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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 muscle characteristics in Multiple Sclerosis: a feasibility study

Kristof Geladé

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

PROMOTOR :
Prof. dr. Bert OP 'T EIJNDE

COPROMOTOR :
De heer Charly KEYTSMAN

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www.uhasselt.be
Universiteit Hasselt
Campus Hasselt:
Martelarenlaan 42 | 3500 Hasselt
Campus Diepenbeek:
Agoralaan Gebouw D | 3590 Diepenbeek

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de Bormanlaan 2, 3730 Hoeselt (Belgium), 25 May 2018 K.G.

Context of the master thesis

This master's thesis is part of the research domain rehabilitation of cardiorespiratory and internal disorders. In particular, it focusses on the cardiorespiratory rehabilitation of 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, exercise therapy is a potent strategy to tackle these secondary deficits and 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]. More importantly, high-intensity interval training (HIIT) combined with resistance training shows superior results on exercise capacity and muscle characteristics compared to continuous endurance training[9]. Furthermore, HIIT is a time-efficient strategy to implement training in daily living[10]. However, PwMS seem to express higher subjective fatigue following HIIT and therapy adherence is rather low[11]. In an attempt to improve high-intense exercise performance, HIIT-related feasibility and adherence, a periodized, HIIT-oriented, home-based, remotely supervised exercise program in combination with supplementation is investigated. β-alanine (BA), an ergogenic aid used to enhance muscle carnosine content[12, 13] (which is lowered in PwMS)[14] and consequently high-intense training efficiency[15, 16], might lead to improved rehabilitation outcomes in PwMS when combined with an exercise program.

This master's thesis is executed in cooperation with two other master students (Ine Nieste and Maarten Van Herck) under the supervision of drs. 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 BA-supplementation on the effects of a home-based rehabilitation program in PwMS.

The experimental study was a master thesis project conducted by Maarten Van Herck, Ine Nieste and Kristof Geladé and 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 is the effect of a home-based, HIIT-oriented periodized rehabilitation program in combination with BA-supplementation for 24 weeks on muscle characteristics, exercise capacity and body composition in PwMS?"

The students have assisted in patient recruitment by phone calls and by attending info sessions. They were actively involved in pre- and post-intervention measurements as well as the data-acquisition, collection and statistical analysis using SPSS statistics 25. The research protocol was designed by mutual agreement between prof. dr. Bert Op 't Eijnde and drs. Charly Keytsman before master thesis topics were assigned.

The topic of this master's thesis was divided in two parts. The first part, which discusses the impact of the protocol on exercise capacity and body composition, was written by Ine Nieste and Maarten Van Herck. The second part, and thus the content of the present thesis, focusses on muscle characteristics and body composition and was written by Kristof Geladé

Reference list

1. Blikman LJ, van Meeteren J, Horemans HL, et al. Is physical behavior affected in fatigued persons with multiple sclerosis? *Arch Phys Med Rehabil*. 2015; 96: 24-9.
2. Wens I, Dalgas U, Vandenabeele F, Krekels M, Grevendonk L and Eijnde BO. Multiple sclerosis affects skeletal muscle characteristics. *PLoS One*. 2014; 9: e108158.
3. Heine M, van de Port I, Rietberg MB, van Wegen EE and Kwakkel G. Exercise therapy for fatigue in multiple sclerosis. *Cochrane Database Syst Rev*. 2015; 11: CD009956.
4. Kent-Braun JA, Ng AV, Castro M, et al. Strength, skeletal muscle composition, and enzyme activity in multiple sclerosis. *J Appl Physiol (1985)*. 1997; 83: 1998-2004.
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. *J Neurol Sci*. 2016; 367: 107-21.
6. Zwibel HL and Smrtka J. Improving quality of life in multiple sclerosis: an unmet need. *Am J Manag Care*. 2011; 17 Suppl 5 Improving: S139-45.
7. Durstine JL, Painter P, Franklin BA, Morgan D, Pitetti KH and Roberts SO. Physical activity for the chronically ill and disabled. *Sports Med*. 2000; 30: 207-19.
8. Latimer-Cheung AE, Pilutti LA, Hicks AL, et al. Effects of exercise training on fitness, mobility, fatigue, and health-related quality of life among adults with multiple sclerosis: a systematic review to inform guideline development. *Arch Phys Med Rehabil*. 2013; 94: 1800-28 e3.
9. 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.
10. Zaenker P, Favret F, Lonsdorfer E, Muff G, de Seze J and Isner-Horobeti ME. High-intensity interval training combined with resistance training improves physiological capacities, strength and quality of life in multiple sclerosis patients: a pilot study. *Eur J Phys Rehabil Med*. 2018; 54: 58-67.
11. Dawes H, Collett J, Meaney A, et al. Delayed recovery of leg fatigue symptoms following a maximal exercise session in people with multiple sclerosis. *Neurorehabil Neural Repair*. 2014; 28: 139-48.
12. 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: 2461-72.
13. 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: 279-89.
14. Keytsman C, Blancquaert L, Wens I, et al. Muscle carnosine in experimental autoimmune encephalomyelitis and multiple sclerosis. *Mult Scler Relat Disord*. 2018; 21: 24-9.
15. Saunders B, Elliott-Sale K, Artioli GG, et al. β-alanine supplementation to improve exercise capacity and performance: a systematic review and meta-analysis. *British Journal of Sports Medicine*. 2017; 51: 658.
16. Bellinger PM. beta-Alanine supplementation for athletic performance: an update. *J Strength Cond Res*. 2014; 28: 1751-70.

Content

1. Abstract

Background: Concurrent high-intensity interval training (HIIT) in a rehabilitation setting improves muscle strength in persons with MS (PwMS). Muscle carnosine content (MCC), an intracellular pH-buffer, is decreased in PwMS. β-alanine (BA) is able to increase MCC and consequently decrease exercise-induced acidosis which may enhance rehabilitation outcomes.

Aim: To investigate the feasibility and effects of a HIIT-oriented, periodized, home-based training program in MS and the ability of BA to fortify these effects.

Methods: This double-blind, placebo-controlled randomized feasibility study consisted of a 24-week periodized, home-based cycling training program and supplementation with either BA or placebo. A 3-week training cycle (comprising a volume, HIIT and recuperation week) was repeated eight times. PwMS (n=23; EDSS=1.83 ± 1.13) and healthy controls (HC; n=22) were allocated to a BA- (MS_{BA}, n=12; HC_{BA}, n=11) or a placebo-group (MS_{PL}, n=11; HC_{PL}, n=11).

Measurements: Lower limb (quadriceps/hamstrings strength at a knee angle of 45°/90°) and core muscle strength (abdominal/lumbar strength at a hip angle of 90°/120°), as well as body composition (fat-mass, lean-mass and fat-percentage) were assessed at baseline and post-intervention.

Results: Lumbar (90°) extension strength (+6.3%; P=0.05), fat-mass (-6.1%; P=0.009) and fat-percentage (-4.0%; P=0.015) improved significantly after six months of intervention. For all participants, right quadriceps strength (45°/90°) decreased (-7.6%; P=0.03, -8.9%; P<0.001) over time, as well within MS_{PL}- (-10.3%; P=0.048), HC_{PL}- (-10.2%; P=0.014) and HC_{BA}-groups (-12.5%; P=0.004) at 90°. Left quadriceps strength (90°) decreased over time (-7.6%; P=0.002) and within the MS_{BA}-group (-7.5%; P=0.03). Training adherence was 86-92%.

Conclusion: Home-based HIIT without resistance training appears feasible and effective to improve body composition, but did not enhance muscle strength in MS (EDSS=0-4), except lumbar extension strength. BA-supplementation does not appear to influence rehabilitation outcomes in MS although further research is warranted.

Keywords: Multiple Sclerosis, β-alanine supplementation, exercise therapy, home-based training, training periodization, muscle

Registration: ClinicalTrials.gov NCT03418376

2. Introduction

Multiple Sclerosis (MS) is a progressive, autoimmune, neurodegenerative disorder characterized by chronic inflammatory processes that cause demyelination and axonal damage throughout the central nervous system[1]. Clinical manifestations include neurological deficits, fatigue, walking impairments and a reduced exercise capacity[2]. These symptoms often lead to a sedentary lifestyle and a vicious circle of physical disability[3]. The inactivity related disuse contributes to muscle atrophy, a dominance of type IIa fibers and a decrease of the oxidative capacity of the muscle[4]. Moreover, muscle strength of the lower limbs, which is decreased in MS, is a key determinant of the ambulatory capacity[5]. Consequently, these skeletal dysfunctions negatively influence the functional capacity and quality of life (QoL)[4]. Moreover, due to limited core stability, required to maintain the centre of gravity into the base of support, instability and risk for falls are a frequent problem in persons with multiple sclerosis (PwMS)[6]. Although pharmalogical therapy addresses MS-related symptoms and exacerbations, it has no impact on this cascade of muscular deconditioning[7]. As such, any strategy that improves muscle strength and characteristics in MS is interesting to investigate.

Exercise therapy has become the cornerstone of rehabilitation in MS and is safe and well-tolerated[8, 9]. Furthermore, exercise therapy is effective to improve physical fitness, muscular strength/function, disease-related symptoms and QoL in PwMS[10]. However, despite these substantial benefits, only 43 percent of PwMS are reported to participate in an organised training program. Here, lack of time, as muscle strengthening programs are time-consuming, and travel distance/transportation are important barriers[11]. To overcome lack of time, high-intensity interval training (HIIT) may be a potential alternative. Although session duration is much shorter, superior results in muscle strength and exercise capacity[12-14] have been reported compared to aerobic endurance training. Interestingly, HIIT on a cycle ergometer has been shown to improve muscle strength and characteristics of the lower limb in patients with muscular deconditioning comparable with PwMS[15-17]. Moreover, electromyography studies demonstrated that cycling increased activity of the trunk musculature[18]. The impact of HIIT, without resistance training, on lower limb and trunk musculature however, has not been investigated yet in MS.

Training at higher intensities is associated with reduced adherence and higher subjective fatigue[19, 20]. This supports the necessity to optimize high-intense training protocols, in order to enhance training efficiency and thus clinical outcome. A possible strategy is the implementation of periodization principles, which are commonly used in the sports community. Here, every one to four

weeks block focusses on a specific target ability of physical fitness[21]. In well-trained cyclists, high-intensity (HI) - training combined with block periodization showed greater improvements in aerobic capacity and peak power output compared to traditional HI-training[22, 23]. As such, the use of periodization principles may be more effective compared to classic progressive training. So far, this training method has not been explored in PwMS. Furthermore, to solve the barrier of transportation to rehabilitation facilities, home-based training could be a potent strategy. Recently, it has been shown that home-based exercise training is feasible and safe in PwMS[24, 25]. Physical rehabilitation at home reduced fall risk and improved functional capacity, muscle strength and balance in this population[26-28]. Since internet-based supervised rehabilitation has proven to be effective with a high patient satisfaction[26], this digital method might be used to increase adherence, which is rather low in a home-based setting[27].

Ergogenic aids are widely used in sport populations to optimise high-intense training performance. In this regard, β-alanine (BA)-supplementation, which enhances muscle carnosine content (MCC), has become a popular ergogenic aid. Muscle carnosine positively influences muscle contractile apparatus by increasing Ca2+-sensitivity[29]. Secondly, Boldyrev, Aldini, and Derave (2013) reported that BA acts as an important muscular lactate buffer during exercise performed at high-intensity[30]. The ergogenic action of BA is optimal in exercise types lasting 1-4 min[31]. Interestingly, recent literature showed that muscle carnosine is reduced in experimental auto-immune encephalomyelitis (EAE) mice and PwMS[32]. A decrease in MCC may contribute to increased exercise-related fatigue and limit HI-performance[33]. Furthermore, oral ingestion of BA has been shown to increase MCC in healthy persons[34] and EAE-mice[35]. Hence, BA-supplementation may increase training volume and feasibility and thereby lead to improved HI-exercise performance[36]. However, this was never investigated in MS.

Therefore, the aim of this study was to explore the impact of a HIIT-oriented, periodized, home-based training program on muscle strength and body composition in MS and the ability of BA to fortify these effects. We hypothesized that this intervention improved muscle strength and body composition in PwMS and that BA-supplementation induced superior clinical outcomes.

3. Methods

3.1. Subjects

Participants were recruited through local advertisement in cooperation with the non-profit association 'Move to Sport' and were included following approved written informed consent. Sixty-six subjects were assessed for eligibility and 45 were enrolled in the study, of which 23 persons with MS (PwMS; EDSS range 0-4, mean ± SD; 1.83 ± 1.13) and 22 healthy controls (HC). Subjects were asked to maintain their usual medication constant during the entire study course and were excluded if they experienced an acute MS exacerbation three months prior to the start of the study, were already taking nutritional supplements in the previous six 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).

3.2. Study design

This double-blind, placebo-controlled, feasibility study was conducted between March 2017 and September 2017. Patient recruitment started in February 2016. All measurements took place at the Rehabilitation Research Centre of Hasselt University (REVAL) at Diepenbeek, Belgium. Medical safety was evaluated by a trained professional before any other measurement took place. Isometric muscle strength and body composition were measured two weeks before start of the intervention (w0) and one week after completion (w26). A detailed overview of the study design can be found in the appendix (figure 2). All subjects underwent baseline measurements prior to randomization. PwMS and HC were assigned to BA-supplementation or placebo (PL) supplementation for 24 weeks using randomization software and sealed enveloppes: a) PwMS + BA-supplementation (MS_{BA}, n=12), b) PwMS + PL-supplementation (MS_{PL}, n=11), c) HC + BA-supplementation (HC_{BA}, n=11) or d) HC + PL-supplementation (HC_{PL}, n=11). Subjects and affect-assessors were blinded (BA vs PL) to group allocation. The intervention consisted of a 24-week home-based training program (identical for all groups) and supplementation with either BA or PL. Personalized training schedules were sent by mail and adherence to it and physical activity (PA) were monitored using smartwatches and an online registration system (flow.polar.com) during the course of the study. Smartwatches (Polar®

M200) were distributed during an information session at baseline. After baseline measurements, one habituation week (w1) was organized to prevent technical issues during the intervention.

3.3. Outcome measures

3.3.1. Muscle Strength

Isometric muscle strength of the hamstrings, quadriceps, abdominal muscles and back extensors was measured at different joint angles using an isokinetic dynamometer (System 3, Biodex®, ENRAF NONIUS, New York, USA). A standardized warm-up of ten minutes on a cycle ergometer is followed by a familiarization trial for each muscle group. Each maximal contraction lasted four seconds and was repeated three times at a specific joint angle. Between each contraction, a short rest period of ten seconds was provided and an alternation between flexion and extension. Standardized verbal encouragements were giving throughout the test. Knee flexion and extension were measured at an angle of 45° and 90°, abdominal flexion and extension were measured in a lumbar isolated (hip angle of 90°) and a semi-standing position (hip angle of 120°). The semi-standing position allows hip involvement in the force development, whereas the lumbar isolated position induces an isolated lumbar movement. Patients had to cross the arms over their chest and were not allowed to hold the devices handles. Belts were used to stabilise the limb during the contraction. The highest peak torque of each movement is elected as maximal isometric muscle strength. Patients were asked to refrain from intense exercise 24 hours before testing. The Biodex (System 3, Biodex®, ENRAF NONIUS, New York, USA) is shown to be a reliable and valid instrument for assessment of isometric muscle strength of the lower extremity and the abdominal muscle function in HC and PwMS[37, 38].

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 assess fat-mass (kg), lean-mass (kg) and fat-percentage (%) of the whole body (with exclusion of the head) pre- and post-intervention. Participants were positioned supine with minimal clothing, without jewellery and were assessed in a rested state to maximize precision[39, 40]. Excellent inter-rater and test-retest reliability are reported

to evaluate body composition using this method[41, 42]. A calibrated analogue weight scale (Seca®) was used to measure total body mass.

3.3.3. Physical activity

Throughout the 24-week training program participants continuously wore a Polar® M200 during daytime. The device registered training data including the amount of training sessions, duration, average HR and HR-pattern. Data was visible for participants and effect-assessors at 'https://flow.polar.com, where adherence was checked. To evaluate high-intensity interval sessions, an analysis was executed to determine the percentage of sprint bouts in which participants could reach a HR above 90% of the HR-max.

3.4. Intervention

3.4.1. Supplementation

Subjects received a daily dose of BA (β-alanine; β-alanine, Cellullose, HPMC, Magnesium Stearaat, Silicium dioxide, Zinc Bisglycinate; Aminolabs® Hasselt, Belgium) that varied across 3.2 $g*day^{-1}$(loading phase, w2-13, 4x800 mg) and 1.6 $g*day^{-1}$ (maintenance phase, w14-25, 2x800 mg) or an equivalent amount of PL (Maltodextrin; Cellullose, Glycine, HPMC, Magnesium Stearaat, Silicium dioxide; Aminolabs® Hasselt, Belgium) for 24 consecutive weeks. Doses did not exceed 800 mg and were sustained-release tablets to prevent paresthesia[43]. Tablets were ingested orally 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 MCC in healthy subjects[34, 44]. Supplements and placebo tablets were provided in identical white tubes and were identical in colour and taste.

3.4.2. Training

Individualized training schedules, based on % of maximal heart rate (HR_{max}) measured at baseline, were provided every 3-week by mail and were executed outdoor (own bike), or indoor (bike rollers or spinning bikes). The smartwatches enabled subjects to train at prescribed exercise intensities (%

HRmax) and monitored adherence to the exercise program. 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 were advised to train on specific days. However, minor deviations were 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 during the intervention period. The 24-week home-based training program consisted of three-week training cycles (meso-cycle) which were 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 recuperation week (week III). Schematic illustration of the training protocol can be found in the appendix (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 moderate intensity and longer duration (2-3 hours, 60-80% HRmax) and one session of higher intensity (HI) and shorter duration (1-1.5 hour, 75-90% HRmax). During HIIT-sessions, three exercise bouts of 60-90 seconds (100% HR-max) were alternated with recuperation bouts of 2-3 minutes (low, self-chosen intensity). The recuperation week consisted of one HIIT-session (100% HRmax, three exercise bouts of 70-90 seconds each, three minutes recuperation bouts) and one, optional volume training (2-3 hours, 70-90%HRmax). Furthermore, each training session included a standardized warming-up (10 min, 50-70% HRmax) and cooling-down (10 min, 60-80%HRmax).

3.5. Statistical analysis

All data were analyzed using SPSS v. 25.0 (IBM). A one-way analysis of variances was used to compare the groups (MS_{BA}, MS_{PL}, HC_{BA} and HC_{PL}) at baseline and to analyze training data. Normality and homoscedasticity were checked (Shapiro-Wilk and Brown-Forsythe test) for all outcome variables (body composition and strength). Since the strength data were not normally distributed, an extra log transformation was executed. The transformed and non-transformed strength data were analyzed by statistical tests and the degree of agreement was compared. A mixed model repeated measures ANOVA with time as a within-subject variable (pre- and post- intervention) and supplementation (BA and PL) and patient (MS and HC) as between-subject variables was used. This model was executed to assess whether muscle strength and body composition changed over time (T1 and T2) and to evaluate time x participant x supplementation interactions. Post-hoc analysis of the difference scores using unpaired t-test with a Bonferonni correction was used to investigate between-group differences. Differences within groups (post minus pre-intervention) were analyzed with a paired student's t-test. All data are presented as means ± SD and percentages and considered significant when $p<0.05$ (2-tailed) or $p<0.008$ (between groups with a Bonferonni correction). Intention-to-treat analysis was applied in case of missing data.

4. Results

4.1. Subject characteristics and baseline measurements

Subject characteristics were not significantly different between groups (P>0.05). A detailed overview can be found in the appendix (Table 1). Primary and secondary endpoints were comparable (P>0.05, Table 2) at baseline between the four groups.

4.2. Adherence and adverse events

During the course of the study, nine subjects (MS, n=6; HC, n=3) dropped out due to MS-exacerbations (n=1), musculoskeletal 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 sessions were due to MS-related exacerbations, holiday, musculoskeletal injuries (not related to the training program) and personal reasons. No adverse events were reported during the course of the study.

When analyzing adherence to prescribed training intensities and more specific HI-bouts (≥90% of HR_{max}), 34.33% ± 25.38% of all HI-bouts were accomplished. PwMS and HC reached 30.34% ± 24.98% and 38.60% ± 25.96% of the HI-bouts with no significant difference between groups (P=0.374). Accomplishment of target heart zones (≥ 90% HR_{max}) was also comparable (P=0.35) between BA-groups (30.39% ± 26.14%) and PL-groups (39.12% ± 24.51%).

4.3. Muscle characteristics

Right knee extension force at 45° and 90° (RE45° and RE90°) decreased 7.6% (MD = -12.54N; P=0.03) and 8.9% (MD = -17.31N; P<0.001), respectively in all subjects over time. Isometric muscle strength of the left quadriceps at 90° (LE90°) decreased 7.6% (MD = -15.21N; P=0.002), whereas isolated lumbar extension strength (LuE90°) increased 6.3% (MD = +16.00N; P=0.05). The transformed data set showed comparable P-values (Table 3). An overall interaction effect (time x group x supplementation) was found for RF90° (P = 0.032, non-transformed data) and in LF90° (P=0.028, transformed data). No differences were observed between all four groups (P>0.008; Table 4), between the two types of participants (MS vs HC; P>0.05; Table 5) or between supplementation

groups (BA vs PL; P>0.05; Table 6) in the difference scores (post minus pre-intervention), except for semi-standing flexion forces at 120° (SF120°; P=0.04).

Within the MS_{PL}-, the HC_{PL}- and the HC_{BA}-group, RE90° decreased significant with 10.3% (MD = -19.00N; P=0.048), 10.2% (MD = -21.62N; P=0.014) and 12.5% (MD = -25.28N; P=0.004), respectively over time. Moreover, LE90° decreased 7.5% (MD = -14.10N; P=0.03) within the MS_{BA}-group. Other within group results did not reach significance (P>0.05; Table 4).

4.4. Body composition

Following 24 weeks of training, a significant reduction in fat mass of 6.1% (MD = -0.985kg; P=0.009) and fat percentage of 4.0% (MD= -0.94%; P = 0.015) was found for all participants (Table 3). Neither an interaction effect (P>0.05) nor a significant difference between groups (P>0.05) in difference scores (post minus pre intervention) was found. Moreover, body composition did not change significantly within groups over time (P>0.05, Table 4).

5. Discussion

The present study was the first to investigate the effect of a 24-week periodized, home-based, high-intensity oriented training program on muscle strength and body composition in PwMS either or not in combination with BA-supplementation. The main findings of the present study are that home-based HIIT improved isolated lumbar extension forces, whereas lower limb muscle strength and other measurements of core stability did not increase. Interestingly, HI-training had a positive impact on body composition. Furthermore, the addition of BA-supplementation did not induce superior effects.

Exercise therapy is a cornerstone in the rehabilitation of PwMS and recent studies have shown that HIIT combined with resistance training was well tolerated and induced superior results on muscle strength and exercise capacity compared to moderate intensity training[12, 16, 45]. Interestingly, since resistance training is time-consuming, the implementation of a HIIT-program without strength training may be a time-efficient alternative[46] in which the elevated workload during HI-cycling bouts could provide a strength stimulus. Indeed, previous studies in severely deconditioned patients confirmed this showing significant improvements in lower limb muscle strength after HIIT without resistance training[15, 17]. However, and in contrast to the above mentioned studies[12, 45], muscle strength of the lower limb did not improve in PwMS and HC after six months of training and even decreased at different angles. A possible explanation is the training principle 'specificity' which means that the impact of the training program depends on the applied exercise mode[47]. Moreover, discordance with previous articles in severely deconditioned patients[15, 17] might be due to the fact that the included MS patients in our study were mildly disabled (mean EDSS score: 1.83) without severe muscle deconditioning and therefore strength gains were rather limited. This hypothesis is confirmed since no significant difference in muscle strength are found between HC and PwMS at baseline. Furthermore, measurements of muscle endurance (isokinetic strength) would have been more sensitive compared to the applied isometric tests, since training on a bicycle consists of repeated cyclical movements and therefore could delay neuromuscular fatigue[48]. In line with the above mentioned reasoning, Bagley et al. (2018) reported that sprint interval training improved fatigue resistance, whereas isometric muscle strength remained unchanged[49].

Core stability, a major determinant of balance and frequency of falls, is decreased in MS[50]. During cycling, trunk musculature is activated to maintain balance and interestingly, HI-cycling has been shown to elicit significant more trunk activity[51, 52]. Under the conditions of the present study, the

trunk extension strength in a lumbar isolated position improved significantly, whereas other core stability measurements did not improve. The posture during this type of training is comparable to the lumbar isolated (90°) test position, which could attribute to the fact that the improvements were only significant in this position. Moreover, this study suggests in general that this training protocol provoked similar strength changes in PwMS as in HC, except for core extension strength in a semi-standing position (SE120°), possibly due to one outlier (> 2SD) (table 5). Probably, the implementation of specific resistance training is required to achieve superior effects on muscle strength in PwMS.

Analysis of the training data demonstrated that both PwMS and HC did not always reach target heart zones above the anaerobic threshold (≥ 90% HRmax) during the HIIT-sessions. However, a wearable heart rate monitor (Polar® M200) was used to register HR during training sessions which could influence the sensitivity of the measurement. Gillinov et al. (2017)[53] revealed that the accuracy of a wrist-worn HR monitor was limited during vigorous exercise with a underestimation of the HR. They concluded that a chest strap with electrodes should be used to accurately determine heart rates during training sessions.[53] The training data of our study support this reasoning, since both PwMS and HC did not always seem to reach maximal target heart rate zones. However, participants were specifically instructed to perform maximally during the HI-bouts ('all-out sprints'). Possibly, a dysfunctional autonomic control and a delay in heart rate increase during exercise might also contribute to the impaired anaerobic training accomplishment[54, 55]. However, further research using a chest strap is warranted to investigate the capacity of PwMS to reach near-maximal and maximal heart rates during short sprint bouts at home and in a rehabilitation setting, since this is never explored before.

Furthermore, analysis of body composition after the intervention period showed a significant decrease in fat-mass and fat-percentage whereas lean mass remained stable. In contrast, previous studies showed that HIIT induced an increase in lean-mass and did not change fat-mass or fat-percentage in PwMS [12, 56]. Unfortunately, food consumption (caloric intake) was not monitored during the course of the study. HI-exercise could lead to an energy deficit by increasing rest energy expenditure (REE)[57] and suppression of appetite signals[58]. Therefore, these factors could lead to a deficit of proteins and other energy sources in the human body and thus limit the process of muscle hypertrophy. Further research should take into account the dietary habits of participants during the course of the study to exclude this confounding variable. Furthermore, body composition did not

change within the four subgroups over time, but this may be attributed to the rather small number of participants.

Since only 43 of the PwMS were reported to participate in organised exercise therapy[11], the HIIT-oriented training program in this study was executed at home with the implementation of periodization to increase therapy adherence and feasibility. Training adherence in this study was excellent (86-92%) and about 25 to 30 percent higher compared to other home-based exercise programs[28, 59]. This may be due to the use of internet-based supervision and feedback. Moreover, since PwMS exhibited higher subjective leg fatigue after HI-exercise compared to other intensities[20], the use of periodization may have improved feasibility by alternating HIIT with other training stimuli. Indeed, the participants reported during a non-standardised questioning that the variation in training intensity made the training protocol more comfortable. In addition, the periodized training scheme in this study was able to enhance exercise capacity in the same group of participants (findings of colleagues Ine Nieste and Maarten van Herck), but the effects on isometric strength were limited. Possibly, the use of a recuperation week in the meso-cyclus may have led to insufficient training incentives to induce a process of muscle overload[60].

Furthermore, the effects of BA-supplementation on HI- training performance and subsequent outcome measures were investigated. In PwMS, a recent study reported that high-intensity exercise was associated with elevated subjective leg fatigue and ratings of perceived exertion (RPE) after exercise[19]. β-alanine (BA), which is an intracellular lactate buffer, may influence recovery from high-intense exercise and thereby improving training feasibility and rehabilitation outcomes. Though, BA-supplementation combined with exercise did not induce greater improvements in muscle strength and body composition compared to exercise alone in PwMS in this study. This is in accordance with previous articles in sedentary subjects where BA-supplementation did not improve muscle strength/power or body composition[61, 62]. Possibly, the subjective fatigue after high-intensity exercise and the impaired training capacity in MS is not solely related to serum lactate, but also to body temperature[20-63]. This is in line with the findings of a recent study, where muscle lactate was not higher during HI-exercise in PwMS compared to healthy controls[56]. Hence, the impact of BA-supplementation on the execution of HIIT and consequently on improvements in muscle strength could be limited in this study. Another possible explanation can be found in the mild disability status of the PwMS in this study. Though Keytsman et al. (2018) revealed a decrease in MCC in PwMS, the degree of disability (mean EDSS: 3.1) was higher in comparison with the present study (mean EDSS:

1.83)[32]. Consequently, the decrease in MCC and the effectiveness of BA-supplementation protocol is not confirmed in this mildly disabled population.

5.1. Limitations of the study

This study holds certain limitations. The MCC was not directly measured and therefore we cannot guarantee that the muscle carnosine was decreased in this mildly disabled MS-population. Consequently, the effectiveness of the supplementation protocol to increase MCC cannot be demonstrated under the present conditions. However, an increase in muscle carnosine can be assumed since an evidence-base supplementation protocol was used[34]. In addition, adherence to the prescribed supplementation scheme was not monitored. Because of practical considerations, the DEXA-scan was not executed in a fasted and euhydrated state, although this is recommended to augment reliability[39, 40]. Another limitation was the absence of a Borg RPE (ratings of perceived exertion) questioning after each training session to assess feasibility of the training and the degree of fatigue. Furthermore, dietary habits and medication intake of the participants during the course of the study were not registered. The fact that only mildly-to moderate disabled MS-patients were included, limits the external validity of the results. Finally, the feasibility of the current results may be limited due to the small sample size and limited power.

6. Conclusion

Home-based HIIT-oriented training appeared to be feasible and provided good adherence in mildly affected persons with MS. This program, without implementation of resistance training, was able to improve body composition, but not lower limb muscle strength in MS. Although strength of the trunk musculature improved significantly following HIIT on a cycle ergometer, other strategies to affect muscle strength should be implemented in MS rehabilitation. Furthermore, supplementation with β-alanine did not affect rehabilitation outcomes.

7. References

1. Tullman MJ. Overview of the epidemiology, diagnosis, and disease progression associated with multiple sclerosis. *Am J Manag Care*. 2013; 19: S15-20.
2. Noseworthy JH, Lucchinetti C, Rodriguez M and Weinshenker BG. Multiple sclerosis. *N Engl J Med*. 2000; 343: 938-52.
3. Veldhuijzen van Zanten JJ, Pilutti LA, Duda JL and Motl RW. Sedentary behaviour in people with multiple sclerosis: Is it time to stand up against MS? *Mult Scler*. 2016; 22: 1250-6.
4. Kent-Braun JA, Ng AV, Castro M, et al. Strength, skeletal muscle composition, and enzyme activity in multiple sclerosis. *J Appl Physiol (1985)*. 1997; 83: 1998-2004.
5. Broekmans T, Gijbels D, Eijnde BO, et al. The relationship between upper leg muscle strength and walking capacity in persons with multiple sclerosis. *Mult Scler*. 2013; 19: 112-9.
6. Amiri B, Sahebozamani M and Sedighi B. The effects of 10-week core stability training on balance in women with Multiple Sclerosis according to Expanded Disability Status Scale: a single-blinded randomized controlled trial. *Eur J Phys Rehabil Med*. 2018; 2: 04778-0.
7. Perry M, Swain S, Kemmis-Betty S and Cooper P. Multiple sclerosis: summary of NICE guidance. *Bmj*. 2014; 349: g5701.
8. Zwibel HL and Smrtka J. Improving quality of life in multiple sclerosis: an unmet need. *Am J Manag Care*. 2011; 17 Suppl 5 Improving: S139-45.
9. Dalgas U, Stenager E, Jakobsen J, et al. Resistance training improves muscle strength and functional capacity in multiple sclerosis. *Neurology*. 2009; 73: 1478-84.
10. Latimer-Cheung AE, Pilutti LA, Hicks AL, et al. Effects of exercise training on fitness, mobility, fatigue, and health-related quality of life among adults with multiple sclerosis: a systematic review to inform guideline development. *Arch Phys Med Rehabil*. 2013; 94: 1800-28 e3.
11. Stroud N, Minahan C and Sabapathy S. The perceived benefits and barriers to exercise participation in persons with multiple sclerosis. *Disabil Rehabil*. 2009; 31: 2216-22.
12. 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.
13. Farup J, Dalgas U, Keytsman C, Eijnde BO and Wens I. High Intensity Training May Reverse the Fiber Type Specific Decline in Myogenic Stem Cells in Multiple Sclerosis Patients. *Front Physiol*. 2016; 7: 193.
14. Wens I, Dalgas U, Verboven K, et al. Impact of high intensity exercise on muscle morphology in EAE rats. *Physiol Res*. 2015; 64: 907-23.
15. Taya M, Amiya E, Hatano M, et al. High-intensity aerobic interval training can lead to improvement in skeletal muscle power among in-hospital patients with advanced heart failure. *Heart Vessels*. 2018; 15: 018-1120.
16. Keogh JWL, Grigg J and Vertullo CJ. Is Home-Based, High-Intensity Interval Training Cycling Feasible and Safe for Patients With Knee Osteoarthritis?: Study Protocol for a Randomized Pilot Study. *Orthop J Sports Med*. 2017; 5: 2325967117694334.
17. Bellumori M, Uygur M and Knight CA. High-Speed Cycling Intervention Improves Rate-Dependent Mobility in Older Adults. *Med Sci Sports Exerc*. 2017; 49: 106-14.
18. Suzuki T, Hirata J, Ohtsuki K and Watanabe S. Electromyographic and haemodynamic activities in lumbar muscles during bicycle ergometer exercise and walking. *Electromyogr Clin Neurophysiol*. 2010; 50: 213-8.
19. Dawes H, Collett J, Meaney A, et al. Delayed recovery of leg fatigue symptoms following a maximal exercise session in people with multiple sclerosis. *Neurorehabil Neural Repair*. 2014; 28: 139-48.
20. Collett J, Meaney A, Howells K and Dawes H. Acute recovery from exercise in people with multiple sclerosis: an exploratory study on the effect of exercise intensities. *Disabil Rehabil*. 2017; 39: 551-8.
21. Issurin V. Block periodization versus traditional training theory: a review. *J Sports Med Phys Fitness*. 2008; 48: 65-75.
22. Issurin VB. Benefits and Limitations of Block Periodized Training Approaches to Athletes' Preparation: A Review. *Sports Med*. 2016; 46: 329-38.

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.
24. Learmonth YC, Adamson BC, Kinnett-Hopkins D, Bohri M and Motl RW. Results of a feasibility randomised controlled study of the guidelines for exercise in multiple sclerosis project. *Contemp Clin Trials*. 2017; 54: 84-97.
25. Paul L, Coulter EH, Miller L, McFadyen A, Dorfman J and Mattison PG. Web-based physiotherapy for people moderately affected with Multiple Sclerosis; quantitative and qualitative data from a randomized, controlled pilot study. *Clin Rehabil*. 2014; 28: 924-35.
26. Finkelstein J, Lapshin O, Castro H, Cha E and Provance PG. Home-based physical telerehabilitation in patients with multiple sclerosis: a pilot study. *J Rehabil Res Dev*. 2008; 45: 1361-73.
27. Hoang P, Schoene D, Gandevia S, Smith S and Lord SR. Effects of a home-based step training programme on balance, stepping, cognition and functional performance in people with multiple sclerosis--a randomized controlled trial. *Mult Scler*. 2016; 22: 94-103.
28. Sosnoff JJ, Finlayson M, McAuley E, Morrison S and Motl RW. Home-based exercise program and fall-risk reduction in older adults with multiple sclerosis: phase 1 randomized controlled trial. *Clin Rehabil*. 2014; 28: 254-63.
29. Dutka TL, Lamboley CR, McKenna MJ, Murphy RM and Lamb GD. Effects of carnosine on contractile apparatus Ca(2)(+) sensitivity and sarcoplasmic reticulum Ca(2)(+) release in human skeletal muscle fibers. *J Appl Physiol (1985)*. 2012; 112: 728-36.
30. Boldyrev AA, Aldini G and Derave W. Physiology and pathophysiology of carnosine. *Physiol Rev*. 2013; 93: 1803-45.
31. Hobson RM, Saunders B, Ball G, Harris RC and Sale C. Effects of beta-alanine supplementation on exercise performance: a meta-analysis. *Amino Acids*. 2012; 43: 25-37.
32. Keytsman C, Blancquaert L, Wens I, et al. Muscle carnosine in experimental autoimmune encephalomyelitis and multiple sclerosis. *Mult Scler Relat Disord*. 2018; 21: 24-9.
33. Blancquaert L, Everaert I and Derave W. Beta-alanine supplementation, muscle carnosine and exercise performance. *Curr Opin Clin Nutr Metab Care*. 2015; 18: 63-70.
34. 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: 279-89.
35. Keytsman Cea. Manuscript under review.
36. Bellinger PM. beta-Alanine supplementation for athletic performance: an update. *J Strength Cond Res*. 2014; 28: 1751-70.
37. Drouin JM, Valovich-mcLeod TC, Shultz SJ, Gansneder BM and Perrin DH. Reliability and validity of the Biodex system 3 pro isokinetic dynamometer velocity, torque and position measurements. *Eur J Appl Physiol*. 2004; 91: 22-9.
38. Gunnarsson U, Johansson M and Strigard K. Assessment of abdominal muscle function using the Biodex System-4. Validity and reliability in healthy volunteers and patients with giant ventral hernia. *Hernia*. 2011; 15: 417-21.
39. Tinsley GM, Morales E, Forsse JS and Grandjean PW. Impact of Acute Dietary Manipulations on DXA and BIA Body Composition Estimates. *Med Sci Sports Exerc*. 2017; 49: 823-32.
40. Nana A, Slater GJ, Stewart AD and Burke LM. Methodology review: using dual-energy X-ray absorptiometry (DXA) for the assessment of body composition in athletes and active people. *Int J Sport Nutr Exerc Metab*. 2015; 25: 198-215.
41. Lohman M, Tallroth K, Kettunen JA and Marttinen MT. Reproducibility of dual-energy x-ray absorptiometry total and regional body composition measurements using different scanning positions and definitions of regions. *Metabolism*. 2009; 58: 1663-8.
42. Glickman SG, Marn CS, Supiano MA and Dengel DR. Validity and reliability of dual-energy X-ray absorptiometry for the assessment of abdominal adiposity. *J Appl Physiol (1985)*. 2004; 97: 509-14.
43. Artioli GG, Gualano B, Smith A, Stout J and Lancha AH. Role of beta-Alanine Supplementation on Muscle Carnosine and Exercise Performance. *Med Sci Sports Exerc*. 2010; 42: 1162-73.
44. 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: 2461-72.

45. Zaenker P, Favret F, Lonsdorfer E, Muff G, de Seze J and Isner-Horobeti ME. High-intensity interval training combined with resistance training improves physiological capacities, strength and quality of life in multiple sclerosis patients: a pilot study. *Eur J Phys Rehabil Med*. 2018; 54: 58-67.
46. Gillen JB, Martin BJ, MacInnis MJ, Skelly LE, Tarnopolsky MA and Gibala MJ. 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.
47. Brody LT. Effective therapeutic exercise prescription: the right exercise at the right dose. *J Hand Ther*. 2012; 25: 220-31; quiz 32.
48. Leary TJ, Collett J, Howells K and Morris MG. Endurance capacity and neuromuscular fatigue following high- vs moderate-intensity endurance training: A randomized trial. *Scandinavian journal of medicine & science in sports*. 2017; 27: 1648.
49. Bagley SL, Al-Shanti SN, Bradburn SS, Baig SO, Slevin SM and McPhee SJ. Sex Comparison of Knee Extensor Size, Strength and Fatigue Adaptation to Sprint Interval Training. *Journal of Strength and Conditioning Research*. 2018.
50. Yoosefinejad AK, Motealleh A, Khademi S and Hosseini SF. Lower Endurance and Strength of Core Muscles in Patients with Multiple Sclerosis. *International Journal of MS Care*. 2017; 19: 100-4.
51. Watanabe S, Eguchi A, Kobara K, Ishida H and Otsuki K. Electromyographic activity of selected trunk muscles during bicycle ergometer exercise and walking. *Electromyogr Clin Neurophysiol*. 2006; 46: 311-5.
52. Bulsink VE, Kiewiet H, van de Belt D, Bonnema GM and Koopman B. Cycling strategies of young and older cyclists. *Hum Mov Sci*. 2016; 46: 184-95.
53. Gillinov S, Etiwy M, Wang R, et al. Variable Accuracy of Wearable Heart Rate Monitors during Aerobic Exercise. *Med Sci Sports Exerc*. 2017; 49: 1697-703.
54. Hansen D, Wens I, Dendale P and Eijnde BO. Exercise-onset heart rate increase is slowed in multiple sclerosis patients: does a disturbed cardiac autonomic control affect exercise tolerance? *NeuroRehabilitation*. 2013; 33: 139-46.
55. Senaratne MP, Carroll D, Warren KG and Kappagoda T. Evidence for cardiovascular autonomic nerve dysfunction in multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 1984; 47: 947-52.
56. Keytsman C, Hansen D, Wens I and B OE. Impact of high-intensity concurrent training on cardiovascular risk factors in persons with multiple sclerosis - pilot study. *Disabil Rehabil*. 2017; 27: 1-6.
57. Hunter GR, Moellering DR, Carter SJ, et al. Potential Causes of Elevated REE after High-Intensity Exercise. *Med Sci Sports Exerc*. 2017; 49: 2414.
58. Hazell TJ, Islam H, Townsend LK, Schmale MS and Copeland JL. Effects of exercise intensity on plasma concentrations of appetite-regulating hormones: Potential mechanisms. *Appetite*. 2016; 98: 80-8.
59. Cakt BD, Nacir B, Genc H, et al. Cycling progressive resistance training for people with multiple sclerosis: a randomized controlled study. *Am J Phys Med Rehabil*. 2010; 89: 446-57.
60. Cunanan A, DeWeese B, Wagle J, et al. The General Adaptation Syndrome: A Foundation for the Concept of Periodization. *Sports Medicine*. 2018; 48: 787-97.
61. Hannah R, Stannard RL, Minshull C, Artioli GG, Harris RC and Sale C. beta-Alanine supplementation enhances human skeletal muscle relaxation speed but not force production capacity. *J Appl Physiol*. 2015; 118: 604-12.
62. Smith AE, Moon JR, Kendall KL, et al. The effects of beta-alanine supplementation and high-intensity interval training on neuromuscular fatigue and muscle function. *Eur J Appl Physiol*. 2009; 105: 357-63.
63. Newland P, Van Aman MN, Smith J and Spencer A. Relationship of Fatigue to Heat Sensitivity in Patients With Multiple Sclerosis: A Review for Management. *JNP-J Nurse Pract*. 2018; 14: 100-+.

8. Appendix

8.1. Figures

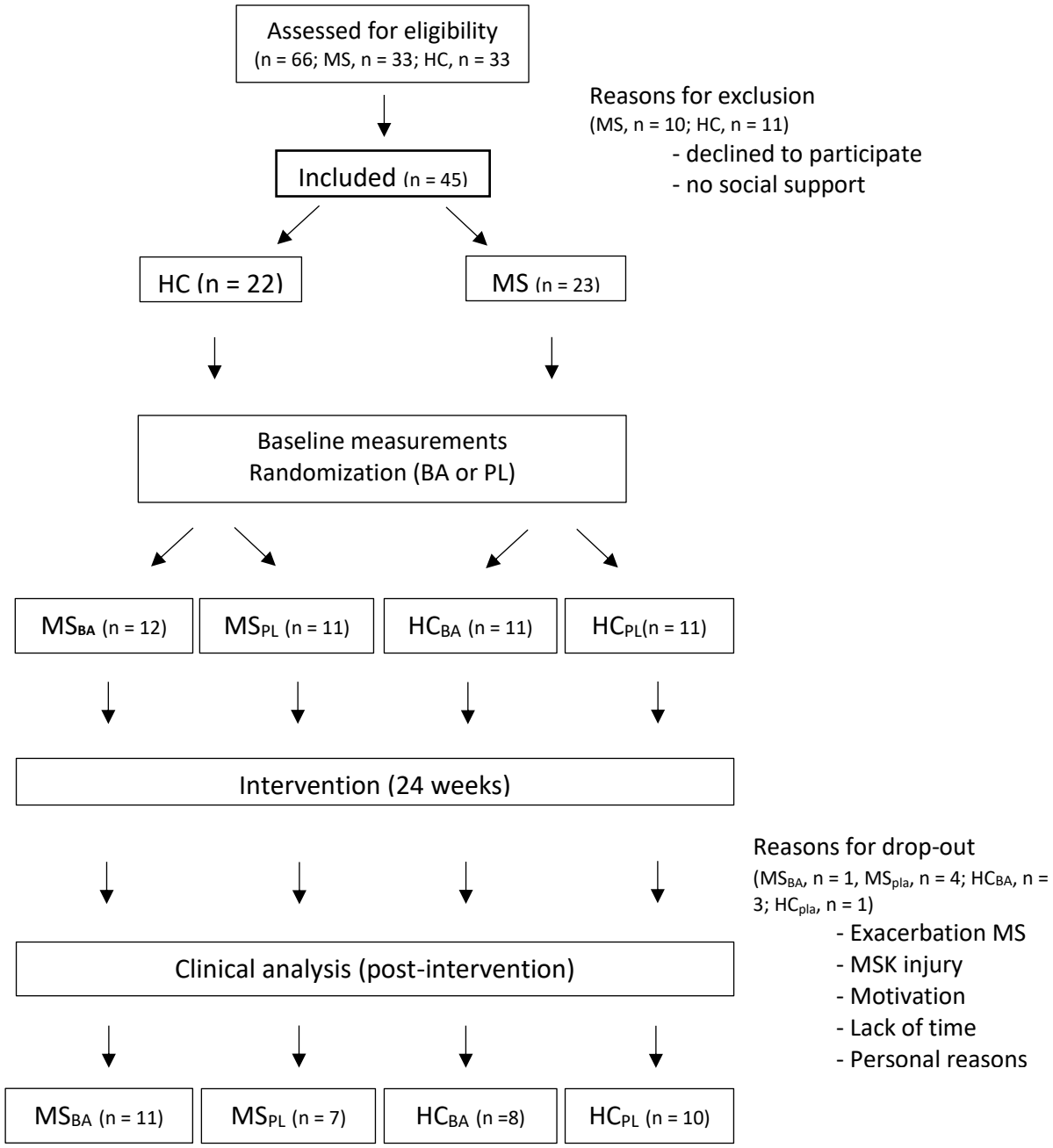

Figure 1. Flowchart

BA: β-alanine; HC: Healthy controls; MS: Multiple sclerosis; MSK: Musculoskeletal; PL: Placebo

Week 0: Pre-intervention (Baseline) measurements

Assessment of medical safety

Muscle strength lower limb (RE45°, RE90°, RF45°, RF90°, LE45°, LE90°, LF45°, LF90°)

Muscle strength core (LuE90°, LuF90°, SE120°, SF120°)

DEXA (FM, LM, TM, FAT%)

Random allocation to supplementation groups (BA or PL)

Week 1: Habituation week

PA registration

Week 2 - week 25: Intervention period

24 weeks during training program

24 weeks during supplementation period

PA registration

Week 26: Post-intervention measurements

Muscle strength lower limb (RE45°, RE90°, RF45°, RF 90°, LE45°, LE90°, LF45°, LF90°)

Muscle strength core (LuE90°, LuF90°, SE120°, SF120°)

DEXA (FM, LM, TM, FAT%)

Figure 2. Study design overview

The muscle strength of the lower limb is represented as isometric right (R) and left (L) extension (E) and flexion (F) forces at 45 degree (45°) or at 90 degree (90°) knee flexion. Isometric core muscle strength is represented as isolated lumbar (Lu) extension (E) and flexion (F) forces at 90 degrees (90°) and semi-standing (S) extension (E) and flexion (F) forces at 120 degrees (120°)
FM: Fat mass; LM: Lean mass; FAT%: Fat-percentage;

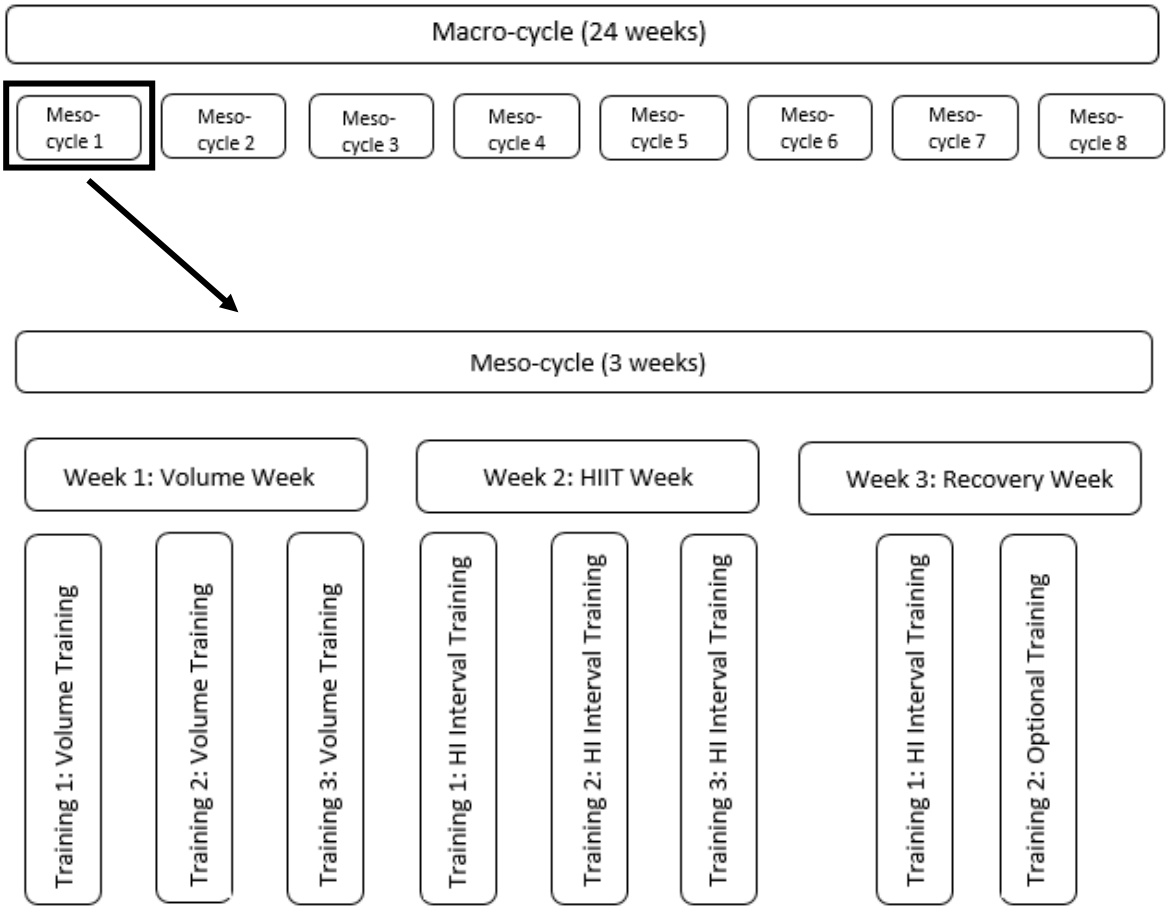

Figure 3. Trainingsprotcol

HI: High Intensity; HIIT: High-Intensity Interval Training

8.2. Tables

Table 1

Subject characteristics

	MS_{BA}	MS_{PL}	HC_{BA}	HC_{PL}	Total group	P-value
EDSS	1.44 ± 1.10	2.42 ± 0.97	/	/	1.83 ± 1.13	0.104
Sex m/f (%)	7/4 (63.6)	4/3 (57.1)	7/1 (87.5)	5/5 (100)	23/13(63.8)	/
Age (years)	41.73 ± 10.02	40.71 ± 7.39	44.13 ±13.00	39.50 ± 11.38	41.44 ± 10.39	0.833
Body weight (kg)	76.22 ± 12.66	73.37 ± 10.89	78.87 ± 12.59	70.91 ± 8.58	74.78 ±11.22	0.484
Body 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/cm2)	25.8 ± 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 the characteristics of the subjects (n=36). EDSS = Expanded Disability Status Scale; m: male; f: female; BMI: body mass index; MS_{BA}: Multiple sclerosis and β-alanine; MS_{PL}: Multiple sclerosis and placebo; HC_{BA}: Healthy control and β-alanine; HC_{PL}: Healthy control and placebo.

* $P < 0.05$: Significant difference between the four groups (MS_{BA}, MS_{PL}, HC_{BA}, HC_{PL}) at baseline.

Table 2

Baseline measurement

Baseline	MS_{BA}	MS_{PL}	HC_{BA}	HC_{PL}	P-value
Fat-mass (kg)	16.82 ± 9.67	16.18 ± 6.31	15.35 ± 5.26	16.50 ± 5.24	0.98
Lean-mass (kg)	51.44 ± 7.05	50.54 ± 8.45	56.79 ± 8.22	50.31 ± 10.81	0.41
Fat-percentage (%)	23.60 ± 10.59	24.04 ± 8.57	20.95 ± 4.75	25.06 ± 8.72	0.79
RE 45 (N)	160.64 ± 25.65	161.86 ± 24.59	175.86 ± 37.50	163.50 ± 31.58	0.74
RF45 (N)	100.18 ± 15.35	92.57 ± 30.05	114.57 ± 24.16	103.90 ± 24.05	0.36
RE90 (N)	189.82 ± 56.42	184.00 ± 41.78	202.14 ± 51.02	202.90 ± 56.89	0.86
RF90 (N)	80.18 ± 15.12	69.14 ± 20.69	92.71 ± 22.19	79.60 ± 23.81	0.22
LE45 (N)	148.91 ± 22.48	162.00 ± 36.15	164.43 ± 28.66	153.20 ± 38.39	0.71
LF45 (N)	100.00 ± 17.35	100.43 ± 35.14	105.43 ± 26.79	98.70 ± 23.46	0.96
LE90 (N)	188.45 ± 57.49	195.57 ± 55.73	194.86 ± 49.26	220.11 ± 53.75	0.62
LF90 (N)	76.40 ± 13.00	71.71 ± 24.06	82.71 ± 27.75	74.11 ± 18.62	0.77
SE120 (N)	279.91 ± 50.90	268.15 ± 66.79	251.71 ± 68.04	262.70± 70.90	0.82
SF120 (N)	148.18 ± 36.62	157.86 ± 46.96	146.29 ± 29.62	145.30 ± 39.37	0.92
LuE90 (N)	257.36 ± 66.19	248.71 ± 74.68	244.29 ± 72.35	256.00 ± 87.67	0.98
LuF90 (N)	132.73 ± 28.89	153.86 ± 45.11	144.71 ± 44.59	149.50 ± 46.62	0.71

Data are expressed as mean (± SD) and represent body composition and muscle strength before (PRE) the start of 24-week intervention. Lower limb muscle strength is represented as isometric right (R) and left (L) extension (E) and flexion (F) forces at 45 degree (45°) or at 90 degree (90°) knee flexion. Isometric core muscle strength is represented as isolated lumbar (Lu) extension (E) and flexion (F) forces at 90 degrees (90°) and semi-standing (S) extension (E) and flexion (F) forces at 120 degrees (120°) hip flexion.

MS_{BA}: Multiple sclerosis and β-alanine; MS_{PL}: Multiple sclerosis and placebo; HC_{BA}: Healthy control and β-alanine; HC_{PL}: Healthy control and placebo.

* $P < 0.05$: Significant difference between the four groups (MS_{BA}, MS_{PL}, HC_{BA}, HC_{PL}) at baseline.

Table 3

Main time effects of the primary outcome measures for all participants

MS + HC				
	PRE	**POST**	**P-values [1]**	**P-values [2]**
Fat-mass (kg)	16.28 ± 6.81	15.29* ± 7.05	0.009*	/
Lean-mass (kg)	52.14 ± 8.75	51.82 ± 8.84	0.24	/
Fat-percentage (%)	23.51 ± 8.42	22.56* ± 9.00	0.02*	/
RE 45 (N)	164.74 ± 29.08	152.20* ± 30.24	0.03*	0.02*
RF45 (N)	102.60 ± 23.18	101.63 ± 22.44	0.93	0.99
RE90 (N)	194.86 ± 51.21	177.54 ± 49.74	0.00*	0.00*
RF90 (N)	80.31 ± 20.91	79.14 ± 19.25	0.35	0.35
LE45 (N)	155.86 ± 30.90	155.66 ± 36.00	0.76	0.65
LF45 (N)	100.80 ± 24.18	100.31 ± 25.28	0.63	0.596
LE90 (N)	199.62 ± 53.59	184.41* ± 53.01	< 0.01*	< 0.01*
LF90 (N)	76.12 ± 20.05	75.91 ± 19.44	0.92	0.96
SE120 (N)	267.00 ± 61.68	267.40 ± 73.34	0.88	0.81
SF120 (N)	148.91 ± 37.02	153.86 ± 39.26	0.20	0.25
LuE90 (N)	252.42 ± 71.46	268.42* ±69.43	0.05*	0.03*
LuF90 (N)	143.82 ± 39.53	148.84 ± 37.77	0.21	0.136

Data are expressed as means (± SD) and represent body composition and isometric muscle strength before (PRE) and after (POST) 24 weeks of intervention. Lower limb muscle strength is represented as isometric right (R) and left (L) extension (E) and flexion (F) forces at 45 degree (45°) or at 90 degree (90°) knee flexion. Isometric core muscle strength is represented as isolated lumbar (Lu) extension (E) and flexion (F) forces at 90 degrees (90°) and semi-standing (S) extension (E) and flexion (F) forces at 120 degrees (120°) hip flexion.

P values[1]: P values non-transformed data; P values[2]: P values transformed data

P <0.05: significant difference between PRE and POST

Table 4

Main time effects of the primary outcome measures within groups

	MS_{BA}		MS_{PL}		HC_{BA}		HC_{PL}	
	PRE	**POST**	**PRE**	**POST**	**PRE**	**POST**	**PRE**	**POST**
Fat-mass (kg)	16.82 ± 9.67	16.41 ± 10.17	16.19 ± 6.31	14.55 ± 5.57	15.35 ± 5.27	14.07 ± 5.49	16.50 ± 5.24	15.57 ± 5.58
Lean-mass (kg)	51.43. ± 7.05	50.45 ± 7.58	50.54 ± 8.45	50.67 ± 8.93	56.79 ± 8.22	56.72 ± 7.86	50.32 ± 10.81.	50.21 ± 10.55
Fat-percentage (%)	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
RE 45 (N)	160.64 ± 25.65	150.36 ± 32.60	161.86 ± 24.59	150.43 ± 25.1	175.86± 37.50	160.00 ± 23.83	163.50 ± 31.58	150.00 ± 37.64
RF45 (N)	100.18 ± 15.35	95.27 ± 15.10	92.57 ± 30.05	97.43 ± 26.46	114.57± 24.16	114.14 ± 22.62	103.90 ± 24.05	102.80 ± 25.59
RE90 (N)	189.82 ± 56.42	181.73 ± 60.34	184.00 ± 41.78	165.00 ± 32.92 [b]	202.14 ± 51.02	176.86 ± 45.52 [b]	202.90 ± 56.89	182.20 ± 55.05 [b]
RF90 (N)	80.18 ± 15.12	76.82 ± 14.55	69.14 ± 20.69	71.86 ± 23.25	92.71 ± 22.19	94.00 ± 18.23	79.60 ± 23.81	76.40 ± 18.85
LE45 (N)	148.91 ± 22.48	153.45 ± 35.30	162.00 ± 36.15	154.57 ± 42.15	164.43 ± 28.66	157.86 ± 31.77	153.20 ± 38.39	157.30 ± 40.49
LF45 (N)	100.00 ± 17.35	92.63 ± 14.63	100.43 ± 35.14	102.86 ± 23.58	105.43 ± 26.79	110.29 ± 34.75	98.70 ± 23.46	100.00 ± 29.10
LE90 (N)	188.45 ± 57.49	174.36 ± 59.11 [b]	195.57 ± 55.73	175.43 ± 42.29	194.86 ± 49.26	181.00 ± 42.53	220.11 ± 53.75	206.33 ± 61.37
LF90 (N)	76.40 ± 13.00	74.00 ± 13.00	71.71 ± 24.06	73.57 ± 18.75	82.71± 27.75	88.86 ± 21.30	74.11 ± 18.62	69.78 ± 21.35
SE120(N)	279.91 ± 50.90	252.90 ± 78.48	268.15 ± 66.79	276.14 ± 69.00	251.71 ± 68.04	276.29 ± 74.30	262.70 ± 70.90	271.00 ± 78.93
SF120(N)	148.18 ± 36.62	143.55 ± 36.64	157.86 ± 46.97	157.71 ± 35.15	146.29 ± 29.62	169.43 ± 44.03	145.30 ± 39.37	151.60 ± 43.35
LuE90(N)	257.36 ± 66.19	252.64 ± 58.52	248.71 ± 74.68	277.57 ± 62.98	244.29 ± 72.35	267.14 ± 64.36	256.00 ± 87.67	283.25 ± 97.28
LuF90(N)	132.73 ± 28.89	140.00 ± 35.32	153.86 ± 45.11	152.86 ± 36.21	144.71 ± 44.59	153.14 ± 46.03	149.50 ± 46.62	153.75 ± 40.18

Data are expressed as means (± SD) and represent body composition and isometric muscle strength before (PRE) and after (POST) 24 weeks of intervention. Lower limb muscle strength is represented as isometric right (R) and left (L) extension (E) and flexion (F) forces at 45 degree (45°) or at 90 degree (90°) knee flexion. Isometric core muscle strength is represented as isolated lumbar (Lu) extension (E) and flexion (F) forces at 90 degrees (90°) and semi-standing (S) extension (E) and flexion (F) forces at 120 degrees (120°) hip flexion.

MS_{BA}: Multiple sclerosis and β-alanine; MS_{PL}: Multiple sclerosis and placebo; HC_{BA}: Healthy control and β-alanine; HC_{PL}: Healthy control and placebo.

[a] P < 0.05: significant difference between the four groups (MS vs HC and BA vs PL).

[b] P < 0.05: significant difference between PRE and POST

[c] P < 0.05 significant difference in difference score (post minus pre) between groups (MS_{BA}, MS_{PL},HC_{BA},HC_{PL})

Table 5

Differences between PwMS and HC

	MS_{PRE}	HC_{PRE}	MS_{POST}	HC_{POST}
Fat-mass (kg)	16.57 ± 8.31	15.99 ± 5.13	15.69 ± 8.52	14.90 ± 5.43
Lean-mass (kg)	51.09 ± 7.39	53.19 ± 10.03	50.53 ± 53.10	53.10 ± 9.77
Fat-percentage (%)	23.77 ± 9.59	23.23 ± 7.35	23.04 ± 10.08	22.09 ± 8.05
RE 45 (N)	161.11 ± 24.51	168.58 ± 33.58	150.39 ± 29.11	154.12 ± 32.18
RF45 (N)	97.22 ± 21.72	108.29 ± 23.95	96.11 ± 19.55	107.47± 24.36
RE90 (N)	187.55 ± 49.97	202.59 ± 52.88	175.22 ± 50.94	180.00 ± 49.89
RF90(N)	75.89 ± 17.86	85.00 ± 23.40	74.89 ± 17.93	83.65 ± 20.11
LE45 (N)	154.00 ± 28.31	157.82 ± 34.20	153.89 ± 36.88	157.53 ± 36.07
LF45 (N)	100.17 ± 24.76	101.47 ± 24.30	96.61 ± 19.66	104.24 ± 30.93
LE90 (N)	191.22 ± 55.25	209.06 ± 51.76	174.78 ± 51.84	195.25 ± 53.86
LF90 (N)	74.47 ± 17.83	77.88 ± 22.63	73.82 ± 16.09	78.13 ± 22.81
SE120 (N)	275.33 ± 55.98	258.18 ± 67.79	261.94 ± 73.75	273.18 ± 74.71
SF120 (N)	151.94 ± 39.89	145.71 ± 34.66	149.06 ± 35.72	158.94 ± 43.20
LuE90 (N)	254.00 ± 67.56	250.53 ± 78.25	262.33 ± 59.76	275.73 ± 81.10
LuF90 (N)	140.94 ± 36.35	147.27 ± 44.10	145.00 ± 35.19	153.47 ± 41.42

Data are expressed as means (± SD) and represent body composition and isometric muscle strength before (PRE) and after (POST) 24 weeks of intervention. Lower limb muscle strength is represented as isometric right (R) and left (L) extension (E) and flexion (F) forces at 45 degree (45°) or at 90 degree (90°) knee flexion. Isometric core muscle strength is represented as isolated lumbar (Lu) extension (E) and flexion (F) forces at 90 degrees (90°) and semi-standing (S) extension (E) and flexion (F) forces at 120° hip flexion.

MS: Multiple sclerosis; HC: Healthy controls

[a] $P < 0.05$: significant difference between the groups (MS vs HC).

[b] $P < 0.05$ significant difference in difference score (post minus pre) between groups (MS vs HC)

Table 6

Differences between BA-supplementation versus placebo-supplementation

	BA	PL	BA	PL
	PRE	**PRE**	**POST**	**POST**
Fat-mass (kg)	16.20 ± 7.95	16.37 ± 5.51	15.43 ± 8.40	15.15 ± 5.42
Lean-mass (kg)	53.69 ± 7.83	50.41 ± 9.621	53.09 ± 8.12	50.40 ± 9.62
Fat-percentage (%)	22.48 ± 8.53	24.64 ± 8.40	21.86 ± 9.57	23.35 ± 8.55
RE 45 (N)	166.56 ± 30.69	162.83 ± 28.08	154.11 ± 29.14	150.18 ± 32.15
RF45 (N)	105.78 ± 19.91	99.25 ± 26.40	102.61 ± 20.11	100.59 ± 25.27
RE90 (N)	194.61 ± 53.19	195.12 ± 50.67	179.83± 53.65	175.12 ± 46.77
RF90 (N)	85.06 ± 18.65	75.29 ± 22.53	83.5 ± 17.77	74.53 ± 20.20
LE45 (N)	154.94 ± 25.45	156.82 ± 36.59	155.16 ± 33.07	156.18 ± 39.88
LF45 (N)	102.11 ± 20.92	99.41 ± 27.81	99.50 ± 25.11	101.18 ± 26.20
LE90 (N)	190.94 ± 53.02	209.38 ± 54.24	176.94 ± 52.01	192.81 ± 54.54
LF90 (N)	79.00 ± 19.85	73.06 ± 20.44	80.12 ± 18.81	71.44 ± 19.69
SE120 (N)	268.94 ± 57.95	264.94 ± 67.15	262.00 ± 75.56	273.12 ± 72.78
SF120 (N)	147.44 ± 33.16	150.47 ± 41.71	153.61 ± 40.52	154.1 ± 39.11
LuE90 (N)	252.28 ± 66.84	252.6 ± 79.04	258.28 ± 59.41	280.60 ± 80.25
LuF90(N)	137.39 ± 35.05	151.53 ± 44.31	145.11 ± 39.05	153.33 ± 37.01

Data are expressed as means (± SD) and represent body composition and isometric muscle strength before (PRE) and after (POST) 24 weeks of intervention. Lower limb muscle strength is represented as isometric right (R) and left (L) extension (E) and flexion (F) forces at 45 degree (45°) or at 90 degree (90°) knee flexion. Isometric core muscle strength is represented as isolated lumbar (Lu) extension (E) and flexion (F) forces at 90 degrees (90°) and semi-standing (S) extension (E) and flexion (F) forces at 120° hip flexion.

BA: β-alanine; PL: Placebo

[a] P< 0.05: significant difference between the groups (BA vs PL).

[b] P< 0.05 significant difference in difference score (post minus pre) between groups (BA vs PL)

www.uhasselt.be
Campus Hasselt | Martelarenlaan 42 | BE-3500 Hasselt
Campus Diepenbeek | Agoralaan gebouw D | BE 3590 Diepenbeek
T + 32(0)11 26 81 11 | E-mail: info@uhasselt.be

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DATUM	INHOUD OVERLEG	HANDTEKENINGEN
19/10/17	Uitleg gebruikte protocol	Promotor: BERT OP 'T EIJNDE UNIVERSITEIT HASSELT Gebouw D Campus Diepenbeek Agoralaan gebouw A 3590 DIEPENBEEK Copromotor: Student(e): Student(e): Velade
31/10/17	Data verdacht	Promotor: BERT OP 'T EIJNDE UNIVERSITEIT HASSELT Gebouw D Campus Diepenbeek Agoralaan gebouw A 3590 DIEPENBEEK Copromotor: Student(e): Student(e): Velade
7/12/17	Overlopen data-analyse + missing data	Promotor: BERT OP 'T EIJNDE UNIVERSITEIT HASSELT Gebouw D Campus Diepenbeek Agoralaan gebouw A 3590 DIEPENBEEK Copromotor: Student(e): Student(e): Velade
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