Exercise-induced lactate response and oxidative muscle characteristics in people with multiple sclerosis

Research questions:

- Part I: “Is there a difference in exercise-induced blood lactate response between healthy controls (HC) and people with Multiple Sclerosis (pwMS).”
- Part II: “To compare skeletal muscle oxidative capacity and related determinants between HC and pwMS.”

Highlights:

- Currently, little research has been performed on exercise-induced lactate values in pwMS.
- Exercise-induced blood lactate content during/after (sub)maximal exercise intensities did not differ in pwMS compared to HC.
- Several intramuscular factors determine the oxidative capacity of a skeletal muscle on peripheral level. In pwMS, significant morphological and functional changes of skeletal muscle tissue that may affect this capacity were observed. These changes include fiber type, muscle fiber cross-sectional area (CSA) and enzyme activities.

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Context of the master thesis

This master thesis fits in a combined research domain of neurological and cardiorespiratory rehabilitation. Multiple sclerosis (MS) is a neurodegenerative disease characterized by complex and heterogeneous symptoms that may negatively affect physical fitness and quality of life. Overall, physical training is well-tolerated in people with multiple sclerosis (pwMS) and has beneficial effects on walking capacity/speed, aerobic capacity and muscle strength. Thereby, physical exercise significantly reduces the sedentary lifestyle. However, the exercise response (the physiological response to exercise (disturbed homeostasis)) is not fully known, and may differ from healthy persons.

This master thesis is part of a broader research project investigating the therapeutic impact of exercise rehabilitation on symptoms and disease progression in MS. It is performed under supervision of Prof. Dr. Bert Op 't Eijnde and co-promotor drs. Jan Spaas at the rehabilitation research centre (REVAL) of Hasselt University (Diepenbeek). The literature study was carried out by both students. They have contributed equally to this master thesis.

This master thesis was conducted to improve the understanding of the exercise response by investigating the lactate response and aerobic capacity of pwMS. Aerobic capacity can be determined by the golden standard (i.e. VO_2 max), but also indirectly by a metabolite called 'lactate'. A better characterization of the exercise response and lactate values in MS may lead to more efficient and goal-oriented refinement of exercise programs. This could result in an improved quality of life, physical fitness and therapy compliance in pwMS. It may also give a better insight into muscle fatigue on peripheral muscle level.

Specifically, the literature search of this master thesis consists of two objectives. The first objective was to compare exercise-induced (blood) lactate values between healthy controls (HC) and pwMS. Second, an analysis of skeletal muscle oxidative capacity and related determinants in pwMS was performed.

This first part of the master thesis is a literature study and was conducted during the first year of the master's degree rehabilitation sciences and physiotherapy at Hasselt University.
For the literature review, the final research questions and strategy were discussed together with drs. Jan Spaas in February 2018. The second part (research protocol) is fictional.

In the second year of the master's degree, exercise-induced (blood) lactate values in MS will be investigated. Data comes from previous studies at the research centre REVAL of Hasselt University (retrospective study). The two master students assisted related studies of drs. Jan Spaas during their first master year.
Central format was used during writing of this duo master thesis.

TABLE OF CONTENTS

PART 1: LITERATURE SEARCH

1. Abstract ……5
2. Introduction ……7
3. Methods ……9
    3.1 Research question ……9
    3.2 Literature search ……10
    3.3 Selection criteria ……11
    3.4 Quality assessment ……11
    3.5 Data extraction ……12
4. Results ……13
    4.1 Results literature search ……13
    4.2 Results quality assessment ……14
    4.3 Results data-extraction ……15
5. Discussion ……21
    5.1 Reflection on the quality of the included studies……21
    5.2 Reflection on the findings in function of the research questions ……22
    5.3 Reflection on the strengths and weaknesses of the literature study ……25
    5.4 Recommendations for further research ……25
6. Conclusion ……27
7. List of references ……29
8. Appendix 1

PART 2: RESEARCH PROTOCOL

1. Introduction 1
2. Aim of the study 3
2.1 Research questions related to the master thesis 3
2.2 Hypotheses 3
3. Methods 5
3.1 Research design 5
3.2 Participants 5
3.2.1 Inclusion criteria 5
3.2.2 Exclusion criteria 6
3.2.3 Participant recruitment 6
3.3 Medical ethics 6
3.4 Measurements 6
3.4.1 Measurement pre- and post-intervention: CPET.....6
3.4.2 Measurement pre- and post-intervention: muscle biopsies 7
3.4.3 Program HIIT training 7
3.5 Outcome measures 8
3.5.1 Primary outcome measures 8
3.5.2 Secondary outcome measures.....8
3.6 Data analysis 8
4. Time planning.....11
5. List of references.....13
6. Appendix 2

PART 1: LITERATURE SEARCH

1 Abstract

Background: Multiple sclerosis (MS) is a progressive neurological disease. A common complaint is fatigue during exercise, which need to understand to adapt and optimize exercise rehabilitation to improve physical fitness and thus quality of life.

Methods: PubMed and ProQuest databases were searched to (1) compare exercise-induced (blood) lactate values between healthy controls (HC) and people with multiple sclerosis (pwMS), and (2) compare skeletal muscle oxidative capacity and related determinants between HC and pwMS.

Results: Blood lactate content did not significantly differ between pwMS and HC during (sub)maximal exercise intensities. PwMS exhibit lower skeletal muscle oxidative capacity compared to HC. Possible contributing factors are the significant differences in muscle fiber type, fiber cross-sectional area (CSA) and altered enzyme activity in pwMS.

Discussion and conclusion: Part I showed no significant difference in blood lactate content during (sub)maximal exercise intensities between pwMS and HC. There is still a lot of research needed (larger sample size, representative mean EDSS) when it comes to exercise-induced lactate response in pwMS. The conclusion for part II is that skeletal muscle oxidative capacity is impaired in pwMS.

Aim of the study: What is the effect of 12 weeks of HIIT training on the aerobic capacity in pwMS compared to HC, measured by blood lactate content and respiratory determinants of blood lactate?

Operationalization: Cardiopulmonary exercise test (CPET) will be performed by pwMS (n= 20) and HC (n= 20) pre- and post-intervention, consisting of 12 weeks of HIIT.

Most important key words: (blood)lactate, multiple sclerosis, exercise, skeletal muscle, oxidative capacity

2 Introduction

Multiple sclerosis (MS) is a chronic demyelinating disease that affects the central nervous system (CNS). It is the most frequent neurological disease among adolescents and young adults that causes impairment (Koch-Henriksen and Sorensen 2010). CNS demyelination causes a wide range of symptoms, such as peripheral muscle weakness, fatigue, disturbed sensation and cognitive impairments (White and Dressendorfer 2004). These components of MS often lead to a reduced level of physical activity, which can result in elevated morbidity and mortality due to further decrease of physical fitness and development of cardiovascular and metabolic diseases (Motl et al., 2009; Motl et al., 2011; Carnethon et al., 2005).
The benefits of physical rehabilitation on aerobic capacity (i.e. peak oxygen consumption) and strength (i.e. one repetition maximum) in people with MS (pwMS) are becoming more and more clear. Over 50 studies have investigated the effect of exercise training on mobility, muscle strength, aerobic capacity and symptoms of fatigue (Latimer-Cheung, Pilutti et al. 2013). Nowadays, exercise rehabilitation therapy has become an important part of overall MS treatment (Bouchard et al., 1994). Therefore, it is important to investigate whether the aerobic capacity of pwMS is altered. This may optimize the treatment and give a better insight on muscle fatigue on peripheral muscle level.

During any type of physical activity, the breakdown of adenosine triphosphate (ATP) delivers the energy required for muscle contraction (Bonora, Patergnani et al. 2012). This universal supplier of energy can be efficiently produced by aerobic breakdown of carbohydrates or fatty acids (Bonora, Patergnani et al. 2012). Aerobic capacity reflects the cardiorespiratory fitness and is an important marker for health (Carnethon, Gulati et al. 2005, Eriksen, Curtis et al. 2013) and performance (Bassett and Howley 2000) in both healthy controls (HC) and pwMS. Furthermore, aerobic capacity is associated with the risk of cardiovascular diseases (Marrie and Hanwell 2013), enhanced cognitive processing speed (Sandroff and Motl 2012), better walking performance (Sandroff, Sosnoff et al. 2013), and potential prophylactic influence on the structural regions of brain tissue in pwMS (Prakash, Snook et al. 2010). Decreased aerobic capacity in healthy persons is related to barriers in daily activities that hinders autonomous living (Cress and Meyer 2003). Maximal oxygen consumption (VO_2max) is considered the golden standard for measuring an individual's aerobic capacity (Stickland, Butcher et al. 2012). The VO_2max is determined by the rate at which a person can take up and use oxygen during exercise. When the energy demand exceeds oxygen delivery and consumption, ATP is resynthesized by the anaerobic metabolism, which produces ATP less efficiently and results in production of lactic acid (Bonora, Patergnani et al. 2012).
Contrary to the fact that this metabolite is produced by the anaerobic metabolism, it can be useful to determine (indirectly) the oxidative capacity of muscle fibers. Change in blood lactate concentration of individuals is frequently used to estimate the relative contribution of aerobic and anaerobic energy metabolism during exercise (Faude, Kindermann et al. 2009). Hence, blood lactate is often interpreted in the context of (muscle) fatigue. In addition, this highly dynamic metabolite can be used indirectly as exercise fuel for the heart muscle and type I muscle fibers (lactate shuttle and Cori cycle).

Interestingly, a recent study found circulating resting lactate values were nearly three times higher in pwMS compared to HC, and concluded that lactate may be an important biomarker for determining the effectiveness of treatments and progression of the disease (Amorini, Nociti et al. 2014).

However, aerobic capacity and exercise-induced lactate values remain not fully understood in this disease. In exercise-related preliminary studies, lactate has only been discussed as a secondary outcome measure. Explanations for these values were not given to date. To further explore the clinical benefits of exercise therapy in pwMS, exercise-induced (blood) lactate values could be interesting parameters to define physical fitness, and oxidative capacity in particular. This can adapt/optimize their rehabilitation which may lead to an enhanced physical fitness, therapy compliance and quality of life.

The literature review consists of two objectives. The first part compares exercise-induced (blood) lactate values between HC and pwMS. The second part gives a complete overview of skeletal muscle oxidative capacity and related determinants in pwMS and HC.
More specifically, the aims of this literature search were the following: (1) (blood) lactate values after any type of physical exercise are compared to HC, and (2) peripheral muscle characteristics that may relate to an altered oxidative capacity in pwMS.

3. Methods

3.1 Research question

Part I:

The first research question is: “Is there a difference in the exercise-induced blood lactate response between healthy controls (HC) and people with MS (pwMS)”.

PICO:

- P: patients with multiple sclerosis (pwMS)
- I: physical exercise
- C: healthy controls
- O: blood lactate content

Part II:

To better understand possible changes in blood lactate content, a secondary aim was set up. A possible factor that would influence lactate production could be changes in the ability to supply energy through the aerobic metabolism. Hereby, intramuscular factors that could influence aerobic capacity were investigated. This literature search immerses in the skeletal muscle fiber on peripheral muscle level, consisting of the composition and size of muscle fibers, but also enzyme activities that occur in the muscle fiber. As such, the second objective is to compare skeletal muscle oxidative capacity and related determinants between HC and pwMS.

PICO:

- P: patients with multiple sclerosis (pwMS)
- I: none
- C: healthy controls
- O: skeletal muscle composition and oxidative capacity

3.2 Literature search

Part I: search strategy

For part I, MeSH terms as well as keywords followed by 'Title-Abstract' referring to pwMS, HC, exercise and lactate were combined with the Boolean operator AND (table 1a-b).

The following search strategies were applied to two databases:

- PubMed database:
  (((((((lactate[Title/Abstract]) OR lactates [MeSH Terms]) OR lactic acid[Title/Abstract]) OR lactic acid[MeSH Terms])) OR ((exercise[Title/Abstract]) OR exercise[MeSH Terms]))) AND ((((healthy volunteers[MeSH Terms]) OR control group[MeSH Terms]) OR control[Title/Abstract]) OR healthy[Title/Abstract])) AND ((multiple sclerosis[Title/Abstract]) OR multiple sclerosis[MeSH Terms])

- ProQuest database:
  (Exact ("multiple sclerosis") OR ti(multiple sclerosis) OR ab(multiple sclerosis)) AND (Exact("lactate") OR ab(lactate))

Part II: search strategy

For the secondary aim of the literature search, MeSH terms and keywords followed by 'Title-Abstract' referring to pwMS and skeletal muscle were used and combined with the Boolean operator AND (table 1c-d). A broad search was conducted because predetermined outcome measures were not given.

The following search strategies were applied to two databases:

- PubMed database:
  ((multiple sclerosis [MeSH Terms]) OR multiple sclerosis [title/abstract])) AND ((((((skeletal muscle [Mesh terms]) OR muscle [title/abstract])) OR skeletal muscle fiber [mesh terms])) OR muscles [mesh terms])

- ProQuest database:
  (Exact("multiple sclerosis") OR ab(multiple sclerosis) OR ti(multiple sclerosis)) AND (ti(muscle) OR ab(muscle))

No restrictions on period of publication, level of evidence or language were used in PubMed. The filter 'scholarly journals' was used in ProQuest to exclude irrelevant results such as newspapers and magazines. All articles were analyzed by two reviewers, where each reviewer has analyzed half of the hits. The final update of the literature search, used to determine the final set of included articles of this master thesis, was performed on February 21, 2018.

3.3 Selection criteria

Part I

Following selection criteria were used for screening of the resulted articles:

1. Does the study measure (blood) lactate content after physical exercise?
2. Full text had to be available
3. Does the article compare HC versus pwMS?
4. The article had to be available in English
5. The study is not allowed to use laboratory animals

Part II

The following selection criteria were implemented for the results of the secondary aim:

1. Does the study compare pwMS with HC?
2. Full text had to be available
3. The article had to be available in English
4. Does the article describe determinants that reflect oxidative capacity on peripheral intramuscular level?
   Aerobic capacity depends on three systems: cardiovascular, muscular and respiratory. This literature search discusses the oxidative capacity on muscular level. There are several intramuscular factors that may influence muscle oxidative capacity such as mitochondria, skeletal muscle fiber type and enzyme activity. Thus, with this fourth criterion, articles were evaluated if they described one of the many possible determinants that influence the oxidative capacity.
5. The study is not allowed to use laboratory animals

3.4 Quality Assessment

A quality assessment for the included articles from medical databases PubMed and ProQuest was performed using the Critical Appraisal Checklist for Cross-Sectional Studies from the Center for Evidence Based Management (March 2018). The studies were reviewed by answering 12 topics that determine the quality. Each full text of every article was searched and studied by two reviewers (Table 3).

3.5 Data extraction (table 5)

Part I

Following data was extracted from the included articles: population characteristics, type of physical exercise, measuring techniques of blood lactate, and the blood lactate values during/after exercise.

Part II

Following data was used from the resulting articles: population characteristics, measuring techniques, and determinants of skeletal muscle oxidative capacity. These determinants may include, among others, the type of muscle fiber and enzyme activity (e.g. SDH and GPDH). Each determinant described by the study is clustered in tables per outcome measure.

Study design

The study design of the included articles were descriptive cross-sectional studies. One article (Hansen et al., 2014) consisted of two parts, of which the second part was a Randomized Controlled Trial (RCT).

4 Results

4.1 Results literature search

A detailed overview of excluded articles with reasons of exclusion (table 2) is provided in the appendix. As a result of the general terms, a large amount of hits (n=2667) was obtained, especially for part II. In total, part I consisted of 548 hits (PubMed n=500, ProQuest n=48) and part II consisted of 2129 hits (PubMed n=1585, ProQuest n=544). The filter 'scholarly journals' was applied in ProQuest. Thereby, only relevant articles were shown and other source types such as articles from magazines, newspapers and reports were excluded. The sets of hits were analysed in more detail by first reading the abstract. If this was not clear, full text was searched and studied. The details on the (number of) included and excluded articles are presented in flowcharts (figure 1 and 2). In total, 16 articles were included (part I: n= 5; part II: n=11), of which one article (Hansen et al., 2012) was a duplicate that was included in both parts of this review. Details on included articles are shown in table 4.

Part I

For part I, following selection criteria were used:

(1) Does the study measure (blood) lactate content after physical exercise?
This criterion was used because lactate is a metabolite that is found in blood, but also in cerebrospinal fluid. Only a few (PubMed n=2, ProQuest n=8) of the studies measured lactate in the cerebrospinal fluid and were therefore excluded.

(2) Full text had to be available
The literature search was not hampered by lack of access to full texts.

(3) Does the article compare pwMS with HC?
Only a small part (PubMed n=40, ProQuest n=0) of the total amount had no healthy controls as comparison. A filter on article type was not applied in PubMed, thereby it was possible that other types of articles were obtained. A filter on source type was used in ProQuest to obtain only relevant scholarly journals.

(4) The article had to be available in English
Only three articles (in PubMed) were not available in English. The other languages that were used were Spanish and Russian.

(5) The study is not allowed to use laboratory animals
In ProQuest, none of the articles used laboratory animals.

The largest amount of hits for part I were articles that were not clinically relevant, and did not answer the research question (PubMed n=446, ProQuest n=36).

Part II

The following selection criteria were implemented for including articles for part II:

(1) Does the study compare pwMS with HC?

Only a few (Pubmed n=16, ProQuest n=2) of the obtained articles did not compare with a healthy control group.

(2) Full text had to be available

Six articles (Pubmed) had no full text available.

(3) The article had to be available in English

The literature search was not hampered by unavailability of English articles.

(4) Does the article describe the oxidative capacity on peripheral intramuscular level?

Only one article in ProQuest did not describe the oxidative capacity on peripheral intramuscular level.

(5) The study is not allowed to use laboratory animals

During the analysis of articles in PubMed, six animal studies were obtained.

The largest amount of hits for part II were articles that were not clinically relevant, and did not answer the research question (PubMed n=1534, ProQuest n=539).

4.2. Results quality assessment

The quality assessment (table 3) on the included articles gave following results:

Part I

Every article addressed a clearly focused research question, which was described at the end of the introduction of every paper. An appropriate research method was applied and clearly described. Not every article applied a clear selection method of the participants. Two articles (Op ‘t Eijnde et al., 2014; Larson et al., 2013) did not clearly describe the participant recruitment. Moreover, the remaining three articles (Hansen et al., 2012; Hansen et al., 2014; Morrison et al., 2008) recruited their participants on advertisements, which may indirectly lead to a small selection bias. Two articles were not representative for the population of pwMS: Larson et al. (2013) had a small sample size (n=15) and the participants of Morrison et al. (2008) had a low EDSS score (≤3). Two (Hansen et al., 2014; Op ‘t Eijnde et al., 2014) out of five articles applied a sample size based on statistical power. None of the articles mentioned whether they achieved a satisfactory response rate. However, every article had reliable and valid measurements and assessed statistical significance ($P<0.05$). Only one article (Larson et al., 2013) used confidence intervals for expressing parameters. No articles contained confounding factors that could affect the study. In general, every article had applicable results for writing this review.

Part II

For part II, every article had a clearly addressed question combined with an appropriate research question. Four (De Haan et al., 2000; Kent-Braun et al., 1994; Kent-Braun et al., 1997; Kumleh et al., 2006) of the 11 articles did not describe how patients were recruited.
Out of 11 articles, only five (Campbell et al., 2013; Garner et al., 2003; Hansen et al., 2012; Hansen et al., 2015; Harp et al., 2016;) had a clear description of the selection method. Due to the fact that the other articles did not have a clear selection method, it was unclear whether they were biased for selection. Subjects of three articles (Hansen et al., 2015; Kumleh et al., 2006; Wens et al., 2014) had a low mean EDSS score and thus were only representative for pwMS with mild disability. It was unclear whether the articles of part II (based on sample size) were representative for the MS population. Two articles (Campbell et al., 2013; Harp et al., 2016) did not describe the EDSS score of their subjects. None of the articles mentioned if the satisfactory response rate was achieved. Statistical significance was assessed on $P<0.05$ for each article. Hansen et al. (2015) was the only article that had a sample size based on statistical power. Campbell et al. (2013) was the only article for part II that contained confidence intervals. Only one article (Carroll et al., 2005) reported a confounding factor.
Out of 11, seven articles (Garner et al., 2003; Wens et al., 2014; Campbell et al., 2013; Kent-Braun et al., 1994; Carroll et al., 2005; Kent-Braun et al., 1997; Kumleh et al., 2006) did not report reliability and validity of their measurements.

4.3. Results data-extraction

Table 5 gives an overview of patient populations, aims, methodology and results of the included studies. For both part I and part II, the studied population consisted of a group of pwMS compared with HC. The number of subjects in all groups varied from seven (Carroll et al., 2005) to 38 (Hansen et al., 2012). All of the studies had a rather small sample size. Each study applied different selection criteria. Six studies (Hansen et al., 2014; Hansen et al., 2012; Op ‘t Eijnde et al., 2014; Hansen et al., 2015; Harp et al., 2016; Kent-Braun et al., 1997) required that participants of the intervention were diagnosed with MS for at least 12 months prior to intervention. Various EDSS scores were used, ranging from zero (Wens et al., 2014) to eight (Kent-Braun et al., 1994). Nine studies (Hansen et al., 2014; Hansen et al., 2012; Morrison et al., 2008; Carroll et al., 2005; Harp et al., 2016; Garner et al., 2003; Kent-Braun et al., 1997; De Haan et al., 2000; Campbell et al., 2013) did research on participants who had a sedentary lifestyle. Two articles (Larson et al., 2013; Carroll et al., 2005) focused on one form of MS called Relapse Remitting. Whereas all others did not exclude based on type of MS, meaning all types were included (clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), primary progressive MS (PPMS), and secondary progressive MS (SPMS)).

Part I

For part I, all studies measured blood lactate at the fingertip during and after exercise. Three articles (Hansen et al., 2014; Hansen et al., 2012; Op ‘t Eijnde et al., 2014) used Lactate Pro as lactate analyzer. The two other studies (Larson et al., 2013; Morrison et al., 2008) used Accutrend Plus. Each study applied a graded cycling test, either maximal (n=2) or submaximal (n=3).

Hansen et al. (2014) consisted of two parts. The first part was an assessment of the ventilatory function during a submaximal exercise test, followed by a six-month training intervention with a healthy control group. In the first part, no significant difference in blood lactate during exercise between the intervention and control group was found. However, significant correlations were observed between exercise blood lactate and the ventilatory equivalent for oxygen (VE/VO_2) and end-tidal tensions of oxygen (PETO2) ($R=0.37$) ($P<0.05$). Blood lactate did not correlate to gender, age, BMI and physical activity level ($P>0.10$). These results suggest that pwMS do not have an altered aerobic metabolism during submaximal exercise. In addition, a six-month training intervention can improve exercise tolerance by decreasing the exercise blood lactate level in pwMS.

Hansen et al. (2012) reported blood lactate values during low to mild intensity cycling (below the anaerobic threshold). The intervention consisted of two exercise bouts (each six minutes) separated by a recovery interval of six minutes. During both bouts, steady-state lactate was not significantly different between both groups. This indicates indirectly that the aerobic capacity during exercise below the anaerobic threshold is not impaired.

Larson et al. (2014) used a unilateral incremental cycling test for measuring bilateral differences in lower-limb performance. Participants had to perform a cycling test until their maximum, limited by symptoms that occurred. Lactate was measured between pwMS and HC, giving no significant differences between both groups.

Morrison et al. (2008) applied a graded aerobic exercise test using a cycle ergometer, with the metabolite blood lactate as secondary outcome measurement. The participants had to continue the exercise test until they reached a maximum, limited by symptoms. The study did not report a significant difference in blood lactate content after the test (after 8 to 12 minutes or at maximal exhaustion (symptom limited maximum)) between pwMS and HC. Within groups, however, lactate showed a significant change from pre- to post-test ($P<0.001$).

Op ‘t Eijnde et al. (2014) measured the impact of whole-body cooling on the muscle oxidative capacity in pwMS. Under normo-and hypothermic conditions, participants performed a submaximal exercise test of two exercise bouts of six minutes. The study reported higher lactate values in hypothermic conditions (steady-state and at rest), but not significantly different between both groups nor thermal conditions.

In general, three studies (Hansen et al., 2012; Hansen et al., 2014; Op ‘t Eijnde et al., 2014) applied submaximal exercise intensities. During this intensity, blood lactate content does not differ between pwMS and HC. Morrison et al. (2008) and Larson et al. (2014) also reported no significant difference in blood lactate content between groups, using a maximal exercise intensity. However, Hansen et al. (2014) reported that a six-month combined endurance and resistance training program may have beneficial effects on blood lactate content (P=0.01).

Part II

The results of the multiple outcome measurements for part II were diverse. As shown in table 6 the outcome measures were: measures of mitochondrial/oxidative capacity, fiber type (proportion), (muscle) fiber cross-sectional area and altered enzyme activity. Table 6 gives an overview of the results, clustered by outcome measures. Following paragraphs show these results. Explanations for (dis)similar results are discussed in the next chapter.

Measures of mitochondrial/oxidative capacity

De Haan et al. (2000) investigated whether adaptations in muscle properties contribute to the higher fatigability of pwMS by using electrical stimulation of the quadriceps muscles through surface electrodes. Results showed that during a series of repeated contractions, isometric force and maximal rate of force rise showed a greater decrease in MS patients when compared with HC. The observed decrease in peripheral fatigue resistance suggests (according to the study) a lower oxidative capacity.

Hansen et al. (2012) examined the skeletal muscle oxidative capacity by calculating exercise-onset VO_2 kinetics. The participants completed a cardiopulmonary exercise test on a cycle ergometer consisting of two submaximal exercise bouts of six minutes separated by a recovery interval of six minutes. The exercise-onset Mean Response Time (MRT) was calculated. This parameter reflects the exercise-onset oxygen uptake (VO_2) kinetics, which can be used to assess skeletal muscle oxidative capacity, by dividing the oxygen deficit with the difference between rest and steady-state VO_2. Exercise-onset MRT during both bouts was significantly slower in pwMS compared to HC. Thereby, the averaged exercise-onset MRT of both bouts was also significantly slower in pwMS compared to HC.

Harp et al. (2016) measured muscle mitochondrial capacity (the rate of recovery of oxygen consumption after exercise) of the m. gastrocnemius using near-infrared spectroscopy (NIRS). PwMS showed 40% lower mitochondrial capacity compared to HC. No differences in mitochondrial capacity between the strong and weak legs in the MS group were observed.

Kent-Braun et al. (1994) measured the rate of intramuscular phosphocreatine (PCr) resynthesis of the dorsiflexor muscles following exercise using phosphorus magnetic resonance spectroscopy. The authors found a relatively faster increase in PCr and decrease in inorganic phosphate in HC when compared to pwMS. Following 10 minutes of recovery, however, PCr was similar (completely recovered) in pwMS and HC. Slowed PCr recovery is suggestive for an impairment in oxidative metabolism in the MS group.

In general, it can be concluded that the mitochondrial/oxidative capacity on peripheral muscle level in pwMS is impaired.

Fiber type (proportion)

Campbell et al. (2013) obtained post-mortem muscle fibers from m. multifidus to investigate muscle fiber size and type. The study reported that HC had a predominance of type I fibers in this stabilizing muscle. However, proportion of this fiber type was significantly decreased in pwMS.

Carroll et al. (2005) studied the abundance of different myosin heavy chain (MHC) isoforms by gel electrophoresis and using mATPase staining in the muscle fibers of the vastus lateralis muscle. They did not find a significant difference in total MHC hybrid between both groups for each fiber type, as well as no significant difference in distribution of MHC I, I/IIa, IIa/IIx or IIx fibers in the vastus lateralis. However, percentage of MHC I/IIa/IIx was significantly higher in pwMS. No differences were found for the ATPase for the three main muscle fiber types.

Garner et al. (2003) also discussed MHC by using the same method on the vastus lateralis muscle and has corresponding results with Carroll et al. (2005) for the relative number of fibers for I, IIa/IIx or IIx MHC. However, type IIa fibers were fewer for pwMS. Moreover, a negative correlation was found between EDSS and type I MHC isoforms, and a positive correlation between EDSS and IIa, IIa/IIx and IIx MHC isoforms.

Kent-Braun et al. (1997) studied muscle biopsies of the m. tibialis anterior using histochemical techniques and determined a significantly lower percent of type I fibers (MS= 65.5 % +- 5.6%; HC= 75.9% +- 2.6%) and a significantly higher percent of type IIa fibers (MS= 28.2% +- 5.9%; HC= 19.2% +- 1.8%) in pwMS compared with HC.

Wens et al. (2014) described, after studying muscles biopsies of m. vastus lateralis by ATPase histochemistry, that the proportion of type I fibers tended to be lower in pwMS, but with no significant p-value. The proportion of type II tended to be higher.

In contrast, Hansen et al. (2015) did not report significant differences in percentage of type I, IIa and IIx fibers of the m. vastus lateralis, using the same ATPase histochemistry technique.

(Muscle) fiber cross-sectional area (CSA)

Campbell et al. (2013) reported that the CSA of both type I and type II muscle fibers were significantly lower in pwMS compared to controls. Furthermore, the CSA of the respiratory enzyme-deficient muscle fibers in the m. multifidus did not significantly differ compared to fibers with intact complex IV activity in both groups.

Carroll et al. (2005) evaluated the single muscle fiber CSA of m. vastus lateralis by photographs and found no differences between groups for any fiber type.

Hansen et al. (2015) studied skeletal muscle CSA by muscle biopsies of the m. vastus lateralis of the weakest leg. The study found a difference in type IIa muscle fiber CSA, which was significantly smaller in pwMS compared to HC.

Kent-Braun et al. (1997) found that the m. tibialis anterior fibers of all types (I, IIa, IIax) were smaller in pwMS compared to HC.

Wens et al. (2014) described a significantly smaller mean muscle fiber CSA and CSA of type I, II and IIa fibers of the m. vastus lateralis in pwMS. And a significantly larger atrophy in type II fibers compared to type I fibers in pwMS.

In conclusion, three out of five studies concluded that the CSA, of all fiber types, is smaller in pwMS. One study (Hansen et al., 2015) found a difference in only type IIa muscle fiber CSA, and one study (Carroll et al., 2005) reported no differences.

Altered enzyme activity

Campbell et al. (2013) reported no difference in the density of respiratory enzyme-deficient fibers (muscle fibers lacking mitochondrial respiratory chain complex IV with an intact complex II) in MS versus HC in the paraspinal muscles.

Hansen et al. (2015) evaluated the skeletal muscle phospho-AMPK∝ in muscle biopsies of the m. vastus lateralis. They found that basal muscle phospho-AMPK∝ and post-exercise phospho-AMPK∝ were significantly higher in pwMS compared to HC. Furthermore, they describe no significant changes as a result of endurance exercise in muscle phospho-AMPK∝ within pwMS and HC.

Kent-Braun et al. (1997) assessed the succinate dehydrogenase (SDH) activity of the m. tibialis anterior, which was found to be significantly lower in pwMS than in HC. No difference between groups were found for α-glycerol-phosphate dehydrogenase (GPDH) activity. Moreover, results for SDH activity weighted for relative fiber area (SDH-W) showed to be lower in pwMS versus HC. Further, no group differences in SDH-%, GPDH-W and GPDH-% were found. The ratio of SDH-to-GPDH activity within a given fiber type (SDH/GPDH) showed to be significantly smaller in MS. Thus, fibers of any type presented greater potential for aerobic vs. anaerobic energy supply in controls than in MS.

Kumleh et al. (2006) isolated mitochondria from fresh quadriceps muscle and determined complex I activity by biochemical studies (spectrophotometry). They measured the activity of NADH-ferricyanide reductase (catalytic activity of complex I), which resulted to be significantly lower in MS compared to HC.

In general, it can be concluded that there are no significant differences in the number of respiratory enzyme-deficient fibers and GPDH activity. In contrast, significant differences were found for muscle phosphoAMPK∝, SDH activity, the activity of NADH-ferricyanide reductase and catalytic activity of complex I. Further, the focus in each study relies on different skeletal muscles. Campbell et al. (2013), for example, studied the paraspinal muscles that consist mainly of type I muscle fibers, whereas Hansen et al. (2015), Kent-Braun et al. (1997) and Kumleh et al. (2006) studied muscles that (in proportion to the total amount of muscle fibers) mainly consist of type II muscle fibers.

5. Discussion

This section reflects on the results for both parts of the literature review.

5.1. Reflection on the quality of the included studies

Quality assessment was performed using the 'Critical Appraisal Checklist for Cross-Sectional Study' from the Center for Evidence Based Management (July 2014), shown in table 3 in the appendix. Based on this checklist, limitations of studies were determined for both parts.
The fourth criterion is a subjective topic and can be interpreted in different ways. Most of the included articles recruited participants by local advertisements. These participants could be more driven and motivated to exercise, which may influence parameters and thus results. Moreover, articles that had no clear description of the selection method could automatically not be evaluated on selection bias. Representativeness and sample size based on statistical power was hard to define, because of the small sample size that is frequently used in the study designs. Achievement of the satisfactory response rate was an irrelevant topic that none of the included articles reported and thus could not be determined. One important lack that is not mentioned in the checklist of CEBM (Center Evidence Based Medicine), however, is if the two groups are comparable for sample size. Most of the articles described matched groups, but the number of participants differed. Only one bias (selection bias) was mentioned, whereby other biases were not defined.

Part I

In general, quality of included articles for part I can be considered as good. Many studies performed well on most of the criteria. By the lack of information, it was unclear if the sample was representative for two articles and based on statistical power for three articles.

Part II

For part II the quality, based on the checklist, can be considered as below average. Due to lack of information, most of the topics (clear selection method, selection bias, sample size based on statistical power, reliability and validity of measurements and achieving response rate) were unclear. Hence, it was hard to answer these important topics.

5.2. Reflection on the findings in function of the research questions

Part I

The characteristics of the participants only slightly differed. EDSS mean scores were not exactly the same, but most of the participants were sedentary. EDSS scores were not higher than six. Thereby, studies were only generalizable for pwMS with low to mild disability. Measurements of blood lactate during/after exercise were similar. The five studies measured blood lactate content during/after exercise by two different portable lactate analyzers (n=2 Lactate Pro and n=3 Accutrend Plus). Moreover, Baldari et al. (2009) reported that Lactate Pro has excellent correlations with other lactate analyzer such as the Accutrend Plus Intensity of exercise was also comparable between studies. The exercise training of three studies (Hansen et al., 2012; Hansen et al., 2014; Op ‘t Eijnde et al., 2014) consisted of a graded submaximal intensity that does not rise above the anaerobic threshold. The other two studies (Larson et al., 2014; Morrison et al., 2008) used a graded maximal exercise intensity, but also did not report significant differences in blood lactate values between both groups. An explanation for these values was not discussed in these studies. One of the arguments is that the EDSS scores, and thus disability, could have been too low in the intervention group to influence the aerobic capacity. EDSS scores varied between low to mild disability. The reason why only low to moderate EDSS scores are more commonly included is because it is hard to complete assessments in pwMS with a high EDSS. Hansen et al. (2014) reported that severe disability (e.g. ataxia and poor coordination) worsens during a maximal cycle tests, which may affect the kinetics during exercise.
It has been unclear at what EDSS score the aerobic capacity differs in pwMS compared to HC. Thus, further research is needed to learn at what point in EDSS scoring the aerobic capacity will alter. Since submaximal and maximal exercise intensities were used, a too low intensity could not have been a limiting factor. The applied sample size requires a sufficient statistical power for determining significant difference between groups. This was only the case in two articles (Hansen et al., 2014; Op ‘t Eijnde et al., 2014) out of five. Thereby, sample size in the other three articles of part I may have been too low to detect significant differences.

The main conclusion of this part is that further research is needed to clarify these exercise-induced lactate responses in pwMS. Arguments for these values on peripheral muscular level are widespread and need further specific research. Therefore, part II of the literature search was set up.

Part II

Measures of mitochondrial/oxidative capacity

De Haan et al. (2000) suggested that pwMS have a lower oxidative capacity, that may lead to a decrease in peripheral fatigue resistance. A reason for this decrease may be explained by a fiber type shift from type I to type II. This determinant is discussed in the next section of the discussion.

Exercise-onset MRT was slower in pwMS, according to Hansen et al. (2012). Poole et al. (2008) reported that these exercise onset kinetics (MRT) may be related to oxidative enzyme activity and mitochondrial chain respiration capacity, and thereby skeletal muscle oxidative capacity. By using NIRS, Harp et al. (2016) reported a lower mitochondrial capacity and thus oxidative capacity in the m. gastrocnemius of pwMS. This may also be explained by a fiber type shift in the muscle. Thereby, it can be suggested that pwMS have a higher ratio of type II fiber types in the m. gastrocnemius and thus lower oxidative capacity, compared to HC. Kent-Braun et al. (1994) reported the phosphocreatine resynthesis in m. tibialis anterior following exercise in pwMS. This is a pathway in the anaerobic metabolism that occurs via oxidative phosphorylation and thus assesses the mitochondrial/oxidative capacity of a muscle. The study finds a slower phosphocreatine resynthesis, and thus an impaired mitochondrial/oxidative capacity.

Fiber type (proportion)

Campbell et al. (2013) did an investigation on the fiber type of m. multifidus. The study reported a decrease in type I muscle fibers of this stabilizer. Because of neurologic impairment and deconditioning caused by this disease (Mahler et al., 2012; Abadi et al., 2009), this decrease could be reasoned. Carrol et al. (2005) and Garner et al. (2003) found, by studying MHC and fiber-type distribution, that the m. vastus lateralis in pwMS was similar to HC. Thereby, this muscle characteristic is not altered in m. vastus lateralis and does not prepossess the oxidative capacity on intramuscular level. Garner et al. (2003) found a correlation that indicates that EDSS scores are related to MHC in type I and type II muscle fibers. The higher the EDSS score, the higher the relative number of MHC isoforms for IIa, IIa/IIx and IIx and the lower the MHC isoforms for type I muscle fibers. This may prepossess the oxidative capacity, because fast MHC is present in muscle fibers with lower oxidative capacity. Kent braun et al. (1997) also reported a shift from fiber type I to type II muscle fibers of the m. tibialis anterior. Wens et al. (2014) reported a similar fiber shift tendency as previous studies, but no significant differences that may have been explained by the small sample size. In contrary, Hansen et al. (2015) did not report a difference in percentages of muscle fibers. The small sample size that the study used could be an explanation for this contradiction.

In general, these results show a fiber type shift and a decrease of type I fibers in pwMS for different groups of muscles. This morphological change may have an effect on the oxidative metabolism, because of the metabolic pathways used by the fiber types. Moreover, type I muscle fibers utilize oxidative pathways for energy supply (in contrary of the glycolytic type II muscle fibers). Thereby, the reported decrease of type I muscle fibers and shift from type I to type II muscle fibers (more fatigable) may lead to an impaired oxidative capacity.

CSA (cross-sectional area)

The significantly smaller CSA of all muscle fiber types in pwMS that was observed in Campbell et al. (2013) for the m. multifidus was most likely related to muscle deconditioning due to the neurological impairment. These findings were in line with the results of Kent-Braun et al. (1997) and Wens et al. (2014) who also found significantly smaller muscle fiber CSA in m. vastus lateralis and m. tibialis anterior. Carroll et al. (2005) on the other hand, reported no differences in single muscle fiber CSA of the m. vastus lateralis in pwMS compared to HC. Explanations for these dissimilar results could be that other muscles might be more affected by inactivity or MS in general, because they are differently activated. They also included pwMS with a wide range of EDSS scores which may have affected the results. Other possible reasons for these results could be that they might not have studied enough subjects to detect significant differences between groups, or that they analyzed an inadequate number of skeletal muscle fibers to represent the m. vastus lateralis appropriately.

Overall skeletal muscle fibers tend to be smaller in pwMS, hereby they can absorb less oxygen during exercise which can result in a lower oxidative capacity.

Altered enzyme activity

The increased basal muscle phospho-AMPK∝ and post-exercise phospho-AMPK∝ in the m. vastus lateralis of pwMS that Hansen et al. (2015) reported, indicates that pwMS have a higher mitochondrial biogenesis. An explanation may be impaired downstream signaling, mitochondrial biogenesis is not aggravated. This is compensated by increasing the phosphorylation, this may ultimately lead to changes in oxidative capacity in pwMS. Hansen et al. (2015) also mentioned that muscle phosphor-AMPK∝ is upregulated during (among others) oxidative stress.

The lower succinate dehydrogenase (SDH) activity of the m. tibialis anterior of pwMS reflects that MS may affect the second pathway (complex II) of oxidative phosphorylation and thus the oxidative capacity of pwMS. Kumleh et al. (2006) reported a significantly lower activity of NADH-ferricyanide reductase. This means that the oxidation of NADH in the mitochondrial matrix that is required for ATP synthesis may be reduced. In general, oxidative phosphorylation is altered in pwMS by changes in SDH activity and catalytic activity of complex I.

In conclusion, altered enzyme activity in pwMS may suggest a diminished ability of the muscle fibers to supply energy via aerobic pathways. As a result, it could be hypothesized that muscle fibers in pwMS supply energy mostly through anaerobic pathways, which would influence lactate production, resulting in elevated concentrations of blood lactate content during exercise. The fact that no difference was found in GPDH activity may indicate that the glycolytic capacity is comparable between pwMS and HC.

5.3. Reflections on the strengths and weaknesses of the literature study

Table 3 summarizes the strengths and weaknesses of the included studies. The major weaknesses of this literature study (for both parts) are the following:

- Sample sizes were small, ranging from six to 38. Only a few articles performed a power analysis to determine the required sample size.
- Sample sizes were not comparable between both groups for most of the articles. The number of participants in the intervention group (pwMS) were frequently higher, compared to the control group.
- EDSS scores varied and were only representative for pwMS with a low to mild disability.

The major strengths are:

- Every study had matched control groups for age, gender and physical activity
- Each protocol of the intervention was described in detail
- A clear description of the in- and exclusion criteria for all articles
- Most of the articles reported similar results, and often referred to included studies.

Finally, the literature study to conduct this master thesis had a number of strengths and weaknesses. The main weakness is the large number of obtained articles, especially for part II. Since only general terms were combined, a large number of articles were found. These articles were often not related to the research question. Thereby, it took a long time to read and analyze each hit on each database. Hits where thereby divided in half, for each half to be analyzed by one reviewer. Another weakness is the limited number of relevant articles for part I. For part II, multiple outcome measures were found, making it difficult to compile a clear overview. Given the broad search strategies and large number of analyzed hits, no articles were overlooked which is the major strength of the literature study.

5.4. Recommendations for further research

Further recommendations could be made after writing this literature review:

Part I

- Graded (sub)maximal exercise intensities were used in the included studies. More research is designated to determine blood lactate content in different forms of exercise intensities varying under and above the anaerobic threshold such as HIIT (High Intensity Interval Training).
- Studies with a larger sample size
- Studies with a mean EDSS score that is representative for the overall population of MS.
- Studies that investigate at what EDSS score aerobic capacity alters, compared with HC.

Part II

- Studies with a larger sample size and a mean EDSS score that is representative for the overall population of multiple sclerosis.
- Further research should be executed to study other muscle characteristics that can influence the oxidative capacity. There are still a lot of possible determinants that have not come across in the literature study. For example: the function of the mitochondria, intermuscular energy supply, the lactate shuttle, intramuscular triglycerides, fire frequency of the motor units, the amount of calcium in the sarcoplasmic reticulum. Further study of these determinants will give us a better insight into the oxidative capacity on peripheral intramuscular level in pwMS and thereby a better understanding of peripheral fatigue.

6 Conclusion

Part I

As conclusion, there is no significant difference in blood lactate content during/after graded submaximal and maximal exercise intensities in pwMS compared to HC.

Part II

After conducting this literature study, it can be concluded that pwMS exhibit lower skeletal muscle oxidative capacity compared to HC. Possible contributing factors are the significant differences in fiber type, muscle fiber cross-sectional area (CSA) and altered enzyme activity in pwMS compared to HC.

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8 Appendix part I – literature search

Table 1: Overview of search terms

Figure 1 and 2: Flowcharts of search strategy

Table 2: Overview of excluded articles

Table 3: Quality assessment of the included articles

Table 4: Data extraction of the included articles (clustered by outcome measurement)

Table 5: Strengths and weaknesses of the included articles

Table 6: Overview outcome measurements included articles

Table 1: Overview of search terms

1a Keywords, search strategy and hits in PubMed; Part I

	Keywords	Results in PubMed
#1	Lactates [MeSH Terms]) OR Lactate [Title/Abstract]	130255
#2	Lactic acid[MeSH Terms]) OR Lactic acid[Title/Abstract]	56503
#3	#1 OR #2	145025
#4	Exercise [MeSH Terms]) OR exercise [Title/Abstract]	316883
#5	Control group [MeSH terms]	1579
#6	Control [Title/Abstract]	2268196
#7	#5 OR #6	2269037
#8	Healthy volunteers[MeSH Terms]	10391
#9	Healthy[Title/Abstract]	701747
#10	#7 OR #8 OR #9	2811091
#11	multiple sclerosis [MeSH terms] OR multiple sclerosis [Title/Abstract]	72534
#12	#3 OR #4 AND #10 AND #11	500

1b Keywords, search strategy and hits in ProQuest; Part I

	Keywords	Results in ProQuest
#1	Exact("multiple sclerosis")	50821
#2	ti(multiple sclerosis)	47450
#3	ab(multiple sclerosis)	112269
#4	#1 OR #2 OR #3	154888
#5	Exact("lactate")	283
#6	ab(lactate)	38215
#7	#5 OR #6	38259
#8	#4 AND #7	71
#9	#8 + Limits applied (Source type: Scholarly Journals)	48

1c Keywords, search strategy and hits in PubMed; Part II

	Keywords in the search bar	**Results in PubMed**
#1	multiple sclerosis[MeSH Terms]	52215
#2	multiple sclerosis[Title/Abstract]	65472
#3	#1 OR #2	72590
#4	Skeletal muscle[MeSH Terms]	242226
#5	Muscle[Title/Abstract]	585938
#6	Skeletal muscle fiber[MeSH Terms]	40403
#7	Muscles[MeSH Terms]	638481
#8	#4 OR #5 OR #6 OR #7	925519
#9	#3 AND #8	1585

1d Keywords, search strategy and hits in ProQuest; Part II

	Keywords in the search bar	**Results in ProQuest**
#1	Exact("multiple sclerosis")	50820
#2	ab(multiple sclerosis)	112269
#3	ti(multiple sclerosis)	47450
#4	#1 OR #2 OR #3	154888
#5	ti(muscle)	189076
#6	ab(muscle)	810967
#7	#5 OR #6	919711
#8	#4 AND #7	3058
#9	#8 + Limits applied (Source type: Scholarly Journals)	544

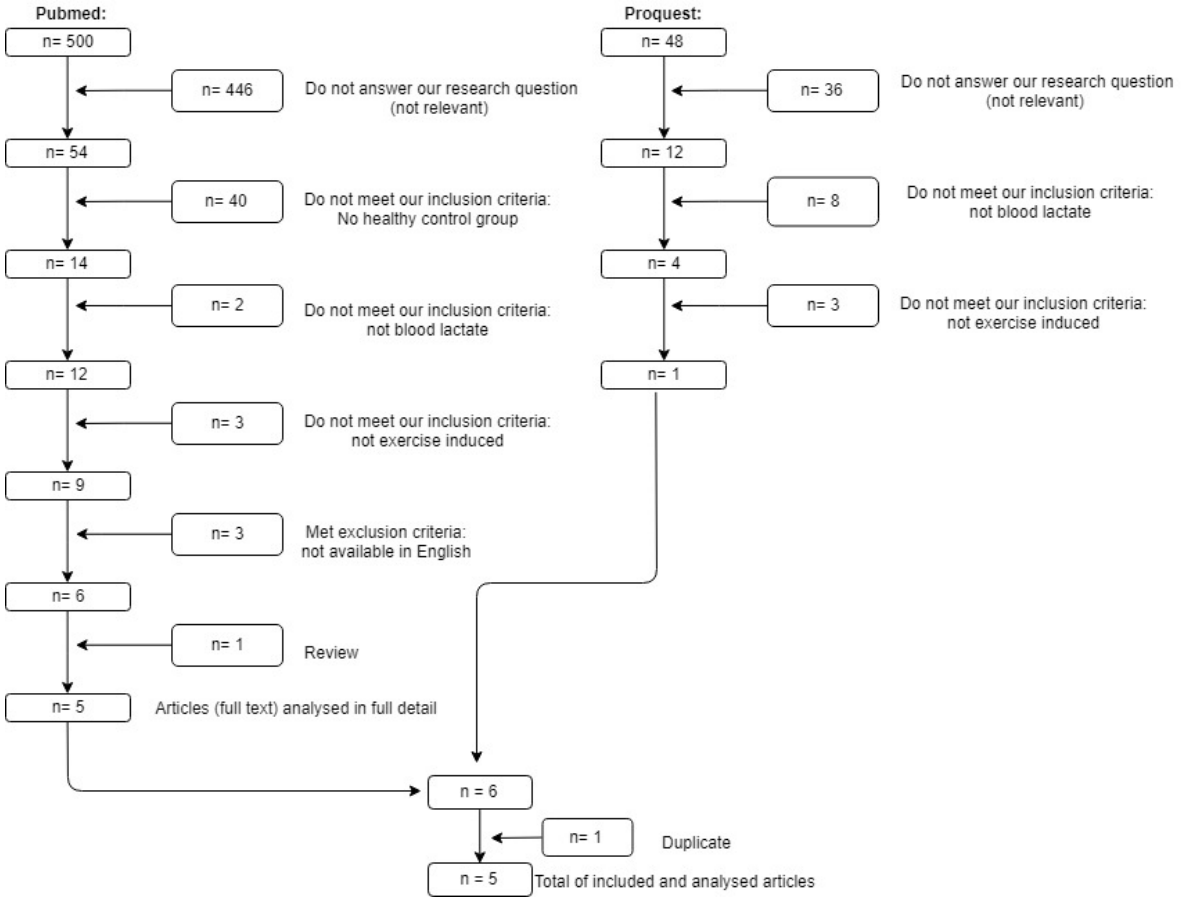

Fig. 1: Flow chart in- and excluded articles Part I PubMed and ProQuest search

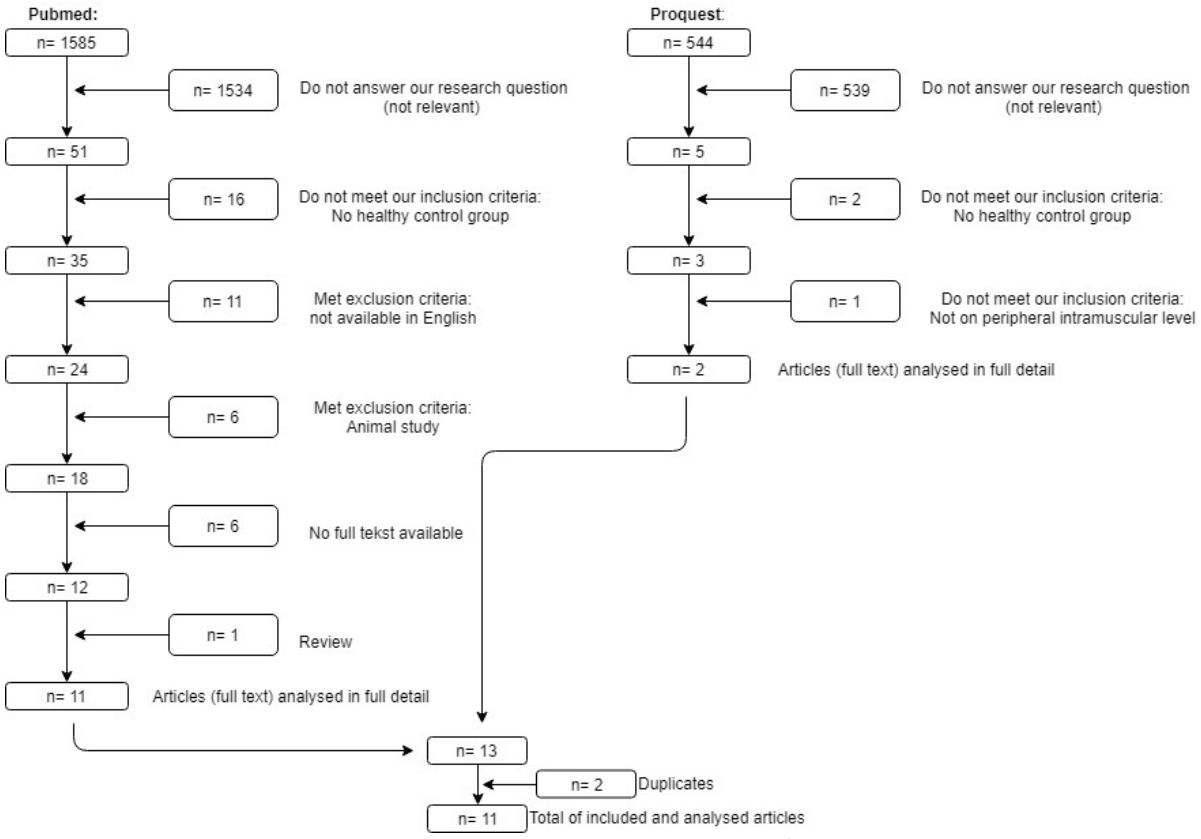

Fig. 2 Flow chart in-and excluded articles Part II PubMed and ProQuest search

Table 2: Overview of excluded articles

Search strategy part I: ProQuest (49 hits)

Reason of exclusion	Number of articles (n=)	Author(s) and year of publication
Do not meet the inclusion criteria (not exercise-induced)	**3**	Vafaeyan et al., 2015; Petzold et al., 2015; Jahromi et al., 2014
Meet the exclusion criteria (not blood lactate)	**8**	Lazzarino et al., 2017; Philips et al., 2017; Pucino et al., 2017; Girard et al., 2017; Yildiz et al., 2015; Campbell et al., 2014; Dong et al., 2012; Mähler et al. 2012
Do not answer the research question	**36**	Guglielmetti et al., 2017; Abdelhak et al., 2017; Ghareghani et al., 2017; Hyun-Hwi et al., 2017; Iglesias et al., 2017; Reis-mendes et al., 2017; Rinholm et al., 2016; Zhang et al., 2016; Albanese et al., 2016; Castro-Nallar et al., 2015; Penesova et al., 2015; Thekkuttuparambil Ananthanarayanan et al, 2014; Martikainen et al., 2013; Bolcaen, 2013; Ghods et al., 2013; Morris et al., 2013; Finsterer et al., 2012; Colledge et al., 2012; Cambron et al., 2012; Polak et al., 2012; Paling et al., 2011; Isohanni et al., 2010; Martínez-Bisbal et al., 2009; Thomas et al., 2008; Lutz et al., 2007; Lindquist et al., 2007; Genc et al., 2006; Enzinger et al., 2005; Malojcic et al., 2004; Schocke et al., 2003; Yonetani et al., 2001; Mader et al., 2001; Lane et al., 2000; Hartmann et al 1999; Iranzo et al., 1999; Jongen et al., 1998; Jongen et al., 1997

Search strategy part II: ProQuest (544 hits)

Reason of exclusion	Number of articles (n=)	Author(s) and year of publication
Do not meet the inclusion criteria (not on peripheral intramuscular level)	**1**	Mona et al., 2016
Meet the exclusion criteria (no healthy control group)	**2**	Dalgas, et al., 2010; Reich et al., 2007
Do not answer the research question	**539**	Hobart et al., 2006; Ghafari et al., 2009; Boudarham et al., 2016; Gijbels et al., 2010; Dalgas et al., 2010; Schyns et al., 2009; Patejdl, et al., 2008; Reich et al., 2007; Taha et al., 2016; Malagoni et al., 2013; Esnouf et al., 2010; Gatti et al., 2008; Keser et al., 2013; Illomei et al., 2017; Claerbout et al., 2012; Zajicek et al.,

		2003; Eftekhari, et al., 2012; Onambélé et al., 2006; Brostrom et al., 2003; Ickmans et al., 2014; Broekmans et al., 2011; Dodd et al., 2011; Caruso et al., 2009; Shimizu et al., 2007; Srour et al., 2013; Ketelhut et al., 2015; Pellegrino et al., 2018; Rodgers et al., 1999; Peterson et al., 2001; Moradi et al., 2015; Gijbels et al., 2011; Habek et al., 2010; Turkoski et al., 2013; Medina-Perez et al., 2016; Eguíluz et al., 2013; Wiens et al., 1999; Giesser et al., 2007; Echaniz-Laguna et al., 2010; Motta et al., 2016; Sicotte et al., 2007; Stangel et al., 2000; Svensson et al., 1994; Miller et al., 2007; Sheean et al., 1997; Chetta et al., 2004; Steens et al., 2012; Cramer et al., 2014; Souza et al., 2010; Ozgocmen et al., 2005; Paoloni et al., 2013; Chang et al., 2011; Kjølhede et al., 2012; Broekmans et al., 2013; Schwid et al., 2002; Thoumie et al., 2002; Pasiut et al., 2015; Ng et al., 2013; Hayes et al., 2007; Manca et al., 2016; Wens et al., 2015; Fry et al., 2015; Johnson et al., 2012; Goodman et al., 2007; Tacconi et al., 2016; Lamarre et al., 2014; Chia et al., 1996; Mutluay et al., 2007; Zeller et al., 2012; Severijns et al., 2015; Mortazavi et al., 2012; Aiello et al., 2008; Mehta et al., 2010; Henze et al., 2014; Leong et al., 2009; Finsterer et al., 2012; Kidd et al., 1998; Sethc et al., 2011; Andreasen et al., 2009; Cofré et al., 2016; Masoudi et al., 2013; Altintas et al., 2007; Scheidegger et al., 2012; Freeman et al., 2012; Puthenparampil et al., 2016; Kobashi et al., 2008; Mitchell et al., 2008; Borisow et al., 2013; Sriram et al., 2018; Hyman et al., 2000; Ingram et al., 1988; Lorna et al., 2014; Shareinia et al., 2017; Hertz et al., 2017; Tallner et al., 2016; Naghdi et al., 2017; Boneschi et al., 2008; Truini et al., 2013; Naghdi et al., 2017; Gottlieb et al., 2000; White et al., 2009; Nance et al., 1997; Tomasevic et al., 2013; Seo et al., 2013; Vermersch et al., 2013; Manca et al., 2017; Sosnoff et al., 2014; Aschenbrenner et al., 2017; Zeller et al., 2011; Freeman, et al., 2016; Johansson et al., 2012; Trojan et al., 2007; Mähler et al., 2015; Levin et al., 2011; Ng et al., 2000; Donnellan et al., 2008; Smith et al., 2000; Siev-Ner et al., 2003; Zajicek et al., 2011; Levy et al., 2017; Jost et al., 2006; Dalgas et al., 2013; Derbich et al., 2016; Mohr et al., 1998; Vazirinejad et al., 2008; Heldner et al., 2014; Tzelepis et al., 2015; Fimland et al., 2010; Katz et al., 2011; Surakka et al., 2004; Berardelli et al., 1988; Hawkes et al., 1980; Halabchi et al., 2017; Hochmeister et al., 2006; Humm et al., 2006; Formica et al., 1997; Lúcio et al., 2014; Zajicek et al., 2005; Dionisiotis et al., 2004; Sedano et al., 2000; Beckmann et al., 2015; Koutsis et al., 2008; Rico et al., 2009; Constantinescu et al., 1998; Vedrenne et al., 2017; Sutherland et al., 2001; Lamers et al., 2015; Martin et al., 2006; Barrett et al., 2009; White et al., 2004; Kostoff et al., 2008; Van Amerongen et al., 2004; Simka et al., 2012; Marsala et al., 2005; Leandri et al., 2003; Gianforcaro et al., 2014; Solaro et al., 2010; Feys et al., 2005; White et al., 2013; Verdun et al., 2002; Vielhaber et al., 2000; Klaren et al., 2016; Cousins et al., 2017; Sotgiu et al., 2009; P-S Tsai et al., 2008; Wirsching et al., 2018; Ghotbi et al., 2011; Pryce et al., 2007; Manetti et al., 2014; Jongen et al., 2015; Minassian et al., 2012; Nefyodov et al., 2015; Malik et al., 2015; Westerdahl et al., 2016; Loeffler et al., 2016; Anonymous et al., 2017; Foran et al., 2005; Kempen et al., 2016; Authier et al., 2001; Fry et al., 2016; Rabadi et al., 2013; Sanford et al., 2014; Nakane et al., 2017; Avandi et al., 2017; Gusev et al., 2008; Surakka et al., 2004; Smith et al., 2000; Cameron et al., 2014; Deckx et al., 2016; Popadic et al., 2012; Shroff et al., 2016; Leuschen et al., 2004; Bethoux et al., 2016; Meca-Lallana et al., 2010; Zajicek et al., 2012; Malojcic et al., 2004; Paradas et al., 2014; de Oliveira et al., 2017; Pappalardo et al., 2006; Tesio et al., 2006; Hedley et al., 1975; Arjmand et al., 2015; Kermode et al., 2006; Romani et al., 2004; Sena et al., 2004;Nair et al., 2014; Huang et al., 2017; Pappalardo et al., 2006; Stephens et al., 2006; La Morgia et

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Search strategy part I: PubMed (500 hits)

Reason of exclusion	Number of articles (n=)	Author(s) and year of publication
Do not meet the inclusion criteria (no healthy control group)	**40**	Brecl Jakob, Remsak, Sega Jazbec, Horvat Ledinek, & Rot, 2017; Bridoux et al., 2015; Conroy, Zhan, Culpepper, Royal, & Wallin, 2017; Coote et al., 2014; Deckx et al., 2015; Dixon-Ibarra, Nery-Hurwit, Driver, & MacDonald, 2017; "Erratum," 2016; Feltham et al., 2013; Finsterer & Mahjoub, 2014; Grover et al., 2016; Gunn, Markevics, Haas, Marsden, & Freeman, 2015; Gutierrez Cruz, Miangolarra Page, & Rojas Ruiz, 2016; Henecke, Hessler, & LaLonde, 2015; Kalron, 2015; Kasser, Jacobs, Ford, & Tourville, 2015; Kasser & Kosma, 2012; Keytsman, Hansen, Wens, & B, 2017; Lazzarino et al., 2017; Magnani et al., 2016; McAuley et al., 2015; McLoughlin, Barr, Crotty, Lord, & Sturnieks, 2015; Miglio, Veglia, & Fantozzi, 2015; Mori et al., 2014; Motl, Dlugonski, Pilutti, & Klaren, 2015; Nedeljkovic et al., 2016; Russo et al., 2015; Sandroff, Benedict, & Motl, 2015; Sandroff, Hillman, Benedict, & Motl, 2016; Sebastiao, McAuley, Shigematsu, & Motl, 2017; Severijns, Lemmens, Thoelen, & Feys, 2016; Sosnoff & Sung, 2015; Straudi et al., 2013; Straudi et al., 2014; Tarakci, Yeldan, Huseyinsinoglu, Zenginler, & Eraksoy, 2013; Wajda, Motl, & Sosnoff, 2013; Wens & Hansen, 2017; White, Vanhaitsma, Vener, & Davis, 2013; Yadav et al., 2014; Learmonth, Paul, Miller, Mattison, & McFadyen, 2012; Ponichtera-Mulcare, 1993
Do not meet the inclusion criteria (not blood lactate)	**2**	Learmonth YC, Paul L, McFadyen AK, 2014; Marongiu E, Olla S, Magnani S, 2015
Do not meet the inclusion criteria (not exercise-induced)	**3**	Amorini AM, Nociti V, Petzold A, 2014; Lazzarino G, Amorini AM, Petzold A, 2017; Vafaeyan H, Ebrahimzadeh SA, Rahimian N, 2015
Met exclusion criteria (not available in English)	**3**	Imenez-Morales RM, Herrera-Jimenez LF, Macias-Delgado Y, 2017; Olgiati R, di Prampero PE., 1986; Pukhov RV, Bisaga GN, Trufanov AG, 2013;
Review	**1**	Langeskov-Christensene et al., 2015
Do not answer the research question	**446**	Aasly J, Gårseth M, Sonnewald U, 1997; Adamson BC, Learmonth YC, Kinnett-Hopkins D, 2016; Adamson BC, Ensari I, Motl RW., 2015; Aidar FJ et al., 2017; Amatya B et al., 2013; Arpin DJ, Davies BL, Kurz MJ., 2016; Aruin AS, Ganesan M, Lee Y., 2017; Azimzadeh E, Hosseini MA, Nourozi K, Davidson PM., 2015; Balk L, Mayer M, Uitdehaag BM, Petzold A., 2013; Baram Y, Miller A., 2007; Baram Y, Miller A., 2006; Barr CJ, Patritti BL, Bowes R, Crotty M, McLoughlin JV., 2017; Belcher JD et al., 2017; Benedict RH et al., 2011; Bisson EJ et al., 2017; Bitsch A at al., 1999; Bjarnadottir OH, Konradsdottir AD, Reynisdottir K, Olafsson E., 2007; Bjurö T, Fugl-Meyer

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Search strategy part II: PubMed (1585 hits)

Reason of exclusion	**Number of articles (n=)**	**Author(s) and year of publication**
Do not meet the inclusion criteria (no healthy control group)	**16**	Brandes et al., 2007; Castro, Kent-Braun, Ng, Miller, & Dudley, 1998; Dionyssiotis et al., 2014; Ferreira, Pegorare, Salgado, Casafus, & Christofoletti, 2016; Gevaert et al., 2015; Hess, Mills, & Murray, 1986; Jongen et al., 2011; Kjolhede et al., 2016; Lambert, Archer, & Evans, 2001; Laxer & Eisen, 1975; Manca et al., 2016; Mutluay et al., 2007; Sangelaji et al., 2016; Vighetto & Tilikete, 2009; Wens et al., 2015; Zaenker et al., 2018
Meet the exclusion criteria (animal study)	**6**	Altuntas et al., 2008; Carroll, Gallagher, Seidle, & Trappe, 2005; de Haan, van der Vliet, Hendriks, Heijnen, & Dijkstra, 2004; Delbono, Garcia, Appel, & Stefani, 1991; Park et al., 2012; Porporato et al., 2013
Meet the exclusion criteria (not available in English)	**11**	Ali et al., 2018; Anonymous et al., 2005; Anonymous et al., 1995; Carter, Han, Mayadev, & Weiss, 2006; Endo, 2004; Kagamihara et al., 1994; Komaroff et al., 1996; Perrigot et al., 1985; Viel, Pelissier, Pellas, Boulay, & Eledjam, 2003; Wagner, Kremer, Van Dillen, & Naismith, 2014; Zaleski, 1999
No full text available	**6**	Islam MT., 2017; Evans WJ. et al., 2007; Ickmans K. et al., 2014; Riggs JE. et al., 1986; Vrach Delo, 1990; Enoka RM. et al, 2016
Review	**1**	Grant & Holick et al., 2005
Do not answer the research question	**1534**	Aguiar, Batista, & Pacheco, 2015; Aisen, Dietz, Rossi, Cedarbaum, & Kutt, 1992; Alfonsi et al., 2017; Amico & Antel, 1981; J. T. Andersen & Bradley, 1976; K. E. Andersson & Pehrson, 2003; Angel & Iannone, 1966; Arai, Tokumaru, Yagishita, Hirayama, & Iwasaki, 1986; Arjmand et al., 2015; Aruin, Kanekar, & Lee, 2015; Asgian, Dobos, & Popoviciu, 1975; Authier et al., 2001; Anonymous et al., 1978; D. Baker et al., 2017; Beer, 2004; Beer et al., 2001; Boerio, Creange, Hogrel, & Lefaucheur, 2007; Borg, Finell, Hakala, & Herrala, 2007; Borg-Stein, Pine,

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Table 3: Quality assessment
Part I

Critical Appraisal of a Cross-Sectional Study (CEBM)	*Hansen et al., 2012*	*Hansen et al., 2014*	*Larson et al., 2013*	*Morrison et al., 2008*	*Op 't Eijnde et al., 2014*
1. Addressing a clearly focused question	Y	Y	Y	Y	Y
2. Appropriate research method	Y	Y	Y	Y	Y
3. Clear selection method subjects	Y	Y	N	Y	N
4. Selection bias (sample)	N	N	?	N	?
5. Representative sample of subjects	Y	Y	N	N	Y
6. Sample size based on statistical power	?	Y	?	?	Y
7. Satisfactory response rate achieved	?	?	?	?	?
8. Reliable and valid measurements	Y	Y	Y	Y	Y
9. Statistical significance assessed	Y	Y	Y	Y	Y
10. Confidence intervals	N	N	Y	N	N
11. Confounding factors	N	N	N	N	N
12. Applicable results	Y	Y	Y	Y	Y

Center for Evidence Based Management (July 2014), Critical Appraisal Checklist for Cross-Sectional Study. Retrieved (March 20, 2018) from https://www.cebma.org
Y: yes
N: no
?: Can't tell

Part II (a)

Critical Appraisal of a Cross-Sectional Study (CEBM)	Campbell et al., 2013	Carroll et al., 2005	De Haan et al., 2000	Garner et al., 2003	Hansen et al., 2012	Hansen al., 2015
1. Addressing a clearly focused question	Y	Y	Y	Y	Y	Y
2. Appropriate research method	Y	Y	Y	Y	Y	Y
3. Clear selection method subjects	Y	N	N	Y	Y	Y
4. Selection bias (sample)	?	?	?	Y	?	Y
5. Representative sample of subjects	?	?	?	?	?	?
6. Sample size based on statistical power	?	N	N	?	N	Y
7. Satisfactory response rate achieved	?	?	?	?	?	?
8. Reliable and valid measurements	?	?	N	?	Y	Y
9. Statistical significance assessed	Y	Y	Y	Y	Y	Y
10. Confidence intervals	Y	N	N	N	N	N
11. Confounding factors	N	Y	N	N	N	N
12. Applicable results	Y	Y	Y	Y	Y	Y

Center for Evidence Based Management (July 2014), Critical Appraisal Checklist for Cross-Sectional Study. Retrieved (March 20, 2018) from https://www.cebma.org
Y: yes
N: no
?: Can't tell

Part II (b)

Critical Appraisal of a Cross-Sectional Study (CEBM)	Harp et al., 2016	Kent-Braun et al., 1994	Kent-Braun et al., 1997	Kumleh et al., 2006	Wens et al., 2014
1. Addressing a clearly focused question	Y	Y	Y	Y	Y
2. Appropriate research method	Y	Y	Y	Y	Y
3. Clear selection method subjects	Y	N	N	N	N
4. Selection bias (sample)	?	?	?	?	?
5. Representative sample of subjects	?	?	?	?	Y
6. Sample size based on statistical power	N	?	N	?	N
7. Satisfactory response rate achieved	?	?	?	?	?
8. Reliable and valid measurements	Y	?	?	?	?
9. Statistical significance assessed	Y	Y	Y	Y	Y
10. Confidence intervals	N	N	N	N	N
11. Confounding factors	N	N	N	N	N
12. Applicable results	Y	Y	Y	Y	Y

Center for Evidence Based Management (July 2014), Critical Appraisal Checklist for Cross-Sectional Study. Retrieved (March 20, 2018) from https://www.cebma.org
Y: yes
N: no
?: Can't tell
1.Did the study address a clearly focused question / issue? 2. Is the research method (study design) appropriate for answering the research question? 3. Is the method of selection of the subjects (employees, teams, divisions, organizations) clearly described? 4. Could the way the sample was obtained introduce (selection)bias? 5. Was the sample of subjects representative with regard to the population to which the findings will be referred? 6. Was the sample size based on pre-study considerations of statistical power? 7. Was a satisfactory response rate achieved? 8. Are the measurements (questionnaires) likely to be valid and reliable? 9. Was the statistical significance assessed? 10. Are confidence intervals given for the main results? 11. Could there be confounding factors that haven't been accounted for? 12. Can the results be applied to your organization?

Table 4: Strengths and weaknesses of the included studies
Part I

Authors & Journal	Limitations	Strengths
Hansen et al., 2014 European Journal of Physical and Rehabilitation Medicine	• In part II, therapists could not be blinded for treatment allocation • Limited by a lack of resting spirometry and respiratory muscle strength assessment • For certain parameter comparisons between groups a low statistical power was observed	• In part II, pwMS were randomly assigned to intervention or control follow-up • In part II, assessors were blinded for treatment allocation • The ethical committee of Hasselt University approved the protocol • Written informed consent was obtained from all participants • Sample size of part I was based on a previous study observing significant effects with sufficient statistical power • No significant differences in subject characteristics were found at baseline in both parts of the study, except for medication intake • No adverse events related to exercise training occurred during the follow-up of six months • Data of the study were in line with those from previous studies, but with proper matching of exercise intensities and subject characteristics between groups • These data were in line with previous observations of relations between exercise tolerance and pulmonary function (although at rest) in pwMS
Hansen et al., 2012 Neurorehabilitation and Neural Repair	• No details were found about possible drop-out(s) • Test discomfort might be too high when using invasive procedures to assess skeletal muscle oxidative capacity. This test might, however, be too difficult in more severely impaired people with MS • Difficult to explain the findings, because there was a great variance in selected endurance intensities, exercise bout and recovery durations, VO_2 kinetics determination methods, and subject characteristics between studies	• The study was approved by the medical ethical committee of Hasselt University • No significant differences at baseline were present • The cardiac (heart rate), ventilatory (expiratory volume), and metabolic (blood lactate content) response to exercise was not different between MS patients and healthy controls. This indicated that the relative exercise intensities used were properly matched between groups, allowing exercise-onset and -offset VO_2 kinetics comparisons between the groups • The author(s) received no financial support for the research, authorship, and/or publication of this article • The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article

Larson et al., 2013 The Journal of Rehabilitation Research and Development	• Data was preliminary at best and would need to be verified in a much larger study because of the small sample size • Lack of ability to distinguish the influence of central and peripheral factors on bilateral differences	• Each participant had physician's clearance and a signed consent form approved by the University of Georgia Institutional Review Board prior to participation • Prior to formal assessments, participants were familiarized with and practiced all testing procedures • To maximize consistency, participants were tested at approximately the same time of day and asked them to abstain from exercise, alcohol, caffeine, and smoking for 12 hours prior to the visit • No different characteristics in the subjects at baseline
Morrison et al., 2008 Archives Physical Medicine Rehabilitation	• Study in an urban university setting that included participants with MS with only mild disability, limiting its generalizability to other groups • Recruited a sedentary control sample, providing the advantage of well-matched study groups but conferring the potential drawback that the controls might not have closely resembled the general young adult population • Did not attempt to screen eligible participants with MS for heat sensitivity, the presence or absence of which might have affected the study results.	• The groups did not differ appreciably on baseline characteristics except for fatigue (MFIS summary scores and physical subscale scores) • Detailed description of drop-outs • Approval was obtained from the University of California, Irvine, Institutional Review Board • First study that systematically uses RPE to assess perceived exertion in MS and control participants during incremental exercise testing
Op 't Eijnde et al. 2014 Neurorehabilitation	• The cycling power output of subject characteristics at baseline was significantly different between groups • A mercury thermometer was used to measure (core) body temperature orally. Such assessment of body temperature was however not always valid (Mazerolle et al., 2011) • The thermometer was not calibrated before each assessment • Rather small sample size	• Sample size of the population was based on sample sizes of similar studies in patients with MS in which significant effects were found • No financial support • No declaration of interest

Part II

Authors & Journal	Limitations	Strengths
Campbell et al., 2013 Multiple Sclerosis Journal (MSJ)	• Assessment was limited to paraspinal muscle because ethical considerations prevented the sampling of limb skeletal muscle at post-mortem • This work was supported by the Wellcome Trust and the Newcastle Healthcare Charity and Newcastle upon Tyne Hospitals NHS charity.	• Ethical approval was granted for this study • No conflict of interest declared
Carroll et al., 2005 Archives of Physical Medicine and Rehabilitation	• It was possible that they might have not studied enough subjects to provide adequate power to detect differences between the MS and control subjects • The study only reported data from one muscle. It is possible that MS affects more other muscles • It was possible that spasticity in the hamstrings of pwMS may have artificially depressed quadriceps strength	• In agreement with others (Ponichtera-Mulcare et al., 1993), eccentric strength was not depressed in the MS group, suggesting that limitations due to hamstring spasticity was limited • Recent study
de Haan et al., 2000 Muscle & Nerve	• Some subjects had difficulty in fully relaxing the left leg. This involuntary activity, as judged from the electromyographic activity in the 'relaxed' muscle, sometimes caused an unsteady force baseline and thus resulted in unreliable measurements. Tese results were therefore not included in the statistical analysis, leading to different numbers of observations for different parameters	
Garner et al., 2003 Muscle & Nerve	• Small sample size • The relationship between MHC isoform content and disability needs to be confirmed in a larger population with a broader range of EDSS	• The data were in agreement with the findings of Kent-Braun et al. (1997)
Hansen et al., 2012 Neurorehabilitation and Neural Repair	• No details were found about possible drop-out(s) • Test discomfort might be too high when using invasive procedures to assess skeletal muscle oxidative capacity: this might be too difficult in more severely impaired people with MS • Difficult to explain the findings, because there is a great	• The study was approved by the medical ethical committee of Hasselt University • No significant differences between both groups at baseline were present • The cardiac, ventilatory, and metabolic response to exercise was not different between MS patients and

	variance in selected endurance intensities, exercise bout and recovery durations, VO_2 kinetics determination methods, and subject characteristics between studies	healthy controls indicating that the relative exercise intensities used were properly matched between groups, allowing exercise-onset and offset VO_2 kinetics comparisons between the groups • The author(s) received no financial support for the research, authorship, and/or publication of this article • The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article
Hansen et al., 2015 The Journal of Laboratory And Clinical Medicine	• The study sample size was low • EDSS was relatively low: only representative for pwMS with a low to mild disability • Dropout rate from the first to the second part of the study was high • It was not examined whether neurologic deficits were present in the biopsied leg of pwMS • Insufficient quantity of muscle tissue was collected to study downstream signaling cascades after phospho-AMPKα (muscle AMP-activated protein kinase phosphorylation) and phospho-mTOR (mammalian target of rapamycin phosphorylation)	• Between groups, subject characteristics were comparable • The observed statistical power for detection of differences in muscle phospho- AMPKα and phospho-mTOR between groups was sufficient • Recent study
Harp et al., 2016 Multiple Sclerosis Journal (MSJ)	• Some of the participants were not able to activate their plantar flexor muscles enough with voluntary exercise to measure recovery rates. In these participants, electrical stimulation was effective • Calf muscle strength was not measured. Participants could accurately identify their stronger and weaker legs, but quantifying the differences would have helped with the comparisons between the stronger and weaker legs and legs with higher and lower mitochondrial capacity • The authors have unpublished data about self-reported fatigue scales such as the Modified Fatigue Impact Scale, or the Mental and Physical State and Trait Energy and Fatigue scales. These may have been useful to quantify symptom severity in terms of perceived fatigue	• Study protocol was well tolerated by the participants • One of the advantages of the NIRS method of measuring mVO_2max was that rate constants could be directly compared between studies • Data agreed with previously published data by Kent-Braun and colleagues using the recovery rate of phosphocreatine measured with P MRS • Recent study

	• There was an inability to make NIRS measures in individuals with excessive adipose tissue thickness over the muscle of interest. This exclusion of people with adipose thickness over the muscle of interest greater than 2 cm limited the participant population, but this is an inherent limitation of the current NIRS technology • Declaration of conflicting interests: K.K. McCully is the president of Infrared Rx Inc. This company develops software analysis solutions for NIRS-based measurements of skeletal muscle • This work was funded in part by the Eula C. and Andrew C. Carlos MS Rehabilitations and Wellness Program	
Kent-Braun et al., 1994 Muscle & Nerve	• No table of subjects characteristics mentioned • The controls performed voluntary exercise but the MS patients were electrically stimulated. The extent to which the difference in exercise stimulus might affected the results of this study cannot be determined • Old study	• The present findings were consistent with a study of mitochondrial oxidative capacity in a model of disuse, in which succinate dehydrogenase (SDH) activity in the tibialis anterior muscle of spinal cord-injured subjects was significantly decreased compared to non- injured control subjects (Martin et al., 1992) • The values for the T1/2 of both PCr (phosphocreatine resynthesis) and ADP (adenosine diphosphate) recovery were in excellent agreement with the results of Arnold et al. (1984)
Kent-Braun et al., 1997 The American Physiological Society	• Old study	

Kumleh et al., 2006 Journal of the Neurological Sciences	• Small sample size	
Wens et al., 2014 PLoS ONE	• Small sample size • Three biopsies from different depths of the muscle and analysing >150 fibers from each sample are recommended to reduce sampling error. Given the ethical concerns were collected only one biopsy and analysed approximately 170 from each sample, being aware of the variation in the study results • Given the cross-sectional nature of the study, these results do not allow conclusions on causality	• No differences in general subject characteristics were found between MS and healthy controls • Findings for reduced muscle fiber size were consistent with Kent-Braun et al. (1997) and Garner et al. (2003)

Table 5: Overview included articles (data extraction)
Part I - blood lactate content

Authors & Journals	Control group and number analyzed	Experimental group and number analyzed	Outcomes/ methodology of the study	Results of the study
Hansen et al., 2012 Neurorehabilitation and Neural Repair	n= 16 healthy sedentary individuals	n= 38 sedentary pwMS diagnosis > 12 months EDSS: 3.1 ± 1.3	Blood lactate measured with Accutrend Plus during a cardiopulmonary exercise test on an electronically braked cycle ergometer that consisted of two six-minute exercise bouts separated by a six-minute resting period. With the resistance set at 25% of predicted Wmax for pwMS and at 35% of predicted Wmax for HC. After each six-minute exercise bout blood was obtained from the fingertip.	Blood lactate during exercise did not differ between groups. First bout lactate (mmol/L): MS = 3.1 ± 0.8 HC = 3.0 ± 1.1 Second bout lactate (mmol/L): MS = 3.0 ± 0.7 HC = 2.6 ± 1.4
Hansen et al., 2014 European Journal of Physical and Rehabilitation Medicine	n=11 healthy sedentary individuals	n= 16 sedentary pwMS diagnosis > 12 months	Blood lactate content during a six-minute constant-workload exercise test on a cycle ergometer. (pwMS: 25% of predicted Wmax; HC: 35% of predicted Wmax) A blood sample was obtained with Accutrend Plus from the fingertip to analyze blood lactate concentration during the final exercise minute.	Blood lactate content (P=0.97) HC = MS → equal relative exercise intensities Exercise blood lactate content did not correlate with subject characteristics for age, gender, BMI, EDSS and physical activity level (P>0.10) Significant correlations between exercise blood lactate content and VE/VO_2 (r=0.42), PETO2 (r=0.37) (P<0.05) Exercise lactate (mmoL/l) initial test: HC= 3.4±0.6 MS= 3.2±0.8

				Exercise lactate (mmoL/l) six months of follow-up: HC= 3.6±10 MS= 2.5±0.7
Larson et al., 2013 The Journal of Rehabilitation Research and Development	n= 7 Healthy individuals	n= 8 pwMS (Relapsing Remitting) EDSS <6,5	Blood lactate measured by finger stick Lactate Pro at rest and 3 minutes after the exercise test that consisted of a single-leg incremental cycling test starting at 0W and increased 1W every 2s until exhaustion.	No statistical differences observed between legs for peak lactate (mmol/L). MS: (P= 0.26) Stronger leg = 5.1 ± 2.6 Weaker leg = 4.2 ± 1.9 HC: (P= 0.91) Stronger leg = 4.67 ± 1.2 Weaker leg = 4.6 ± 1.5
Morrison al., 2008 Archives Physical Medicine Rehabilitation	n= 12 (age and sex matched) sedentary healthy individuals	n=12 sedentary pw mild MS EDSS score < 3 Current adherence to one of the approved disease-modifying therapies for MS	Measuring lactate with Lactate Pro as metabolite (secondary outcome) during a graded aerobic exercise test on a cycle ergometer with an increasing workload of 5 to 20W/min lasting 8 to 12minutes or till exhaustion.	Pretest serum lactate: MS: 1.81 +- 0.70 mmol/L HC: 1.89 +- 0.49 mmol/L → P= 0.74 Postexercise lactate: MS: 6.80 ± 1.85 mmol/L HC: 8.96 ± 3.64 mmol/L → P= 0.09 Significant increase in lactate from pre- to post-test. → P< 0.001
Op ‘t Eijnde et al., 2014 Neurorehabilitation	n=12 healthy individuals	n=12 pwMS diagnosis > 12 months EDSS: 3,5 ± 1,5	Cardiopulmonary exercise test on an electronically braked cycle ergometer consisting of two six-minute exercise bouts separated by a six-minute resting period. With the resistance set at 25% of predicted Wmax for pwMS and at 35% of predicted Wmax for HC. Blood samples were obtained with Accutrend Plus from	<u>1st exercise bout:</u> lactate rest (mmol/l): HC= 2.5 ± 0.8; MS= 2.9 ± 0.8 (P>0.05) steady-state lactate (mmol/l): HC= 3.0 ± 1.1; MS= 2.7 ± 0.9 (P>0.05)

			the fingertip to analyze blood lactate during each exercise bout.	<u>2nd exercise bout:</u> steady-state lactate (mmol/l): HC= 2.3 ± 0.7; MS= 2.7 ± 0.9 (P>0.05) <u>Combined data: 1 + 2nd bout:</u> steady-state lactate (mmol/l): HC= 2.6 ± 0.8; MS= 2.7 ± 0.8 (P>0.05)

Part IIa - Measurements of mitochondrial/oxidative capacity

Authors & Journals	Control group and number analyzed	Experimental group and number analyzed	Outcomes/ methodology of the study	Results of the study
De Haan et al., 2000 Muscle & Nerve	n=16 inactive or mildly physically active healthy individuals	n=17 ambulatory pwMS EDSS: 2-6	Investigate whether adaptations in muscle properties contribute to the higher fatigability of these patients. Electrical stimulation of the quadriceps muscles through surface electrodes (proximal and distal of the upper anterolateral and the lower anterior thigh). During a series of repeated contractions isometric force and maximal rate of force rise were observed.	Decrements MS>HC MS= (31.3 ± 10.4% and 50.1 ± 10.0%, respectively; n=13) HC= (23.8 ± 6.6% and 39.0 ± 8.1% n=15) → suggesting a lower oxidative capacity
Hansen et al., 2012 Neurorehabilitation and Neural Repair	n= 16 healthy sedentary individuals (sports <2h/week)	n= 38 sedentary pwMS diagnosis > 12 months EDSS: 3.1 ± 1.3	Cardiopulmonary exercise test on a cycle ergometer that consisted of two six-minute exercise bouts separated by a six-minute resting period. With the resistance set at 25% of predicted Wmax for pwMS and at 35% of predicted Wmax for HC. Examining skeletal muscle oxidative capacity by calculating exercise-onset Vo_2 kinetics	Exercise-onset MRT during both bouts: MS is significantly slower than HC (P =0.01 and P=0 .04) The averaged exercise-onset MRT of both bouts: MS is significantly slower

			Exercise-onset Mean Response Time (MRT): the exercise-onset Mean Response Time (MRT) was calculated by dividing the oxygen deficit with the difference between rest and steady-state VO_2	than HC (P =0.007) MS: 46 ± 17 seconds HC: 32 ± 14 seconds
Harp et al., 2016 Multiple Sclerosis Journal (MSJ)	n= 9 sedentary healthy individuals	n= 16 ambulatory pw MS diagnosis >12 months Stable use of disease modifying drugs	<u>NIRS mitochondrial capacity assessment of the gastrocnemius muscle:</u> Muscle mitochondrial capacity was quantified as the rate of recovery of muscle metabolism after a short bout of exercise or electrical stimulation to increase metabolic rate → muscle metabolism measured as in NIRS-measured oxygen saturation. <u>Exercise:</u> -able to exercise calf muscles: 5-7s of rapid voluntary plantar flexion (full ROM against resistance by red thera-band) -not able to exercise both legs: electrical stimulation (15s 4Hz)	MS 40% lower mitochondrial capacity compared to HC. MS= 1.13 ± 0.29 min-1; HC= 1.68 ± 0.37 min-1 (P= 0.001) No difference in mitochondrial capacity between strong and weak legs in the MS group. (P=0.27)
Kent-Braun al., 1994 Muscle & Nerve	n= 8 healthy individuals	n= 13 pwMS EDSS: 2.5-8	Rate of intramuscular phosphocreatine resynthesis (PCr) following exercise measured by phosphorus magnetic resonance spectroscopy. MS = electrically stimulated exercise protocol: 9min of intermittent tetanic contractions via surface electrode at the peroneal nerve HC = voluntary exercise protocol: intermittent isometric contractions of the dorsiflexor muscles (4s contract- 6s relax) 6 contractions/min for 16 min. Both protocols resulted in comparable muscle fatigue.	<u>Recovery of PCr following exercise:</u> T1/2 of PCr resynthesis during 10min recovery: MS = significantly longer (2.3 ± 0.3 min) compared to HC (1.2 ± 0.1 min) (P<0.02) by 10min of recovery PCr MS = HC MS= 94.4 ± 4.7% recovered; HC= 97.7 ± 2.4% → slowed PCr recovery suggestive of impairment of oxidative capacity in MS vs HC.

Part IIb - Fiber type (proportion)

Authors & Journals	Control group and number analyzed	Experimental group and number analyzed	Outcomes/ methodology of the study	Results of the study
Campbell et al., 2013 Multiple Sclerosis Journal (MSJ)	n =15 mobile healthy individuals	n=17 non-ambulatory pwMS	Post-mortem muscles (multifidus) from MS and controls were obtained. The proportion of muscle fiber types was identified using myosin heavy chain slow and fast and assessed by taking images.	Predominance of type I fibers in controls (82.30% of all muscle fibers). Proportion of type I fibers was significantly decreased to 61.48% in MS (p =0.006).
Carroll et al., 2005 Archives of Physical Medicine and Rehabilitation	n=7 sedentary healthy individuals non-smoking	n=7 sedentary pwMS in clinical remission (Relapse Remitting) EDSS: 2.5 - 6.5 non-smoking	Single muscle fiber myosin heavy chain (MHC) distribution MHC analysis with gel electrophoresis Muscle biopsy from vastus lateralis for ATPase analysis.	<u>MHC distribution:</u> The proportion of total MHC hybrid (I/IIa+I/IIa/IIx+IIa/IIx) fibers: no difference between the groups. (MS: 36.1±4.7; HC: 25.2±2.8) Distribution of MHC I, I/IIa, IIa/IIx or IIx fibers: no difference between groups MHC I/IIa/IIx fibers %: MS > HC (p=0.041) (MS: 5.6±1.5; HC: 1.6±1.0) <u>ATPase fiber type:</u> No differences were noted between MS and HC in the distribution of any fiber type. Fiber type %: I: MS= 46.8±7.4; HC= 43.0±2.8 IIa: MS= 28.1±6.3; HC= 37.9±3.8 IIx: MS= 25.0±7.6; HC= 19.1±2.9
Garner et al., 2003 Muscle & Nerve	n= 6 sedentary healthy individuals	n=6 ambulatory pwMS EDSS: 4.0-6.0	Muscle biopsies from vastus lateralis (weakest leg pwMS, left leg healthy individuals) were obtained. Fiber MHC isoform content determined by gel electrophoresis.	<u>Fiber type %</u> Relative number of fibers containing type I, IIa/IIx or IIx MHC was similar between groups. MS had relatively fewer fibers containing type IIa I: MS= 45.5±5.2; HC= 39.9±3.1 IIa: MS= 30.7±4.0; HC= 45.6±3.9 → P<0.05

				IIa/IIx: MS= 13.3±3.4; HC= 9.5±1.9 IIx: MS= 7.9±3.1; HC= 2.5±1.0 Significant negative relationship between EDSS and type I MHC expression (R2=0.77; P<0.05) Positive correlation between EDSS and relative expression of pooled fibers containing fast MHC isoforms, i.e., the IIa, IIa/IIx, and IIx fibers (R2=0.70; P<0.05)
Hansen et al., 2015 The Journal of Laboratory And Clinical Medicine	n= 10 healthy individuals	n= 14 pwMS Diagnosis >12 months	Skeletal muscle fiber type composition by muscle biopsies [middle part of m. vastus lateralis (MS = weakest leg, HC = random leg)]. Stained by means of ATPase histochemistry.	<u>Muscle characteristics:</u> Type 1 %: MS= 44.6 ± 58; HC= 50.0 ± 14.2 (P=0.29) Type 2a %: MS= 33.6 ± 10.7; HC= 34.1 ± 12.4 (P=0.75) Type 2x %: MS= 22.9 ± 8.9; HC= 18.7 ± 11.6 (P=0.51)
Kent-Braun et al., 1997 The American Physiological Society	n= 8 sedentary healthy individuals	n= 9 pwMS diagnosis: 11 ± 2 years EDSS: 2-6	Skeletal muscle biopsies: tissue samples from m. tibialis anterior Fiber type % Each sample was processed using histochemical techniques.	<u>%:</u> I: MS= 65.5 ± 5.6; HC= 75.9 ± 2.6 IIa: MS= 28.2 ± 5.9; HC= 19.2 ± 1.8 IIax: MS= 6.3 ± 1.7; HC= 4.9 ± 1.4 → % type I: HC > MS; % type IIa: MS > HC (P<0.05)
Wens et al., 2014 PLoS ONE	n= 18 healthy individuals > 18 years No other chronic disorders	n= 34 pwMS EDSS: 0-6 >18 years No exacerbation 6 months prior to start of study No other chronic disorders	Muscle biopsies of m. vastus lateralis Fiber type proportion by ATPase histochemistry.	<u>Fiber type distribution (%):</u> Type I: HC= 46.1 +- 2.8; MS= 41.6 +- 2.3 Type IIa: HC= 32.6 +- 2.7; MS= 36.4 +- 2.1 Type IIx: HC= 23.2 +- 2.9; MS= 21.8 +- 1.9 Fiber type I proportion tended to be lower in pwMS (P=0.1) Type IIa proportion tended to be higher in pwMS (P=0.1)

Part IIc - CSA

Authors & Journals	Control group and number analyzed	Experimental group and number analyzed	Outcomes/ methodology of the study	Results of the study
Campbell et al., 2013 Multiple Sclerosis Journal (MSJ)	n =15 mobile healthy individuals	n=17 non-ambulatory pwMS	Post-mortem muscle (multifidus) from MS and controls were obtained. Peri-operative samples were obtained from lumbar paraspinal and deep cervical paraspinal muscles. Determining whether respiratory enzyme deficiency in MS was in excess of age-related changes within muscle with histochemical technique (COX/SDH histochemistry).	CSA of respiratory enzyme-deficient muscle fibers: not significantly different, compared to fibers with intact complex IV activity in both groups (p =0.059 and p =0.258, respectively) CSA of both type I and type II muscle fibers in MS: significantly lower compared with controls (data not shown)
Carroll et al., 2005 Archives of Physical Medicine and Rehabilitation	n=7 sedentary healthy individuals non-smoking	n=7 sedentary pwMS in clinical remission (Relapse Remitting) EDSS: 2.5 - 6.5 non-smoking	Single muscle fiber cross-sectional area (CSA) was determined by tracing the individual muscle fibers from photographs of each mATPase-stained cross-section.	<u>CSA:</u> No differences were observed between groups on any fiber type. Fiber CSA (μm²): I: MS= 3682±448: HC= 3496±200 IIa: MS= 4112±439; HC= 4022±478 IIx: MS= 3246±492; HC= 3398±467
Hansen et al., 2015 The Journal of Laboratory And Clinical Medicine	Part I: n= 10 healthy individuals Part II: n= 7 healthy individuals	Part I: n= 14 pwMS Part II: n= 9 pwMS Diagnosis >12 months	Skeletal muscle CSA by muscle biopsies of the middle part of the m. quadriceps femoris vastus lateralis (MS = weakest leg, HC = random leg). ATPase histochemistry was used.	<u>Muscle characteristics:</u> Type I CSA: MS= 4.235 ± 977; HC= 4.843 ± 1236 (P= 0.20) Type IIa CSA: MS= 3.911 ± 1475; HC= 5.171 ± 1705 (P=0.046) Type IIx CSA: MS= 3.167 ± 1404; HC= 3.404 ± 926 (P=0.31) → type IIa muscle fiber CSA: MS < HC

Kent-Braun et al., 1997 The American Physiological Society	n= 8 sedentary healthy individuals	n= 9 pwMS diagnosis: 11 ± 2 years EDSS: 2-6	Skeletal muscle biopsies: tissue samples from m. tibialis anterior CSA and relative fiber type CSA: % times CSA for each fiber type divided by sum of these values for all fiber types Each sample was processed using histochemical techniques.	<u>CSA (μm²):</u> I: MS= 3.438 ± 288; HC= 4.572 ± 438 IIa: MS= 4.443 ± 410; HC= 6.988 ± 769 IIax: 3.476 ± 320; HC= 5.054 ± 782 → HC CSA > MS CSA (P<0.05) These measurements were used to calculate the following results: <u>Relative fiber type CSA %:</u> I: MS= 62 ± 6; HC= 69 ± 3 IIa: MS= 32 ± 7; HC= 26 ± 2 IIax: MS= 6 ± 2; HC= 5 ± 2 → p > 0.05
Wens et al., 2014 PLoS ONE	n= 18 healthy individuals > 18 years No other chronic disorders	n= 34 pwMS EDSS: 0-6 >18 years No exacerbation 6 months prior to start of study No other chronic disorders	Muscle biopsy of m. vastus lateralis was stained by means of ATPase histochemistry. Skeletal muscle fiber cross-sectional area	<u>Fiber CSA (μm²):</u> Mean: HC= 4621 +- 302; MS= 3827 +- 200 → atrophy compared to HC: -17.2 +- 4.4% Type I: HC= 4880 +- 313; MS= 4109 +- 223 → atrophy compared to HC: -15.8 +- 4.6% Type II: HC= 4353+- 332; MS= 3502 +- 219 → atrophy compared to HC: -19.5 +- 5.1% Type IIa: HC= 4985 +- 342; MS= 3862 +- 234 → atrophy compared to HC: -22.5 +- 4.7% Type IIx: HC= 3566 +- 277; MS= 3165 +- 226 → atrophy compared to HC: -11.2 +- 6.4% With p<0.05 for mean, type I, type II and type IIa compared to corresponding HC. Larger atrophy in type II fibers compared to type I fibers in pwMS (p<0.05) Significantly smaller in pwMS (p<0.05): • Mean muscle fiber CSA • CSA of type I, II, and IIa fibers

Part IId - Altered enzyme activity

Authors & Journals	Control group and number analyzed	Experimental group and number analyzed	Outcomes/ methodology of the study	Results of the study
Campbell et al., 2013 Multiple Sclerosis Journal (MSJ)	n =15 mobile healthy individuals	n=17 non-ambulatory pwMS	Post-mortem muscle (multifidus) from MS and controls were obtained. Peri-operative samples were obtained from lumbar paraspinal and deep cervical paraspinal muscles. Determining whether respiratory enzyme deficiency in MS was in excess of age-related changes within muscle with histochemical technique (COX/SDH histochemistry).	Density of respiratory enzyme-deficient fibers in MS (6.85 ± 7.44) was not significantly different compared with the healthy control group (4.51+-3.39%) → no difference in number of respiratory enzyme-deficient fibers (P=0.48)
Hansen et al., 2015 The Journal of Laboratory And Clinical Medicine	Part I: n= 10 healthy individuals Part II: n= 7 healthy individuals	Part I: n= 14 pwMS Part II: n= 9 pwMS Diagnosis >12 months	Skeletal muscle phospho-AMPK∝ by muscle biopsies [middle part of m. quadriceps femoris vastus lateralis (MS = weakest leg, HC = random leg)]. Incremental exercise test till exhaustion on an electronically braked cycle ergometer. MS: 3x 6minute exercise bouts at 70% of Wpeak with a six-minute recovery. HC: 3th bout was shorter or absent	<u>Part I:</u> Muscle phosphoAMPK∝: MS > HC (P<0.01) MS: 1.57 ± 0.42mg/mL HC: 1.14 ± 0.24mg/mL <u>Part II:</u> Basal muscle phospho-AMPK∝: MS > HC (P<0.05) MS: 1.46 ± 0.24mg/mL HC: 1.09 ± 0.26mg/mL Post-exercise phospho-AMPK∝: MS > HC (P<0.01) MS: 1.66 ± 0.51mg/mL HC: 1.12 ± 0.23mg/mL Within MS and HC: no significant changes (P>0.05)

Kent-Braun et al., 1997 The American Physiological Society	n= 8 sedentary healthy individuals	n= 9 pwMS diagnosis: 11 ± 2 years EDSS: 2-6	Skeletal muscle biopsies: tissue samples from m. tibialis anterior SDH + GPDH quantitative histochemistry was used to determine enzyme activities SDH-W: SDH activity weighted for relative fiber area SDH-%: SDH-W of given fiber type relative to that of all fiber types GPDH-W: GPDH activity weighted for relative fiber area GPDH %: GPDH-W of given fiber type relative to that of all fiber types SDH/GPDH: ratio of SDH-to-GPDH activity	<u>SDH (µmol):</u> I: MS= 272 ± 50; HC= 425 ± 62 IIa: MS= 179 ± 28; HC= 318 ± 44 IIax: MS= 185 ± 28; HC= 293 ± 45 → SDH activity: HC > MS (P= 0.001) <u>GDPH (µmol):</u> I: MS= 53 ± 13; HC= 33 ± 18 IIa: MS= 89 ± 13; HC= 70 ± 13 IIax: MS= 94 ± 16; HC= 82 ± 14 → No difference between groups these measurements were used to calculate the following results: SDH-W: MS < HC (P= 0.01) SDH-%, GPDH-W, GPDH-%: MS = HC SDH/GPDH: MS < HC (P<0.01)
Kumleh et al., 2006 Journal of the Neurological Sciences	n= 11 healthy individuals age between 20 and 28 years	n= 10 pwMS EDSS: 2.5-4.5 age between 20 and 28 years	Muscle specimens obtained from quadriceps muscle. Mitochondria were isolated from fresh skeletal muscle. Complex I activity was determined by biochemical studies (spectrophotometry).	Catalytic activity of complex I is significantly decreased in pwMS (P=0.007) → decrease of activity in complex I of pwMS may be involved in pathogenesis of MS

Table 6: Overview outcome measurements included articles Part II

Outcome measures				
Article	**Measures of mitochondrial/oxidative capacity**	**Fiber type (proportion)**	**Muscle fiber CSA (cross-sectional area)**	**Altered enzyme activity**
Campbell et al., 2013		X	X	X
Carroll, et al., 2005		X	X	
De Haan et al., 2000	X			
Garner al., 2003		X		
Hansen et al., 2012	X			
Hansen et al., 2015		X	X	X
Harp et al., 2016	X			
Kent-Braun al., 1994	X			
Kent-Braun et al., 1997		X	X	X
Kumleh et al., 2006				X
Wens et al., 2014		X	X	

Research protocol

1. Introduction

People with multiple sclerosis (pwMS) often suffer from increased fatigability that is correlated with muscle fatigue (Steens et al., 2012). This fatigability leads to a cascade of general physical deconditioning and thus influences the quality of life negatively (Miller et al., 2005). Therefore, physical exercise modalities could be interesting interventions and are being explored to inhibit this cascade.

Various exercise interventions were described and used in randomized controlled trials and cross-sectional studies. Studies often use parameters of the cardiac and respiratory capacity to determine the effect of exercise in this population (Hansen et al., 2012; Grassi et al., 2011). One of the (secondary) outcome measures is blood lactate content, this metabolite is measured during and after physical exercise. However, this metabolite is not widely discussed.

Previous studies (Hansen et al., 2012; Hansen et al., 2015; Op ‘t Eijnde et al., 2014; Morrison et al., 2008; Larson et al., 2013) have reported (indirectly) that blood lactate content during/after exercise did not differ between pwMS and healthy controls (HC). Knowledge about blood lactate values after exercise above the anaerobic threshold are limited, and thus needs more research. The impact of high intensity interval training (HIIT) on the aerobic capacity of pwMS needs further research.

This protocol was designed to investigate training effects on this capacity of pwMS after a HIIT program of 12 weeks. The aerobic capacity will be determined by metabolic and respiratory parameters. Blood lactate content, by fingertip samples, will be the metabolic parameter. Together with the respiratory determinants of the aerobic and anaerobic thresholds. All parameters will be assessed at baseline, during and after the intervention to compare exercise effects. Cardiac parameters will be assessed by a 12-lead ECG for determining exercise intensities during CPET and HIIT training. Muscle biopsies will be taken to investigate whether HIIT training has beneficial effects on the oxidative capacity on peripheral muscle level.

To be executable for pwMS, the HIIT program needs adaptation because of the clinical features of the neurological disease. Duration of the intervals will be adjusted together with the workload so that participants can complete the full protocol, and drop out during the intervention is minimized.

Commonly used HIIT protocols (Wens et al., 2017; Wens et al., 2015; Keytsman et al., 2017) are described for pwMS with different outcome measures. The HIIT protocol is based on these studies, but slightly adapted. The progression of this program happens in smaller increments so that participants can better adapt to training stimuli.

This research protocol fits in a combined domain of cardiorespiratory and neurological rehabilitation. Currently, effects of exercise interventions on the aerobic capacity of pwMS are limited and thus needs more investigation.

2. Aim of the study

This research is part of a broader research project investigating the impact of physical exercise on symptoms and progression of multiple sclerosis. The aim of this investigation is to determine whether high intensity interval training (HIIT) of 12 weeks may have beneficial effects on the aerobic capacity of pwMS and HC, measured by the golden standard for measuring the aerobic capacity in pwMS and HC: Cardio Pulmonary Exercise Test (CPET) (Heine et al., 2014). These measurements take place pre- and post-intervention to determine the exercise effects.

2.1. Research question related to the master thesis

- What is the effect of 12 weeks HIIT training on the aerobic capacity in pwMS compared to HC, measured by blood lactate content and respiratory determinants of blood lactate?

2.2. Hypotheses

- We expect that parameters of CPET, post intervention, will be significantly improved in both groups and thus may have beneficial effects on the aerobic capacity.
- We expect that, due to a higher rate of perceived exertion and muscle fatigability, pwMS may have a lower exercise tolerance and thus have a higher BORG score during the assessment and intervention.

3. Methods

3.1. Research design

An experimental prospective longitudinal design will be applied for this study.

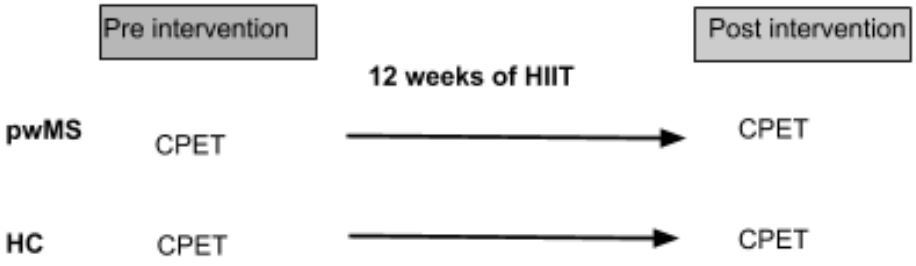

Fig 1. design of the study

3.2. Participants

This study will focus on sedentary pwMS with a mild disability, with an EDSS score not higher than six (n=20). This population will be compared with HC (n=20).

3.2.1. Inclusion criteria

Patients with MS that participate in this study should correspond with following criteria:

- EDSS score not higher than six (mean score 4.0-4.5)
- Age between 18 and 75 years
- Diagnosed with MS for at least 12 months
- Sedentary (< two hours any form of physical exercise per week), evaluated by a survey called 'Physical Activity Scale for Individuals with Physical Disabilities' (PASIPD)
- No chronic (cardiovascular) diseases

Healthy controls should correspond with similar criteria, except for diagnosis and EDSS score:

- Age between 18 and 75 years
- Sedentary (< two hours any form of physical exercise per week), evaluated by a survey called 'Physical Activity Scale for Individuals with Physical Disabilities' (PASIPD)
- No chronic (cardiovascular) diseases

3.2.2. Exclusion criteria

Patients with following characteristics will be excluded:

- EDSS score higher than six
- Participating in another study
- Exacerbation up to six months prior to intervention
- Pregnant

During the intervention of the study, patients will be excluded when:

- An exacerbation occurs
- They are diagnosed with a chronic (cardiovascular) disease
- They become pregnant
- Are not able to perform CPET due to excessive ataxia, lack of coordination or muscle weakness

3.2.3. Patient recruitment

In general, 40 participants (pwMS n= 20; HC n= 20) will be recruited over different paths. Social media (Facebook) posts will be made and shared to recruit participants. Flyers and mails will be spread in the environment.

3.3. Medical ethics

A request for approval of this study will be submitted to the medical ethical committee of Hasselt University. Participants will receive an informed written consent.

3.4 Measurements

3.4.1 Measurement pre- and post-intervention: Cardiopulmonary (maximal) exercise test (CPET)

Before testing, every subject will be screened by a physician to ensure cardiac safety. Thereafter, subjects will perform a cardiopulmonary exercise test at baseline on an electronically braked cycle ergometer (♂: 20W+15W/min, ♀: 15W+10W/min). Just before every increase of resistance (wattage), blood lactate content will be determined by blood samples of the fingertip by the Accutrend Plus. Respiratory determinants of blood lactate will be obtained by breath-by-breath gas analysis. Heart rate of participants will be continuously monitored. Subjects will be advised not to exercise the day before, or on the day of testing and only to eat a light meal (meal with low glycemic index) at least two hours prior to testing. These precautions will be taken to avoid that subjects start hypoglycemic or fatigued. This may negatively affect the performance, and thus results. Maximal workload (wattage) and heart

rate will be determined during this test to determine the intensity of the HIIT training. This assessment will take place three days pre- and post-intervention of 12 weeks HIIT training.

3.4.2 Measurement pre- and post-intervention: muscle biopsies from m. vastus lateralis

Muscle biopsies samples from the m. vastus lateralis of the weakest leg will be taken under local anesthesia, three days pre- and post-intervention using a 5-mm Bergstrom biopsy needle. This will determine whether the intervention of 12 weeks will have an impact on the oxidative capacity on peripheral muscle level.

3.4.3 Program HIIT training

After the baseline assessment, participants of both groups will be enrolled in the same exercise program performing at a training frequency of five training sessions per two weeks. The program is based on other studies that implemented HIIT training in pwMS at REVAL (Wens et al., 2015 and Wens et al., 2017). Each session will start with a five-minute warm-up on a cycle ergometer. Thereafter, high intensity interval training will be performed. The intensity of the program will be individually determined by the maximal heart rate and workload of the CPET (pre-intervention). Thereby, duration and workload will be will be gradually increased (fig 2.) The first four weeks, an intensity of 100% of the maximal workload will be applied. One-minute intervals will be performed followed by one-minute rest. The next four weeks, maximal workload will be increased with 10 % and a duration of 1,5 min, followed by one-minute rest. The last four weeks, 120% of maximal workload will be applied during two-minute intervals followed by one-minute rest. The metabolic parameter blood lactate content will be measured after one minute, followed by a two-minute interval measurement during the entire trainings session. Every training will be supervised by two master students and physiotherapists. The program will take place at REVAL (Rehabilitation Research Centre) of Hasselt University. To ensure a decent recovery, each training will be followed by 48h rest. Number and reason for drop-out during the program will be clearly inventoried.

Weeks	**Maximal workload (%)**	**Frequency interval and rest period (times)**	**Duration interval (min)**	**Duration rest (min)**
Week 1-4	100	5	1	1
Week 5-8	110	5	1,5	1
Week 9-12	120	5	2	1

Fig 2. HIIT Program

3.5. Outcome measures

3.5.1. Primary outcome measures

Blood lactate content and respiratory determinants of blood lactate will be determined as primary outcome measures. Blood lactate content will be measured by capillary blood samples on the fingertip by Accutrend Plus (portable lactate analyzer). Measurements will be performed during CPET and during each training session. Blood samples will be taken after one minute of exercise, followed by a two-minute interval measurement during the entire training session.
Reflecting respiratory determinants, for aerobic and anaerobic thresholds, will be assessed by a breath-by-breath gas analysis that is averaged every 10 seconds. Following respiratory parameters will be assessed during CPET (pre- and post-intervention):

- Respiratory exchange ratio (RER): carbon dioxide over oxygen uptake (VCO_2/VO_2) (will also be used to determine if the test was maximal (RER=1.1-1.2))
- Ventilation over carbon dioxide uptake (V-slope method: VE/ VCO_2)

3.5.2. Secondary outcome measures

For verifying exercise intensity and whether exertions were maximal, cardiac parameters will be assessed as secondary outcome measure by continuous monitoring of heart rate (12-lead ECG) by the Jaeger Oxycon system, measured during CPET and training.
Moreover, to investigate whether oxidative capacity may be changed on peripheral muscle level, muscle biopsy parameters will be taken three days pre- and post-intervention for investigating muscle fiber type (proportion) and muscle fiber cross-sectional area (CSA). The muscle biopsy samples will be immediately frozen in isopentane cooled with liquid nitrogen and stored at -80°C for further analysis. Muscle samples will be cut in transverse sections (9µm) at -20° and stained by means of ATPase histochemistry. Procedure of Brooke and Kaiser (1970) will be followed.

3.6. Data analysis

All calculations will be performed using JMP to compare continuous data of 2 independent groups (pwMS and HC) at 2 moments in time (pre- and post-intervention). Statistical significance will be assessed at $P<0.05$. To compare baseline characteristics between pwMS and HC, an independent-measures t-test will be performed assuming a normal distribution evaluated by the Shapiro-Wilk test and constant variance (homoscedasticity) evaluated by the Brown-Forsythe test. When these assumptions are not met, Mann-Whitney U test will be used instead.
Because repeated measurements are made on the same statistical units (longitudinal study) a “mixed model” approach will be used. With MS or HC as fixed effect and the patient as random effect. Among others, we will compare the lactate values between the groups (pwMS and HC) pre- and post-intervention, as well as within each group (pre- and post-intervention). Relationships between all parameters (primary and secondary outcome measures) will be examined by Pearson correlations.

Data will be expressed as the mean ± SD. The Shapiro-Wilk test will be used to evaluate if the data (each group on every point in time) are normally distributed. Other assumptions that will be checked are linearity (Goodness of Fit test) and constant variance (Brown-Forsythe test).

4. Time planning

1. September 2018: sending request to the medical ethical committee of Hasselt University for approval of this study
2. October 2018: starting recruitment of participants by advertisements (e. g. flyer and mail) and social media
3. January - May 2019: data acquisition
4. May - April 2019: data analysis
5. April - June 2019: writing master's thesis based on findings

5. References

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6. Appendix part II – Research protocol

Table 1: Self-evaluation form

Table 2: Progress form

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Table 1: Self-evaluation form

ZELFEVALUATIERAPPORT **WETENSCHAPPELIJKE STAGE - DEEL 1** **RWK**

Naam & Voornaam STUDENT: Schepers Tim
Naam & Voornaam (CO)PROMOTOR & PROMOTOR: Promotor: Prof. Dr. B. Op't Eijnde **Co-promotor:** Drs. J. Spaas
TITEL-masterproef: Exercise-induced lactate response and oxidative muscle characteristics in people with multiple sclerosis

LITERATUURSTUDIE	Gestelde deadline	Behaald op	Reflectie
De belangrijkste concepten en conceptuele kaders van het onderzoekdomein uitdiepen en verwerken	05/01/2018	03/01/2018	G
De belangrijkste informatie opzoeken als inleiding op de onderzoeksvraag van de literatuurstudie	27/11/2017	27/11/2017	G
De opzoekbare onderzoeksvraag identificeren en helder formuleren in functie van de literatuurstudie	13/11/2017	13/11/2017	G
De zoekstrategie op systematische wijze uitvoeren in relevante databanken	31/01/2018	25/01/2018	ZG
De kwaliteitsbeoordeling van de artikels diepgaand uitvoeren	16/04/2018	23/04/2018	ZG
De data-extractie grondig uitvoeren	08/05/2018	10/05/2018	G
De bevindingen integreren tot een synthese	15/05/2018	15/05/2018	G

ONDERZOEKSPROTOCOL	Gestelde deadline	Behaald op	Reflectie
De onderzoeksvraag in functie van het onderzoeksprotocol identificeren	08/05/2018	07/05/2018	G
Het onderzoeksdesign bepalen en/of kritisch reflecteren over bestaande onderzoeksdesign	10/05/2018	10/05/2018	G
De methodesectie (participanten, interventie, uitkomstmaten, data-analyse) uitwerken	15/05/2018	13/05/2018	ZG

ACADEMISCHE SCHRIJVEN	Gestelde deadline	Behaald op	Reflectie
Het abstract tot he point schrijven	20/05/2018	20/05/2018	G
De inleiding van de literatuurstudie logisch opbouwen	16/04/2018	15/04/2018	G
De methodesectie van de literatuurstudie transparant weergegeven	04/04/2018	02/04/2018	G
De resultatensectie afstemmen op de onderzoeksvragen	15/05/2018	17/05/2018	V, niet gehaald o.w.v. examens en omnistage
In de discussiesectie de bekomen resultaten in een wetenschappelijke tekst integreren en synthetiseren	20/05/2018	22/05/2018	V, niet gehaald o.w.v. examens en omnistage
Het onderzoeksprotocol deskundig technisch uitschrijven	21/05/2018	21/05/2018	G
Referenties correct en volledig weergeven	23/05/2018	22/05/2018	G

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ZELFSTUREND EN WETENSCHAPPELIJK DENLEN EN HANDELEN	**Aanvangsfase**	**Tussentijdse fase**	**Eindfase**
Een realistische planning opmaken, deadlines stellen en opvolgen	G	G	G
Initiatief en verantwoordelijkheid opnemen ten aanzien van de realisatie van de wetenschappelijke stage	G	G	G
Kritisch wetenschappelijk denken	ZG	G	G
De contacten met de promotor voorbereiden en efficiënt benutten	G	G	ZG
De richtlijnen van de wetenschappelijke stage autonoom opvolgen en toepassen	G	G	G
De communicatie met de medestudent helder en transparant voeren	ZG	G	ZG
De communicatie met de promotor/copromotor helder en transparant voeren	G	G	G

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ZELFEVALUATIERAPPORT **WETENSCHAPPELIJKE STAGE - DEEL 1** **RWK**

Naam & Voornaam STUDENT: Verstraeten Rani
Naam & Voornaam (CO)PROMOTOR & PROMOTOR: Promotor: Prof. Dr. B. Op't Eijnde **Co-promotor:** Drs. J. Spaas
TITEL-masterproef: Exercise-induced lactate response and oxidative muscle characteristics in people with multiple sclerosis

LITERATUURSTUDIE	Gestelde deadline	Behaald op	Reflectie
De belangrijkste concepten en conceptuele kaders van het onderzoekdomein uitdiepen en verwerken	05/01/2018	03/01/2018	G
De belangrijkste informatie opzoeken als inleiding op de onderzoeksvraag van de literatuurstudie	27/11/2017	27/11/2017	ZG
De opzoekbare onderzoeksvraag identificeren en helder formuleren in functie van de literatuurstudie	13/11/2017	13/11/2017	G
De zoekstrategie op systematische wijze uitvoeren in relevante databanken	31/01/2018	25/01/2018	ZG
De kwaliteitsbeoordeling van de artikels diepgaand uitvoeren	16/04/2018	23/04/2018	ZG
De data-extractie grondig uitvoeren	08/05/2018	10/05/2018	G
De bevindingen integreren tot een synthese	15/05/2018	15/05/2018	G

ONDERZOEKSPROTOCOL	Gestelde deadline	Behaald op	Reflectie
De onderzoeksvraag in functie van het onderzoeksprotocol identificeren	08/05/2018	07/05/2018	G
Het onderzoeksdesign bepalen en/of kritisch reflecteren over bestaande onderzoeksdesign	10/05/2018	10/05/2018	G
De methodesectie (participanten, interventie, uitkomstmaten, data-analyse) uitwerken	15/05/2018	13/05/2018	ZG

ACADEMISCHE SCHRIJVEN	Gestelde deadline	Behaald op	Reflectie
Het abstract tot he point schrijven	20/05/2018	20/05/2018	G
De inleiding van de literatuurstudie logisch opbouwen	16/04/2018	15/04/2018	G
De methodesectie van de literatuurstudie transparant weergegeven	04/04/2018	02/04/2018	ZG
De resultatensectie afstemmen op de onderzoeksvragen	15/05/2018	17/05/2018	G
In de discussiesectie de bekomen resultaten in een wetenschappelijke tekst integreren en synthetiseren	20/05/2018	22/05/2018	G
Het onderzoeksprotocol deskundig technisch uitschrijven	21/05/2018	21/05/2018	V
Referenties correct en volledig weergeven	23/05/2018	22/05/2018	G

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Een realistische planning opmaken, deadlines stellen en opvolgen	G	G	ZG
Initiatief en verantwoordelijkheid opnemen ten aanzien van de realisatie van de wetenschappelijke stage	G	G	G
Kritisch wetenschappelijk denken	ZG	G	G
De contacten met de promotor voorbereiden en efficiënt benutten	G	ZG	ZG
De richtlijnen van de wetenschappelijke stage autonoom opvolgen en toepassen	G	ZG	ZG
De communicatie met de medestudent helder en transparant voeren	ZG	G	ZG
De communicatie met de promotor/copromotor helder en transparant voeren	G	ZG	ZG

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VOORTGANGSFORMULIER WETENSCHAPPELIJKE STAGE DEEL 1

DATUM	INHOUD OVERLEG	HANDTEKENINGEN
13/11 2017	Bespreking onderzoeksvraag	Promotor: Bert Op't eijnde Copromotor: Jan Spaas Studente: Rani Verstraeten Student: Tim Schepers
27/11 2017	Bespreking literatuuronderzoek	Promotor: Bert Op't eijnde Copromotor: Jan Spaas Studente: Rani Verstraeten Student: Tim Schepers
15/01 2018	Samenstelling zoekstrategie	Promotor: Bert Op't eijnde Copromotor: Jan Spaas Studente: Rani Verstraeten Student: Tim Schepers
31/01 2018	Bespreking resultaten artikels in- en exclusie	Promotor: Bert Op't eijnde Copromotor: Jan Spaas Studente: Rani Verstraeten Student: Tim Schepers

04/04 2018	Methode + kwaliteitscontrole bespreking / feedback	Promotor: Bert Op't eijnde Copromotor: Jan Spaas Studente: Rani Verstraeten Student: Tim Schepers
15/05 2018	Bespreking Resultaten	Promotor: Bert Op't eijnde Copromotor: Jan Spaas Studente: Rani Verstraeten Student: Tim Schepers
29/05 2018	Verbetering draft 1 Masterproef 1	Promotor: Bert Op't eijnde Copromotor: Jan Spaas Studente: Rani Verstraeten Student: Tim Schepers
06/06 2018	Verbetering Draft 2 Masterproef 1	Promotor: Bert Op't eijnde Copromotor: Jan Spaas Studente: Rani Verstraeten Student: Tim Schepers
		Promotor: Bert Op't eijnde Copromotor: Jan Spaas Studente: Rani Verstraeten Student: Tim Schepers