UHASSELT

KNOWLEDGE IN ACTION

Faculteit Revalidatiewetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

The effect of exercise on clinical disability in experimental autoimmune encephalomyelitis

Steven Slegers

Eerste deel van het scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie

PROMOTOR :

Prof. dr. Bert OP 'T EIJNDE

BEGELEIDER :

De heer Jan SPAAS

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The effect of exercise on clinical disability in experimental autoimmune encephalomyelitis

Research question:

- "Which training parameters have been used in EAE exercise training?"
- "What is the effect of exercise on clinical disability in EAE compared to a control group?"

Highlights:

- Forced or voluntary running or forced swimming were selected in most studies with different levels of intensity. Exercise was given before or after disease induction, with varying exercise program duration.
- Most studies show a positive effect on clinical disability, which can be seen in daily clinical score, disease onset, peak score and peak onset.
- Future research should focus on directly comparing the effects of forced treadmill running and forced swimming on clinical disability.

Steven Slegers

Promotor: Prof. Dr. Bert Op 't Eijnde

Co-promotor: Drs. Jan Spaas

Context

Multiple Sclerosis (MS) is an immune-mediated disease of the central nervous system that usually starts with periods of inflammation leading to demyelination and ultimately axonal degeneration (Mäurer & Rieckamnn, 2000). Typical symptoms of this disease are walking impairments, cognitive dysfunction, fatigue, pain, depression, and reduced quality of life and participation in activities of daily living. This master thesis discusses the possible therapeutic effects of exercise in experimental autoimmune encephalomyelitis (EAE), an animal model for neuroinflammation that shares many pathophysiological features with human MS.. In this way, this master thesis fits into the research domain of both neurological and cardiorespiratory rehabilitation. The aim of this systematic review is to compare different training parameters used in EAE exercise interventions, and to investigate the effect of exercise on clinical disability. This thesis fits in the research project "impact of muscle carnosine loading on exercise capacity and muscle contractile characteristics in EAE" (project code R-8156, Hasselt University). During the second year of the Master's degree (2019-2020), data from ongoing animal research involving EAE and exercise will be analysed and reported. This master thesis is a mono thesis which fits into a central format, and the research questions were formulated in consultation with promotor prof. dr. Bert Op 't Eijnde and co-promotor drs. Jan Spaas.

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Part 1: Literature search

1. Abstract

Background: Multiple Sclerosis (MS) is an immune-mediated disease of the central nervous system. The animal model of MS, experimental autoimmune encephalomyelitis (EAE), can be used to investigate the effect of physical exercise on MS pathology, based on clinical disability score.

Methods: PubMed and Web of Science databases were consulted. Quality of included studies was assessed by an adapted 'ARRIVE' checklist. Data of training parameters (exercise modality, exercise intensity, program duration and timing of exercise delivery) and outcome measures of clinical disability were extracted.

Results: Eighteen studies were included. Forced or voluntary running or forced swimming were selected in most studies with different levels of intensity. Exercise was given before or after disease induction, with varying exercise program duration. In 14 out of 18 (78%) included studies, a positive effect of exercise was shown for at least one outcome measure of clinical disability.

Discussion and conclusion: Exercise on clinical disability shows various results which may be explained by the individual effect of each training parameter, since a lot of training parameter combinations have been used. Most studies showed that exercise had a positive effect on clinical disability in EAE.

Aim of the study: Investigate the effect of forced treadmill running versus forced swimming at moderate and high intensity on clinical disability in EAE.

Operationalization: First, a pilot experiment is set up to determine matching running and swimming intensities. Next, daiiy clinical score will be compared in swimming and running at high and moderate intensity.

Most important key words: Exercise, EAE, clinical disability

2. Introduction

Multiple Sclerosis (MS) is an immune-mediated disease of the central nervous system, which occurs in approximately one out of 1000 adults in Belgium (Kurtzke, 2005). This disease usually starts with periods of inflammation leading to demyelination and ultimately axonal degeneration (Mäurer & Rieckmann, 2000).

Typical symptoms of this disease are walking impairment and cognitive dysfunction, fatigue, pain, depression, and reduced quality of life and participation in activities of daily living (Lublin, 2005). In addition, MS patients frequently suffer from secondary complications including loss of physical fitness(Motl, McAuley, &Snook, 2005), muscle weakness (Garner & Widrick, 2005), and cardiovascular health risks (Christiansen et al., 2010).

Although pharmacological treatments are able to decrease MS relapse rate and severity, they do not stop the progression of this disease.
To date, exercise therapy (e.g. endurance and strength training) is being used to reduce or prevent the secondary complications in MS. Interestingly, however, it may be possible this positive effect also affects primary characteristics of MS. For example, a study of Zhang et al. showed that in an animal stroke model 'middle cerebral artery occlusion (MCAO)', physical exercise improved neurological functioning possibly by reduction of autophagosome accumulation, attenuation of apoptosis and improvement of neurogenesis. (Zhang et al., 2013)

To investigate such effects in MS, experimental autoimmune encephalomyelitis (EAE), the animal MS model, can be used. EAE is a T-helper cell-mediated autoimmune disease, where T-cells and monocytes have been infiltrated in the central nervous system, linked with local inflammation (Robinson, Harp, Noronha, &Miller, 2014). This injection results in demyelination of axonal tracks, impaired axonal conduction and progressive hind-limb paralysis, which is daily measured by a self-scored observational clinical scale (Robinson, Harp,

Noronha, &Miller, 2014). In this way, studying the effect of exercise on clinical disability in EAE can be useful for developing a possible therapeutic intervention for MS.

Interestingly, Klaren, Motl, Woods and Miller (2014) already summarized EAE exercise intervention studies (n=5) in a review. The authors concluded that some of the existing studies found a positive effect of exercise on the clinical symptoms related to EAE, and that further research on different types of training modalities is needed. Since 2014, multiple new studies on exercise interventions in EAE have been conducted. The aim of this systematic review is to summarize different training parameters used in EAE exercise interventions, and to investigate the effect of exercise on clinical disability.

3. Methods

3.1. Research question

This systematic review investigated exercise interventions in EAE and aimed to answer following research questions:

- "Which training parameters have been used in EAE exercise training?" These parameters include exercise modality, exercise intensity, program duration and timing of exercise delivery.
- "What is the effect of exercise on clinical disability in EAE compared to a control group?" Effects on clinical disability can be seen in daily clinical score, time of disease onset, disease peak score and time of peak onset.

This second research question relies on the following PICO:

P: EAE animals

I: physical exercise

C: control group with no additional exercise

O: clinical disability in EAE measured by a self-scored observational clinical scale.

3.2. Literature search:

To answer these questions, two databases have been consulted: PubMed and Web of Science. The search strategy consisted of synonyms and abbreviations of experimental autoimmune encephalomyelitis and exercise.

On PubMed, "Mesh Terms" and "Title/Abstract" were selected. This resulted in following keywords: "experimental autoimmune encephalomyelitis[MeSH Terms]", experimental autoimmune encephalomyelitis[Title/Abstract], experimental Allergic Encephalomyelitis[Title/Abstract], and "EAE[Title/Abstract]" which were combined with 'or'.

Synonyms of exercise led to following keywords: exercise[MeSH Terms], exercise [Title/Abstract], exercise therapy[MeSH Terms], exercise therapy [Title/Abstract], physical therapy modalities[MeSH Terms], physical therapy modalities[Title/Abstract], physical therapy[MeSH Terms], physical therapy[Title/Abstract], physical activity[MeSH Terms],

physical activity[Title/Abstract], training[Title/Abstract], running[Title/Abstract], and swimming[Title/Abstract] which were also combined with ‘or’ as conjunction.

The same strategy was applied in Web of Science, with the field tag TOPIC instead of MeSH and Title/Abstract. The number of hits for each keyword and their combinations can be seen in Table 1.

This literature search was terminated on May 12, 2019. After removal of the duplicates, studies were first excluded based on abstract and title evaluation. After this, studies retrieved for more detailed evaluation were excluded based on full text assessment.

Table 1

number of hits for each keyword and their combinations

Zoektermen	#hits pubmed	#hits WOS
experimental autoimmune encephalomyelitis [MeSH Terms]	10.523	
experimental autoimmune encephalomyelitis [Title/Abstract]	7.566	
experimental Allergic Encephalomyelitis [Title/Abstract]	3.164	
(experimental autoimmune encephalomyelitis[MeSH Terms]) OR experimental autoimmune encephalomyelitis[Title/Abstract]) OR experimental Allergic Encephalomyelitis[Title/Abstract]) OR (EAE[Title/Abstract])	14.821	
TOPIC: (EAE)		11.155
TOPIC: (Experimental allergic encephalomyelitis)		10.888
TOPIC: (Experimental autoimmune encephalomyelitis)		21.534
(TOPIC: (EAE)) OR (TOPIC: (Experimental allergic encephalomyelitis)) OR (TOPIC: (Experimental autoimmune ecephalomyelitis))		29.092
exercise [MeSH Terms]	172.742	
Exercise [Title/Abstract]	240.283	
Exercise therapy [MeSH Terms]	44.707	
Exercise therapy [Title/Abstract]	4.108	
Physical therapy modalities [MeSH Terms]	140.107	
Physical therapy modalities [Title/Abstract]	350	
Physical therapy [Title/Abstract]	18.578	
Physical activity [MeSH Terms]	172.742	
Physical activity [Title/Abstract]	94.111	
Training [Title/Abstract]	363.563	
Running [Title/Abstract]	54.617	

Swimming [Title/Abstract]	25.976	
(exercise [MeSH Terms]) OR (Exercise [Title/Abstract]) OR (Exercise therapy [MeSH Terms]) OR (Exercise therapy [Title/Abstract]) OR (Physical therapy modalities [MeSH Terms]) OR (Physical therapy modalities [Title/Abstract]) OR (Physical therapy [Title/Abstract]) OR (Physical activity [MeSH Terms]) OR (Physical activity [Title/Abstract]) OR (Training [Title/Abstract]) OR (Running [Title/Abstract]) OR (Swimming [Title/Abstract])	845.695	
TOPIC: (exercise)		419.094
TOPIC: (exercise therapy)		39.798
TOPIC: (physical therapy modalities)		3.393
TOPIC: (physical therapy)		71.039
TOPIC: (physical activity)		260.158
TOPIC: (training)		820.821
TOPIC: (running)		487.122
TOPIC: (swimming)		56.945
(TOPIC: (exercise)) OR (TOPIC: (exercise therapy)) OR (TOPIC: (physical therapy modalities)) OR (TOPIC: (physical therapy)) OR (TOPIC: (physical activity)) OR (TOPIC: (training)) OR (TOPIC: (running)) OR (TOPIC: (swimming))		1.839.620
((experimental autoimmune encephalomyelitis[MeSH Terms]) OR experimental autoimmune encephalomyelitis[Title/Abstract]) OR experimental Allergic Encephalomyelitis[Title/Abstract]) OR (EAE[Title/Abstract])) AND (exercise [MeSH Terms]) OR (Exercise [Title/Abstract]) OR (Exercise therapy [MeSH Terms]) OR (Exercise therapy [Title/Abstract]) OR (Physical therapy modalities [MeSH Terms]) OR (Physical therapy modalities [Title/Abstract]) OR (Physical therapy [Title/Abstract]) OR (Physical activity [MeSH Terms]) OR (Physical activity [Title/Abstract]) OR (Training [Title/Abstract]) OR (Running [Title/Abstract]) OR (Swimming [Title/Abstract]))	67	

((TOPIC: (EAE)) OR (TOPIC: (Experimental allergic encephalomyelitis)) OR (TOPIC: (Experimental autoimmune ecephalomyelitis))) AND ((TOPIC: (exercise)) OR (TOPIC: (exercise therapy)) OR (TOPIC: (physical therapy modalities)) OR (TOPIC: (physical therapy)) OR (TOPIC: (physical activity)) OR (TOPIC: (training)) OR (TOPIC: (running)) OR (TOPIC: (swimming)))	248

3.3. selection criteria:

Articles were included if they fulfilled the following criteria:

1. Study on EAE animals
2. Written in English or Dutch
3. A certain type of exercise was given as intervention
4. Comparison to a control group
5. Effect of exercise on clinical disability was discussed

Articles were excluded if they fulfilled the following criteria:

1. Human research
2. Review or meeting abstract
3. No assessment of the daily clinical score
4. Different topic
5. Exercise in combination with pharmacological treatment
6. No exercise intervention

3.4. Quality Assessment

An adapted version of the 'ARRIVE Checklist' was used for quality assessment. This checklist consists of 17 criteria and can be consulted in the results of this systematic review, in the section 'quality assessment'. Next, an analysis of the strengths and weaknesses of each study was made, which can also be consulted in the results of this systematic review.

3.5. Data extraction

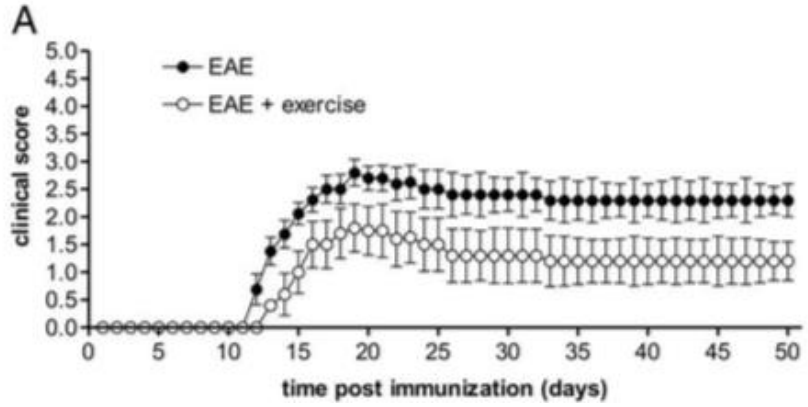
Animal species and type of EAE were analysed. Exercise training in EAE consisted of following parameters. Exercise modality was analysed, which refers to the type of exercise given to animals including forced treadmill running, voluntary wheel running, strength training and forced swimming. Since a variety of different exercise intensities were investigated, this parameter was also analysed. Program duration was analysed to show the number of days or weeks exercise was given. Timing of exercise delivery was analysed, which tells if exercise was given before or after the induction of EAE.

Different outcome measures including daily clinical score, disease onset, peak score and peak onset were analysed to investigate the effect of exercise on clinical disability in EAE. Daily linical score was measured daily on a self-scored observational scale ranging from 0 to 5. An example of disease course in chronic (Bernardes et al., 2016), monophasic (Le Page et al., 1996), and relapse-remitting (Klaren et al., 2016) type of EAE can be seen in Figure 2, where clinical signs were monitored daily, and the exercised mice were compared with the unexercised mice. (0 = healthy; 1 = limp tail; 2 = ataxia and/or paresis of hindlimbs; 3 = paralysis of hindlimbs and/or paresis of forelimbs; 4 = tetraparalysis; 5 = moribund or death) Disease onset represents the day animals show their first clinical symptoms. Peak score represents the highest value of the daily clinical score, and peak onset shows the day this score was reached.

Figure 2:

Disease course in chronic (A), monophasic (B) and relapse-remitting (c) type of EAE.

A



B

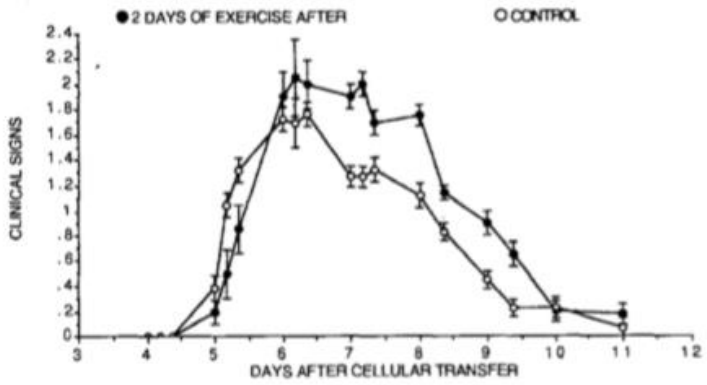
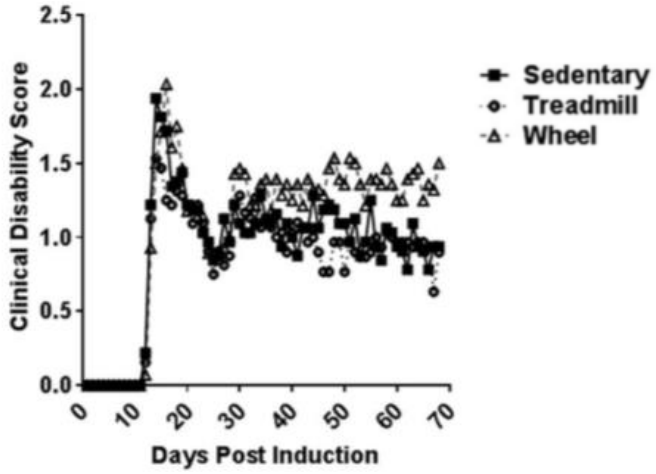


Fig. 1 Time course of mobility score (see Methods) in adoptive experimental auto-immune encephalomyelitis (first experiment): effect of 2 consecutive days of severe exercise after cell transfer. Values are means and SEM

C



4. Results

4.1. Results of study selection

A schematic version of the results of study selection can be consulted in Figure 1. In total, 315 studies were assessed for eligibility. 67 studies were found on PubMed, and 248 studies were found on Web Of Science. After the removal of 35 duplicates, 280 studies were screened for inclusion based on title and abstract. Reasons for exclusion were different topic (221), no exercise intervention (14), human research (10), review or meeting abstract (6) or exercise in combination with pharmacological treatment (1). This led to 28 studies that were retrieved for more detailed evaluation by full text. After this, eight studies were excluded because there was no assessment of the daily clinical score, and three studies were excluded for the absence of an exercise intervention. An overview of the excluded studies can be consulted in Table 2.

This led to 17 relevant studies who were included in this systematic review. However, one additional study of Wens (2015) was found through reference search in the review of Klaren, Motl, Woods and Miller (2014).

Figure 1

Search strategy flowchart

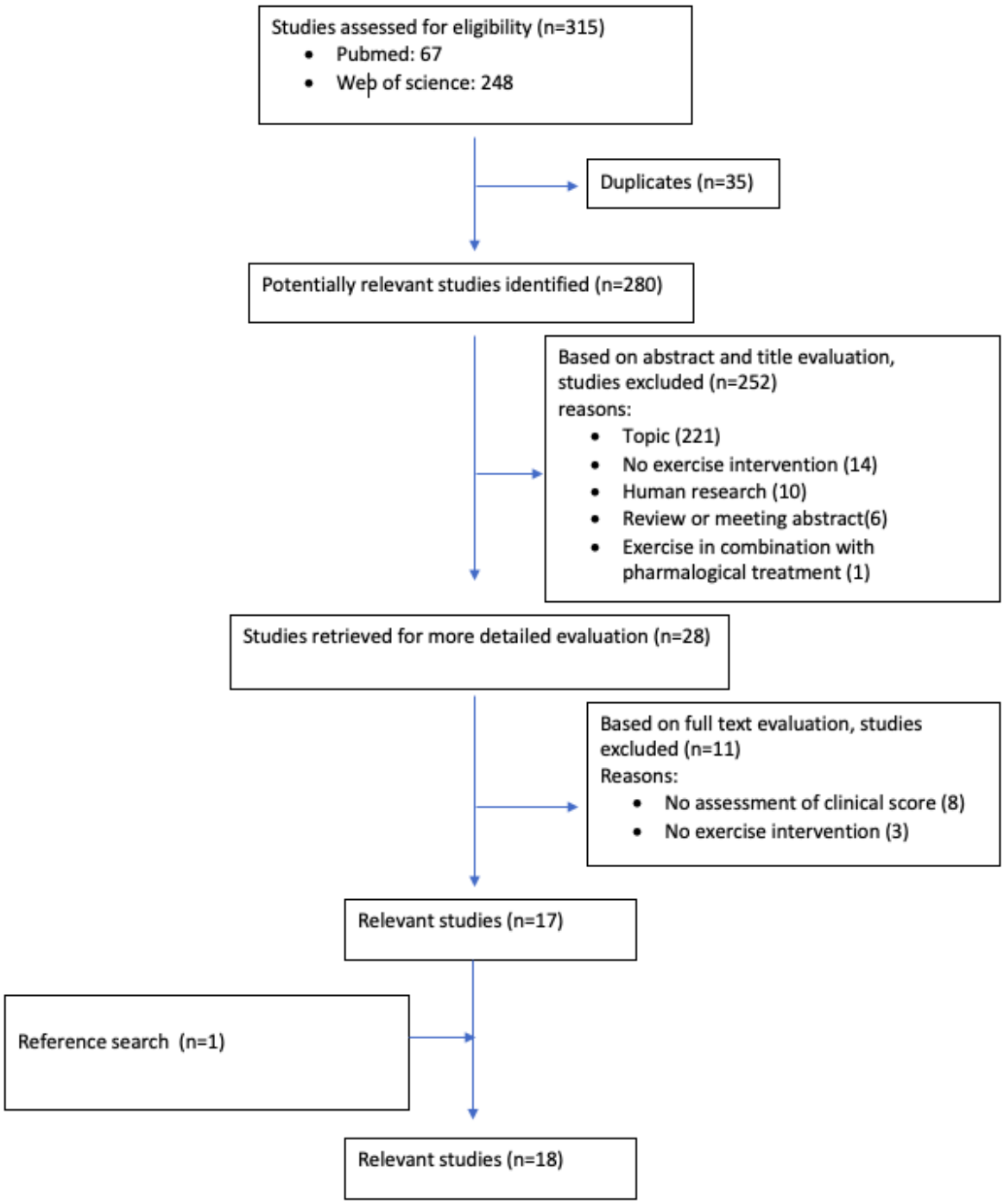


Table 2

Overview of excluded studies (n=263)

Reden exclusie	Aantal studies	Auteur(s), jaartal
No assessment of daily clinical score	8	Keytsman et al. 2018; Flander et al. 2017; Kim et al 2017; Mifflin et al. 2018; Mifflin et al. 2019; Houdebine et al. 2017; Bernardes et al. 2016; Wens et al. 2013
Review or meeting abstract	6	Klaren et al. 2014; Devasahayam et al. 2017; Barry et al. 2016; Brown et al. 2005; Philips et al. 2015; Broekmans et al. 2009
No exercise intervention	17	Acharjee et al. 2013; Madsem et al. 2017; Hosseini et al. 2017; Koutrolos et al 2014; Buddeberg et al 2004; Magalon et al. 2007; De Haan et al. 2004; Arrieta-cruz et al. 2009; Ludwig et al. 2017; Grace et al. 2017; Li et al. 2019; Baker et al. 2014; Ayoobi et al. 2013; Forte et al. 2007; Furlan et al. 2004; Yao et al. 1996; Hosseini et al. 2019;
Different topic	221	Dalgas et al 2012; Liu et al. 2013; Fernandez et al. 2017; Liu et al. 2010; Guest et al. 2015; Vignes et al. 2009; Ruiz-Juan et al. 2013; Xie et al. 2011; Herrara-Ruiz et al. 2007; Dugan 2008; Sicari et al. 2008; Malik 2011; Sahrani et al. 2014; Feng et al. 2019; Kroon et al. 2002; Dehkordi et al. 2014; Kopp et al. 1985; Du et al. 2019; Luc et al. 2018; Brown et al. 2018; Scheinberg et al. 2017; Jaehne et al. 2014; Gargani et al. 2012; Mertens et al. 2011; Galderisi et al. 2011; Sicari et al. 2011; Popescu et al. 2009; Quintana et al. 2008; Itabashi et al. 2018; Marucci et al. 2011; Pogodina et al. 1982; Simmons et al. 1981; Kies et al. 1958; Cutler et al. 2019; Gholamzad et al. 2019; Thompson et al. 2019; Kosari-Nasab et al. 2018; Munshi etal. 2018; Schiffman et al. 2018; Seifert et al. 2018;

Jensen et al. 2018, Spavenello et al. 2018; Itabashi et al. 2018; Hu et al. 2018; Camara-Lemarroy et al. 2018; Nghibzadeh et al. 2018; Bassi et al. 2018; Jungwirth et al. 2018; Larson et al. 2018; Khan et al. 2018; Cooper et al. 2018; Barbau-Piednoir et al. 2018; Brown et al. 2018; Andreas et al. 2018; Heath et al. 2018; Orhan et al. 2018; Barbado et al. 2018; Labuschage et al. 2018; Khaluoi et al. 2018; Chitnis et al. 2018; Hewing et al. 2017; Ayatollahi et al. 2017; Kim et al. 2017; Pozdniakova et al. 2017; Gupta et al. 2017; Michael et al. 2017; Hosseini et al. 2017; Ton et al. 2017; Goncalves et al. 2017; Petit et al. 2017; Ghasemi et al. 2017; Scheinberg et al. 2017; St Clair et al. 2017; Hadadianpour et al. 2017; Fedotova et al. 2017; Yellamma et al. 2016; Cekanaviciute et al. 2016; Tatsumi et al. 2016; Harris et al. 2016; Yang et al. 2016; Arnao et al. 2016; Dugan et al. 2016; Thomas et al. 2016; Voldsgaard et al. 2016; Rosenzweig et al. 2015; Cao et al. 2015; De Vries et al. 2015; Lee et al. 2015; Kooij et al. 2015; Mirtaheri et al. 2015; Schipper et al. 2015; Calik et al. 2015; Ryan et al. 2015a; Ryane et al. 2015b; Sankowski et al. 2015; Gentile et al. 2015; Gil-Ad et al. 2015; Russi et al. 2015; Rasool et al. 2015; Riccio et al. 2014; Quintana et al. 2014; Chevalier et al. 2014; Harris et al. 2014; Chew et al. 2014; Wang et al. 2014; Wrotek et al. 2014; Nissinen et al. 2014; Gullace et al. 2014; Sharahni et al. 2014; Gokahle et al. 2014; Harrison et al. 2014; Du et al. 2014; Boerlage-van deyck et al. 2014; Davies et al. 2013; Thoene et al. 2013; Adriani et al. 2013; Sato et al. 2013; Acharjee et al. 2013; Alvaraz et al. 2013; Coseyns et al. 2013; Loftis et al. 2013; Lancellotti et al. 2013; Karussis et al. 2013; Pellikka et al. 2013; Nomura et al. 2013; Swardfager et al. 2013; Kostic et al. 2013; Mertens et al. 2013; Carvalheiro et al. 2013; Rahn et al. 2013; Schumann et al. 2012; Maehler et al. 2012; Moon et al. 2012; Pollard et al. 2012; Arima et al.

2012; Gargani et al. 2012; Maverakis et al. 2012; Wijesinghe et al. 2011; Cannon et al. 2011; Andersen et al. 2011; Lam et al. 2011; Mifsud et al. 2011; West et al. 2011; Coisne et al. 2011; Swanson et al. 2011; Mozafari et al 2011; Galderisi et al. 2011; Sicari et al. 2011; Ropelle et al. 2010; Prakash et al. 2011; Heraud et al. 2010; Korpos et al. 2010; Coyle et al. 2009; Engelhardt et al. 2009; Korpos et al. 2009; Beutin et al. 2009; Poffenberger et al. 2009; Johannesson et al. 2009; Husted et al. 2009; Andrade-talavera et al. 2008; Cheng et al. 2008; Van Wijmeersch et al. 2008; Sicari et al. 2008; Tsutsui et al. 2008; Zarraonandia et al. 2008; Dinunzio et al. 2008; Kern et al. 2008; Ebensen et al. 2007; Scheele et al. 2007; Schott et al. 2007; Wiendl et al. 2007; Mastronardi et al. 2007; Defer et al. 2007; Zabad et al. 2007; Harris et al. 2007; Baranzini et al. 2006; Soukhareva et al. 2006; El Allali et al. 2006; Teft et al. 2006; Finaud et al. 2006; Schulz et al. 2005; Schwarz et al. 2005; Schreiner et al. 2005; Penkowa et al. 2005; Killestein et al. 2005; Boneschi et al. 2005; Waxman 2005; Calabrese et al. 2004; Kanwar et al. 2004; Weilbach et al. 2004; Althaus et al. 2004; Heesen et al. 2003; Fischer 2003; Wax et al. 2003; Badawi 2003; Elenkov et al. 2002; Smith et al. 2001; Adorini 2001; Li et al. 2001; Boles et al. 2000; Martino et al. 2000; Akenami et al. 2000; Majumder et al. 1998; Vold et al. 1998; Sztajnbok et al. 1998; Goldman-Brezinski et al. 1998; Inoue et al. 1997; Hollister et al. 1997; Bilzer et al. 1996; Mannie et al. 1995; Shrikant et al. 1994; Mao et al. 1994; Beutin et al. 1994; Gautam et al. 1994; Whitaker et al. 1994; Torre et al. 1993; Mannie et al. 1993; Lohse et al. 1993; Chung et al. 1992; Bianco et al. 1992; Hoyer et al. 1991; Ransohoff et al. 1991; Inouye et al. 1991

Exercise in combination with pharmacological treatment	1	Bernardes et al. 2018
Human research	10	Riemenschneider et al. 2018; Barry et al. 2018; Feter et al. 2018; Kierkegaard et al. 2016; Giesser et al. 2015; Motl et al. 2015; Dalgas et al. 2011; White et al. 2008a; White et al. 2008b; Smith et al. 1999;

4.2. Results of quality assessment

Detailed information about the quality assessment of each individual study can be consulted in Table 3. In general, study quality was sufficient and no articles were excluded from this systematic review. For several criteria, almost all studies acquired the same outcome. However, there were some differences among the studies regarding five criteria. First, eleven studies provided no accurate summary of the background in the abstract (Benson et al., 2015; Bernardes et al., 2013; Bonfiglio et al., 2019; Einstein et al., 2018; Le Page et al., 1994; Le page et al., 1996; Mifflin et al., 2017; Patel et al., 2016; Souza et al., 2016; Wens et al., 2015a; Xie et al., 2019). However, these details were found in the section 'Introduction' or 'Methods' in most studies. Second, only four studies checked if blinding of the assessors of the daily clinical score was mentioned (Klaren et al., 2016; Le Page, Ferry, &Rieu, 1994; Le Page et al., 1996; Rossi et al., 2009)

Third, only half of the studies checked if there was a report of the number of animals in each group that are included in each analysis and if there is an explanation if any animals or data were not included. (Benson et al., 2015; Bernardes et al., 2013; Einstein et al., 2018; Klaren et al., 2016; Patel et al., 2013a; Patel et al., 2016; Pryor et al., 2014; Wens et al., 2015a; Wens et al., 2015b). Fourth, only six studies mentioned limitations of the study, including potential sources of bias, limitations to the animal model or imprecision associated with results (Klaren et al., 2016; Le Page et al., 1994; Patel et al., 2013; Patel et al., 2016; Wens et al., 2015a; Wens et al., 2015b). At last, seven studies did not mention how findings of the study were likely to translate to other species of systems, including any relevance to human biology. (Bernardes et al., 2013; Bernardes et al., 2017; Bonfiglio et al., 2019; Patel et al., 2013; Patel et al., 2016; Pryor et al., 2014; Rossie et al., 2009)

All studies have also been analysed for their strengths and weaknesses (Table 4). In general, there are two common strengths which were seen in most studies. The first strength is the fact that seven studies had a sample size of 30 animals or more, which can be considered as a big sample size (Bensen et al., 2015; Bernardes et al., 2016; Klaren et al., 2016; Mifflin et al., 2017; Patel et al., 2016; Wens et al., 2015a; Wens et al., 2015b).

Secondly, five out of 14 studies who used the chronic type of EAE assessed the daily clinical score for more than 35 days post disease induction (Einstein et al., 2018; Klaren et al., 2016;

Rossi et al., 2009; Souza et al., 2016; Xie et al., 2019). Two common weaknesses can be found in most studies. The first one is the randomization of animals into exercise and control groups. Although this is an important factor, this was only mentioned in half of the studies. (Bernardes et al., 2017; Bonfiglio et al., 2019; Le Page et al., 1996; Patel et al., 2013; Patel et al., 2016; Pryor et al., 2014; Rossi et al., 2009; Souza et al., 2016; Wens et al., 2015a; Xie et al., 2019). Secondly, five studies had a sample size of 12 animals or less (Bernardes & Oliveria, 2017; Le Page et al., 1996; Patel & White, 2013; Pryor, Freeman, Larson, Edwards, &White, 2014; Rossi et al., 2009). Further details of the strengths and weaknesses of each individual study can be consulted in Table 4.

Table 3

Quality assessment of included studies in alphabetical order(n=18)

Criteria	Benson, C. et al., 2015	Bernardes, D. et al., 2013	Bernardes, D. et al., 2016	Bernardes, D. & Oliveira, A. L. R., 2017	Bonfiglio, T. et al., 2019	Einstein, O. et al., 2018	Klaren, R. E. et al., 2016	Le Page, C., Ferry, A. & Rieu, M., 1994	Le Page, C. et al., 1996	Mifflin, A., Frieser, E., Benson, C., Baker, G. & Kerr B., 2017	Patel, D. I. & White, L. J., 2013	Patel, D. I., White, L. J., Lira, V. A. & Criswell D. S., 2016	Pryor, W., Freeman, K., Larson, R., Edwards, G. & White, L., 2014	Rossi, S. et al., 2009	Souza, P. S. et al., 2016	Wens, I. et al., 2015a	Wens, I. et al., 2015b	Xie, Y. et al., 2019
1	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y
2	N	N	Y	Y	N	N	Y	N	N	N	Y	N	Y	Y	N	N	Y	N
3	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
4	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
5	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
6	1Y 2N 3Y	1N 2N 3Y	1Y 2N 3Y	1Y 2N 3Y	1Y 2N 3N	1N 2N 3Y	1Y 2Y 3Y	1Y 2Y 3Y	1Y 2Y 3Y	1Y 2N 3Y	1Y 2N 3Y	1Y 2N 3Y	1Y 2N 3Y	1Y 2Y 3Y	1Y 2N 3Y	1Y 2N 3Y	1N 2Y 3Y	1Y 2N 3Y
7	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
8	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
9	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
10	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
11	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	N

12	Y	Y	N	N	N	Y	Y	N	N	N	Y	Y	Y	N	N	Y	Y	N
13	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
14	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
15	1Y 2N	1N 2N	1Y 2N	1N 2N	1Y 2N	1Y 2N	1Y 2Y	1Y 2Y	1Y 2N	1Y 2N	1Y 2Y	1Y 2Y	1N 2N	1Y 2N	1Y 2N	1Y 2Y	1Y 2Y	1Y 2N
16	Y	N	Y	N	N	Y	Y	Y	Y	Y	N	N	N	N	Y	Y	Y	Y
17	Y	N	Y	Y	Y	Y	N	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y

Adaptive version: ARRIVE checklist

Title	1	Provides a description of the content of the article as accurate and concise as possible.
Abstract	2	Provides an accurate summary of the background, research objectives, including details of the species or strain of animal used, key methods, principal findings and conclusions of the study.
Background	3	There is sufficient scientific background, this includes: references to previous work, an explanation of the experimental approach, rationale and why or how the animal model is used, to understand the motivation and context for the study. This explanation can address the scientific objectives.
Objectives/experimental outcomes	4	There is a description of the objective of this study and a definition of the primary and secondary outcomes that are assessed
Ethical statement	5	Indicates the nature of the ethical review permissions, relevant licenses (e.g. Animal [Scientific Procedures] Act 1986), and national or institutional guidelines for the care and use of animals, that cover the research.
Study design	6	1. The number of experimental and control groups are given and if or how their allocation was randomized. 2. The blinding of the therapist who set up and controlled the exercise interventions, assessors of clinical disability, as well as the statistician, are mentioned. 3. The order of treatment and assessment is given. If possible, time-line diagrams or flow charts are used to illustrate how study designs were carried out
Experimental procedures	7	For each experiment and each experimental group, including controls, precise details are provided of all procedures carried out. → How (e.g. drug formulation and dose, site and route of administration), When (e.g. time of day), Where (e.g. home cage, laboratory, water maze) and Why.
Experimental animals	8	Details of the animals used are provided, including species, strain, sex, developmental stage (e.g. mean or median age plus age range) and weight (e.g. mean or median weight plus weight range).
Housing and husbandry	9	There are details provided of the housing type, de husbandry conditions and the welfare-related assessments and interventions that were carried out prior to, during, of after the experiment.
Sample size	10	The number of animals used in each experiment, how the number of animals was arrived and the number of independent replications of each experiment is specified.
Statistical methods	11	Detailed explanation of the statistical methods used for each analysis, the unit of analysis for each dataset and any methods used to assess whether the data met the assumptions of the statistical approach.
Numbers analysed	12	There is a report of the number of animals in each group that are included in each analysis and explanation if any animals or data were not included.

Outcomes and estimation	13	The results of each analysis are carried out, with a measure of precision.
Adverse events	14	Details are given of all important adverse events and any modifications made to reduce the adverse effects in each experimental group.
Interpretation/scientific implications	15	1. There is an interpretation of the results, taking into account the study objectives and hypotheses, current theory and other relevant studies in the literature. 2. Limitations of the study are mentioned, including potential sources of bias, limitations to the animal model or imprecision associated with results.
Generalizability/translation	16	There is a comment section on whether, and how, the findings of this study are likely to translate to other species or systems, including any relevance to human biology.
Funding	17	There is a list of all funding sources, the role of the funder(s) in the study and if there are any conflicts of interests.

Table 4

Analysis of strengths and weaknesses of included studies in alphabetical order (n=18)

Author(s), year	Strength	Weakness
Benson, C. et al., 2015	• Drop-outs are mentioned and explained • Big sample size: n=30 in exercise and control group (n=60 in total)	• No mentioning of blinding of assessors of the daily clinical score • No mentioning of randomisation of animals into groups
Bernardes, D. et al., 2013	• First study using a swimming exercise protocol	• No mentioning of blinding of assessors of daily clinical score • No mentioning of randomisation of animals into groups
Bernardes, D. et al., 2016	• Big sample size: n=47 in total	• No mentioning of blinding of assessors of the daily clinical score • No mentioning of drop-outs

Bernardes, D. & Oliveira, A. L. R., 2017	• Mice were randomly assigned to groups	• No mentioning of blinding of assessors of daily clinical score • Low sample size in groups: n=12 per group • Weak interpretation of results
Bonfiglio, T. et al., 2019	• Randomisation of mice between EE and SE-group • A lot of secondary outcome measures are analysed	• Weak description of statistical analysis • No mentioning of blinding of assessors of daily clinical score
Einstein, O. et al., 2018	• Long assessment of clinical score: 50 days • No animal was excluded from the experiments	• No mentioning of randomisation • No mentioning of blinding of assessors of clinical score • Intensity of treadmill running was not mentioned in the first 2 weeks of training program

Klaren, R. E. et al., 2016	• Large sample size (n=47) • Long assessment of the clinical score: 70 days • Blinded assessor for clinical disability scores • Inclusion of both voluntary wheel running and forced wheel running	• Amount of exercise: not all mice were compliant with the forced wheel running protocol • Low overall volume of exercise in the running wheel and treadmill conditions
Le Page, C., Ferry, A. & Rieu, M., 1994	• Induction of 3 types of EAE • Blinding of assessors of the clinical score	• No mentioning of drop-outs and reasons of drop-outs • Clinical signs were only assessed every 2 days
Le Page, C. et al., 1996	• Randomisation of rats into groups • Blinding of assessors of the clinical score	• Small sample size for each individual experiment (n= 7 – 10) • Weak description of statistical analysis
Mifflin, A., Frieser, E., Benson, C., Baker, G. & Kerr B., 2017	• Big sample size: n=60 • Inclusion of both male and female mice	• No mentioning of blinding of assessors of daily clinical score • No mentioning of randomisation of animals into groups

Patel, D. I. & White, L. J., 2013	• Randomisation of animals into 4 groups • Reason of drop-out was mentioned	• No mentioning of blinding of assessors of daily clinical score • Small sample size: n=10 per group
Patel, D. I., White, L. J., Lira, V. A. & Criswell D. S., 2016	• Randomization of rats into groups • Big sample size: n=40	• The protocol provides an inherent limitation • No mentioning of blinding of assessors of daily clinical score
Pryor, W., Freeman, K., Larson, R., Edwards, G. & White, L., 2014	• Explanation of drop-outs was mentioned • Randomisation of animals into groups	• Low sample size: n=8 • No blindation of the assessors of the daily clinical score
Rossi, S. et al., 2009	• Long assessment period of clinical score: 50 days • Mice were randomly allocated in groups	• Small sample size: n=8 in both groups • No mentioning of blinding of assessors of daily clinical score • Weak description of exercise protocol

Souza, P. S. et al., 2016	• 2 independent obersvers assessed clinical signs of EAE • Mice were randomised into groups • Long assessment of clinical score: 35 days	• Duration of endurance exercise sessions not mentioned • Exact number of mice in each group was not mentioned
Wens, I. et al., 2015a	• Big sample size: n = 80 • Randomization of ratis into groups	• Short duration of the applied exercise program • The researchers could not be blinded to group allocation
Wens, I. et al., 2015b	• Big sample size: n = 67 • Mentioning of drop-outs (n=5)	• Randomisation of rats in sedentary and training groups not mentioned
Xie, Y. et al., 2019	• Randomisation of mice into three groups • Long assessment of clinical score: 30 days	• Duration of endurance exercise sessions not mentioned • Exact number of mice in each group was not mentioned

4.3. Results of data extraction

Different genders of animals and types of EAE have been investigated. To sum up, five studies used female Lewis rats (Le Page et al., 1996; Patel & White, 2013; Patel, White, Lira, &Criswell, 2016; Wens et al., 2015a; Wens et al., 2015b), and one study used both male and female Lewis rats (Le Page, Ferry, &Rieu, 1994). Next, seven studies used female C57BL/6(J) mice (Benson et al., 2015; Bernardes et al., 2013; Bernardes et al., 2016; Bernardes et al., 2017; Bonfiglio et al., 2019; Rossie et al., 2009; Souza et al., 2016; Xie et al., 2019), one study used male C57BL/6(J) mice (Pryor, Freeman, Larson, Edwards, &White, 2014), and one study uses both male and female C57BL/6(J) mice (Mifflin, Frieser, Benson, Baker, &Kerr, 2017). At last, two studies used female SJL/(JCrHsd) mice (Einstein et al., 2018; Klaren et al., 2016). Details of age and weight of experimental animals can be consulted in Table 5.

Three different types of EAE have been induced to the experimental animals: monophasic, chronic and relapse-remitting EAE. Monophasic EAE is characterised by a single exacerbation of disease symptoms, which spontaneously recovers after seven to 11 days. This type of EAE can be seen in four studies (Le Page, Ferry, &Rieu, 1994; Le Page et al., 1996; Wens et al., 2015a; Wens et al., 2015b). In the chronic type of EAE, clinical symptoms do not recover. The relapse-remitting type is characterized by alternating periods of exacerbations and remissions of the symptoms. A chronic type of EAE was used in 14 studies (Benson et al., 2015; Bernardes et al., 2013; Bernardes et al., 2016; Bernardes et al., 2017; Bonfiglio et al., 2019; Einstein et al., 2018; Le Page et al., 1994; Mifflin et al., 2017; Patel et al., 2013; Patel et al., 2016; Larson et al., 2014; Rossi et al., 2014; Souza et al., 2016; Xie et al., 2019), where daily clinical score was assessed for a longer period, ranging from 10 days (Patel, White, Lira, &Chriswell, 2016) to 50 days (Rossi et al., 2009, Einstein et al., 2018) after disease induction. Only two studies used a relapse-remitting type where daily clinical score was assessed for 40 days (Le Page, Ferry, &Rieu, 1994) or 70 days (Klaren et al., 2016) after disease induction.

4.3.1. Training parameters (research question 1)

4.3.1.1. exercise modality

Three different exercise modalities were used: running, swimming and exercise training. In the running program, exercise was forced in eight studies, whereby animals were placed on a small treadmill (Bernardes et al., 2017; Einstein et al., 2018; Le Page et al., 1994; Le Page et al., 1996; Patel et al., 2013; Patel et al., 2016; Wens et al., 2015a; Wens et al., 2015b), and exercise was voluntary in five studies where animals had a continuous access to a running wheel in their cages (Benson et al., 2015; Bonfiglio et al., 2019; Mifflin, Frieser, Benson, Baker, &Kerr, 2017; Pryor, Freeman, Larson, Edwards, &White, 2009; Rossi et al., 2009). One study compared the forced treadmill running program with a strength training program, where animals had to climb a ladder with a progressive load secured to the tail (Souza et al., 2016). One study compared the voluntary wheel running program with the forced treadmill running program (Klaren et al., 2016). At last, three studies selected a forced swimming program, where mice had to swim inside a small plastic tube which was partly filled with water (Bernardes et al., 2013; Bernardes et al., 2016; Xie et al., 2019).

4.3.1.2. Exercise intensity

Different exercise intensities were investigated. Exercise intensity was either gradually increased trough the training program, remained at a constant intensity or divided into light, moderate or high intensity.

Regarding the forced treadmill running program, exercise intensity was gradually increased in five studies (Einstein et al., 2018; Le Page, Ferry, &Rieu, 1994; Patel & White, 2013; Patel, White, Lira, &Chriswell, 2016; Souza et al., 2016). Exercise intensity remained constant in three studies (Bernardes & Oliveira, 2017; Klaren et al., 2016; Wens et al., 2015a), and there was a comparison between of low, moderate or high intensity in two studies (Le page et al., 1996; Wens et al., 2015b). Studies who used the forced swimming program modulated exercise intensity by attaching a load to animals tail, corresponding with a percentage of the body weight (BW). This percentage was held constant at 7% in two studies (Bernardes et al.,

2013; Bernardes et al., 2016), and was either 0% or 4% in a study who compared moderate with high exercise intensity (Xie et al., 2019). Since animals had free access to a running wheel in the voluntary wheel running program, exercise intensity could not have been modulated. Details of training bout durations and running speed can be consulted in Table 5.

4.3.1.2. exercise program duration and time of exercise delivery

A lot of different exercise programs were used in the forced treadmill running program. Exercise was given before EAE induction with a program duration of six weeks (Einstein et al., 2018). Exercise was given after EAE induction with a program duration of 10 days (Le Page, Ferry, &Rieu, 1994; Patel & White, 2013; Patel, White, Lira, &Chriswell, 2013; Wens et al., 2015a; Wens et al., 2015b) or only during remission perdiods in the relapse-remitting type of EAE (Klaren et al., 2016). Exercise was given before and after EAE induciton with a program duration of six weeks (Bernardes & Oliveira, 2017) or four weeks (Souza et al., 2016), and in one study exercise was given before or after EAE induction for two or five days (Le page, Ferry, &Rieu, 1994).

All voluntary wheel running programs started after disease induction, but there was a wide variation in program duration going from 21 days (Mifflin, Frieser, Benson, Baker, &Kerr, 2017) to 50 days (Rossi et al., 2009). Animals only had access to a running wheel during remission periods after a peak in the relapse-remitting type of EAE (Klaren et al., 2016). Program duration of other studies who also used voluntary wheel running exercise can be consulted in Table 5.

Only two different training protocols were seen in the forced swimming program. In the first one, animals had to swim for four weeks before EAE induction, and 10 or 14 days after (Bernardes et al., 2013; Bernardes et al., 2016). In the second one, animals were given six weeks of swimming exercise before EAE induction, and the exercise continued until sacrification of the animals (Xie et al., 2019). Details of exercise frequency and individual training durations can be consulted in Table 5.

4.3.2. Clinical disability (research question 2)

In general, 14 out of 18 studies (77,78%) showed a positive effect of exercise on clinical disability. This positive effect can be seen in a significant change in at least one of following outcome measures: daily clinical score, disease onset, peak score and peak onset.

4.3.2.1. Daily clinical score

Daily clinical score was assessed in twelve studies, were eight of these studies showed a significant positive effect of exercise. Three studies reported a significant reduction of the mean clinical score (average of all daily scores per animal) in the exercise group compared to control (Mifflin, Frieser, Benson, Baker, &Kerr, 2017; Pryor, Freeman, Larson, Edwards, &White, 2014; Xie et al., 2019). However, this was only the case in male mice in the study of Mifflin, Frieser, Benson, Baker and Kerr. One study found a significant effect on the cumulative disease score (sum of all daily clinical scores per animal) (Bernardes et al., 2016). Another study reported a significant reduction of the burdon of disease (BOD), which represent the area under the curve and is therefore comparable to the cumulative disease score (Einstein et al., 2018). Daily clinical score was significantly reduced starting from onset of disease in two studies (Bonfiglio et al., 2019; Rossi et al., 2009). At last, one study showed a significant reduction in daily clinical score from day 10 to 14 (Bernardes et al., 2013). However, daily clinical score was not reduced in three studies (Bernardes & Oliveira, 2017; Klaren et al., 2016; Patel & White, 2013), and daily clinical score was reduced in the control group instead of the exercise group in two studies (Mifflin, Frieser, Benson, Baker, &Kerr, 2017; Patel, White, Lira, &Chriswell, 2016). Exact values of disease score and p-values can be consulted in Table 5.

4.3.2.2. Disease onset

Disease onset was reported in 11 studies, where nine of these studies found a positive effect on disease onset in the exercise group compared to control.

Three studies using a voluntary wheel running program showed a significant delayed disease onset of the exercise group (Benson et al., 2015; Bernardes et al., 2016; Pryor, Freeman, Larson, Edwards, &White, 2014), and one study showed a delay in disease onset without a p-value (Mifflin, Frieser, Benson, Baker, &Kerr, 2017).

Disease onset was analysed in only one study with a forced swimming program, which showed a significant delay of disease onset (Bernardes et al., 2016). One study who compared light, moderate and high intensity exercise showed only a significant delay of disease onset in the high intensity exercise group (Wens et al., 2015b). Another study found a significant delay only in the relapse-remitting type of EAE (Le Page, Ferry, & Rieu, 1994), and disease onset was only delayed with two days of high-intensity exercise after disease induction in one study (Le Page et al., 1996). A study who compared a strength training with an endurance training, showed only a delayed disease onset in the endurance training without a p-value (Souza et al., 2016). At last, Disease onset only tended to be delayed in one study (p=0,1) (Wens et al., 2015a). However, disease onset was not delayed in two studies (Bonfiglio et al., 2019; Einstein et al., 2018). Data of disease onset and p-values can be consulted in Table 5.

4.3.2.3. Peak score and peak onset

Four studies reported results of peak score, where only two studies found a positive effect of exercise. Peak onset was reported in three studies, who all found a positive effect of exercise.

One study reported a significant reduction of the peak score of the exercise group compared with control (Einstein et al., 2018), and the study of Souza et al. (2016) also mentioned a reduction of the peak score without any p-value. However, two studies reported that peak score was not affected in the exercise group (Le Page, Ferry, &Rieu, 1994; Le Page et al., 1996). Two studies showed a significant delay in peak onset in the exercise group (Le Page et al. 1996; Wens et al., 2015a) and one study reported a delay in peak onset without any p-value (Bonfiglio et al., 2019). Exact values of peak score, peak onsets and p-values can be consulted in Table 5.

Table 5

Data extraction of included studies in alphabetical order (n=18)

Author(s), year	Animal species	Type of EAE	Training parameters	Daily clinical score	Disease onset	Peak score Peak onset
Benson, C. et al., 2015	Female C57/BL6 mice, age 10 to 12 weeks	Chronic	• Voluntary wheel running • 20 days • post disease induction	/	Delayed in exercise group by an average of 3-4 days($p<0.05$)	/
Bernardes, D. et al., 2013	Female C57BL/6 mice, Age 6 to 8 weeks	Chronic	• Forced swimming • 30 min/day, 5 days/week, 7%BW attached to tail • 4 weeks • post disease induction	Reduced from disease onset (10 days post induction) to peak (14days post inductioni) ($p<0.05$)	/	/
Bernardes, D. et al., 2016	Female C57BL/6 mice, age 7 weeks	Chronic	• Forced swimming • 30 min/day, 5days/week, 7%BW attached to tail • 4 weeks • post disease induction	cumulative disease score (sum of daily clinical score during assessment period) reduced in exercise group: 29.6±6.7	Delayed in exercise group: day 21.7±2.6, compared to control group: day 15.7±1.3, ($p<0.05$)	/

				compared to controup group: 52.2±8.2		
Bernardes, D. & Oliveira, A. L. R., 2017	Female C57BL/6 mice, age 4 to 6 weeks	Chronic	• Forced treadmill running • 30 min/day, 5 days/week, 11m/min • 4 weeks • pre disease induction	not reduced	/	/
Bonfiglio, T. et al., 2019	Female C57BL/6J mice, age 4 weeks at the start of exercise	Chronic	• Access to voluntary wheel running in enriched environment (EE) • 4 weeks • post disease induction	Reduced in exercise group compared to control group ($p<0.05$) since disease onset	Not delayed	**Peak onset** Delayed in exercise group (day 21) compared to control group (day 15)

Einstein, O. et al., 2018	Female SJL/JCrHsd mice, age 6 to 7 weeks or 12-13 weeks	Chronic, passive	• Forced treadmill running
			• Intensity:
			  ○ First week: 10 min/day
			  ○ Second week: 20 min/day
			  ○ Thirth to sixth week:
				Significant reduction of burdon of disease (area under the curve)	Not delayed	**Peak score**
						Reduced in exercise group: 2.5±0.4, compared to conrol group: 3.8±0.1 ($P<0.05$)

			30 min day at 23cm/s ○ 5 days/week • 6 week • pre disease induction			
Klaren, R. E. et al., 2016	Female SJL-mice, age 6 to 8 weeks	Relapse-Remetting	• Voluntary wheel running, forced wheel running • 30 min/day, 14m/min, 5% grade • Only exercise during remission periods	No significant effect of exercise delivered during remission after initial disease onset, and among conditions over 68 days post disease induction	/	/
Le Page, C., Ferry, A. & Rieu, M., 1994	Female and Male Lewis Rats, age 8 weeks	Monophasic, acute and chronic-relapsing EAE(CR-EAE)	• Forced treadmill running • Gradually increased from 60 to 120 min/day and from 15 to 20 m/min • 10 days • post disease induction	Development of clinical signs tended to be significant	Delayed in the exercise group in CR-EAE (p=0.001)	**Peak score** not modified by exercise

Le Page, C. et al., 1996	Female Lewis rats, age 8 weeks	Monophasic	• Forced treadmill running • Moderate or severe intensity • 2 or 5 days • pre or post disease induction	/	Delayed in group who received 2 days of severe intensity exercise after disease induction (p=0.008)	**peak score** delayed in group who received 2 days of severe intensity exercise after disease inducton(P=0.016) **Peak score** not affected in group who received 2 days of severe intensity exercise after disease inducton (p>0.05)
Mifflin, A., Frieser, E., Benson, C., Baker, G. & Kerr B., 2017	Male and Female C57/B16 mice, age 6 to 8 weeks	Chronic	• Voluntary wheel running • 30 days • Starting from 4 days post disease induction	Male mice: average clinical score reduced in exercise group: 2.2±1.2 compared to conrol group: 3.3±0.8	Female mice: delayed by approximately 3 days: 16.6±3.0 in exercise group, 14.1±4.3 in control group Male mice: delayed by approximately 1 day: 18.3±2.8 in	/

				Female mice: **average clinical score reduced in control group:** 2.1±1.3 compared to exercise group: 3.1±0.9	exercise group, 17.3±3.5 in control group	
Patel, D. I. & White, L. J., 2013	Female lewis rats, age 8 weeks	Chronic	• Forced treadmill running • Gradually increased from 60 to 90 min/day, 15 to 20 m/min • 10 days • post disease induction	No significant difference between exercise and control group at day 10 of the study	/	/
Patel, D. I., White, L. J., Lira, V. A. & Criswell D. S., 2016	Female Lewis Rats, age 8 weeks	Chronic	• Forced treadmill running • Gradually increased from 60 to 120 min/day and from 15 to 30 m/min • 10 days • post disease induction	Reduced in **control group** on days 5-9 ($p<0.001$)	/	/

Pryor, W., Freeman, K., Larson, R., Edwards, G. & White, L., 2014	Male C57BL/6J mice, age 10 weeks	Chronic	• Voluntary wheel running • 25 days • post disease induction	Mean clinical score reduced in exercise group: 1.86±0.21 compard to control group: 3.15±0.53	Delayed in exercie group: day 13.75±0.95 compared tot control group: day 12±0.81 ($p<0.05$)	/
Rossi, S. et al., 2009	Female C57BL/6 mice, age 8 weeks	Chronic	• Voluntary wheel running • 50 days • post disease induction	Reduced in exercise group starting from day 12 post disease induction ($p<0.05$)	/	/

Souza, P. S. et al., 2016	Female C57BL/6 mice,
	Age 6 to 12 weeks
		Chronic	• Strength training (ST):
			  ○ climbing a ladder with progressive load attached tot tail
			  ○ 5 days/week
			• Endurance training (ET)
				/	Significant delayed in ET (day 16) (no p-value given)
					
					Not delayed in ST
						Peak score
						Reduced in ST (score = 1.5)
						
						Reduced in ET (score = 0.5)

			- Forced treadmill running - Gradually increased from 13 to 17 m/min 5 days/week 2 weeks before and 2 weeks after disease induction			
Wens, I. et al., 2015a	Female Lewis Rats, age 6-7 weeks, body weight 100 - 120g	Monophasic	- Forced treadmill running 18 m/min, 1h/day 10 days - post disease induction	/	Tended to be delayed by 0.7±0.4 days in the exercise group (p=0.1)	Peak onset of the exercise group was delayed by 1.0 ±0.3 days (p<0.05)
Wens, I. et al., 2015b	Female Lewis Rats, age 6-7 weeks, body weight 120 - 170 g	Monophasic	- Forced treadmill running - Light, moderate or high intensity 10 days - post disease induction	/	delayed in high intensity exercise group: day 11.6±0.3 compared to control group: day 11.0±0.1 (p<0.05)	/

Xie, Y. et al., 2019	Female C57BL/6 mice, age 6 to 8 weeks	Chronic	• Forced swimming
			• Intensity
			  ○ High intensity exercise (HE): 4%BW
			  ○ Moderate intensity exercise (ME): 0%BW
			  ○ 50 min/day, 5 days/week
			• 6 weeks before disease induction
			• 4 weeks after disease induction until sacrification
				High intensity swimimng exercise reduced daily clinical score compared to control group ($p<0.01$)	/	/

5. Discussion

5.1. Reflection of quality of studies

Eighteen studies who examined the effect of exercise on clinical disability in EAE have been investigated. Differences among the studies were seen in the quality assessment regarding five criteria: information in abstract, blinding of assessors, number of animals and drop-outs, study limitations and translation to human biology. However, quality was sufficient and no articles were excluded. This systematic review included seven articles with a big sample size of 30 animals or more, and five studies assessed the daily clinical score for at least 35 days. However, randomisation of animals into exercise and control groups was only mentioned in half of the studies, and six studies selected a small sample size of 12 animals or less.

5.2. Effect of training parameters on clinical disability

This systematic review aimed to compare different training parameters of exercise in EAE, and to investigate the effect of exercise on clinical disability. Forced or voluntary running and swimming exercise are mostly selected, with varying intensities. Exercise was given before or after EAE induction for two days to six weeks. Most studies showed that exercise had a positive effect on the outcome measures of clinical disability. However, results of these outcome measures show many differences which may be explained by the individual effect of each training parameter.

5.2.1. Effect of training parameters on daily clinical score

5.2.1.1. exercise modality

Only two out of five (40%) of studies handling a forced treadmill program showed a positive effect of exercise on daily clinical score. This was the case in four out of six (66,67%) studies handling a voluntary wheel running program, and in all studies handling a forced swimming program (n=3).

In this way, forced treadmill running may have a limited capacity of reducing the daily clinical score. This hypothesis was also mentioned in a study conducted by Patel, White, Lira and

Chriswell (2016) using a forced treadmill exercise program. This study reported that forced exercise may cause a stress response, which is associated with suppressed brain-derived neurotrophic factor (BDNF) concentrations and counteract the positive effect of exercise on daily clinical score (Jacobsen & Mork, 2006). The swimming exercise modality also includes forced exercise, but this stress response may be counteracted by the benefits of swimming exercise as already mentioned. However, since animals in this study were euthanised the day after the last exercise session (day 10), positive effects of exercise on daily clinical score may not have occurred due to this reason.

Since all studies using a forced swimming program showed a positive effect of exercise on daily clinical score, this modality may be particularly suitable for reducing daily clinical score. Two studies may have an explanation for this effect. First, Bernardes et al. (2016) mentioned that a forced swimming exercise modality was used because swimming has been found to trigger cardiovascular fitness (Evangelista, Brum, &Krieger, 2003) muscle endurance (Oh-ishi et al., 1996), and immune function (Almeida et al., 2009) in mice. Second, Xie et al. (2019) reported that swimming exercise can increase muscle endurance (Shei et al., 2016), delay tumor development (Almeida et al., 2009), promote antiinflammation and neuroprotective effects in mice (Bernardes et al., 2013). In this way, swimming exercise may be particularly suitable for reducing daily clinical score and future research should also use this exercise modality.

At last, Bernardes et al. (2016) conducted two studies where exercise was given to EAE animals. The first study selected a forced swimming program, which contained four weeks of exercise before and 10 to 14 days after disease induction for five days a week and 30 minutes a day (Bernardes et al., 2016). The second study used the same exercise protocol, but the only difference was the fact that a forced treadmill running program was selected instead of a forced swimming program (Bernardes & Oliveira, 2017). Although Bernardes et al. did not directly compare these two modalities, results showed that daily clinical score was only reduced in the swimming program. In this way, future research should directly compare effects of exercise on daily clinical score in a forced treadmill running and a swimming program.

5.2.1.2. exercise intensity

Two different swimming protocols were used in the included studies. The first one is a protocol selected by Bernardes et al. (2013), where a high intensity exercise was selected by attaching 7%BW to the tail. The second protocol was selected in the study of Xie et al. (2019), which used a moderate exercise intensity (0%BW) and a high exercise intensity (4%BW). Results show that daily clinical score was only significantly reduced in exercise at high intensity. Due to the fact that daily clinical score was not significantly reduced in exercise at moderate intensity, exercise intensity may be important in reducing daily clinical score.

5.2.1.3. program duration

Duration of exercise may also be an important factor in reducing the daily clinical score due to two reasons. First, eight studies who reported a significant reduction in daily clinical score used an exercise program that lasted at least 21 days (Bernardes et al., 2013; Bernardes et al., 2016; Bonfiglio et al., 2019; Einstein et al., 2018; Mifflin et al., 2017; Pryor et al., 2014; Rossi et al., 2009; Xie et al., 2019), and three studies with an exercise program that lasted 10 days or less reported no significant reduction in daily clinical score in exercise group (Klaren et al., 2016; Patel & White, 2013; Patel, White, Lira, &Chriswell, 2016). Second, a study of Klaren et al. (2016) used both forced wheel running and voluntary wheel running as exercise modality. However, none of these modalities resulted in a significant reduction of the daily clinical score among conditions over 68 days post disease induction. This study used a relapse-remitting type of EAE, where exercise was only given during remission periods after acute disease relapses. Since these remission periods only lasted a few days, a long exercise program could not be given. In this way, exercise duration may be the reason why there was no significant reduction of the daily clinical score among this study instead of exercise modality.

5.2.1.4. timing of exercise delivery

Only one study with a forced treadmill running program who assessed the daily clinical score used an exercise program given exclusively before disease induction (Einstein et al., 2018).

This study reported a significant reduction in daily clinical score (burdon of disease). In this way, time of delivery may also be an influencing factor in reducing daily clinical score

5.2.2. Effect of training parameters on disease onset

In general, peripheral immunomodulation is the main mechanism in delaying disease onset in EAE mice. In a study of Aharoni et al. (2005), a peripheral immunomodulatory treatment for MS or EAE called glatiramer acetate (GA), led to sustained reduction in the axonal damage typical to the neurodegenerative disease course which led to a delay in disease onset.
However, training parameters of exercise intervention may also play an important role in delaying disease onset, which may support the mechanism of peripheral immunomodulation.

5.2.2.1. exercise modality

Four studies using a voluntary wheel running exercise program analysed the disease onset. This parameter was significantly delayed in three studies (Benson et al., 2015; Mifflin, Frieser, Benson, Baker, &Kerr, 2017; Pryor, Freeman, Larson, Edwards, &White, 2014), and not delayed in one study (Bonfiglio et al., 2019). This was also the case in studies using a forced treadmill running exercise program, where three studies reported a significant delayed disease onset (Le Page, Ferry, &Rieu, 1994; Le Page et al., 1996; Souza et al., 2016), but this was not delayed in one study (Einstein et al., 2018). Only one study using a forced swimming exercise program analysed this parameter. In this way, exercise modality may not have a clear effect on delaying disease onset.

5.2.2.2. exercise intensity

Disease onset was significantly delayed in five studies who used high intensity exercise or where the exercise program was gradually increased until high intensity was reached (Bernares et al., 2016; Le Page, Ferry & Rieu, 1994; Le Page et al., 2016; Wens et al., 2015b).
Since disease onset was not delayed in only one study with an incremental exercise program (Einstein et al., 2018), exercise intensity may be an influencing factor for delaying disease onset.

5.2.2.3. timing of exercise delivery

Six studies using a forced treadmill exercise program also analysed this disease outcome. A clear effect of timing of exercise delivery can be seen. Five of these studies where exercise was given after disease induction showed a significant delay of disease onset (Le Page, Ferry, &Rieu, 1994; Le Page et al., 1996; Souza et al., 2016; Wens et al., 2015b) and tended to be delayed in the study of Wens et al. (2015a), while one study where exercise was given before disease induction reported no delay of disease onset (Einstein et al., 2018). In this way, timing of exercise delivery may be an important factor in delaying disease onset.

5.2.2.3. timing of exercise delivery

No clear differences can be seen regarding program duration in modifying disease onset.

5.2.3. Effect of training parameters on peak score and peak onset.

5.2.3.1. exercise modality

Since peak score was only analysed by four studies using a forced treadmill running program (Einstein et al., 2018; Le Page, Ferry, &Rieu, 1994; Le Page et al., 1996; Souza et al., 2016), it is not clear how different exercise modalities can influence the peak score.

5.2.3.2. exercise intensity

Due to the fact that peak score was only analysed in studies who used a high or gradually increased intensity forced wheel running program, it is also not clear if exercise intensity modifies the peak score, since two studies reported a significant reduction (Einstein et al., 2018, Souza et al., 2016) and two studies showed that peak score was not affected (Le Page, Ferry & Rieu, 1994; Le Page et al., 1996).

As already mentioned in results, only three studies analysed the onset of peak score, whereby a (significant) delay of peak onset was found in all three studies. Since no study showed that peak onset was not delayed, the effect of each training parameter on peak onset is not clear. However, a conclusion regarding exercise intensity can be drawn when two studies using the

forced treadmill running program are compared. The first study used a medium intensity exercise intervention (Wens et al., 2015a), and the second one used a high intensity exercise intervention (Le Page et al., 1996). Since both studies reported a significant delay in peak onset, exercise intensity may not be a contributing factor that modifies peak onset.

5.2.3.3. program duration

A clear effect of exercise program duration can be seen. Two studies where the exercise program lasted four to six weeks showed a significant reduction in peak score (Einstein et al., 2018, Souza et al., 16), while two studies with an exercise program duration of two to 10 days reported peak score was not affected (Le Page, Ferry, &Rieu, 1994; Le Page et al., 1996).

5.2.3.4. timing of exercise delivery

A second important parameter affecting the peak score may be the timing of exercise delivery, since two studies with an exercise program given before disease induction show a significant reduction in peak score (Einstein et al., 2018; Souza et al., 2016), while two studies with an exercise program given after disease showed that peak score was not affected (Le Page, Ferry, &Rieu, 1994; Le Page et al., 1996). In this way, selection of an exercise program given before disease induction may lead to a reduction of peak score.

5.3. Reflections of strengths and limitations of this systematic review

After the review of Klaren, Motl, Woods and Miller (2014), many studies investigating the effect of exercise on clinical disability have been published. Due to this reason, a first strength is the fact that this systematic review was able to make a descriptive comparison of the effects of different training parameters on the outcome measures of clinical disability.
Second, there was an inclusion of a recent relevant article conducted by Xie et al. (2019) dating from March 15 2019, since the literature search was terminated on May 12 2019. Due to this study, this systematic review included of two various swimming protocols instead of one. Third, this systematic review contains a comprehensive search strategy, since a lot of synonyms of ‘exercise’ and ‘EAE’ were included.

Since this systematic review is a mono master thesis, there may be an assessor bias regarding the screening procedure of the studies assessed for eligibility, and the quality assessment of included studies.

5.4. Recommendations for future research

This systematic review included four different training modalities: forced treadmill running, voluntary wheel running, strength training and forced swimming. Two studies directly compared two different exercise modalities. The study of Klaren et al. (2016) compared the effects of forced treadmill running with voluntary wheel running, and the study of Souza et al. (2016) compared the effects of forced treadmill running with strength training. Although Bernardes et al. conducted two studies using a forced swimming program (Bernardes et al., 2013; Bernardes et al., 2016) and one study using a forced treadmill running program (Bernardes & Oliveira, 2017), a study which directly compared these two modalities was never conducted. Since there was only a positive effect of exercise on clinical disability in the forced treadmill running program of Bernardes et al., future research should focus on directly comparing the effects of forced treadmill running and forced swimming on clinical disability.

6. Conclusion

A lot of training parameter combinations have been used regarding exercise modality, exercise intensity, program duration and timing of exercise delivery and most studies showed that exercise had a positive effect on at least one outcome measure of clinical disability.

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Part 2: Research Protocol

1. Introduction

Multiple Sclerosis (MS) is an immune-mediated disease of the central nervous system, which has an estimated prevalence of one out of 1000 adults in Belgium. (Kurtzke, 2005).
Periods of inflammation are initial markers of this disease, which leads to demyelination and ultimately axonal degeneration (Maurer and Rieckmann, 2000).
MS patients experience typical symptoms including walking impairment and cognitive dysfunction, fatigue, pain, depression, and reduced quality of life and participation in activities of daily living (Lublin, 2005).

Loss of physical fitness (Motl, McAuley and Snook, 2005), muscle weakness (Garner and Widrick, 2005) and cardiovascular health risks (Christiansen et al., 2010) are secondary complications of this disease. Although pharmacological treatments are able to decrease MS relapse rate and severity, they do not stop the progression of this disease.
To date, exercise therapy (e.g. endurance and strength training) is being used to reduce or prevent these secondary complications in MS. Interestingly, however, it may be possible this positive effect also affects primary characteristics of MS.

Before therapeutic exercise interventions can be applied on human patients, the effect of exercise is being tested in experimental autoimmune encephalomyelitis (EAE), an animal model of MS. EAE is a T-helper cell-mediated autoimmune disease, where T-cells and monocytes have been infiltrated in the central nervous system, linked with local inflammation (Robinson, Harp, Noronha and Miller, 2014).
This injection results in demyelination of axonal tracks, impaired axonal conduction and progressive hind-limb paralysis, which is daily measured by a self-scored observational clinical scale (Robinson, Harp, Noronha and Miller, 2014).
In this way, possible therapeutic interventions for MS patients can be developed by studying the effect of exercise on clinical disability in EAE.

Several studies already investigated the effect of exercise on clinical disability. In these studies, a lot of training parameter combinations have been used regarding exercise modality, exercise intensity, program duration and timing of exercise delivery. Most studies showed that exercise had a positive effect on clinical disability.

To reduce clinical disability, four training modalities have been used including forced treadmill running, voluntary wheel running, strength training and forced swimming. However, the effects of different training modalities have only been directly compared in two studies. One study compared the effects of forced treadmill running with voluntary wheel running (Klaren et al., 2016), and one study compared the effects of forced treadmill running with strength training (Souza et al., 2016).

Although Bernardes et al. conducted two studies using a forced swimming program (Bernardes et al., 2013; Bernardes et al., 2016) and one study using a forced treadmill running program (Bernardes & Oliveira, 2017), a study which directly compared these two modalities has been never conducted. Results showed that there was only a positive effect of exercise on clinical disability in the forced swimming program in the studies of Bernardes et al. (2013, 2016). This leads to the assumption that forced swimming may be more suitable for reducing clinical disability than forced wheel running.

Due to this assumption, the aim of this study is to directly compare the effects of forced treadmill running and forced swimming on clinical disability in EAE.

2. Study objective

2.1. Research question

"What is the effect of forced treadmill running versus forced swimming at moderate and high intensity on clinical disability in experimental autoimmune encephalomyelitis?"
Effects on clinical disability can be seen in daily clinical score, time of disease onset, disease peak score and time of peak onset.

2.2. Hypothesis

Wens et al. already conducted a study which compared exercise effects of forced treadmill running at light, moderate and high intensity (Wens et al., 2015b). Since disease onset, which represents the day animals showed their first clinical symptoms, was only significantly reduced in the high intensity exercise group, we hypothesize that clinical disability will only be reduced in the high intensity running group.
Xie et al. conducted a study which compared exercise effects of a moderate and high intensity exercise program (Xie et al., 2019). Daily clinical score was only significantly reduced in the high intensity exercise group. Due to this reason, we hypothesize that clinical disability will only be reduced in the high intensity swimming group.
A possible effect of exercise modality on daily clinical score has already been discussed in the systematic review. Since only two out of five studies handling a forced treadmill program, and all three studies handling a forced swimming program showed a positive effect of exercise on daily clinical score, the forced swimming modality may be more suitable for reducing daily clinical score.

3. Method

3.1. study design

Exercise intensity is modulated by adjusting running speed in the forced treadmill program. In the forced swimming program, exercise intensity is modulated by attaching a load to the animal's tail, corresponding with a percentage of the body weight (BW).

First, a pilot experiment is set up to match a specific running speed with a percentage of BW. In this way, animals in the running and swimming program can exercise at the same intensity. Swimming and running intensities will be compared using blood lactate level. Mice have to complete a total of 12 exercise sessions. This pilot experiment is a prospective study with repeated measurements.

The second experiment will be a randomized prospective animal study investigating the effect of exercise modality and intensity on clinical disability, including four training groups and one sedentary.

3.2. Animals

Female C57/BL6 mice (age 10 to 13 weeks) are purchased from Envigo (The Netherlands). Animals will be obtained in a controlled environment with a 12:12h light:dark cycle, and will be provided with water and food *ad libitum* (Xie et al., 2019).

3.2. Medical Ethics

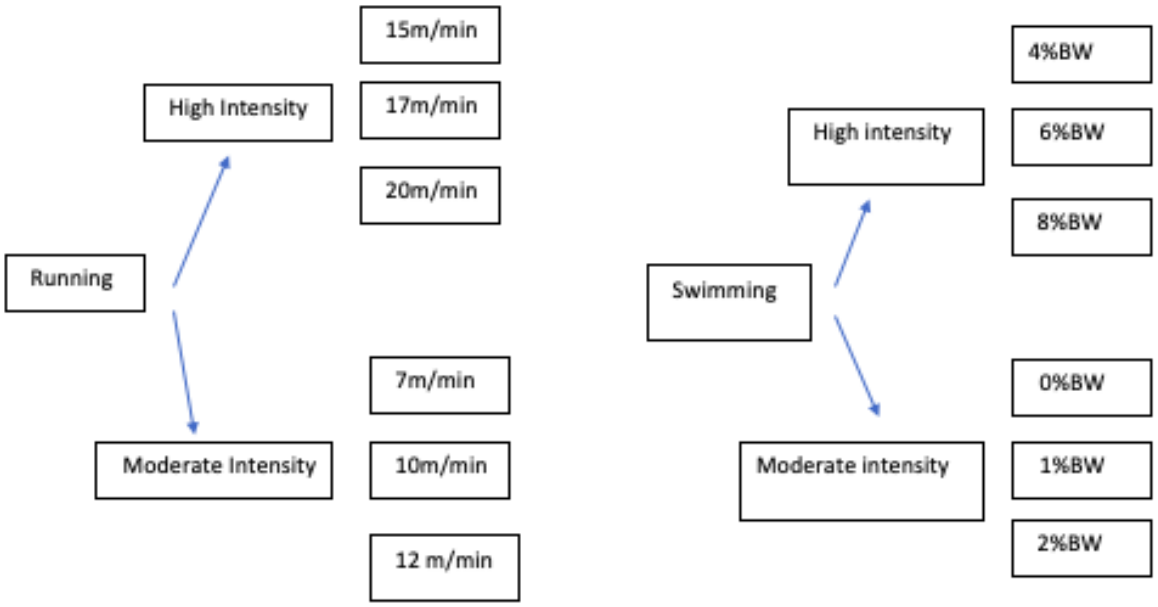
All procedures are approved by the 'Ethical Committee on Animal Experiments (ECAE)' from Hasselt University.

3.4. Intervention

3.4.1. Pilot experiment

Animals (n=10) have to complete 12 different training sessions, consisting of two different exercise modalities (forced treadmill running and forced swimming), each at moderate and high intensity. Exercise intensity will be set at 4%, 6% or 8% BW in the high intensity forced swimming program, and 0%, 1% or 2% BW in the moderate intensity forced swimming program. Exercise intensity will be set at 15, 17 or 20m/min in the high intensity forced treadmill program, and 7, 10 or 12m/min in the moderate intensity forced treadmill program. This results in an exercise program of 12 different exercise sessions. Order or exercise will be randomised and there will be a resting period of 48 hours between each session to minimise possible training effects. Each session will last 30 minutes, since this duration was also used in the study of Bernardes et al. (2016).

Blood lactate will be monitored pre and post exercise session, and after 15 minutes of exercise. These values of blood lactate will be used for matching a specific running speed with a percentage of BW in the main experiment. For example, if blood lactate level after 30 minutes of forced running at 20m/min matches the blood lactate level after 30 minutes of swimming with 8%BW attached to the animal's tail, these training intensities are selected for high intense training in the main experiment.



3.4.2. Main experiment

3.4.2.1. Disease induction

The Hooke Laboratories (MA, USA) protocol will be used for the induction of EAE. First, animals will be subcutaneously injected with 100 µL MOG/CFA antigen emulsion in the neck region, and another 100 µL in the lower back. Second, there will be an intraperitoneal injection of 100 µL pertussis toxin (PTX), followed by another 100 µL after 24 hours. After the exercise protocol, mice will be sacrificed by overdose injection of Dolethal (200 mg/kg BW, i.p.) (Xie et al 2019). In order to monitor the wellbeing, animals were sacrificed before ending of the exercise progam if they reached at least one out of five 'human endpoints' including: weight loss of >25% compared to maximum weight in combination with a daily clinical score of 4/5, dehydration in combination with a daily clinical score of 4/5, a score of 4/5 during more than two consecutive days, a score of 4.5/5, and a continuous roll of animals in their cages.

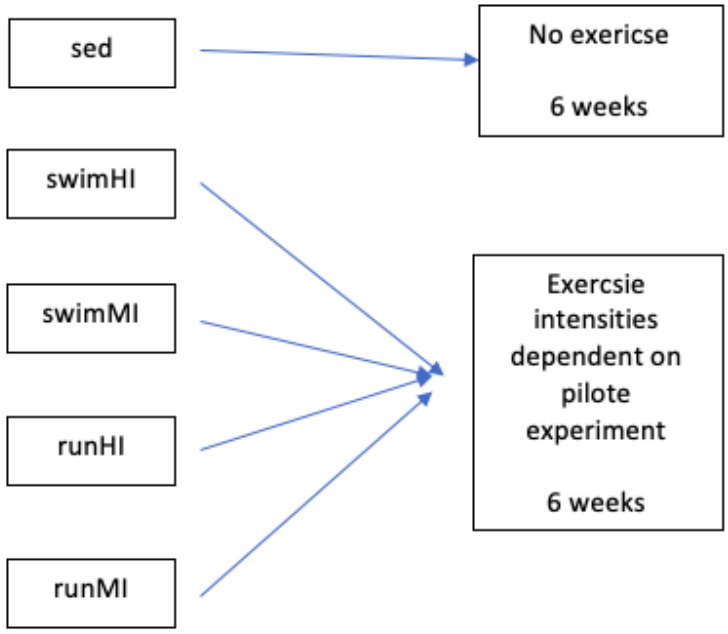
3.4.2.2. Design

Animals (n=60) will be randomly assigned to five different groups: sedentary (sed), high intensity swimming (swimHI), moderate intensity swimming (swimMI), high intensity treadmill running (runHI) and moderate intensity treadmill running (runMI).

Before exercise intervention, animals receiving the swimming program will be progressively adapted to the water for one week. Animals receiving the forced treadmill running program will also receive an adaptation period where intensity will be gradually increased from 5 to 15m/min over a period of one week.

Animals will be subjected to a six-week exercise program: five days per week, one session per day of 30 minutes (Einstein et al., 2018). This protocol of Einstein et al. was selected because this study showed the greatest reduction of peak score of all studies included in the systematic review. Animals in the swimHI-group and the runHI-group will exercise at the same exercise intensity, which will be determined in the pilot experiment. Animals in the swimMI-group and the runHI-group will also exercise at the same intensity. Exercise intensities will be based on the results of the pilot experiment, where intensities of swimming and running will be matched based on blood lactate levels. Since blood lactate will reach the highest values at the

end of each training session, values of blood lactate after each session will be used. EAE will be induced after five weeks of the exercise program, and animals will exercise for another week during the induction phase of the disease.



3.5. Outcome measures

3.5.1. Primary outcome measures

Daily clinical score, disease onset, peak score and peak onset will be assessed from day 1 to 42.

Daily Clinical score

Daily clinical score will be measured daily on a self-scored observation scale ranging from 0 to 5 by blinded assessors Different stages of clinical disability with their corresponding score can be consulted in Figure1.

Disease onset

Disease onset represents the day animals show their first clinical symptoms, which will occur 9 to 14 days after immunization according to Hooke's protocol.

Peak score

Peak score represents the highest value of the daily clinical score, which will be 3.0 to 3.5 in sedentary mice according to the Hooke's protocol. Peak score of exercise groups will be expected lower.

Peak onset

Peak onset represents the day animals reach their highest value of the daily clinical score.

3.5.2. Secondary outcome measures

Body weight

Body weight (BW) will change during both experiments. Animals will be weighted before and after each exercise session in the pilot experiment. BW will be measured every week during the exercise period of the main experiment

Blood lactate

Blood lactate level will be measured pre, post, and at 15 minutes of exercise in each training session of the pilot experiment. Values of blood lactate will be expected higher in high intensity exercise compared to moderate intensity. Blood lactate will be expressed in mmol/L.

3.6. Data-analysis

"SAS JUMP" statistical software will be used in the data-analysis, and level of significance will be set at $p<0,05$.

3.6.1. Pilot experiment

Repeated measures analysis of variance (rANOVA) will be used to compare the effects of different exercise intensities (independent variable) on blood lacate levels (depended variable). In this model, two assumptions must be applied. First, the dependent variable (blood lactate) has to be normally distributed, which can be checked with the Shapiro-Wilk test. Second, the order of training session has to be randomly distributed over the animals.

3.6.2. Main experiment

Mixed-factor ANOVA will be used to compare differences in daily clinical score, disease onset, peak score, peak onset and body weight in a running versus swimming exercise program at different intensities. In this model, dependent variables (daily clinical score, disease onset, peak score, peak onset and BW) have to be normally distributed. This can be checked by the Shapiro-Wilk test, and distribution of animals over the experiment groups also have to be randomised.

4. Time planning

- October 2019: ethical approval
- November – December 2019: implementation of pilot experiment
- January 2020: statistical analysis of results
- January – March 2020: implementation of main experiment
- March 2020: statistical analysis of results
- April – May 2020: Writing

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6. Appendix research protocol

Figure 1

Mouse EAE scoring guide

Score	Clinical observations
0.0	No obvious changes in motor function compared to non-immunized mice. When picked up by base of tail, the tail has tension and is erect. Hind legs are usually spread apart. When the mouse is walking, there is no gait or head tilting.
0.5	Tip of tail is limp. When picked up by base of tail, the tail has tension except for the tip. Muscle straining is felt in the tail, while the tail continues to move.
1.0	Limp tail. When picked up by base of tail, instead of being erect, the whole tail drapes over finger. Hind legs are usually spread apart. No signs of tail movement are observed.
1.5	Limp tail and hind leg inhibition. When picked up by base of tail, the whole tail drapes over finger. When the mouse is dropped on a wire rack, at least one hind leg falls through consistently. Walking is very slightly wobbly.
2.0	Limp tail and weakness of hind legs. When picked up by base of tail, the legs are not spread apart, but held closer together. When the mouse is observed walking, it has a clearly apparent wobbly walk. One foot may have toes dragging, but the other leg has no apparent inhibitions of movement. - OR - Mouse appears to be at score 0.0, but there are obvious signs of head tilting when the walk is observed. The balance is poor.
2.5	Limp tail and dragging of hind legs.

	Both hind legs have some movement, but both are dragging at the feet (mouse trips on hind feet). - OR - No movement in one leg/completely dragging one leg, but movement in the other leg. - OR - EAE severity appears mild when picked up (as score 0.0-1.5), but there is a strong head tilt that causes the mouse to occasionally fall over.
3.0	Limp tail and complete paralysis of hind legs (most common). - OR - Limp tail and almost complete paralysis of hind legs. One or both hind legs are able to paddle, but neither hind leg is able to move forward of the hind hip. - OR - Limp tail with paralysis of one front and one hind leg. - OR - ALL of: ere head tilting, king only along the edges of the cage, hing against the cage wall, ning when picked up by base of tail.
3.5	Limp tail and complete paralysis of hind legs. In addition to: Mouse is moving around the cage, but when placed on its side, is unable to right itself. Hind legs are together on one side of body. - OR - Mouse is moving around the cage, but the hind quarters are flat like a pancake, giving the appearance of a hump in the front quarters of the mouse.
4.0	Limp tail, complete hind leg and partial front leg paralysis.

	Mouse is minimally moving around the cage but appears alert and feeding. Often euthanasia is recommended after the mouse scores 4.0 for 2 days. However, with daily s.c. fluids most C57BL/6 mice may recover to 3.5 or 3.0, while SJL mice may fully recover even if they reach score 4.0 at the peak of disease. When the mouse is euthanized because of severe paralysis, a score of 5.0 is entered for that mouse for the rest of the experiment.
4.5	Complete hind and partial front leg paralysis, no movement around the cage. Mouse is not alert. Mouse has minimal movement in the front legs. The mouse barely responds to contact. Euthanasia is recommended. When the mouse is euthanized because of severe paralysis, a score of 5.0 is entered for that mouse for the rest of the experiment.
5.0	Mouse is spontaneously rolling in the cage (euthanasia is recommended). - OR - Mouse is found dead due to paralysis. - OR - Mouse is euthanized due to severe paralysis.

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KNOWLEDGE IN ACTION

VOORTGANGSFORMULIER WETENSCHAPPELIJKE STAGE DEEL 1

DATUM	INHOUD OVERLEG	HANDTEKENINGEN
19/11	Algemeen overleg B. op 't Eijnde	Promotor: Copromotor/begeleider: Student(e): Student(e):
3/12	1e overleg literature search	Promotor: Copromotor/begeleider: Student(e): Student(e):
14/12	overleg zoekstrategie	Promotor: Copromotor/begeleider: Student(e): Student(e):
21/12	overleg zoekstrategie Pubmed + WOS	Promotor: Copromotor/begeleider: Student(e): Student(e):
16/5	overleg data - extractie	Promotor: Copromotor/begeleider: Student(e): Student(e):
21/5	overleg tekst t.e.m methode + tabel exclusie	Promotor: Copromotor/begeleider: Student(e): Student(e):
27/5	overleg tekst results + aanpassen data-extractie	Promotor: Copromotor/begeleider: Student(e): Student(e):
3/6	overleg discussie + tekst	Promotor: Copromotor/begeleider: Student(e): Student(e):
10/6	overleg protocol	Promotor: Copromotor/begeleider: Student(e): Student(e):
	Niet-bindend advies: De promotor verleent hierbij het advies om de masterproef WEL/NIET te verdedigen.	Promotor: Copromotor/begeleider: Student(e): Student(e):

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3590 DIEPENBEEK

12/6/2018

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