Suitability of High-Intensity Interval Training for people with Multiple Sclerosis

A scoping review

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Master's thesis
January 2025
Master's Degree of Sport and Exercise Physiotherapy

Jyväskylän ammattikorkeakoulu
University of Applied Sciences

jamk

Description

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Suitability of high-intensity interval training for people with multiple sclerosis, a scoping review

Jyväskylä: Jamk University of Applied Sciences, December 2024, 57 pages

Degree Programme in Sport and Exercise Physiotherapy. Master's thesis.

Permission for open access publication: Yes

Language of publication: English

Abstract

For years, people with multiple sclerosis (pwMS) were told to avoid physical activity and exercising due to risk of symptom exacerbation. Nowadays exercise is essential part of rehabilitation and clinical management of the disease. Nevertheless, recommended intensity has generally been restricted to moderate-level at highest.

High-intensity interval training (HIIT) has become fundamental part of endurance athletes' training. Larger volume of training at high-intensity and needed boost for performance is enhanced with HIIT. Several benefits of HIIT have also been found in health context. For example, reduction in post-operative complications and decreased risk of cardiovascular disease have been reported.

Aim of the study was to find out suitability of high-intensity interval training for pwMS. Objectives were to explore possible benefits and adverse effects of HIIT for pwMS. Finally, a recommendation of suitable HIIT-program for pwMS was formed.

Scoping review approach was chosen to gather existing evidence of the subject. Data search for the review covered four databases: Cinahl, Pubmed, Medline and Cochrane. Eight articles were finally included from the official datasearch and one from manual search covering author's own archives. Data was then extracted by using an extraction table in Excel.

Increased cardiorespiratory fitness, improvements in parts of cognitive performance and anti-inflammatory and neuroprotective changes in serum biomarkers were beneficial effects of HIIT for pwMS. In addition, HIIT generated sense of achievement, improved energy levels and ability to cope. Conflicting results indicated that HIIT might reduce fatigue or at least not worsen it. On the other hand, overexertion, symptom exacerbation and nausea were adverse effects experienced when participating in HIIT intervention. HIIT can be concluded to be suitable exercise modality for some pwMS although risk for short-term discomfort and symptom exacerbation exists. Appropriate intensity is 85-100% of HRmax or 70-90% of peak power (RPE=hard or very hard) for work bout and 50-60% of HRmax or 0-50% of peak power (RPE=very comfortable) for rest interval.

Keywords/tags (subjects)

Multiple sclerosis, people with multiple sclerosis, high-intensity interval training, benefits, adverse effects, scoping review

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List of appreviations

CIS	clinically isolated syndrome
CNS	central nervous system
CRF	cardiorespiratory fitness
CSF	blood-cerebrospinal fluid
HIIT	high-intensity interval training
HR	heart rate
ICF	International Classification of Functioning, Disability and Health
JBI	Joanna Briggs Institute
PPMS	primary progressive multiple sclerosis
pwMS	people with multiple sclerosis
MICT	moderate-intensity continuous training
MS	multiple sclerosis
MSIF	Multiple Sclerosis International Federation
RIS	radiologically isolated syndrome
RPE	rate of perceived exertion
RRMS	relapsing-remitting multiple sclerosis
SPMS	secondary progressive multiple sclerosis
VO2 max	maximal oxygen consumption

1 Introduction

Exercising has become important part of management and treatment of many neurological diseases. Benefits of exercising in the context of neurological diseases are better acknowledged nowadays. Regular long-term exercise is known to support and enhance well-being, health and functioning of people with neurological diseases in many ways. (Neuroliitto, 2024a.)

Rehabilitation and training of people with multiple sclerosis (pwMS) has conventionally been low or at most moderate in intensity. Physicians instructed to avoid exercising and this practice lasted for years (Halabchi et al., 2017, p. 2). Nowadays regular exercise is recommended as essential part of clinical management of the disease (Richardson et al., 2020, pp. 1–2). Recently the question of suitability of more intense training modes, including high intensity interval training (HIIT), has risen and become under research. This thesis reviews existing research of this subject.

People with MS (pwMS) seem to have decreased aerobic capacity and cardiorespiratory fitness (CRF). When comparing to healthy controls, pwMS had approximately 30% lower VO^2max or maximal oxygen consumption. (Halabchi et al., 2017, p. 2.) Casey et al. (2018, p.1966) also reported lower levels of physical activity among pwMS when compared to general population. Thus, HIIT can be important and good way to train for pwMS and improve their cardiorespiratory fitness. Overall, the goal of this thesis is to map possible benefits and adverse effects of HIIT for pwMS. This is done by undertaking a scoping review of the subject.

Outcome of the thesis can benefit pwMS by offering one more exercise-option and diversifying training or rehabilitation. Thesis can also be beneficial for (physio)therapists as it helps them to make evidence-based decision of application of HIIT in rehabilitation with pwMS. Subject of the thesis is particularly relevant for those pwMS who are used to being active and have exercised vigorously before MS-diagnosis. This might cover large portion of pwMS as the average onset of the disease happens around 30 years which generally is active time of life (Dendrou et al., 2015, p. 545; The Multiple Sclerosis International Federation [MSIF], 2020, p. 25).

The commissioner of the thesis is Suomen Aikuisneurologinen Fysioterapiayhdistys Ry (Finnish Adult Neurological Physiotherapy Association). The goal of the association is to bring adult's neurological physiotherapy more visible and offer high-quality education concerning adults' neurological physiotherapy. Sanfy also connects those interested in adult's neurological physiotherapy, follows research of the subject and develops the field. (Suomen Aikuisneurologinen Fysioterapiayhdistys ry, n.d.)

Purpose of this thesis is to find out if HIIT is suitable training modality for pwMS. This will be fulfilled by gathering and reporting evidence of the effects of HIIT among pwMS by using a scoping review as method. Based on the findings, objective is also to form a recommendation of suitable HIIT-program for pwMS.

2 Multiple sclerosis

2.1 Definition and statistics

Multiple sclerosis (MS) is a chronic neurological disease where neuroinflammation causes demyelination in central nervous system (CNS). MS affects about 2.8 million people worldwide and causes serious physical disability especially among young women. The disease tends to begin around the age of 30, during phase of life that is commonly important for career and family planning. (Dendrou et al., 2015, p. 545; MSIF, 2020, pp. 21, 25.) Multiple sclerosis is progressive disease and leads to approximately 50% of patients using wheelchair permanently by 25 years from diagnosis (Dendrou et al., 2015, p. 545). Prevalence of MS is increasing in both developed and developing countries, but it varies geographically. Highest rates are reported in the Americas and Europe whereas lowest in Africa and Western Pacific region. There seems to be a link between prevalence of MS and latitude; closeness to equator lowers the risk of MS. This is potentially because of exposure to sunlight and gaining more vitamin D. Estimation of mean incidence rate of multiple sclerosis is 2.1/100,000 per year. Lack of data and inconsistent reporting prevents stating whether the incidence is truly increasing or not. (MSIF, 2020, pp. 21–23.)

It is estimated that currently there are over 12 000 pwMS in Finland (Neuroliitto, 2024b). According to research from national register (Laakso et al., 2019, p. 1), crude prevalence was 180-200/100 000 in 2018 and it peaked at 50-54 years.

2.2 Pathophysiology and risk factors

The exact cause of multiple sclerosis is still unclear and pathophysiological processes behind the disease are complicated and multicellular. Onset of MS is thought to be sum of genetic predisposition, random events and environmental factors. (Dendrou et al., 2015, pp. 546, 551.) Different processes seem to drive different phases of the disease so that pathophysiology of the disease evolves along its course. Inflammation causes onset and relapses and other process drives chronic progression and neurodegeneration. (Dendrou et al., 2015, pp. 547, 551; Jakimovski et al., 2024, p. 190.) Although pathological inflammatory changes are present also in progressive multiple sclerosis, they are more prevalent in relapsing-remitting form (RRMS) and acute phases (Dendrou et al., 2015, p. 547; Dobson & Giovannoni, 2019, p. 29). RRMS can be said to be inflammation dominant phase or subtype and progressive MS neurodegeneration dominant phase/subtype of the disease. The composition of inflammatory infiltrate is similar in these forms, but there are differences in proportions of B- and plasma-cells. (Dobson & Giovannoni, 2019, p. 29.) T and B lymphocytes are said to be the key driver in MS-pathogenesis and contribute especially to focal lesions and clinical relapses. T cells seem to shift from normally reacting immune cells into autoimmune state. (Jakimovski et al., 2024, pp. 188, 190.)

Inflammatory process appears to be triple factorial process involving:

1. Infiltration of peripheral immune cells (T and B cells, macrophages) into CNS.
2. Activation of autoreactive lymphocytes in blood-cerebrospinal fluid (CSF).
3. CNS's innate macrophages rising inflammation inside the CNS itself. (Dendrou et al., 2015, 547; Dobson & Giovannoni, 2019, pp. 28–29.)

This process leads to damage to the CNS including variable loss of myelin, oligodendrocytes and axons (Jakimovski et al., 2024, p. 188). In addition to autoreactive T and B cells, progression of multiple sclerosis is due to defective regulatory cells. Dysfunction of effector-regulatory cell interaction is detected in pwMS and this leads to emergence of autoreactive adaptive immune cells and infiltration of these into CNS. This dysfunction can be due to inadequate suppression capacity of regulatory cells, decreased frequency of the regulatory cells or increased resistance of effector cells to suppression mechanisms. (Dendrou et al., 2015, pp. 552–554.)

Inflammation causes the key feature of multiple sclerosis which is the process of demyelination happening in white and grey matter of CNS (Dendrou et al. 2015, p. 547). Demyelinated sites in brain and spinal cord are called plaques which can be classified into active, chronic active and chronic inactive plaques. Whereas active and chronic active plaques are characterized with densely populated phagocytic cells, chronic inactive plaques lack relevant active myelin degradation although number of myelin-forming oligodendrocytes is lower in them. Remarkable gliosis (sclerosing) is characteristic feature in chronic inactive plaques. (Jakimovski et al., 2024, p. 188.) Active lesions are more typical in RRMS as it is inflammation-dominant phase or type of the disease. In progressive form of the disease, lesions dominantly have an inactive core surrounded by rim of activated microglia and macrophages. Remyelination (creating shadow lesions) is plausible and in all stages of the disease, but these remyelinated axons might remain functionally defective. (Dobson & Giovannoni, 2019, pp. 28–29; Jakimovski et al., 2024, p. 189.)

Although neurons and axons are mostly preserved at early stages, they end up being affected as the disease progresses and increasingly destructive inflammatory milieu keeps overriding body's buffering mechanisms. It can be said that there happens a shift from initial inflammation and autoimmune response into CNS-innate inflammation and finally self-sustaining chronic neurodegeneration. (Dendrou et al., 2015, pp. 547, 553–554.) Hence, brain atrophy and neurodegeneration in multiple sclerosis can progress without obvious inflammation (Dendrou etl al., 2015, p. 554; Dobson & Giovannoni, 2019, p. 34). The process includes CNS-resident cells initiating oxidative stress responses which end up causing mitochondrial injury and dysfunction, metabolic stress, protein misfolding in endoplasmic reticulum, energy deficiency and loss of neuronal fitness. (Dendrou et al., 2015, p. 553.) Inhibition of remyelination and disruption of neuroprotective mechanisms enhances the process. (Dendrou et al., 2015, p. 554; Jakimovski et al. 2024, p. 190.) Neurodegeneration also involves redistribution of ion channels as an attempt to preserve homeostasis. Unfortunately, this redistribution and excess accumulation of excitatory neurotransmitter glutamate from neuronal injury lead to increased ionic imbalance which further advances tissue damage. The process of degeneration can spread backwards towards neuronal cell body (retrograde degeneration) or forwards toward distal axon terminal (anterograde degeneration). Spreading can also reach nearby pre- or postsynaptic neurons and eventually cause neuronal apoptosis or necrosis. (Dendrou et al., 2015, p. 553.)

2.2.1 Risk factors

In multiple sclerosis, genetic factors are thought to bear around 30% of overall disease risk (Dendrou et al., 2015, p. 546). Although this genetic influence is smaller than environmental one, genetic factors are better known and knowledge of these keeps increasing. Genome-wide association studies have found over 200 genetic variants that are linked to multiple sclerosis risk. Most of these are affecting peripheral immune cell pathways and resident microglia. Thus, genetic risk factors work as triggers of autoreactivity and in broader scale as modulators of immune cell activation thresholds. Nevertheless, heritability of the disease requires polymorphism in many genes and each variant carries only small portion of total risk. (Dendrou et al., 2015, pp. 546–547, 550; Dobson & Giovannoni, 2019, p. 28; Jakimovski et al., 2024, p. 188)

Environmental risk factors thought to contribute to onset of multiple sclerosis are those affecting the same immunological pathways that genetic factors do. For example, viral and microbial factors can trigger autoreactive T cells through molecular mimicry. Low serum levels of vitamin D, human cytomegalovirus infection and circadian disruption are environmental factors that have been variably linked to multiple sclerosis. Also, childhood obesity, ultraviolet B light exposure and diet-related changes in gut microbiome have been reported to increase the risk for multiple sclerosis. Best confirmed contributors are smoking and Epstein-Barr virus infection. (Dendrou et al., 2015, p. 550; Dobson & Giovannoni, 2019, pp. 27–28.) Jakimovski et al. (2024, p. 188) also mention that EBV and other viral infections could work as triggers for susceptibility genes that influence pathological processes. Smoking, among some other lifestyle risk factors, can contribute to faster disease progression and decreased disease-modifying therapies' effectiveness (Jakimovski et al., 2024, p. 188).

2.3 Diagnosis

There is still lack of single MS-typical clinical feature or diagnostic test to confirm MS diagnosis. Hence the diagnosis is an integration from typical symptoms and examination findings which include clinical, imaging and fluid indicators. McDonald diagnostic criteria (figure 1) is widely used additional criteria in diagnosis when there is strong suspicion of multiple sclerosis. (Thompson et al. 2018, p. 164.) Finnish Current Care guideline for MS states that McDonald criteria must be fulfilled in order to MS-diagnosis to be made (MS-tauti: Käypä hoito -suositus, 2024).

McDonald criteria in Multiple Sclerosis.

Attacks	Number of lesions with objective clinical evidence	Additional Criteria for diagnosis of MS
≥2	≥2	None
≥2	1	DIS: further attack or MRI
1	≥2	DIT: further attack or MRI or OB
1	1	DIS and DIT
0 progression from onset		One year of disease progression and 2/3: • Cranial ≥1 lesions: periventricular, cortical / juxtacortical or infratentorial • Cord ≥2 lesions • Positive cerebrospinal fluid

Figure 1. McDonald criteria for diagnosis of multiple sclerosis (copied from McNicholas et al., 2018, p. 49)

Because of different characteristics of subtypes of MS, there are also differences in diagnostic process. According to Finnish Current Care Guideline for multiple sclerosis, a diagnosis of relapsing-remitting MS (RRMS) requires a presence of attack period which is also called clinically isolated syndrome (CIS) if being first episode. This means an episode in which the symptoms originate neuroanatomically from CNS without presence of fever or infection and last minimum of 24 hours. (MS-tauti: Käypä hoito -suositus, 2024; Thompson et al., 2018, p. 163.) Diagnosis of primary progressive MS (PPMS) is more time consuming and requires steady progress of symptoms and disability from the onset without obvious relapse periods for at least a year. In addition, at least two of three of next criteria must be fulfilled 1) at least one cortical or juxtacortical, periventricular or infratentorial lesion 2) at least two spinal lesions 3) positive oligoclonal band finding. (MS-tauti: Käypä hoito -suositus, 2024.) Furthermore, Thompson et al. (2018, p. 164) emphasize the importance of careful differential diagnosis before confirming any MS-diagnosis. This is to avoid common issue of misdiagnosis of multiple sclerosis that is result of several factors such as heterogeneity of both clinical and imaging manifestations of the disease and lack of single feature or diagnostic test for the disease.

Brain and spinal cord MRI are important paraclinical tests in diagnosis of multiple sclerosis. Brain MRI is recommended to be obtained in all suspected MS-patients. In some cases, it is justified to use also a spinal MRI. (Thompson et al., 2018.) MRI helps to determine dissemination in space (development of lesions in multiple places in CNS) and dissemination in time (development of new lesions within CNS over time) which are essential for diagnosis. It also allows recognizing MS mimics when experienced professional is doing the interpretation. (Dobson & Giovannoni, 2019; Thompson et al., 2018.) Fluid biomarkers are important addition to diagnosis and prognosis of multiple sclerosis. They can increase diagnostic confidence by supplementing insufficient clinical and MRI evidence. (Jakimovski et al., 2024; Thompson et al., 2018.)

2.4 Subtypes of multiple sclerosis

Several subtypes of the disease can be recognized according to general patterns in disease presentation (Dendrou et al., 2015, p. 546). Three main subtypes that are presented in this thesis are relapsing-remitting (RRMS), secondary progressive (SPMS) and primary progressive (PPMS). RRMS is the most common form and it affects about 85-90% of MS-patients. Presentation of this subtype involves recurring relapses after which clinical recovery occurs during a period called remission. (Dendrou et al., 2015, p. 546; Jakimovski et al., 2024, p. 185; MS-tauti: Käypä hoito -suositus, 2024.) During a relapse, new neurological symptoms appear, or existing symptom gets worse slowly over hours to days (Jakimovski et al. 2024, p. 185; MS-tauti: Käypä hoito -suositus, 2024). Relapse involves inflammatory reaction in central nervous system (CNS) and often detectable demyelination. To be accounted as relapse period, the symptom or symptoms have to last at least 24 hours, and they shouldn't be caused by confounding factors like ongoing infections. Finnish Current care guideline for MS still states that physiological stress from infections and other diseases may expose for relapse. (Dendrou et al., 2015, p. 546; Jakimovski et al., 2024, p. 185; MS-tauti: Käypä hoito -suositus, 2024.) Usually, these symptoms increase or plateau for several weeks before gradual recovery begins. Some damage can remain after relapse, for example visual deficits or abnormalities after optic neuritis. (Dobson & Giovannoni, 2019, p. 29.)

Finally, the disease progresses, remissions bring less improvements, and disability accumulates as neurons lose their reserve (Dobson & Giovannoni, 2019, p. 29). Due to this, the disease develops into secondary progressive form in time course of 10-20 years from diagnosis (Dendrou et al., 2015, p. 546; Jakimovski et al., 2024, p. 185). Previously this happened to 50-80% of people with RRMS (Dendrou et al., 2015, p. 546; Jakimovski et al., 2024, p. 185), but nowadays the proportion is considerably lower, 15-20%. This is probably because of improved capability to diagnose MS at earlier stages and start required disease-modifying therapies. (Jakimovski et al., 2024, pp. 185, 187.) In the SPMS, neurological deterioration is a result of CNS atrophy instead of inflammatory lesions (Dendrou et al., 2015, p. 546). Overall, as Jakimovski et al. (2024, p. 185) specify, long-term disease worsening (even before transition into secondary progressive stage), is due to activity-free progression. Hence, disability progression can't be predicted by frequency of relapses or signs of disease activity. Secondary progressive subtype is characterized with fluctuating symptoms which, among other factors like age-related functional decline, slows down the reclassification. (Jakimovski et al., 2024, p. 187).

Third recognizable form of MS is primary progressive disease affecting approximately 5-15% of patients (Dendrou et al., 2015, p. 546; Dobson & Giovannoni, 2019, p. 29; Jakimovski et al., 2024, p. 187). This form is characterized by progressive decline without distinct relapse periods right from the onset. There is usually one dominant neuronal system affected. (Dendrou et al., 2015, p. 546; Dobson & Giovannoni, 2019, p. 29.) It is actually uncertain if this form should be separated from secondary progressive form and classified as independent subtype of MS (Dobson & Giovannoni, 2019, p. 29; Jakimovski et al. 2024, p. 187). According to Jakimovski et al. (2024, p. 187) people might be experiencing long prodromal and undiagnosed stage which reaches secondary progressive phase before the diagnosis is made. To support this, Dobson & Giovannoni (2019, pp. 28–29) suggest that MS should be seen as one disease where different subtypes present different points on a continuum. On the other hand, they report how research has recently found genetic differences between RRMS and PPMS. Furthermore, Dendrou et al. (2015, p. 546) contemplated in their paper that improved characterization of different subtypes or presentations could justify classification of these into different diseases. This variable feature/nature of the disease poses pressure on accuracy of diagnosis since different forms can have shared but also distinct pathophysiological mechanisms behind them and these have implications on therapeutic targeting. (Dendrou et al., 2015, p. 546.)

2.5 Symptoms and functioning

Symptoms of multiple sclerosis can be diverse and early signs can actually show up even a decade before diagnosis. Retrospective data from Canada shows that preceding the diagnosis, pwMS had more hospital admissions, physician claims and prescriptions than people without MS. Similar data from UK reports increases (higher rates than matched controls) in health care usage 10 years before official diagnosis. Common reasons for these visits were for example fatigue, insomnia and pain. Even people with radiologically isolated syndrome, (RIS, MRI showing lesions typical for multiple sclerosis but lacking the clear neurological symptoms) can have increased prevalence of headaches, greater cognitive impairment or slower manual dexterity. For 20-50% of people with RIS, the condition transitions into actual multiple sclerosis over 5 years. Trials are still ongoing for finding out if treatment could prevent this transition. (Jakimovski et al., 2024, pp. 183–184.)

Unilateral optic neuritis, brainstem-, cerebellar- and spinal cord syndromes are most common signs when a person is experiencing first ever relapse-period (Dobson & Giovannoni, 2019, p. 29; Thompson et al., 2018, p. 163). Clinically these syndromes can present themselves as a decrease in visual acuity and tenderness with eye movement, unilateral sensory deficits or weakness, balance disturbance and double vision for example. Most common early symptom in PPMS is spastic paraparesis causing walking and balance difficulties. (MS-tauti: Käypä hoito -suositus, 2024.) Variety of symptoms that are involved with multiple sclerosis along the disease course can be seen in figure 2.

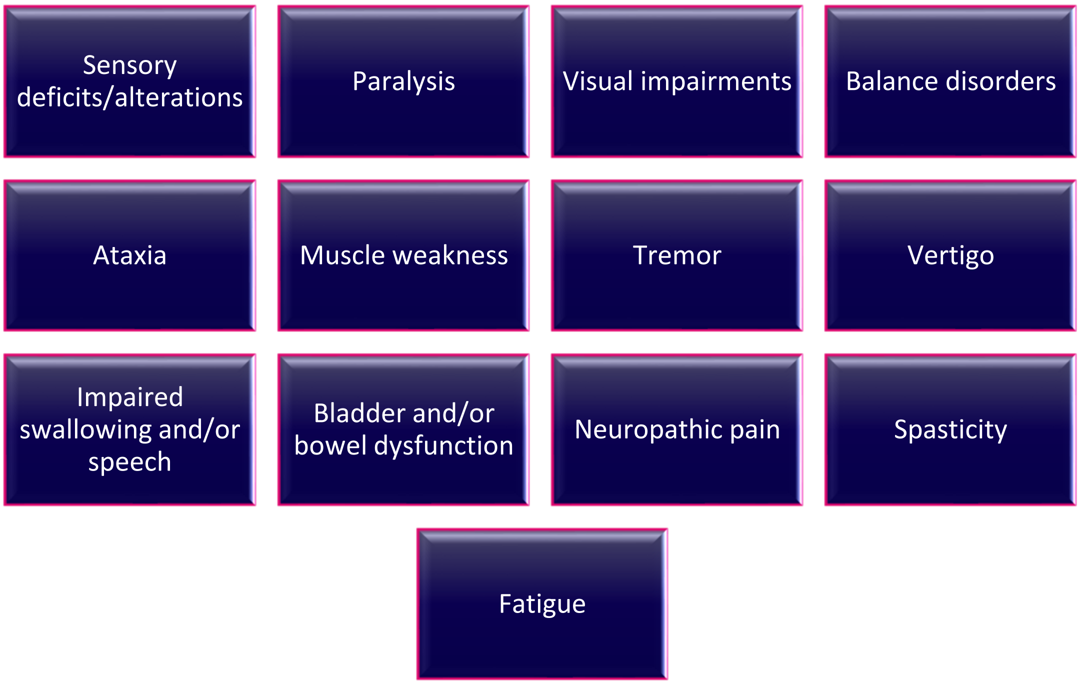

Figure 2. Symptoms of multiple sclerosis (Halabchi et al., 2017, p. 2; MS-tauti: Käypä hoito -suositus, 2024)

As many of these symptoms impact on functioning, it is not surprising that about 50% of pwMS end up using movement aid following 15 years from the disease onset and wheelchair permanently by 25 years from the beginning of the disease. (Dendrou et al., 2015, p. 545; Halabchi et al., 2017, p. 2.) Extended disability severity scale (EDSS), developed by neurologist John Kurtzke, is an indicator that is used to assess and follow disability progression of pwMS. The scale has ten levels (0-10) where level 0 refers to no disability in any functional system and level ten indicates a death that is related to MS. Appendix 1 shows the whole EDSS scale. (Multiple Sclerosis Trust, 2024.)

One common and significant consequence of multiple sclerosis is cognitive impairment. This can develop at very early stage of the disease, even in radiologically isolated syndrome. (Jakimovski et al., 2024, p. 187.) Dobson and Giovannoni (2019, p. 30) actually report that children who are later diagnosed with MS perform worse at school and even quarter of people with RIS present similar cognitive deficit than people with diagnosed MS. Cognitive impairment has significant negative impact on person's life since it can affect on employment status, social life/personal relationships and driving fitness. It is also linked to depression and anxiety. Among people with RRMS prevalence of cognitive deficit is around 30-40% but in the case of PPMS it is even up to 70%. Areas of cognitive performance that are often affected by multiple sclerosis are information processing speed, working memory and episodic memory. Less common ones are higher executive function, verbal fluency, and visual-spatial processing. (Jakimovski et al., 2024, p. 187.)

When reflected through International Classification of Functioning, Disability and Health (ICF), there are in total 138 categories included in ICF core set for multiple sclerosis which means that these are possible areas that MS can be involved with. These related categories cover 40 different body functions, seven body structures, 53 different aspects of activities and participation, and 38 environmental factors. (ICF Research Branch, 2017.)

Holper et al. (2010) further investigated relationship between MS and ICF. In their study, more than 5% of pwMS reported 129 ICF categories (of total 156) they had problems with. These included 34 'Body functions', 13 'Body structures', 51 in 'Activities and participation' and 31 in 'Environmental factors'. Over 50% of pwMS identified challenges in 10 categories related to gait and movement including 'Muscle power functions', 'Gait pattern functions', 'Structure of lower extremity' and 'Structure of upper extremity'. Many reported problems with four ICF categories related to urinary functions and structures, and sexual or reproductive functions and structures. Also, cognitive and psychological areas were included which was reflected in eight ICF categories. For example, attention-, emotional-, memory- and higher-level cognitive functions were mentioned. Regarding ICF category of activities and participation, limitations in 'Recreation and leisure', 'Community life', 'Remunerative employment' and 'Intimate relationships' seemed to be common. In ICF component 'Environmental factors', participants reported almost every category being either a facilitator or a barrier. Yet, notable point is that most of the environmental factors were experienced as facilitators. These included 'Immediate- 'and 'Extended family', 'Friends' and 'Health professionals'. 'Climate' was most frequently reported as a barrier by participants. There were differences between three main MS subtypes (RRMS, SPMS and PPMS); problems and limitations were more common among people with secondary progressive MS which responds to this form being a phase/type dominated by neurodegeneration and increasing disability.

2.6 Treatment

There are two categories of treatment for multiple sclerosis; disease-modifying therapies (DMTs) and symptomatic therapies (Dobson & Giovannoni, 2019, p. 34). DMTs are able to decrease disease activity including relapse-rate and short-term increase of disability when administered during relapse. There is also strong evidence for DMTs delaying long-term disability progression. (Jakimovski et al., 2024, p. 1.) The aim in the treatment of active MS-disease is to reach remission within first years (MS-tauti: Käypä hoito -suositus, 2024). Classical disease-modifying therapies are immunosuppressant or immunomodulatory and require on-going intake for the inflammation to remain suppressed. More novel therapies, immune reconstitution therapies, aim to produce long-lasting effects already when given as short courses. (Dobson & Giovannoni, 2019, p. 34) For the treatment of PPMS, only one approved drug exists (Jakimovski et al., 2024, p. 193).

Symptomatic therapies include pharmaceutical and physical therapies that aim to manage/alleviate symptoms following from CNS damage (eg. spasticity, fatigue, pain and bladder dysfunction). They are not MS-specific but several of them have been licensed specifically for MS. In addition, managing comorbid diseases such as hypertension and diabetes can further benefit pwMS. (Dobson & Giovannoni, 2019, p. 37; Jakimovski et al., 2024, p. 197)

2.7 Multiple sclerosis and exercise

Benefits of exercising for pwMS include managing symptoms, restoring function and enhancing quality of life and participation in activities of daily living (Motl et al., 2017, p. 854). Exercise is sub-category of physical activity and it is planned, structured, repetitive and it aims to improve or maintain physical fitness, performance or health. Physical activity is defined as movement that re-quires energy expenditure and is produced by skeletal muscles (Office of Disease Prevention and Health Promotion, 2018.) Neuroliitto states that people with neurological diseases can basically participate in almost any kind of exercise. Nevertheless, individual features of the disease, symp-toms and baseline fitness should be considered. (Neuroliitto, 2024a.) Examining the effectiveness of controlled exercise regimens in pwMS is increasingly popular in research field (Jakimovski et al. 2024, p. 197). Exercise can affect positively on for example physical capacity of pwMS and possibly even symptoms like fatigue (Latimer-Cheung et al., 2013, p. 1822). Hence it is essential for clinical management of MS-disease (Richardson et al. 2020, pp. 1–2) and is especially a key component of proper self-care (MS-tauti: Käypä hoito -suositus, 2024). Evidence suggests that pwMS should ex-ercise at least according to general health recommendations (3x at least 30min/week) care. (MS-tauti: Käypä hoito -suositus, 2024). It seems that even large doses of exercise don’t exacerbate the disease (MS-tauti: Käypä hoito -suositus, 2024) and for example Dobson& Giovannoni (2019, p. 37) recommend 4-5 sessions of aerobic exercise in a week. According to guidelines of Kim et al. (2019, p. 6), 2-3x 10-30min/week of moderate-intensity aerobic training and 2-3x/week of resistance training consisting of 5-10 exercises with 1-3 sets between 8 to 15 repetition maximum is generally recommended for pwMS. Vigorous exercise on the other hand, is not recommended during re-lapse due to possibly excessive energy demand for already compromised pathway which then could theoretically lead to increased neuroaxonal loss. Overall, “patients who exercise do better than those who do not”. (Dobson & Giovannoni, 2019, p. 37).

Regardless of existing evidence showing the benefits of exercising in pwMS, physical activity levels have remained low among them. Amount by which pwMS engage in physical activity is similar to those with other chronic diseases. Interestingly, pwMS seem to exercise less than people with such clinical conditions as stroke or spinal injury. (Kinnett-Hopkins et al., 2017, p. 42.) In particular, participating in moderate-to-vigorous exercise is lower to general population (Klaren et al., 2013, pp. 2346–2347). Marrie et al. (2009, p. 108) report that as disability increases, intensity of physical activity decreases. Findings of Motl et al. (2008, p. 141) are similar as they discovered relationship/association between worsening symptoms and decreased levels of physical activity. Limiting activities exposes to deconditioning and this seems to lead to increased disability and disuse-related muscle weakness. Compared to healthy controls, pwMS seem to have even 30% lower cardiorespiratory fitness (CRF). (Gallien et al., 2007, pp. 373, 375; Halabchi et al., 2017, p. 2.) This might explain at least partially the increased risk of pwMS for different chronic, physical inactivity related comorbidities including cardiovascular disease, chronic lung disease, obesity and type 2 diabetes (Halabachi et al., 2017, p. 2; Heine et al., 2016, p. 231; Marrie et al., 2015a, p. 327; Marrie et al., 2015b, p. 338; Wens et al., 2013, p. 1562). Another phenomenon increasing risk of comorbidities is adaptation of adverse health behaviors that occurs frequently among pwMS (Marrie et al., 2009, p. 109).

Compliance doesn't seem to be the issue as most pwMS participating in randomized trials have been able to complete the prescribed structured regimen (Motl et al., 2017, p. 851; Pilutti et al., 2014, p. 6). Main barrier for exercising and living active life appears to be fear of symptoms exacerbation (Gallien et al., 2007, p. 373; Halabchi et al., 2017, p. 2; Pilutti et al., 2014, p. 3). However, exacerbation is rather rare as mentioned before (MS-tauti: Käypä hoito -suositus, 2024). Furthermore, occurrence of adverse and serious adverse events (safety profile for exercise) is similar for pwMS and general population of adults and also risk for relapse doesn't seem to increase from exercising (Pilutti et al., 2014, p. 6). Nevertheless, rising body temperature can cause an Uthoff symptom in which existing neurological symptoms are temporarily emphasized as the conduction speed of neurons decreases. This is harmless and temporary as it wades off with decreasing body temperature. (MS-tauti: Käypä hoito -suositus, 2024.)

Learmonth and Motl (2016, p. 1235) list several different environmental, social, health- and cognition & behaviour-related barriers for physical activity among pwMS. Unsuitable facilities and surroundings including inappropriate temperature, and inappropriate exercise are some of common environmental barriers mentioned by them/the authors. Social barriers include for example bad/poor quality advice for exercising from healthcare professionals and social isolation. Personal level barriers for being physically active cover most typically fatigue and symptom fluctuations (related to health condition) and such cognitive and behavioural issues as fear and apprehension, poor self-management and loss of self-control. (Learmonth & Motl, 2016, p. 1235.)

Figure 3 shows benefits of exercising in more detail. Physical activity can also prevent or improve some comorbidities and impairments related to MS (Dalgas et al., 2008, p. 36; Motl et al., 2017, p. 851). There also exist some evidence of disease-modifying properties of exercising (Dalgas & Stenager, 2012, p. 89). This still needs more evidence as quality of only a few studies of this subject are heterogenous (Proschinger et al., 2022, pp. 2922, 2929, 2935–2936). Also the study of Schlagheck et al. (2023, p. 04) shows that being physically active is related to lower disability severity and fatigue. This supports the slowing/postponing effect of exercising on disease progression. However, physical activity didn't correlate with/decrease annual relapse-rate in this study.

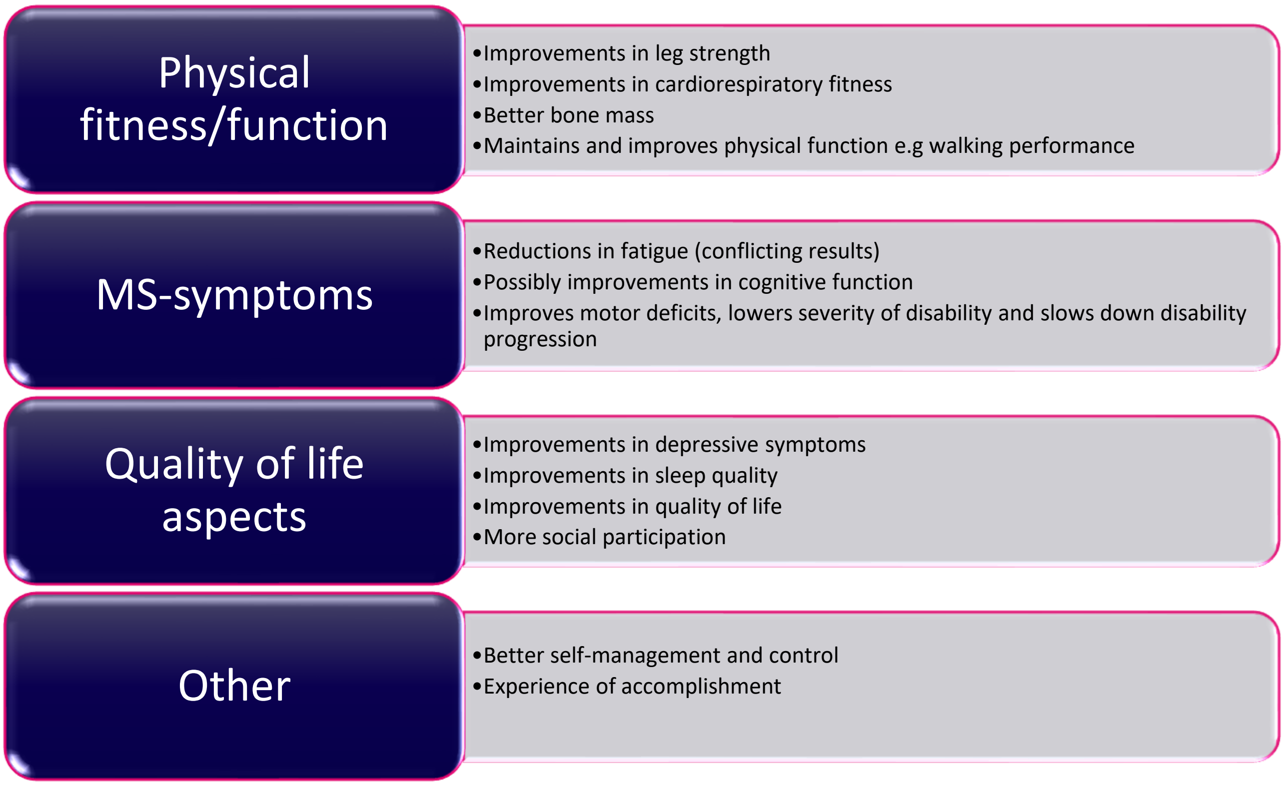

Figure 3. Benefits of exercising for pwMS (Halabchi et al., 2017, pp. 2-4; Heine et al., 2019, p. 4; Learmonth & Motl, 2016, p. 1234; Motl et al., 2017, pp. 848–851; Pearson et al., 2015, p. 1345; Schlagheck et al., 2023, p. 04)

Physical activity still doesn't come without disadvantages or adverse effects. Uthoff symptom mentioned earlier can be imagined being uncomfortable experience no matter of being harmless and temporary. In addition, Learmonth and Motl (2016, p. 1234) mention various other unfavourable consequences of exercise or physical activity. These include physical effects like increased fatigue, non-specific symptom worsening and relapse, and muscle soreness and self-evaluative effects like frustration and lost control. Overall, physical activity and exercising can still be seen as beneficial and generally safe for pwMS.

3 High Intensity Interval Training

Endurance athletes have utilized high-intensity interval training (HIIT) as essential part of their training programs for over a century. HIIT enables bigger volume of training at high intensity level than continuous training. (Coates et al., 2023, pp. 585–586.) It can also rapidly improve cardiorespiratory fitness – significant increases can be gained with just approximately 100 weekly minutes of intense training (Clifford et al., 2023, p. 10). For highly trained athletes, HIIT can offer a good boost for performance: according to Laursen and Jenkins (2002, p. 53) there is a point where increase in submaximal training stops further enhancing endurance performance but HIIT on the other hand, seems to be able to do that. HIIT's application for improving health including rehabilitative context isn't novel phenomena either; it has been advanced for decades (Coates et al., 2023, p. 586).

3.1 Definition of HIIT

Lack of standardized terminology, especially of classification of intensity, means that common definition for HIIT still doesn't exist; e.g Coates et al. (2023, p. 587) define HIIT differently in performance context than in health context. In performance context they define HIIT as intermittent exercise bouts performed above heavy-intensity domain whereas in health context HIIT is seen as intermittent exercise performed above moderate intensity. Figure 4 shows different definitions or prescriptions for HIIT. Common feature is that exercise includes repeated bouts of hard work with recovery periods of lighter work or total rest in between them. Definition of American College of Sport Medicine (ACSM) (Kravitz, 2014) also shows the typical "rule": higher the intensity, shorter the working bout, longer the rest period. Rest periods allow recovery but only partially.

Figure 4. Different prescriptions for HIIT program (Atakan et al., 2021, p. 3; Kravitz, 2014; Laursen & Jenkins, 2002, p. 56)

3.2 Intensity of HIIT

Demanded intensity is what leads many people astray when thinking about HIIT. Even in health context, HIIT has been erroneously thought to demand very high intensity, even “all out” efforts due to early reviews being based on studies that used sprint interval training (SIT) interventions. Evolution of the field has led to development and widening of terminology. Thus, definitions such as “target intensity of 80-100% of peak heart rate” for HIIT and “target intensity ≥100% VO2max or maximal power” for SIT, have been taken to use. SIT can hence be considered as intense form of HIIT and is mainly used in performance context. (Atakan et al., 2021, pp. 1, 3–4; Coates et al., 2023, pp. 587.) HIIT can also be divided into low and high-volume HIIT based on total times spent in active intervals. In low-volume HIIT active intervals last less than 15 minutes in total whereas total active intervals longer than 15 minutes are categorized as high-volume HIIT. (Atakan et al., 2021, p. 3.)

In addition to definition of HIIT being rather diverse, so are the different indicators of intensity. For example, Coates et al. (2023, pp. 587–588) list that in health context, indicators of sufficient intensity are perceived exertion, oxygen uptake or heart rate as defined in public health and exercise prescription guidelines. In performance context, indicators such as critical power or speed, second lactate threshold, maximal lactate steady state or lactate turnpoint are used. MacInnis & Skelly, (2023, p. 179) add heart rate reserve, ratings of perceived exertion, peak power output, VO2 reserve, maximal lactate steady state, critical speed and critical power as possible indicators to use in HIIT prescription. Using heart rate as a measure of intensity is problematic due to heterogeneity of heart rate. For example, cardiovascular disease can lead to overestimation of training HR. (Atakan et al., 2021, p. 3.) Also, in the context of this thesis, pwMS can have impaired chronotropic regulation (heart rate not rising along the increase in activity) due to cardiac autonomic dysfunction (Wens et al., 2015, pp. 9–10). Furthermore, obtaining true HRmax from untrained person using incremental treadmill or cycle ergometer test has its challenges: leg fatigue can end the test prematurely (Atakan et al., 2021, p. 3).

3.3 Benefits of HIIT

HIIT has several benefits, equal or superior to moderate intensity continuous training (MICT). For instance, preoperative HIIT-intervention was noticed to reduce postoperative complications and associate with increased VO2max (Clifford et al., 2023, pp. 10–11). It has been reported that cardiovascular adaptations following HIIT are similar and even superior to those of endurance training. There are also indications that single weekly HIT/HIIT training can be enough to reduce the risk of cardiovascular disease. Exercising in intervals allows beginners to reach bigger work volume with less fatigue. Key is to choose appropriate work and recovery intervals. This principal also allows HIIT to be used in improving cardiorespiratory fitness among insufficiently active people. Challenge is that research concerning HIIT is heterogenous and there is variation in both definition and protocols of HIIT. (Clifford et al., 2023, p.12; Coates et al., 2023, pp. 585–587; Milanović et al., 2015, pp. 1470, 1477, 1479). Overall, there are plenty of benefits of interval training programs. These include improvements in VO2max, endurance capacity, resting metabolic rate, substrate metabolism, body composition, insulin sensitivity and cognitive functions; decreases in risk for cardiovascular diseases, breast cancer, metabolic syndrome, osteoarthritis and rheumatoid arthritis. (Atakan et al., 2021, p. 3.)

3.4 Physiological mechanisms of high-intensity interval training

One of the reasons behind HIIT's suggested superiority to MICT lies in powerful stimulus to central cardiovascular adaptations and metabolic stress that it provides. Higher intensity causes higher metabolic stress because process relies more on substrate-level phosphorylation and anaerobic metabolism even with low amounts of total work. Thus, HIIT covers both aerobic and anaerobic components. Furthermore, during interval training, also resting intervals impact on physiological adaptation. (Atakan et al., 2021, p. 15–17; Fisher, 2010, p. 27; MacInnis & Skelly, 2023, pp. 179–180.) High-intensity interval training seems to occupy mostly type II muscle fibers. This means that to meet increased energy demand, ATP production is raised up to 100 times. This leads to process by which HIIT seems to have inflict changes in muscle at mitochondrial level by increasing mitochondrial biogenesis and possibly increasing mitochondrial content more than MICT. Protein signaling and gene expression responses are similar or greater for HIIT than moderate intensity continuous training. (Atakan et al., 2021, p. 17; MacInnis & Skelly, 2023, pp. 180, 186.) As mentioned before, HIIT induces improvements in VO2max. Increased stroke volume, maximal cardiac output, skeletal-muscle oxidative enzyme capacity, capillary density, red blood cell volume and hemoglobin mass are thought to be some mechanism behind VO2max improvements elicited by HIIT. Hence, the effects are both central and peripheral. (Atakan et al., 2021, p. 15.)

In addition to positive physiological adaptations that improve cardiorespiratory fitness, HIIT also has some more questionable effects. These include acute immune and oxidative stress responses. More specifically this means that HIIT impairs immune system during recovery phase by releasing stress hormones and peripheral leukocytes and increasing formation of reactive oxygen species. (Fisher, 2010, pp. 57, 59, 62 ; Shiu, 2016, p. 58.) Shiu (2016, pp. 59–60) found out that single HIIT session was able to disrupt T cell homeostasis by recruiting hypersensitive T cells into bloodstream which then activated immunosuppressive Treg cells. Exercise associated immune response and oxidative stress can be harmful at recovery stage but turn out to be beneficial in long term according to principle of hormesis (stress and toxins are only detrimental or lethal at large doses, small doses beneficial for health) (Fisher, 2010, p. 27). In addition, findings of Shiu (2016, p. 60) reveal persistent effect of HIIT on come T cell functions which indicates stronger immune function. It is also notable than in the study of Fisher (2010, pp. 20, 56) HIIT didn't elicit post-exercise lymphopenia (decrease of lymphocytes below basal values) which is typical after intense exercise.

The purpose of this thesis was to find out suitability of HIIT for pwMS. More precisely, the objectives were to explore possible benefits and adverse effects of HIIT for pwMS. Finally, a suggestion of suitable HIIT regime was formed based on the findings of the review.

4 Research design

4.1 Purpose and objectives

Purpose of this thesis was to find out if high intensity interval training (HIIT) is suitable for people with MS-disease (pwMS). Thus, main objective was to recognize and report effects of HIIT among pwMS. This will be achieved by completing next sub-objectives:

1) explore what are possible benefits of HIIT for pwMS
2) explore what are possible adverse effects of HIIT for pwMS
3) form a recommendation of what kind of HIIT is suitable for pwMS and to what functioning level is required from pwMS in order to participate in it.

Results are presented in this thesis and aim is also to report them to thesis commissioner Sanfy (Suomen Aikuisneurologisen Fysioterapian yhdistys; Finnish Adult Neurological Physiotherapy Association) and its members.

4.2 Inclusion criteria

For eligibility criteria the JBI concept of PCC (participants, concept, context) was followed (Peters et al., 2022, pp. 961–962).

4.2.1 Participants

Study population (participants) had to be adult people with certain diagnosis of MS (according to McDonald criteria) and more precisely only three main subtypes (RRMS, SPMS and PPMS) were included. Hence, studies involving participants with other subtypes of MS, un-diagnosed MS-disease or non-human subjects, were excluded. Other exclusion criteria based on for example age, gender or EDSS level weren’t set in order to keep the scope wide and enable enough search results.

4.2.2 Concept

As a concept, eligible studies needed to research the effects of high intensity interval training (HIIT). Both aerobic- and resistance-types of HIIT were initially included. HIIT could be either the intervention or comparator in research setting. Studies were excluded if they combined HIIT with other training modality, for example resistance training.

4.2.3 Context

Context of this thesis was set to be in rehabilitation. Both in- and outpatient settings were included. Rehabilitation was set as context because it is seen important to find out suitability of HIIT for pwMS in that context first before examining the concept in general training-context. Latter will still be relevant in the future if HIIT proves to be suitable training type in multiple sclerosis. At protocol creation stage, further specification of context to include only in-/out-patients was seen too limiting.

4.2.4 Types of sources

The scope in this thesis was focused on research articles. This narrowed the breadth of the scope but on the other hand, possibly ensured certain quality in the evidence of the effects of HIIT. Both experimental and quasi-experimental studies were considered, and these included randomized controlled trials, non-randomized controlled trials, before- and after studies, interrupted time-series studies. Also, prospective cohort studies and case reports could be included. In the case of qualitative research, those appropriate for research objectives were eligible. Only finished studies were included so study protocols were excluded. Free full text was required. Only studies written in English were accounted as eligible because of limited translation and time resources.

5 Implementation

5.1 Scoping review

In this thesis a scoping review was undertaken to collect and summarize existing evidence of the effects of high-intensity interval training for people with multiple sclerosis. Scoping review has become increasingly popular method in health research but for long time it lacked proper universal definition and purpose, and also methodology was inadequate. Rather recently (Munn et al., 2022,

p. 950) provided the next formal definition to enhance understanding of scoping reviews: “Scoping reviews are a type of evidence synthesis that aims to systematically identify and map the breadth of evidence available on a particular topic, field, concept, or issue, often irrespective of source (ie, primary research, reviews, non-empirical evidence) within or across particular contexts. Scoping reviews can clarify key concepts/definitions in the literature and identify key characteristics or factors related to a concept, including those related to methodological research.” This is usually done without assessing the quality of evidence source. Overall, rehabilitation science being emerging science and conciseness of randomised trials hinders undertaking systematic reviews, scoping review becomes relevant and ideal methodology as range of study design can be incorporated and findings complementary to clinical trials can be generated. Research questions can also be other than related to intervention effectiveness and they don’t need to be so specifically defined as in systematic review. (Arksey & O’Malley, 2005, p. 8; Levac et al., 2010, p. 1; Munn et al., 2022, pp. 950–951)

When it comes to methodological quality, first six-step framework for conducting a scoping review was presented by Arksey and O’Malley in 2005. It was then refined by Levac, Colquhoun & O’Brien in 2010 and further enhanced by the research group of Joanna Briggs Institute (JBI), Peters et al, in 2015, 2017 and 2020. Even more recently, in 2022, JBI published best practice guidelines for developing high quality scoping review protocol. The framework and guidelines of JBI were fundaments of this thesis research. It is good to remember that in scoping review, the process is iterative, so repeating and refining steps were naturally taken along the process. (Peters et al., 2020; Peters et al., 2022).

Usually, a scoping review demands a review team undertaking the research. Multiple reviewers are especially recommended for creating search strategy, selection and data extraction processes. (Levac et al., 2010, pp. 5–6; Peters et al., 2020; Peters et al., 2022) As this thesis will be undertaken by one person, this issue will be handled by regular consultations with the thesis supervisor and possibly also with the commissioner presentative if seen necessary and appropriate.

5.2 Data collection

5.3 Search strategy

The search strategy aimed to locate published studies from selected databases. In addition, some manual search was executed in existing computer files of the researcher. Search process began with building an initial search strategy for conducting a pilot search. This was done by first brain-storming and searching glossaries for initial search terms. Next, pilot searches were undertaken in CINAHL Ultimate (EBSCO), Cochrane Library and MEDLINE (PubMed). Pilot results were analyzed at title and abstract level for identification of all relevant keywords and index terms. These were then used in developing the final search query (seen in table 1). Final search was carried out from 4 to 10 May 2024 in MEDLINE (PubMed), CINAHL Ultimate (EBSCO), Medline (EBSCO) and Cochrane Library. Time limits were not set as the aim was to achieve as broad scope as possible of the subject.

Table 1. Final search query

OR		OR
"multiple sclerosis"		"high intensity interval training"
"disseminated sclerosis"		"high intensity interval exercis*"
"encephalomyelitis disseminata"		"high intensity intermittent training"
"ms-disease"		"high intensity intermittent exercis*"
"relapsing-remitting multiple sclerosis"	AND	"aerobic high intensity interval training"
"chronic progressive multiple sclerosis"		"aerobic high intensity exercis*"
"primay progressive multiple sclerosis"		"resistance high intensity interval training"
"secondary progressive multiple sclerosis"		"resistance high intensity interval exercis*"
		"interval training"
		"interval exercis*"
		"aerobic interval training"
		"aerobic interval exercis*"
		"resistance interval training"
		"high intensity circuit training"

5.4 Study selection

After undertaking the data search, data selection took place. Duplicates were removed and results were first screened at title and abstract level. Potentially relevant sources were retrieved in full text. Selection continued with screening of full text. During these two screenings, irrelevant reports were excluded. Figure 5 shows the Prisma flow chart of selection process. At selection phase, studies involving high intensity resistance training were also categorized as illegible due to different physiological effects than aerobic high-intensity interval training. This decision was also made for cohesion of the thesis results as resistance HIIT in the studies involved repetitions and sets instead of time intervals like in aerobic HIIT. Selection phase also included brief quality assessment of final reports included. JBI Critical Appraisals tools were utilized here (Barker et al., 2023; Moola et al., 2020).

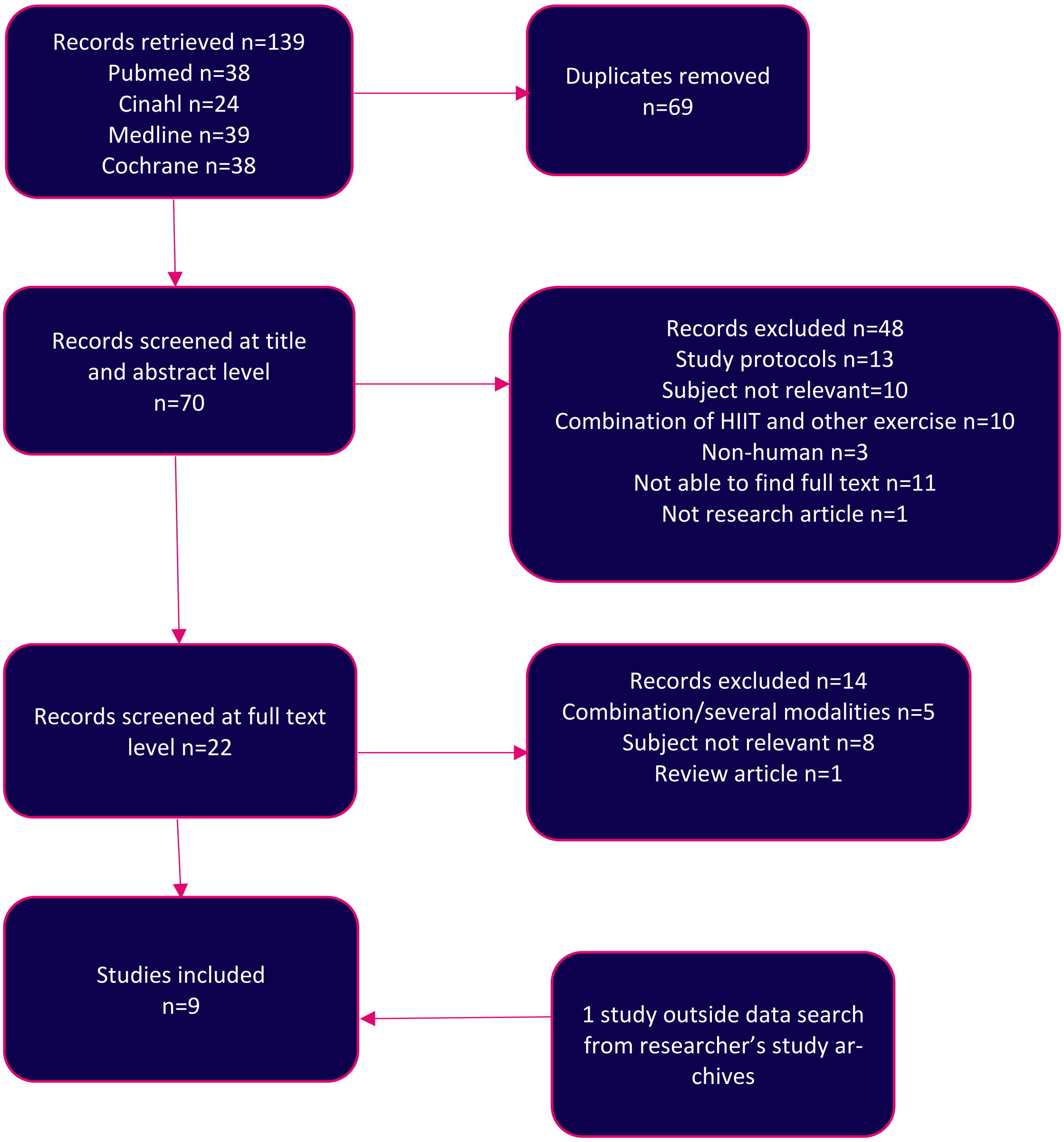

Figure 5. Prisma Flow chart

Initially, 139 records were retrieved from the four databases chosen for the datasearch (CINAHL Ultimate [EBSCO], MEDLINE [Pubmed], Cochrane Library and Medline [EBSCO]). 69 duplicates were first removed before screening the records. During title and abstract screening, 48 records were excluded. Full text screening resulted in 14 excluded reports. Specific reasons for exclusion were report being just a study protocol (n=13), study population being non-human (n=3), study topic being irrelevant and not covering effects of HIIT among pwMS (n=18) or study intervention combining some other training modality with HIIT (n=15). Common training modality used in combination with HIIT was resistance training. Examples of irrelevant topics were high-intensity functional training and high-intensity physiotherapy. Issues with full text availability ended up in exclusion of 11 records. One record was excluded for not being a research article and one for being a review. Finally, eight reports were included from the official datasearch and one from manual search of researcher's archives.

5.5 Data extraction

Data was extracted by using an extraction table/form based on recommendations of JBI (Pollock et al., 2023, p. 522). The extraction form was piloted with three sources from pilot search and necessary changes were made in the final form. Data extracted can be seen in appendix 2.

In addition to eight quantitative studies included, one mixed-methods feasibility study was used here to reveal perceptions of pwMS themselves of HIIT training. This study didn't go through the official data extraction. Relevant findings were highlighted and written as notes in Microsoft Word- formed thesis diary (that supported the Microsoft Excel-formed notes of thesis progress).

6 Data analyses and presentation

6.1 Summary of the studies

9 studies were finally included in this review. Table 2 shows a summary of included studies. As the table 2 shows, only 4 of the 9 included reports were primary studies. Furthermore, four reports out of five secondary/sub-analysis studies use the same population/sample of inpatients at the Valens clinic in Switzerland.

Table 2. Summary of included studies

Parameter	n of total studies	Parameter	n of total studies
Number of publications	9	*Method of data collection*	
Types of studies/sources		Multiple methods	5
Primary research article	4	Testing	1
Secondary/sub analysis	5	Survey/questionnaires	1
Methodology used		Other (i.e. blood sampling)	2
Quantitative	8	*Outcome measures*	
Mixed or multimethods	1	Cardiorespiratory fitness/response	5
Qualitative		Cognitive performance	3
Sample size		Fatigue	3
<10	0	Depression	1
10-30	2	Serum biomarkers	3
31-50	1	Other	1
51-70	3	*Setting*	
71-100	1	Inpatient/clinic	6
>100	2	Outpatient	3

Outcome measures used in the studies were cardiorespiratory fitness/response, cognitive performance, fatigue, depression and serum biomarkers. Only two studies used outpatient-setting where exercise sessions were undertaken at fitness centre, clinical exercise and rehabilitation centre or community leisure centre.

Summary of the study populations is presented in table 3. Most of the participants had relapsing-remitting form of MS. For 10 participants of mixed-methods study by Humphreys et al. (2022), data of the MS subtypes of participants was not available. Mean age of participants in the studies ranged from 41.6 to 51.02 years for HIIT groups and from 42.8 to 49.7 years for control groups.

Table 3. Summary of study population

Parameter	**n(%) from total population**
Population	
Total	277(100%)*
Type of MS	
Relapsing-remitting	172(62,1%)**
Secondary progressive	91(32,9%)**
Primary progressive	3(1,1%)**
Drop-outs	
Total	16(5,8%)
HIIT	8(2,9%)
Control	8(2,9%)
Intervention/control	
HIIT	144(52%)
Other	133(48%)

*Inconsistencies in reporting participant numbers **Not reported for 10 participants

144 participated in HIIT interventions of the studies and 133 did control exercise which was continuous exercise at medium intensity. Both interventions and control exercises were performed with cycle ergometer. Total of 16 drop-outs were reported (HIIT 8, control 8), but in some studies there were inconsistencies and even lack of information in this aspect. Mean EDSS scores are not shown in the table but for HIIT groups they ranged from 2.29 to 4.5 and for control groups from 2.17 to 4.6. This refers to disability ranging from mild (scoring 2.) to significant (scoring 4.) with capability to work full day and walk without aid or rest for 300m (Multiple Sclerosis Trust, 2024). The study of Feltham et al. (2013) used Barthel index as a measure of functional capability. Mean scores were 19 for both groups in their study. This indicates total dependency in activities of daily living (Physiopedia, 2024). For the study of Humphreys et al. (2022) details of participant characteristics were unavailable but the inclusion criteria mentioned that only pwMS with mild disability were included.

Figure 6 shows details of HIIT-interventions and figure 7 of control group regimes used in the studies. Notable detail is that the study of Zimmer et al. (2018) used different session frequencies for HIIT- and control groups, 3 and 5 times a week respectively. In the study of Humphreys et al. (2022) number of repetitions was increased progressively on weekly basis from six to ten. There was no control group in their study.

1 Zimmer et al., 2018; 2 Wolf et al., 2021; 3 Rademacher et al., 2021a; 4 Rademacher et al., 2021b; 5 Joisten et al., 2021a; 6 Joisten et al., 2021b; 7 Wonneberger & Schmidt, (2019); 8 Feltham et al., 2013; 9 Humphreys et al., 2022

Figure 6. Details of HIIT-interventions used in the included studies

1 Zimmer et al., 2018; 2 Wolf et al., 2021; 3 Rademacher et al., 2021a; 4 Rademacher et al., 2021b; 5 Joisten et al., 2021a; 6 Joisten et al., 2021b; 7 Wonneberger & Schmidt, (2019); 8 Feltham et al., 2013

Figure 7. Details of control interventions used in included studies

This scoping review showed that beneficial effects of HIIT focus on factors of cardiorespiratory fitness, cognitive performance and serum biomarkers of MS. Three out of eight studies reported positive and significant changes in these areas. Results regarding fatigue were controversial. Adverse effects reported in the studies include for example exacerbation of symptoms and nausea. Figure 8 summarizes both beneficial and adverse effects of HIIT in this scoping review.

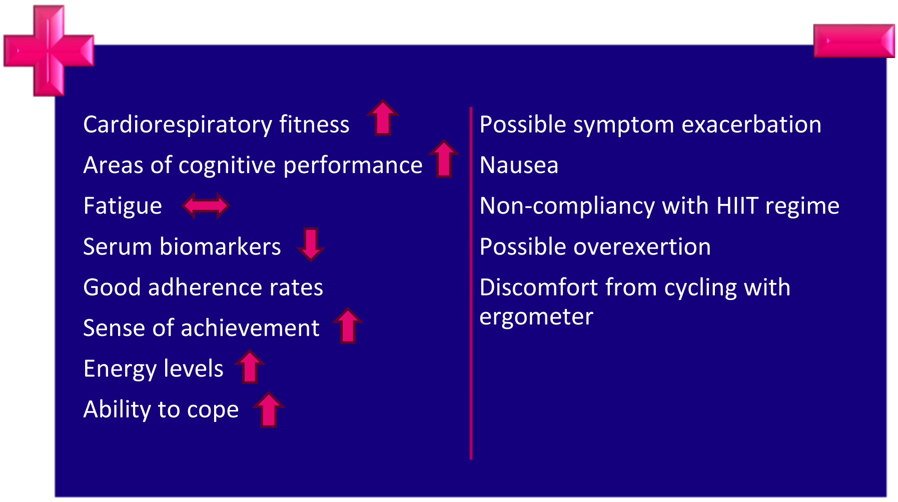

Figure 8. Summary of benefits and adverse effects of HIIT

6.2 Beneficial effects of high-intensity interval training for pwMS

Cardiorespiratory fitness (CRF) seemed to improve in all five studies that used it as one of the outcomes. This happened regardless of parameter used (VO2max, VO2peak, VO2norm) (Feltham et al., 2013, pp. 768-770; Rademacher et al., 2021a, p. 4; Wolf et al., 2022, pp. 3-4; Wonneberger & Schmidt, 2019, p. 561; Zimmer et al., 2018, p. 1639.) Wonneberger and Schmidt (2019, p. 563) found out that HIIT was able to elicit mean improvement of 3.0ml/min/kg within 8 weeks. All three studies that measured cognitive performance found positive changes in processing speed and verbal learning. Processing speed improved in both HIIT and control groups whereas changes in verbal learning were more linked to HIIT groups in two of the studies. Zimmer et al. (2018, p. 1639) also reported significant improvement of response inhibition in HIIT group. (Rademacher et al., 2021a, pp. 4-5; Rademacher et al., 2021b, pp. 3-6; Zimmer et al., 2018, p. 1639.) Regarding serum biomarkers, studies revealed several beneficial effects. Zimmer et al. (2018, p. 1639) found significant decrease in levels of MMP-2 (matrix metalloproteinases) in HIIT group. MMPs can disrupt blood-brain barrier and acts in inflammatory process and pathogenesis of MS. There was also a negative association between VO2peak increase and MMP-2 levels supporting the suggestion of anti-inflammatory effects of regular exercising. Study of Joisten et al., (2021a, p. 1137) supports this with other inflammatory indicators; researchers reported decrease in neutrophil-to-lymphocyte ratio (NLR) and systemic-immune-inflammation index (SII) in HIIT group. Joisten et al. (2021b, pp. 2, 4-6) focused on possible neuroprotective effects of HIIT by measuring the levels of plasma neurofilament light chain (pNFL) and rerouting of kynurenine (KYN) pathway. KYN pathway seems to be deregulated in pwMS. This means that pathway produces more of neurotoxic agent of quinolinic acid (QA) than neuroprotective agent kynurenic acid (KA). Study showed that HIIT acutely decreased pNfl levels and increased KA levels. Positive correlation between pNfl and KA changes and negative correlation between pNfl and quinolinic acid-to-KA ratio was also found. All changes observed were larger in HIIT than MCT (moderate continuous training) group.

From the outcomes used in these eight studies, fatigue seems to be the most controversial one. Research of Wonneberger and Schmidt (2019, p. 561) proposes that HIIT might reduce fatigue among pwMS with increased fatigue. This is supported by interviews of Humphreys et al. (2022, p. 11) in their study. On the other hand, other studies didn’t find significant impact on fatigue. Furthermore, most of the drop-outs in the study of Wonneberger and Schmidt (2019, p. 564) were pwMS with significant fatigue. Nevertheless, there was equal distribution of drop-outs in both the HIIT and the control group suggesting that exercise frequency (3x/week) lead to an overexertion instead of exercise modality being a reason for dropping out.

Study of Humphreys et al. (2022, p. 9-11) shows how meaningful the attitudes and words of people close to a person with MS can be. Fear for patients’ well-being can enforce the idea of incapability to do more intense exercise. On the other hand, positive encouragement can support confidence and drive the decision to participate. Especially an expert (consultant) opinion holds a certain value. Many participants of the study were concerned of their body’s reaction to intense exercise (HIIT). Encouragement and will to try non-pharmacological treatment facilitated the decision to take part in intervention. Participants also mentioned a desire to be/feel fitter or get fit again. Positive changes that HIIT-intervention brought were increased energy levels (ability to do more and be more alert), sense of achievement (being actually able to complete HIIT sessions), better ability to cope and reduced perceived fatigue. Participants were able to complete 87% of all HIIT sessions and average attendance rate was 10.5 (+/- 3) of 12 scheduled sessions/participant.

6.3 Adverse effects of high-intensity interval training for pwMS

In addition to mixing results concerning HIIT’s effect on fatigue, some contradiction exists also in other findings especially regarding adverse effects of HIIT; although eight quantitative studies in this review reported barely any symptom exacerbations, qualitative part of the study of Humphreys et al. (2022, pp. 12-13) reported that eight out of 10 participants experienced symptoms like tingling in extremities, blurred vision, partial deafness and one-sided weakness. This could refer to Uthoff syndrome taking place. In addition, some participants experienced nausea during HIIT-session and muscle ache and felling wiped out afterwards. Bike as exercise mode was also experienced uncomfortable. Study of Wonneberger and Schmidt (2019, p. 564) also brought up that potential reason for drop-outs in their study was overexertion from exercising 3 times a week. This phenomenon was linked to both exercise modalities, HIIT and continuous training.

6.4 Recommendation of suitable HIIT-program

HIIT can be considered as part of rehabilitation of pwMS as it is generally safe as number of possible adverse effects is relatively low. HIIT seems to be beneficial and time-efficient way to exercise for pwMS. Moreover, some pwMS might enjoy the more vigorous intensity of exercising than traditionally used. Recommendation of suitable HIIT- program is presented in figure 9.

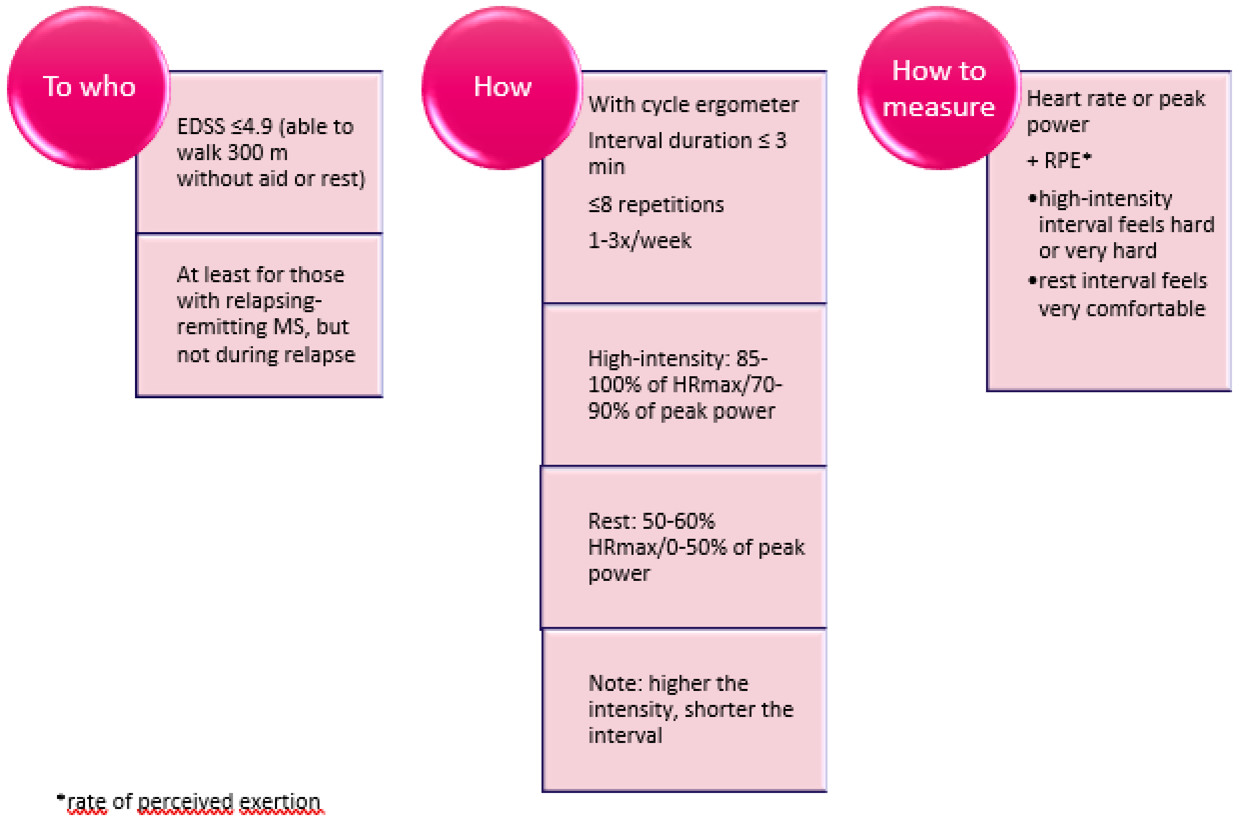

Figure 9. Recommendation of suitable HIIT-program for pwMS

7 Discussion

Purpose of this thesis was to find out if high intensity interval training (HIIT) is suitable for people with MS-disease (pwMS). In order to do this, aim was to recognize and report effects of HIIT among pwMS. Hence, the research objectives were to explore possible benefits and adverse effects of HIIT for pwMS and then form a recommendation of suitable HIIT-program including advisable functioning level of participants.

In addition to improving cardiorespiratory fitness, HIIT may improve parts of cognitive function, generate neuroprotective and/or anti-inflammatory changes in important serum biomarkers, reduce or at least not increase fatigue and enhance such positive feelings as sense of achievement and better coping. Logically, these should improve functioning and quality of life of pwMS. PwMS were mostly able to participate in HIIT sessions and complete the programs mainly without significant adverse events. From this they got sense of achievement, better ability to cope and increased energy levels. On the other hand, symptom exacerbation, nausea and discomfort were adverse effects experienced by some participants. There was also indication of overexertion and challenge with correct execution of HIIT session.

7.1 Possible benefits of high-intensity interval training for pwMS

This scoping review revealed that potential benefits of HIIT for pwMS are increasing of cardiorespiratory fitness, improvements in some areas of cognitive performance and positive changes in serum biomarkers indicating anti-inflammatory and even neuroprotective effects. Contradicting findings were discovered regarding effects of HIIT on fatigue.

Increased cardiorespiratory fitness is in line with the findings of Atakan et al. (2021, p. 15), Campbell et al. (2018, p. 22), Halabchi et al. (2017, p. 3), Latimer-Cheung et al. (2013, p. 1825), Milanovic et al. (2015, p. 1479) and Platta et al. (2016, p. 1571) which have showed exercise-induced improvements in CRF in both healthy adults and populations with multiple sclerosis, obesity, cancer, metabolic syndrome. In addition, Clifford et al. (2023, pp. 10–12) found that HIIT-intervention improved CRF and significantly reduced post-operative complications in population going through major surgery. However, there is no clear consensus of how much VO2peak should increase to produce clinically significant improvements in pwMS. Increase of about 3.5ml/min/kg is suggested as it reduces mortality by 13 % and incidence of cardiovascular diseases by 15% but in healthy people (Kodama et al. 2009 in Wonneberger and Schmidt 2019, p. 563).

Evidence of benefits of exercise on cognitive performance among pwMS is inconsistent as the review of Sandroff et al., (2016, p. 284) reveals. On the other hand, these researchers found possible association between better physical fitness and better cognitive performance. Among healthy people, exercise appears to have small positive effects on cognition (Chang et al., 2012, p. 91). All the studies measuring cognitive outcomes in this thesis found beneficial effects; some improvements only took place in HIIT-intervention group, but many were observed also in active control groups. However, Langeskov-Christensen et al. (2021, p. 1594) found that progressive aerobic exercise involving interval training had no effect on cognitive domains in pwMS. The exception was clinically relevant improvement in processing speed among cognitively impaired subgroup. Similar findings were observed in this thesis in the study of Rademacher et al. (2021b, p. 5) as baseline lower cognitive status and HIIT-group predicted bigger improvements in verbal learning. Inconsistency of findings might be due to variable quality of studies and differences in methodology

(Sandroff et al., 2016, p. 284). Chang et al. (2012, p. 87) specify that exercise duration and intensity, type of cognitive performance assessed and participants' fitness are potential factors effecting on findings. Also, the choice of cognitive performance being primary instead of secondary outcome seems to impact on results; the studies measuring cognitive performance as primary outcome more often find positive effects from exercise or physical activity (Sandroff et al., 2016, p. 285).

HIIT's positive effects on different serum biomarkers and possibly having anti-inflammatory or neuroprotective influence is supported by meta-analyses of Shobeiri et al. (2022) and review of Dalgas and Stenager (2012). Shobeiri et al. (2021, p. 10–14) found that physical activity increases peripheral levels of brain-derived neurotrophic factor (BDNF) in pwMS which can indicate neuroregenerative or neuroprotective effects of exercising. Dalgas and Stenager (2012, p. 93) also concluded that although findings are conflicting, exercise may have an impact on levels of different neurotrophic factors with neuroprotective properties in pwMS. On the other hand, it still can't be concluded that exercise would have disease-modifying effects in pwMS (Proschinger et al., 2022, p. 2922).

7.2 Possible adverse effects of high-intensity interval training for pwMS

As mentioned earlier, the number of reported adverse events in this scoping review was very low. This is accordingly with Pilutti et al. (2014, p. 7) and Halabchi et al. (2017, p. 9) who declare exercising as safe for pwMS. Campbell et al. (2018, pp. 20, 25) agree with this although one study in their review reported six adverse events. It should be mentioned that Uthoff phenomenon seemed to be present in the study of Humphreys et al. (2022) as participants reported of short-term symptom exacerbation. Although it has no lasting effects, it can be very unpleasant and reduce willingness to engage in more permanent active behavior (Richardson et al.2020, p. 4). Some participants also experienced nausea and discomfort. Moreover, the review revealed indication of overexertion and challenge with correct execution of HIIT session. Atakan et al. (2021, p. 4) seem to agree with this as they claim that high-exertion that HIIT requires is too strenuous for sedentary people. Contradicting findings were discovered regarding effects of HIIT on fatigue. Whereas no significant change was seen in the studies of Wolf et al. (2022) and (Rademacher et al., 2021a) two other research groups showed reduced fatigue in their trials (Humphreys et al., 2022; Wonneberger & Schmidt, 2019). Earlier findings about effects of exercise on fatigue among pwMS are equally inconsistent although they seem to favor slightly more the findings of latter researchers. Both Gallien et al. (2007, p. 375) and Latimer-Cheung et al. (2013, p. 1825) stated in their reviews that exercise can improve fatigue. Learmonth and Motl (2015, p. 1235) disagree with this view and list increased fatigue as an adverse consequence of exercise for pwMS. One of the reasons for this inconsistency at least in this thesis, might be use of different measuring methods of fatigue. In larger scale, variable dosage of exercise might confuse findings.

7.3 Suitable HIIT-program for pwMS

This scoping review indicates that HIIT inflicts increases in cardiorespiratory fitness also among pwMS. This is meaningful finding considering that CRF of pwMS is lower than general population and they also have more inactivity-related comorbidities. Improved CRF has secondary health benefits (Motl et al., 2017, p. 849; Wonneberger & Schmidt, 2019, p. 563) and evidence suggests that HIIT is either superior or equally efficient than continuous training in improving cardiovascular risk factors (Campbell et al., 2018).

Although HR might be the easiest way to measure intensity, there is a risk for unreliable measuring due to possible impairment in autonomic regulation of HR and unreliable baseline measurement (untrained person finishing the test because of leg fatigue instead of reaching true HRmax). Due to this, RPE scale can be used as additional measurement method. (Atakan et al., 2021, p. 3; Halabchi et al., 2017, p. 6.) Supervision is advisable in case of serious medical event. Risk for Uthoff syndrome/short-term symptom exacerbation exists (Humphreys et al., 2022, pp. 12-13) and person with MS willing to try HIIT should acknowledge it. The risk of symptom exacerbation and rising core temperature can be minimized by using cooling vest and properly air-conditioned environment (Richardson et al., 2020, p. 4).

7.4 Limitations

For a scoping review serving its role as a thesis and carried out by only one person, 9 studies located by data search can be established as sufficient result. Unfortunately, due to the limited resources, search from the reference lists of already identified studies was left out. This could have broadened the scope. Being a first time for the researcher in executing a scoping review, the whole process could have been more organized. Proper research plan kept the overall process in control, but some smaller part and phases lacked efficiency and structure (e.g. removing duplicates). In addition, even further thought could have been put in choosing databases for data search. For example, Cochrane Library appeared to be quite ineffectual. More precise search term would have been more effective especially by saving time in the beginning of report selection.

What it comes to limitation of the study, there was a lack of diversity and variability in findings as many of included studies used the similar setting and same sample of participants. This has an impact on generalizability of the results. Furthermore, most participants had relapsing-remitting MS so less is known about suitability and effects of HIIT for people with progressive multiple sclerosis. For most of the secondary analysis -studies, locating the primary study was unsuccessful regardless of the effort. Hence, it seemed that for example reporting dropouts and adverse events was incomplete. Furthermore, any of included studies didn't report activity levels of the participants so it is impossible to conclude whether HIIT is advisable for pwMS of all activity or fitness levels. To increase reliability of findings, two instead of one researcher carrying out study selection and data extraction would have been justifiable.

7.5 Ethics and reliability

Reliability, honesty, respect and accountability are key principles of research integrity and best effort was put to follow those in this research. Reliability refers to ensuring quality of research throughout the design, methodology, analysis and resources. (All European Academies [ALLEA], 2023, p. 5.) In this thesis quality of the design and methodology were ensured by following the principles of scoping review and using a framework specially created for scoping review. Good research conduct was also complied with by keeping a detailed research diary and being systematic through all the steps of research. Using official JBI critical appraisal tools for quality assessment of the included studies aimed in ensuring quality of resources. There was some variation in quality of included studies which will be addressed in more detail later in this chapter. It must also be acknowledged that appraisal was taken by only one person although at least two is recommended. Principle of honesty demands transparency and fairness through all the aspects and steps of research process, from planning to reviewing and communicating research (ALLEA, 2023, p. 5). The researcher aimed to report everything clearly and comprehensively so that understanding of results and repeating the research process would be easy. Table and figures were used to support the written text and facilitate interpretation of the results. Data extraction form used in this review is available in appendices and other raw data can be delivered if requested. Some ways to guarantee transparency of this research were presenting of both beneficial and adverse effects of HIIT for pwMS and reporting shortcomings of this research process. To follow the principle of respect, proper in-text citing and reference listing were used to give credit for other researchers of their work.

Recurring issues with the quality of included studies were partial lack of blinding and missing of proper follow up period after intervention. All randomized controlled trials included used only single blinding (blinding of assessors) which, on the other hand, is understandable since blinding of participants and those delivering the interventions would be challenging or even impossible in this kind of intervention setting. In addition to lack of follow up period, duration of majority of the studies was very short (3 weeks). Hence, it is impossible to make conclusions of persistence or longer-term effects of HIIT among pwMS. Reporting and dealing with confounding factors were inadequate throughout the sample which weakens repeatability and reliability of the studies. Finally, since some of the studies were short reports and also secondary analyses, some elements of the appraisal remained unclear if retrieving primary study was unsuccessful.

7.6 Conclusions and future research proposals

To conclude, high-intensity interval training is generally suitable for pwMS. Benefits seem to outweigh adverse effects, but individual differences, preferences and health should be considered.

Future research should focus on investigating HIIT's effect on MS-symptoms more precisely and maybe more broadly. For example, no study using spasticity as outcome was found during this thesis process. Specific symptoms also have to be placed as primary outcomes. Studies need to include more people with primary or secondary progressive multiple sclerosis, and higher disability levels (≥5.0 EDSS), as participants. This subject also needs more primary studies, especially interventions lasting longer than 3 weeks, and happening in outpatient setting or so that other therapies or treatments as confounding factors can be minimized as well as ethically possible. Finally, all the studies here used cycle ergometer in performing HIIT-sessions so studying other methods for HIIT training is relevant.

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Appendices

Appendix 1. EDSS scoring[1]

Score	Description
0	Normal neurological exam, no disability in any functional systems (FS)
1.0	No disability, minimal signs in one FS
1.5	No disability, minimal signs in more than one FS
2.0	Minimal disability in one FS
2.5	Mild disability in one FS or minimal disability in two FS
3.0	Moderate disability in one FS or mild disability in three or four FS. No impairment to walking
3.5	Moderate disability in one FS and more than minimal disability in several others. No impairment to walking
4.0	Significant disability but self-sufficient and up and about some 12 hrs a day. Able to walk without aid or rest for 500m.
4.5	Significant disability but up and about much of the day, able to work a full day, may therewise have some limitation of full activity or require minimal assistance. Able to walk without aid or rest for 300m
5.0	Disability severe enough to impair full daily activities and ability to work a full day without special provisions. Able to walk without aid or rest for 200m
5.5	Disability severe enough to preclude full daily activities. Able to walk without aid or rest for 100m.
6.0	Requires a walking aid (cane, crutch, etc.) to walk about 100m with or without resting
6.5	Requires two walking aids (pair of canes, crutches, etc) to walk about 20m without resting
7.0	Unable to walk beyond approximately 5m even with aid. Essentially restricted to wheelchair; though wheels self in standard wheelchair and transfers alone. Up and about in wheelchair some 12 hrs a day
7.5	Unable to take more than a few steps. Restricted to wheelchair and may need aid in transferring. Can wheel self but cannot carry on in standard wheelchair for a full day and may require a motorized wheelchair
8.0	Essentially restricted to bed or chair or pushed in wheelchair. May be out of bed itself much of the day. Retains many self-care functions. Generally has effective use of arms
8.5	Essentially restricted to bed much of day. Has some effective use of arms retains some self-care functions.
9.0	Confined to bed. Can still communicate and eat
9.5	Confined to bed and totally dependent. Unable to communicate effectively or eat/swallow
10	Death due to MS

[1] Multiple Sclerosis Trust, 2024

Appendix 2. Data extraction table of sources 1-4

	Source 1	Source 2	Source 3	Source 4
Author(s), year	Zimmer et al., 2018	Wolf et al., 2021	Rademacher, Joisten, Proschinger, Bloch et al., 2021	Rademacher, Joisten, Proschinger, Hebchen et al., 2021
Country	Switzerland? Germany, UK, Denmark	Germany, Switzerland	Germany, Switzerland, UK	Germany, Switzerland
Study type/source	RCT (single-blinded)	Secondary analyses of two parallel group RCTs (Zimmer et al.2018; Joisten et al.2019)	Parallel group (1:1) RCT	Secondary analyses of two parallel group RCTs (Zimmer et al. 2018 and Joisten et al. 2019 same as the other one)
Aim	1.Test the hypothesis that 3-week HIT endurance exercise programme can improve cognitive performance in pwMS compared to moderate exercise programme. 2.evaluate whether exercise programmes differentially influenced basal serum levels of BDNF, serotonin, MMP-2 and MMP-9	1. reproduce reported associations between aerobic capacity and fatigue on a cross-sectional and interventional level 2. investigate intervention effects on fatigue in a severely fatigued subgroup 3.analyze differences in changes of fatigue between peak-oxygen uptake responders and non-responders	1. compare the effects of 3-weeks HIIT and moderate continuous exercise training on cognitive perfromance and cardiorespiratory fitness of pwMS 2.investigate potential effects based on baseline cognitive status in a subgroup analysis	1. analyse the effects of 3-week HIIT compared to moderate continuous exercise on cignitive performance 2. investigate potential predictors for changes of cognitive performance following 3-week aerobic exercise intervention
Population				
Sample size	60 in total, 29 HIT, 31 CT	131 in total, 65 HIIT, 66 MCT	Total 75; HIIT 38; Control 37	Total 130, HIIT 65; MCT 65
Age	HIT 51 (9.9); CT 48 (12.1)	HIIT 51.02 (10.46); MCT 48.85 (10.97)	HIIT 51 (10.97); CG 49 (10.12)	HIIT 51.02 (10.46); MCT 48.75 (11.03)
Gender	Overall 38/19 (F/M); HIT 20/7; CT 18/12	Overall 86/45 (F/M) HIIT 47/18; MCT 39/27	Overall 48/26 (F/M); HIIT 27/11; CG 21/15	Overall 86/44 (F/M); HIIT 47/18; MCT 39/26
Other demographics			Participants divided into subgroups according to cognitive status	Participants divided into subgroups accroding to cognitive status
			Impaired: HIIT 15, CG 19; Intact HIIT 23, CG 16	Impaired: HIIT 25, MCT 30; Intact HIIT 40, MCT 35
Disease characteristics				
Type	Total 30/27 (RRMS/SPMS); HIT 14/13; CT 16/14	T otal 78/53; HIIT 39/26; MCT 39/27	Overall 45/29 (RRMS/SPMS); HIIT 23/15; CG 22/14	Overall 77/53 (RRMS/SPMS); HIIT 39/26; MCT 38/27
Last relapse				
Years since dg	HIT 11.98 +/-11.34; CT 13.33 +/-9.3			
EDSS	HIT 4.37 (1.39); CT 4.37 (0.98)	Total 4.5 (1.11); HIIT 4.45 (1.20); MCT 4.45 (1.03)	HIIT 4.5 (1.05); CG 4.53 (1.08)	HIIT 4.45 (1.20); MCT 4.46 (1.04)
Activity level				
Methodology/methods				
Setting	Clinic (inpatient)	Clinic (inpatient)	Clinic (inpatient)	Clinic (inpatient)
Follow up	No	No	No	No
Co-interventions	Yes, other therapies during clinic stay, but not reported in detail	Yes, other therapies during clinic stay, but not reported in detail	Yes, other therapies during clinic stay, details not reported	Yes, other therapies during clinic stay, details not reported
Adherence	100%		HIIT 79% and CG 70% of planned sessions; Subgroups: 77% HIIT&impaired c, 81% HIIT&intact c, 72% CG&impaired c, 67% CG&intact c	
Drop outs	HIT n=2; CT n=1	RCT1: HIT n=2; CT n=1; RCT2 ?	n=1 (from control group) lost to follow up=0	

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	Source 1	Source 2	Source 3	Source 4
Outcomes and measurement method	1. Cognitive performance	1. Fatigue	Aerobic fitness with CPET	Cognitive performance with BICAMS
	BICAMS	FSMC	Fatigue with FSMC	
	TMT-A/B	2. Cardiorespiratory fitness (VO2peak)	Cognitive Performance with BICAMS	
	Go/No go tasks of TAP	CPET		
	2. Basal serum levels of BDNF, serotonin, MMP-2 and MMP-9	3.Depression		
	Resting blood samples			
	Cardiorespiratory fitness (VO2-peak)	HADS		
Results	HIT improved verbal memory significantly more than CT	No significant correlation between CRF and fatigue at baseline	Significant improvement over time in both groups in levels of relative VO2peak and processing speed	Significant improvement over time for both groups in all cognitive outcomes
	Improvements over time in processing speed, cognitive flexibility/task shifting, response inhibition (executive functions) in both groups	No significant improvements in fatigue in either group	No time or interaction effects for fatigue outcome	Significant and superior improvement in verbal learning for HIIT group
	Significant increase in CRF in both groups, higher in HIT	No significant differences in fatigue changes between VO2peak-responders and non-responders	Significantly higher relative power outputs in HIIT group	HIIT group and lower cognitive status at baseline predicted higher change in verbal learning score
	Significant decrease of serum MMP-2 levels in HIT		Time effects for processing speed, verbal learning and visuospatial memory but no group or groupxtime interaction	
	Significant improvement in response inhibition test performance in HIT			
Adverse events	Nothing (except exacerbation of blood pressure during		No adverse events	
	clinic stay and one drop-out being non-compliant with the HIT protocol)			
Limitations	Learning effects	Assessment of CRF with CPET and VO2peak might not be valid method for pwMS as they might be unable to reach required exertion levels e.g because of spasticity, muscle weakness	Inpatient setting not comparable to outpatient setting (time limit, other therapies)	Setting taking place at clinic where additional individual therapies confound the generalizability of the results in larger MS population
	Short duration	Therapies during inpatient stay having possible impact on results		
		Own critique: depression-outcome was not handled in results in anyway (used only as covariate?)		
		Possible learning effects		
Conclusion	HIT is time-efficient way to increase CRF of pwMS	No confirmation of aerobic capacity-fatigue relationship in pwMS	No superiority of one exercise regime with regard to cognitive performance	Indication that pwMS with cognitive impairment respond differently to aerobic exercise (larger changes) than pwMS with intact cognition
	Regular exercise has anti-inflammatory effects	No evidence of HIIT's larger effect on fatigue than MCT although rate of VO2peak-response was higher	HIIT had positive impact on physical fitness (and adherence rates were good throughout several disability ranges)	Lower cognitive status, HIIT exercise regime and higher EDSS potentially impact changes of cognitive performance in pwMS

Appendix 3. Data extraction table of sources 5-8

	Source 5	Source 6	Source 7	Source 8
Author(s), year	Joisten & Proschinger et al., 2021	Joisten & Rademacher et al., 2021	Wonneberger & Schmidt, 2019	Feltham, et al., 2013
Country	Germany, Switzerland	Germany, Switzerland, UK	Germany	UK
Study type/source	Secondary analyses of two-armed single blinded RCT (Joisten et al.2019)	Secondary analysis of prospective single-blinded RCT	Prospective, monocentric, randomized, single-/unblinded cohort study	Sub-analysis of two-group, single blinded RCT
Aim	Examine the immediate (single-bout) and training (3-week intervention) effects of HIIT versus classical moderate continuous training (MCT) during inpatient rehabilitation on NLR, systemic immune-inflammation index (SII) and platelet-to-lymphocyte-ratio (PLR) in pwMS	Examine acute (single-bout) and training effects of HIIT vs MCT on plasma neurofilament light chain (pNfL) and kynurenine (KYN) pathway to tryptophan degradation metabolites in pwMS	To determine the effects of short-term HIIT on aerobic fitness and fatigue in MS patients	Explore the response during maximal and submaximal exercise in pwMS prior to and following two different 12-week exercise programmes
Population				
Sample size	Total 68, HIIT 35, MCT 33	Total 69; HIIT 35; MCT 34	Total 40; HIIT 22; MT 18	Total 21, Interval 9; Cont 12
Age	Overall 50.3 (10.2); HIIT 50.9.(10.3), MCT 49.7 (10.2)	Overall 50.28(10.12); HIIT 50.89 (10.31); MCT 49.65 (10.04)	Overall 42.1; HIIT 41.6; MT 42.8	I 49.3 (3.5); Cont 52.3 (2.08)
Gender	Overall 42/26 (F/M); HIIT 24/11; MCT 18/15	Overall 43/26 (F/M); HIIT 24/11; MCT 19/15	Total 31/9 (F/M); HIIT 17/5; MT 14/4	
Other demographics				
Disease characteristics				
Type	Overall 42/26 (RRMS/SPMS); HIIT 21/14; MCT 21/12	Overall 42/27 (RRMS/SPMS); HIIT 21/14; MCT 21/13	All RRMS	I 4/4/1 (RRMS/SPMS/PPMS; Cont 5/5/2
Last relapse				
Years since dg		Overall 13.54 (7.95); HIIT 14.8 (8.26); MCT 12.24 (7.5)	Overall 10.9; HIIT 11.1; MT 10.6	
EDSS	Overall 4.5 (1.1); HIIT 4.4 (1.1); MCT 4.6 (1.1)	Overall 4.51 (1.06); HIIT 4.44 (1.06); MCT 4.59 (1.08)	Overall 2.24; HIIT 2.29; MT 2.17	Barthel index used instead: I 19 (18-20); Cont 19 (13-20)
Activity level				
Methodology/methods				
Setting	Clinic (inpatient)	Clinic (inpatient)	Fitness centre (out-patient)	Clinical exercise and rehabilitation centre, community leisure centre (out-patient)
Follow up	No	No	No	No
Co-interventions	Yes, other therapies during clinic stay, details not reported	Yes, other therapies during clinic stay, details not reported	Not reported	Not reported
Adherence			Overall 73% (+/-22%); HIIT 75% (+/-23%);MT 71% (+/-22%)	
Drop outs			Total 11 (27.5%); HIIT 5; MT 6	None? But only 15 session on average completed so no 100% compliance/commitment

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	Source 5	Source 6	Source 7	Source 8
Outcomes and measurement method	Neutrophil-to-lymphocyte ratio (NLR)	Plasma neurofilament light chain (pNfL)	1. Cardiorespiratory fitness (VO2peak)	Cardiovascular and respiratory response
	Systemic immune-inflammation index (SII)	Plasma concentration of tryptophan (TRP), kynurenic acid (KA), kynurenine (KYN) and quinolinic acid (QR)	Ramp test	Stepwise incremental cycle ergometer
	Platelet-to-lymphocyte ratio (PLR)	Interleukin-6 (IL-6)	2. Fatigue	HR- monitor
	All from blood samples	All from blood samples	FSS	RPE
			2. Walking speed	BP
			T25-FW	
Results	Significant reduction in NLR and SII after HIIT intervention	Indication of negative association between pNfl and processing speed and visuospatial memory at baseline correlations	Significant increase in aerobic fitness in HIIT group	No change in BP or RER
	Greater immediate alterations in all three cellular inflammation markers from HIIT than MCT	Decreased pNfl and increased KYN pathway flux toward neuroprotective end product (kynurenic acid=KA) from acute exercise	Mean improvement of 3.0ml/min/kg can be achieved with 8 weeks of HIIT	Significant increase in normalised oxygen uptake (VO2norm) in both exercise groups
		Positive correlation between pNfl and KA changes, negative correlation between pNfl and quinolinic acid-to-KA ratio	Significant decrease in fatigue among sub-group with elevated fatigue in both groups	Change in cardiovascular response for submaximal exercise: Adrupt/non-linear HR reversed to linear
		Greater changes in HIIT than MCT group	No change in T25-FW (walking speed) but EDSS low in both groups meaning no significant gait impairment at baseline	
		KYN pathway activation in HIIT group after 3-week training		
Adverse events			1 relapse, 1 LBP (both dropped out)	
Limitations		Short duration, clinic setting	Dropouts mainly pw fatigue indicating possible overexertion from 3x/week sessions, but not related to ex modality since equal distribution between both groups	Some participants struggeled to maintain required cycling RPM
			Difference in aerobic fitness at baseline	Limited compliance to rx sessions
Conclusion	Physical rx and especially HIIT can attenuate inflammation in MS and hence possibly contribute to disease-specific symptom alleviation	Acute rx diminishes pNfL levels and indicates potential alleviation of ongoing neurogeneration	HIIT seems to be safe and time-efficient way to improve aerobic fitness in pwMS	Maximal rx capacity increased but less than expected in both continuous and interval group
		"Exercise mediated KYN pathway rerouting toward KA as end product is associated with pNfL reductions and might be responsible for neuroprotective effects. Overall, HIIT leads to greater responses than MCT, emphasizing the importance of higher exercise intensities when exercising with pwMS"	Could reduce fatigue among those with it	Non-linear HR response reversing to linear may suggest decontioning rather than autonomic dysfunction for the baseline reason/autonomic dysfuntion can improve from rx in pwMS