Archives of Physical Medicine and Rehabilitation
journal homepage: www.archives-pmr.org
Archives of Physical Medicine and Rehabilitation 2024;105: 1545−58

SYSTEMATIC/META-ANALYTIC REVIEWS

Is High-Intensity Interval Training More Effective Than Moderate Continuous Training in Rehabilitation of Multiple Sclerosis: A Comprehensive Systematic Review and Meta-analysis

Hussein Youssef, MSc,[a,b,c] Mine Nur Gönül, BSc,[a,b,d] Mohamed Gomaa Sobeeh, PhD,[e,f] Kardelen Akar, MSc,[a,b] Peter Feys, PhD,[c,g] Koen Cuypers, PhD,[c,h,i] Atay Vural, MD, PhD[a,b,j]

From the [a]Koç University Research Center for Translational Medicine (KUTTAM), İstanbul, Türkiye; [b]Koç University Graduate School of Health Sciences, İstanbul, Türkiye; [c]Hasselt University, Faculty of Rehabilitation Sciences, REVAL Rehabilitation Research Center, Diepenbeek, Belgium; [d]University of Health Sciences, Department of Physical Therapy, İstanbul, Türkiye; [e]Cairo University, Faculty of Physical Therapy, Department of Physical Therapy for Musculoskeletal and its surgeries, Giza, Egypt; [f]Sinai University, Faculty of Physical Therapy, Department of Physical Therapy for Orthopedics and Orthopedic Surgery, Ismailia, Egypt; [g]Universitair MS Centrum Hasselt-Pelt, UMSC, Belgium; [h]Movement Control and Neuroplasticity Research Group, Biomedical Sciences, KU Leuven, Tervuurse Vest 101, Leuven 3001, Belgium; [i]Leuven Brain Institute, KU Leuven-LBI, Leuven, Belgium; and [j]Koç University School of Medicine, Department of Neurology, İstanbul, Türkiye.

Abstract

Objectives: The present study aimed to conduct meta-analysis to determine whether the high intensity interval training (HIIT) protocol is more beneficial in improving outcome measures compared to moderate continuous training (MCT) in people with multiple sclerosis (PwMS). It also aimed to systematically review the exercise protocols differences.

Data Sources: A search strategy, locating HIIT in PwMS, was executed in six databases, PubMed, EMBASE, Web of Science, Central Cochrane, Pedro, and Ovid MEDLine.

Study Selection: Randomized control trials of HIIT utilizing cycle ergometer or recumbent stepper as exercise modalities were included in analysis. Intervention arms should include at least two intervention arms, including HIIT in one arm, and MCT in the other group.

Data Extraction: Data extracted from each study includes the following items: basic details of the study (such as author, date of publication, location, and study design), participant characteristics (sample size, mean age, sex, mean disease duration, and extended disability status scale), specifications of the HITT protocol (exercise modality, session duration, number of intervals/session, interval intensity, recovery intensity, recovery interval, and adverse effect), as well as primary outcomes at baseline and post-intervention (cardiorespiratory fitness, fatigue, body composition, cognitive functions, and blood biomarkers).

Data Synthesis: 22 studies included in the systematic review, 11 were included in random effects model pooled analysis. There was a significant effect in favor of HIIT for VO2max of cardiorespiratory functions compared to MCT (ES=0.45 95%, CI [0.14, 0.76], *P*=.004), and for memory domain of cognitive functions (ES=0.34 95% CI [0.05, 0.63], *P*=.02). Statistical significance was not achieved for the other variables.

Conclusion: HIIT and MCT yield similar results in terms of fatigue, body composition, cognitive functions, and blood biomarkers. However, VO2max of cardiorespiratory functions and memory domain of cognitive functions were in favor of HIIT protocol.

Archives of Physical Medicine and Rehabilitation 2024;105:1545−58

Multiple sclerosis (MS) is a chronic inflammatory neurological disorder,[1] which is a serious cause of disability, characterized by a progressive course of disease followed by frequent relapses.

Protocol Registration: The protocol of this study was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the number CRD42023392168.

Funding: No funding was received for this research.

Disclosures: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

0003-9993/$36 - see front matter © 2024 by the American Congress of Rehabilitation Medicine.
https://doi.org/10.1016/j.apmr.2023.12.012

Recurrent attacks accumulate various visible defects, such as motor, sensory, and urinary dysfunctions,[1] but also invisible (silent) complications, such as fatigue, pain, emotional, and cognitive manifestations.[2] PwMS usually undergo disease-modifying therapies (DMTs), however, pharmacological DMTs alone did not meet the expectations of PwMS and the MS community in stopping the disease progression, and it is not sufficient to rely solely on DMTs to stop or slow down the disease progression.[3] In addition to pharmacological DMTs, nonpharmacological options are gaining more and more interest.[3] Exercise therapy is a promising and safe alternative DMT for PwMS,[4] as an integral part of improving health-related physical fitness, the Canadian Physical Activity Guidelines for adults with mild to moderate disability caused by MS prescribe two times per week of 30 minutes of moderate-intensity aerobic activity.[5] Exercise therapy include many different forms such as aerobic exercises,[6] high-intensity interval training (HIIT),[7] etc. HIIT provides evidence in improving cognitive[8] working memory,[9] fatigue, and cardiorespiratory[10] in PwMS. HIIT's main advantage is the shorter duration required to achieve a greater benefit, this feature is attained by the severe intensity of HIIT protocols in comparison to the low to moderate intensity of aerobic exercises.[11]

Main difference between HIIT and moderate continuous training (MCT) is the intensity of the training, MCT intensity is 50-70% of maximum heart rate (HR_{max}), maximal oxygen consumption, or work load for duration lasting 30-60 minutes,[12,13] on the other hand, intensity of the HIIT protocols is considered high, since it could reach up to 85-95% HR_{max} during the bursts of active intervals of around 30-60 seconds, interspersed with active recovery periods.[14] Most HIIT protocols in PwMS implement recumbent stepping or cycle ergometer as exercise modality. While fitness programs for people without mobility disabilities often employ treadmills,[12] these may not be suitable for people with critical mobility problems. Recumbent stepping has been suggested by the American College of Sports Medicine as a suitable and effective diagnostic tool to assist in determining aerobic fitness in neurological patients.[15] A systematic review supported the effectiveness and safety of HIIT in boosting fitness in MS patients with mild impairment.[7]

Research studies have shown that PwMS tend to have lower levels of cardiovascular fitness compared to healthy individuals.[16] Furthermore, it has been found that there is an inverse relationship between the severity of the disease and level of impairment, and cardiovascular fitness; as the disability and fatigue caused by MS increase, cardiovascular fitness decreases,[17,18] Therefore, although cardiovascular fitness is an essential component of overall health and wellness, PwMS may struggle with maintaining optimal levels of cardiovascular fitness. The primary objective of the current systematic review and meta-analysis is to determine the effectiveness of the HIIT protocol in improving outcome measures such as enhancing cardiorespiratory fitness, reducing fatigue, impacting associated functional, cognitive, and biomarkers measures in comparison to MCT. In addition to identify the variations between the two training intervention protocols within PwMS, as a secondary objective.

List of abbreviations:

DMT	**disease-modifying therapy**
EDSS	**expanded disability status scale**
FSMC	**Fatigue Scale for Motor and Cognitive Functions**
HIIT	**high intensity interval training**
HR_{max}	**maximum heart rate**
MCT	**moderate continuous training**
MICT	**moderate-intensity continuous training**
MS	**multiple sclerosis**
PROSPERO	**International Prospective Register of Systematic Reviews**
PwMS	**people with multiple sclerosis**
RER_{max}	**maximum respiratory exchange ratio**
RCT	**randomized controlled trials**

Methods

This study was a systematic review and meta-analysis that followed the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions.[19] The article search and data extraction were carried out independently by three investigators, and any disagreements were resolved through discussion or with the help of a third author (HY, MG, and MS).

Protocol registration

Before initiating our search strategy, we checked both the Prospero database and Cochrane Library of systematic reviews to make sure that similar work was not already published or in progress. The study was registered and got approval in the International Prospective Register of Systematic Reviews (PROSPERO) (with PROSPERO ID CRD42023392168).

Search strategy

Our systematic search contained all relevant studies reported in the PubMed, EMBASE, Web of Science, Central Cochrane, Pedro, and Ovid MEDLine databases. Publication dates ranged from January 1, 2009, to January 20, 2023. The keywords used in the literature search included multiple sclerosis and high intensity interval training. A combined search was performed in different databases as follows: (HIIT and MS) OR (High intensity interval training and multiple sclerosis) (((multiple sclerosis) OR (relapsing remitting) OR (chronic progressive) or (secondary progressive) OR (primary progressive))) AND (((High intensity interval training) OR (interval training) or (High intensity interval exercise) OR (interval exercise) OR (aerobic interval training) OR (high intensity) OR (high-intensity) OR (exercise intensity) or (HIIT) or (HIT))). There were no restrictions on study design or publication date during the search. Duplicate articles were eliminated by using Endnote software, then, the selection of research was done through a two-step process, which involved preliminary screening of titles and/or abstracts and secondary screening of full-text articles. The reference lists of relevant review articles and meta-analyses were also checked to ensure that all potentially eligible studies were included.

Selection criteria

The research included studies with specific types of designs (randomized controlled and cohort), published in English, and that focused on persons diagnosed with MS, without regard to age, sex, or MS phenotype. Included studies looked at the effects of HIIT on MS and the data from these studies was used to estimate outcomes including mean and standard deviation values. The intervention arms should include at least two intervention arms, including HIIT in one arm, to be included in the meta-analysis. The HIIT protocols must have been conducted using a bicycle ergometer or recumbent stepper, however, protocols conducted on treadmill machines[20] have been excluded. Our decision to exclude treadmill-based protocols was based on specific criteria chosen to maintain consistency and minimize variability between the studies included in our meta-analysis, this would ensure maintaining the homogeneity in exercise modalities. We aimed to focus on exercise modalities that are more universally applicable to individuals with various levels of mobility and to evaluate the safety and efficacy of these specific modalities, as they are more likely to be used in clinical settings, treadmill training may not be suitable for individuals with critical mobility problems. Treadmill training may indeed require different motor capabilities and involve additional musculoskeletal efforts compared to bicycle ergometers or recumbent steppers.[6]

Studies that included high-intensity aerobic training protocols without specifying a definitive interval of high intensity, where only one of the following is achieved during the short burst interval for each exercise cycle (≥80% HR_{max}, ≥80% maximal oxygen consumption (VO_{2max}), or ≥80% workload)[14] have been excluded. The intervals of HIIT protocols should be repeated over more than one bout/cycle per session and should be specified within the study design.

Studies were excluded if they did not have enough or complete information after the authors were contacted for additional data. Studies that were case reports, abstracts, reviews, or animal experiments were excluded.

Data extraction

Two researchers (HY and MG) screened the articles, which were then verified by a third researcher (MS). Next basic details of the study (such as author, date of publication, location, and study design), participant characteristics (sample size, mean age, sex, mean disease duration, and expanded disability status scale (EDSS) score), specifications of the HITT protocol (exercise modality, session duration, number of intervals/session, interval intensity, recovery intensity, recovery interval, and adverse effect), as well as primary outcomes at baseline and post-intervention (cardiorespiratory fitness, fatigue, body composition, muscle power, cognitive functions, and blood biomarkers) were extracted (HY, MG and KA). The authors of the study provided us with the data that we had requested.[21]

Outcome assessment

The outcome analysis involved evaluating changes from baseline to specific time points. Short-term effects were considered to be those that occurred within two weeks after the end of the intervention. The earliest post-intervention data was used for short-term effect evaluation if more than one time point was available in the study. Fatigue improvement was measured using the Fatigue Scale for Motor and Cognitive Functions (FSMC).[22] Cardiorespiratory fitness improvement was assessed by examining changes to VO_{2max}, HR_{max}, and maximum respiratory exchange ratio (RER_{max}). Body composition was evaluated by changes in lean tissue mass/fat-free mass (kg) and fat percentage (%). Cognitive functions were measured using the Brief International Cognitive Assessment for MS;[23] which includes three tests evaluating the main cognitive domains affected by MS: information processing speed, verbal and visual memory, including the Symbol Digit Modalities Test,[24] California Verbal Learning memory Test-II (CVLMT-II),[25] and Brief Visuospatial Memory Test-Revised.[26] Lastly, the blood markers which is mentioned in some HIIT studies are included within the review, such as the serum neurofilament light chain and kynurenine.[21]

Quality assessment

The quality of each study was assessed by two authors (HY and MS) using the PEDro scale,[27] a reliable and validated tool for evaluating the quality of randomized controlled trials (RCTs) in physiotherapy. It has 11 items that assess important aspects of trial methodology, including randomization, blinding, reporting, allocation concealment, selective reporting, and other potential biases. If there was any disagreement, it was resolved through negotiation with a third author.

Statistical analysis

A meta-analysis of the pooled effect sizes of all outcomes using the DerSimonian-Liard model was performed. This random effect model takes into account the possibility of inconsistencies and incorporates a larger standard error by assigning a slightly higher weight to smaller studies and a lower weight to larger studies. To analyze the data, we utilized the RevMan meta-analysis software and employed an inverse variance statistical method based on a random effects analysis model. The results of the meta-analysis were reported as the between-groups effect size with a 95% confidence interval, comparing the standardized mean difference of the HIIT group with the active comparator (MICT or medium-intensity cardiovascular training) for each study. The threshold for statistical significance was set at P=.05, and effect sizes were categorized as small (0.20), medium (0.50), large (0.80), and very large (1.20).[28]

Assessment of heterogeneity

The heterogeneity of each meta-analysis was estimated using three measures: Tau,[2] which is the estimate of the between-study variance of the group; chi-square, which represents the probability that the differences in results are due to chance alone; and I,[2] which reflects the heterogeneity caused by between-study variance. Absolute thresholds are not recommended in this regard.[29] In this review, a chi-square P-value less than or equal to 0.05 was considered as an indication of heterogeneity. The values of I^2 were interpreted as mentioned in Cochrane Handbook for Systematic Reviews of Interventions[19] as follows: 0−40%: might be low heterogeneity, 30−60%: may represent moderate heterogeneity, 50−90%: may represent substantial heterogeneity, and 75%: considerable heterogeneity.

Results

Literature search results

The initial search for articles resulted in 701 potential articles found through electronic search and 8 additional articles found through manual search of reference lists. After eliminating 178 duplicate articles, 523 articles were evaluated based on their titles and abstracts. Out of these, 492 were determined to be ineligible

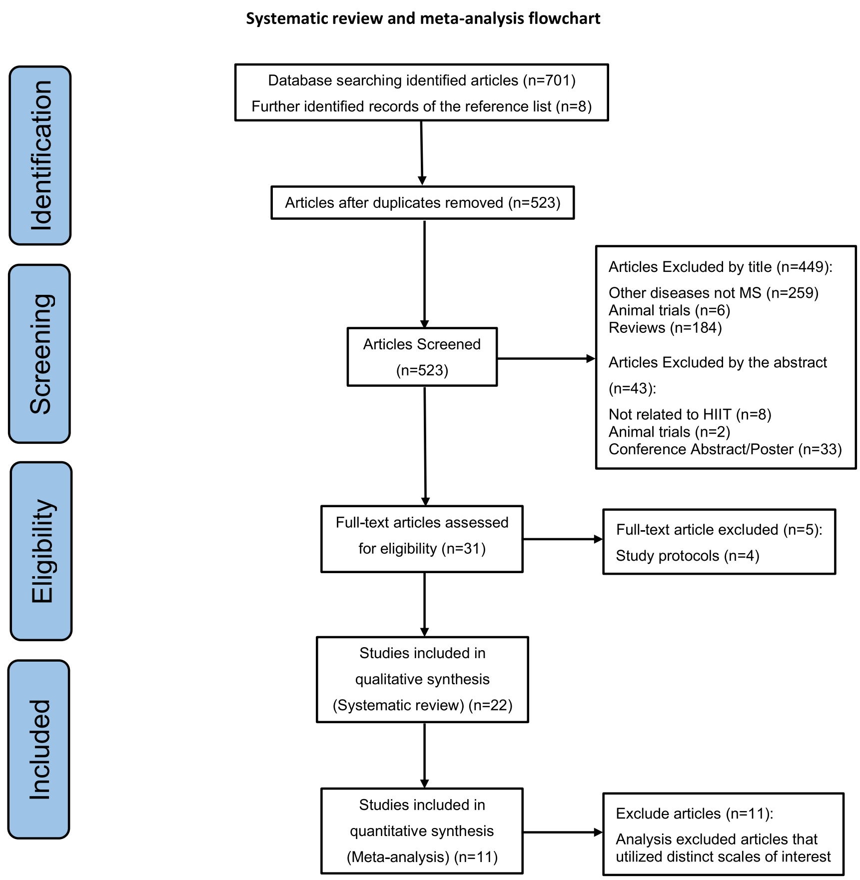

Fig 1 PRISMA flow diagram of studies' screening and selection.

and 31 were chosen for further evaluation by reading the full texts. After a review by three members of the research team, 9 were excluded from the meta-analysis,[21,30-35] and 11 articles were included in the meta-analysis.[8,21,36-46] Included in the meta-analysis were a total of 11 randomized controlled trials (RCTs).

The PRISMA flow diagram of the study selection process is shown in figure 1.

Study characteristics

The authors of this study would like to emphasize that only RCTs were included in the meta-analysis to assess the effect of either HIIT or MCT, while other study designs, such as cohort studies, were not considered in the data analysis.

The characteristics of the eligible studies for the meta-analysis are summarized in table 1. Twenty-two articles, of which nineteen were RCTs and three were cohort studies[10,33,42] were included in this review.

Many studies refer to the active comparison groups in aerobic training programs by different terms such as moderate-intensity continuous training (MICT), medium-intensity cardiovascular training,[45] or active control training group.[8,30] These names reflect the moderate intensity of the programs, which typically involve a maximum of 70% HR_{max}, VO_{2max}, or workload. These different names for the same concept are all considered to be moderate continuous training (MCT) in the program specifications as shown in table 1. In this review, the use of a cycle bike as an intervention method is discussed. It is referred to by various names, including bicycle ergometer, cycle ergometer, or static cycle. However, for the purposes of this review, it referred to as a cycle ergometer.

In total, 947 PwMS with the following MS phenotypes: relapse-remitting MS (RRMS, n=553), secondary progressive MS (SPMS, n=277) and primary progressive (n=10), were included. Regarding the phenotype, seventeen studies involved RRMS, twelve studies involved SPMS, five study studies involved PPMS and three studies did not provide this information. Study characteristics and summary of intervention protocols are shown in tables 2 and 3.

Three studies had a three-arm parallel design that compared HIIT protocol to the MCT protocol, or resistance training.[40,43,47] Two other studies also had one-arm that compared or combined resistance training with the HIIT protocol.[10,31,42,43] Only two studies included a recumbent stepper as intervention modality,[33,44] the rest of the studies considered a cycle ergometer instead. One study reported side effects; HIIT (n=4), during cycling; pain (n=2), exacerbation of MS symptoms (n=1), loss of consciousness (n=1), and combined group (n=3), one patient for; tachycardia, leg pain, exacerbation of a knee injury, however no adverse effects has reported for the continuous group,[47] other studies reported no adverse effects noticed during the interventions.[8,30,33,35,38,40,42-44,46,48] The rest of the studies did not report detail regarding the adverse effects of the interventions.[10,21,31,32,34,36,37,39,41,45]

The frequency each outcome measure was mentioned in each study is displayed in figure 2.

Table 1 Characteristics of the studies (n=11) that were included in the meta-analysis to evaluate the effect of High intensity interval training in comparison to the active comparator group within the multiple sclerosis population

Author and Year	Study Design	Country	Intervention	Sample Size (M/F)	Age (Years) Mean ± SD	Participants Condition Disability	Clinical Trials Gov (yes/no)	Disease Type (RR/PP/SP)	Disease Severity (EDSS)	Disease Duration (Years)	Groups
Feltham et al., 2013[45]	RCT	United Kingdom	Cycle ergometer	NR	51 ± 3	NR	No	9/3/9	NR	NR	HIIT, MCT
Skjerbæk et al., 2014[44]	RCT	Denmark	Recumbent Cross-Trainer	3/8	58.9 ± 7.5	6.5 ≤ EDSS ≤ 8.0	Yes	0/3/8	NR	NR	HIIT, CG
Wens et al., 2015[43]	RCT 3 arms	Belgium	Cycle ergometer	12/22	45.5 ± 3.4	McDonald criteria (EDSS range 1−5)	Yes	26/ CP=8	2.49 ± 0.33	NR	HIIT, HCT, and CG
Bansi et al., 2018[41]	RCT	Switzerland	Cycle ergometer	19/38	49.4 ± 11.11	revised McDonald criteria (EDSS range 1.0−6.5)	Yes	33/0/24	4.37 ± 1.18	4.37 ± 1.18	HIIT, MCT
Zimmer et al., 2018[46]	RCT	Switzerland	Cycle ergometer	19/38	49.4 ± 11.11	revised McDonald criteria (EDSS range 1.0−6.5)	Yes	30/0/27	4.37 ± 1.18	4.37 ± 1.18	HIIT, MCT
Guillamó et al., 2018[40]	RCT 3 arms	Spain	Cycle ergometer	8/21	42.3 ± 1.07	EDSS < 3.0	No	29/0/0	1.5 ± 0.5	NR	HIIT, MCT, and CG
Rademacher et al., 2020[8]	2 RCT	Switzerland	Cycle ergometer	44/86	49.9 ± 10.7	Revised McDonald criteria (EDSS range 1.0−6.5)	Yes	77/0/53	4.45 ± 1.11	NR	HIIT, MCT
Lea Schlagheck et al., 2021[39]	RCT	Switzerland	Cycle ergometer	45/86	49.92 ± 10.73	Revised McDonald criteria (EDSS range 1.0−6.5)	Yes	78/0/53	4.5 ± 1.1	NR	HIIT, MCT
Rademacher et al., 2021[37]	RCT	Switzerland	Cycle ergometer	26/48	50 ± 10.5	Revised McDonald criteria (EDSS range 3.0−6.0)	Yes	45/0/29	4.5 ± 1.05	NR	HIIT, MCT
Keytsman et al., 2021[38]	RCT	Belgium	Cycle ergometer	11/17	41.9 ± 8.9	EDSS	Yes	29/0/2	2.3 ± 1.3	NR	HIIT, MCT
Wolf et al., 2022[36]	RCT	Switzerland	Cycle ergometer	45/86	49.92 ± 10.73	Revised McDonald criteria (EDSS range 1.0−6.5)	Yes	78/0/53	4.5 ± 1.1	NR	HIIT, MCT

Abbreviations: CG, control group; CP, chronic progressive; ET, exercise training; HIIT, high-intensity interval training; HCT, high intensity continuous training; MCT, moderate continuous training; NR, not reported; PP, primary progressive; RCT, randomized controlled trial; RR, relapse remitting; RT, resistance training; SP, secondary progressive.

Effect of HIIT Versus MCT on cardiorespiratory fitness outcome

Cardiorespiratory fitness outcome was investigated in total eight studies (n=360) as shown in figure 3.[20,37-40,43-46] VO_{2max} shows significant difference between groups in favor of HIIT group (Effect size (ES)=0.45, 95% CI [0.14, 0.76], *P*=.004). For VO_{2max}, low heterogeneity was evident, with two of eight studies reporting significant findings in active comparator of MCT. HR_{max} investigated in five studies (n=99)[38,40,43-45] shows no significant difference between HIIT versus comparator group (ES=0.35 95% CI [-0.31, 1.01] *P*=.3). For HR_{max}, there was a moderate heterogeneity. RER_{max} was investigated in five studies (n=88),[38,40,43,45] however, no significant difference between HIIT versus comparator group (ES=-0.13; 95% CI [-0.55, 0.29] *P*=.54) was reported. For RER_{max}, no heterogeneity was evident.

Effect of HIIT versus MCT on fatigue outcome

Fatigue outcome assessed by FSMC was investigated in three studies (n=215), see figure 4A.[8,36,44] and did not show significant differences between HIIT versus comparator group (ES=0.2 95% CI [-0.07, 0.47] *P*=.15). For FSMC, no heterogeneity was evident.

Effect of HIIT versus MICT on body composition outcome

Body composition outcomes was investigated in two studies (n=51) as shown in figure 4B.[20,38,43] Lean tissue/fat free mass shows no significant differences between HIIT versus comparator group (ES=-0.32 95% CI [-0.52, 1.17] *P*=.45). For lean tissue, moderate heterogeneity was evident. Fat percentage shows no significant differences between HIIT versus comparator group (ES=-0.03 95% CI [-01.40, 1.34] *P*=.96). For fat percentage, heterogeneity was substantial.

Effect of HIIT versus MICT on cognitive functions outcome

Cognitive functions were measured in two studies (n=187) using the Brief International Cognitive Assessment for MS as shown in figure 4C.[8,20,37,46] The Symbol Digit Modalities Test was investigated in two studies (n=187)[8,20,37,46] but no significant difference between HIIT versus comparator group was found (ES=0.06 95% CI [-0.23, 0.34] *P*=.7). No heterogeneity was evident. VLMT was investigated in three studies (n=187)[8,37,46] and shows significant difference between HIIT versus comparator group (ES=0.34 95% CI [0.05, 0.63] *P*=.02). No heterogeneity was evident. Brief Visuospatial Memory Test-Revised was investigated in two studies (n=187)[8,20,37,46] shows no significant difference between HIIT versus comparator group (ES=0.08 95% CI [-0.22, 0.36] *P*=.63). No heterogeneity was evident.

Effect of HIIT versus MICT on blood biomarkers

Blood biomarkers measures outcomes were investigated in two studies (n=68) as shown in figure 4D.[21,41] kynurenine shows no significant difference between HIIT versus active comparator group (ES=-0.16 95% CI [-0.51, 0.19] *P*=.38). No heterogeneity was evident. Serum neurofilament light chain shows no significant difference between HIIT versus active comparator group (ES=0.04 95% CI [-0.39, 0.47] *P*=.87). No heterogeneity was evident.

Risk-of-bias analysis

PEDro scores ranged from three to eight out of ten as shown in table 4. Eight articles were regarded to be of high quality with a score of seven[32,35,41,43-45,48] or eight.[8,21,30-32,34,36,38,39,46] Points were commonly lost because of a lack of blinding of either participants or therapists.

Table 2 Training protocol characteristics of the studies (n=22).

			Training Protocol Characteristics													
			General Specifications			HIIT Protocol							Comparator Protocol			
Author and Year	Study Design	Groups	Exercise Modality	Duration (Weeks)	Sessions/ Week	Session Duration (min)	Intervals/ Session	Interval Intensity (%)	Interval (sec)	Recovery Intensity	Recovery (sec)	Warm Up / Cooling Down (min)	Name	Session Duration (min)	Session Intensity (%)	Warm Up / Cooling Down (min)
Collett et al., 2011[47]	RCT 3 arms	Continuous Intermittent Combined	Static Bike	12	2	20	20	90% W_{peak}	30	NR	30	NR	Cont Combined	20 20	45% W_{peak} Intermittent 90% W_{peak} Cont 45% W_{peak}	NR NR
Feltham et al., 2013[45]	RCT	Cont Int	Static Bike	12	2	20	20	90% W_{peak}	30	NR	30	NR	Cont	20	45%W_{peak}	NR
Skjerbæk et al., 2014[44]	RCT	EXE CG	Recumbent Cross-Trainer	4	Total 10	60	6	65%–75% VO_{2peak}	180	NR	NR	5 / NR	CT	-	-	-
Wens et al., 2015[43]	RCT 3 arms	SED $H_{TR}R$ $H_{CT}R$	Cycle ergometer	12	5/2	NR	5	80–90% HR_{max} (0-6w) 90-100% HR_{max} (6-12w)	60	NR	60	5/ NR	SED $H_{CT}R$	- NR	- 80–90% HR_{max}	- NR
Farup et al., 2016[31]	RCT	HC $H_{TR}R$ $H_{CT}R$	Bicycle ergometer	12	5/2	NR	5	100% to 100-120 HR_{max}	From 60 to 120	NR	60	NR	$H_{CT}R$	From 6 up to 20	80-90% HR_{max}	NR
Wens et al., 2017[48]	RCT 3 arms	SED $H_{TR}R$ $H_{CT}R$	Cycle ergometer	12	5/2	NR	5	80–90% HR_{max} (0-6w) 90-100% HR_{max} (6-12w)	60	NR	60	5/ NR	SED $H_{CT}R$	- NR	- 80-90% HR_{max}	- NR
Zaenker et al., 2018[10]	Cohort	Combined (ET, RT, AS)	Cycle ergometer	12	1	20	5	90% and 110% MTP	60	~55% VO_{2peak}	180	10/ NR (ET) NR/15-20 (RT)	-	-	-	-
Keytsman et al., 2019[42]	Cohort	HICT	Cycle ergometer	12	5/2	NR	5	85-90% HR_{max} (0-6w) 100% HR_{max}	From 60 up to 120	NR	60	NR	-	-	-	-
Bansi et al., 2018[41]	RCT	HIT CT	Cycle ergometer	3	3 (HIT) 5 (CT)	20	5	85-90% HR_{max}	180	50-60% HR_{max}	90	2/2	CT	26	70% HR_{max}	2/2
Zimmer et al., 2018[46]	RCT	HIT CT	Cycle ergometer	3	3 (HIT) 5 (CT)	20	5	85-90% HR_{max}	180	50-60% HR_{max}	90	2/2	CT	26	70% HR_{max}	2/2
Guillamo et al., 2018[40]	RCT 3 arms	CFTFG HG CG	Cycle ergometer	40	6	90	3	Borg 13-15	30	NR	30	NR	HG	90	50-85% age predicted HR_{max}	5-15 / 5-15 (HG)
Rademacher et al., 2020[8]	2 RCT	HIIT MCT	Bicycle ergometer	3	3 (HIIT) 3-5 (MCT)	NR	5	85-90% HR_{max} (RCT1) 95-100% HR_{max} (RCT2)	180 (RCT1) 90 (RCT2)	50-60% HR_{max}	NR	NR	MCT	29 (RCT1) 31 (RCT2)	60-70% HR_{max}	2/3
Lea Schlagheck et al., 2021[39]	RCT	HIIT MCT	Bicycle ergometer	3	3 (HIIT) 3-5 (MCT)	NR	5	85-90% HR_{max} (RCT1) 95-100% HR_{max} (RCT2)	180 (RCT1) 90 (RCT2)	50-60% HR_{max}	90 (RCT1) 120 (RCT2	2-3/2-3	MCT	30	65% to 70% HR_{max}	2/3
Rademacher et al., 2021[37]	RCT	HIIT CG	Bicycle ergometer	3	3	23.5	5	95-100% HR_{max}	90	60% HR_{max}	120	3/3	CG	30	65% HR_{max}	3/3
Joisten, Proschinger, et al., 2021[34]	RCT	HIIT MCT	Bicycle ergometer	3	3	23.5	5	95-100% HR_{max}	90	60% HR_{max}	120	3/3	MCT	30	65% HR_{max}	3/3
Keytsman et al., 2021[38]	RCT	Periodized HIIT CCEEP	Cycle ergometer	12	1-3 (HIIT) 2-3 (CCEEP)	12	3	NR	20	NR	120	2/3	CCEEP	60	60-70% HR_{max} (0-3w) 70-80% HR_{max} (3-12w)	5/5
Wolf et al., 2022[36]	RCT	HIIT MCT	Cycle ergometer	3	3 (HIIT) 3-5 (MCT)	27.5 (RCT1) 22.5 (RCT2)	5	85-90% HR_{max} (RCT1) 95-100% HR_{max} (RCT2)	180 (RCT1) 90 (RCT2)	50-60% HR_{max} (RCT1) 60% HR_{max} (RCT2)	90 (RCT1) 120 (RCT2)	2/3	MCT	30	70% HR_{max} (RCT1) 65% HR_{max} (RCT2)	2/2 (RCT1) 3/3 (RCT2)
Collett et al., 2017[30]	RXT		Cycle ergometer	1-2	Total 3	20	20	90% W_{peak}	30	50 rpm	30	NR	45% Con 60% Con	20 20	45% W_{peak} 60% W_{peak}	NR NR

(*continued on next page*)

Table 2 (*Continued*)

Author and Year	Study Design	Groups	Training Protocol Characteristics: General Specifications: Exercise Modality	Duration (Weeks)	Sessions/ Week	HIIT Protocol: Session Duration (min)	Intervals/ Session	Interval Intensity (%)	Interval (sec)	Recovery Intensity	Recovery (sec)	Warm Up / Cooling Down (min)	Comparator Protocol: Name	Session Duration (min)	Session Intensity (%)	Warm Up / Cooling Down (min)
Jorissen et al., 2018[32]	RCT	45% Con 60% Con %90 Intermittent HIIT MIT	Cycle ergometer	12	5/2	NR	5	~100-120 VO	From 60 to 120	NR	60	5/ NR	MIT	NR	60% VO_{2peak}	NR
Hubbard et al., 2019[33]	Cohort	HIIT Con	Recumbent stepper	NR	Total 1	30	10	90% VO_{2max}	60	15W	60	5/5	Con	20	50-60% VO_{2peak}	5/5
Wonneberger &Schmidt, 2019[35]	RCT	MT HIIT	Bicycle ergometer	8	3	30	8	70% W_{peak}	60	50% W_{peak}	60	7.5/7.5	MIT	30	50% W_{peak}	7.5/7.5
Joisten, Rademacher, et al., 2021[21]	RCT	HIIT MCT	Bicycle ergometer	3	3	23.5	5	95-100% HR_{max}	90	60% HR_{max}	120	3/3	MCT	30	65% HR_{max}	3/3

Abbreviations: AS, autonomous session; CCEEP, classic continuous endurance exercise program; CFTFG, combined face-to-face group; Cont, continuous; CG, control group; ET, exercise therapy; EXE, intervention group; $H_{IT}R$, high intensity interval + resistance training; HICT, high intensity concurrent training; HIIT+RT, $H_{CT}R$ high intensity continuous endurance + resistance training; HIT, high intensity training; HIAE, high intensity aerobic exercise; HG, home based exercise group; Int, interval; MTP, maximal tolerated power; MT, moderate training; MIT, medium-intensity cardiovascular training; NR, not reported peak; VO_{2peak}, peak rate of oxygen consumption, RCT, randomized controlled trial; RT, resistance training, W_{peak}, peak workload/work rate; SED, sedentary control group

Discussion

The aim of this review was to assess and compare the current evidence regarding changes in objective outcome measures in PwMS in response to moderate continuous and high-intensity interval exercise training. In terms of functional outcome measures, despite, most studies reported on cognition, fatigue, cardiorespiratory function, and body composition, few studies aimed to study blood-based biomarkers. The current meta-analysis indicated no significant difference in the improvements of those outcome measures between HIIT and MCT, except for VO_{2max}, which increased more in the HIIT group, and improving of the verbal retrieval and recalling of information related to the memory domain assessed by VLMT of cognitive functions.

There were some variances related to exercise protocols between studies; the range of interval and recovery durations were variable between studies, ranging from 30 to 180 seconds per interval, as shown in table 2. Also, the intervention duration was different ranging from 3 weeks (8 studies) to 40 weeks (one study), patients of 9 studies performed the intervention over 12 weeks. The mean disease duration mentioned in 2 out of 11 studies included in the meta-analysis. Overall EDSS of PwMS varied from 1.0 to 6.5, with a study average between 2.0 to 4.0, which could be considered as another confounding factor.

The main advantage of HIIT is that it requires less time to achieve better results due to its high intensity compared to the low to moderate intensity of MCT, for example, the present guidelines from the American College of Sports Medicine and the UK Chief Medical Officers suggest that adults, including older adults, should aim for 150 minutes of moderate-intensity activity (corresponding to 55-70% of maximum heart rate or 40-60% of maximum oxygen uptake) or 75 minutes of vigorous-intensity activity (70-90% of maximum heart rate or 60-85% of maximum oxygen uptake) every week as part of their physical activity routine.[12,13] The current review provides insight into the effectiveness of HIIT in achieving similar outcomes to MCT, making it a more time-efficient option for PwMS.[49] This could enhance the enjoyment of training and increase motivation to engage in regular exercise.[50]

Our finding showing no superior extra beneficial effects of HIIT protocols, except for VO_{2max}, is in agreement with another review in a population of healthy older people. In this study, no superiority of HIIT over MCT regarding the functional movement outcomes was reported.[51] However, other reviews showed that HIIT was more efficient than MCT in improving cardiorespiratory functions and VO_{2max} in particular in patients with heart failure,[52] coronary artery disease[53] and cerebral stroke.[54] Data from a cohort of 469 PwMS revealed a decline in cardiorespiratory fitness, specifically measured as VO_{2peak}, as they age. This trend was observed to be consistent when compared with a control group of healthy individuals. These findings underscore the significance of incorporating exercise interventions as preventive measures for PwMS. HIIT emerged as particularly effective in mitigating the decline in cardiorespiratory fitness, demonstrating superior outcomes compared to MCT.[55]

The history of HIIT protocols did not originate with a focus on patients or even the general population's health, however, coaches have traditionally utilized HIIT to enhance the performance of elite endurance athletes who already possess the required cardiorespiratory fitness and physiological capacity for such exercise programs.[56] Highly trained endurance athletes typically precede their HIIT training programs with an initial phase focused on building an 'aerobic base', which is then followed by HIIT sessions closer

Table 3 Summary of the studies (n=22) included in the review.

Author and Year	Criteria EDDS Score, Number of Patients, MS Phenotypes, Drop Out	Outcome Measures	Study Results
Collett et al., 2011[47]	EDSS score NR, PwMS (n=61) MS Types NR, Drop outs (n=6)	Pri: 2 min walk Sec: TUG, Leg extensor power Peak power Barthel Index, SF36 FSS 0, 6, 12, 24 weeks	All groups showed significant improvement of 2 MWT, TUG and leg power at t1, SF-36 score decreased at t2, and FSS showed no significant change. Intermittent group showed the greatest improvement in 2 MWT. MCT showed improvement in 2 MWT, TUG, and leg power, but significant reduced SF-36. Leg power showed improvement more within intermittent and combined groups.
Feltham et al., 2013[45]	EDSS score NR, PwMS (n=21) RRMS (n=9), SPMS (n=9), PPMS (n=3) Drop outs NR	BP, Cardiorespiratory functions (VO_{2max}, HR_{max}, RER, VO_{2norm}), Peak power — T 0,6,12 w	Significant increase in $VO_{2\text{-norm}}$, peak power and trend increase in VO_{2max}, but RER values remained similar, for both groups, however there is no significant difference between groups for HRmax, VO_{2max}, or peak power.
Skjerbæk et al., 2014[44]	6.5 ≤ EDSS score ≤ 8.0, PwMS (n=11), SPMS (n=8), PPMS (n=3), Drop outs (n=1)	Cardiorespiratory functions (VO_{2max}, HR_{max}), 6 minWC, FSMC, MDI, MSIS-29, 9HPT, HGT, BBT — T 0, 4 w	Improving VO_{2max} in HIIT group. No time group interaction was found in outcome measures (MDI, MSIS-29, FSMC, 9-HPT, handgrip power, Box and Block, 6-MWT), but a trend toward a time*group interaction was seen for VO_{2max}.
Wens et al., 2015[43]	EDSS score 1.0-5.0, PwMS (n=34) RRMS (n=26), CPMS (n=8), Drop outs (n=0)	Pri: Muscle fiber CSA and proportion Sec: Isometric muscle strength Endurance capacity (RER VO_{2max} HR_{max} Test duration), Body composition, PA level; PASIPD — T 0, 12 w	- In CG muscle fiber CSA and proportion did not change. Mean CSA significantly increased in HITR and HCTR. Muscle fiber type I CSA increased in HCTR, whereas muscle fiber type II and IIa increased in HITR. Fiber type IIx CSA did not change. No changes in fiber type proportion were observed in any exercise group. Muscle strength of CG remained stable during 12 weeks of usual care. HITR group improved knee flexion and extension strength of the weakest leg, only hamstring strength of the strongest leg. HCTR flexion and extension strength improved, from pre- to post trial, in the weakest leg, but the strongest leg remained stable.
Farup et al., 2016[31]	EDSS score 1.0 - 6.0, PwMS (n=23), HC (n=18) MS types NR, Drop outs NR	Pri: SC/type I fiber SC/type II fibre, SC/mm^2 type I and II fiber Myonuclei, and central nuclei analysis Sec: Muscle tissue fibrosis and lipid content	The training intervention in PwMS elicited an increase in SCs per fiber associated with type II fibers, but not in type I fibers. However, an increase of SCs per mm2 fiber area, but not per mm2 fiber area in type I fiber. The myonuclear content of type II fibers displayed a tendency to an increase following training, but no changes in type I fibers. No changes in the size of the myonuclear domain and the difference between the myonuclear domain size of type I and type II fibers persisted following training. No changes were observed in the number of central nuclei of either type I or type II fibers, and no difference between both types. At baseline there was a difference in muscle tissue fibrosis between MS and HC, no difference was detected from pre-to post-training in MS. For lipid content there was no differences at baseline between MS and HC there was a significant increase post-training in MS.
Wens et al., 2017[48]	EDSS score 0.5 - 6.0, PwMS (n=34), RRMS (n=26), CPMS (n=8), Drop outs (n=0)	Pri: AUC from OGTT Fasting glucose conc Sec: GLUT4 content vastus lateralis — T 0, 12 w	Fasting glucose concentrations of HITR and HCTR significantly decreased, but stable in CG. HITR and HCTR, glucose tAUC significantly decreased, but stable in CG. There were no significant changes in fasting insulin concentrations for any groups. 1-hour post-load insulin concentrations significantly decreased in HCTR. Muscle GLUT4 content significantly increased in HITR, but not in HCTR. No significant correlations between the change of the primary and secondary outcome measures on pooled data.
Zimmer et al., 2018[46]	EDSS score 1.0-6.5, PwMS (n=60) HIIT (n=29) -RRMS (n=14), SPMS (n=13)-CT (n=31) -RRMS (n=16), SPMS (n=14)-Drop outs HIT (n=3) CT (n=1)	Pri: BICAMS: TMT, TAP test (errors and speed), SDMT, VLMT, BVMT Sec: Serum levels of serotonin, BDNF, MMP-2, MMP-9, Cardiorespiratory functions (VO_{2max}), HADS, FSMC, MWT-A — T 0, 3 weeks	SDMT, TMTB, TAP errors and VO2-peak significantly improved. Interaction effects (time × group) showed significant differences for VLMT, VO2-peak and serum MMP-2 levels. Significant improvement of verbal memory in the HIIT, whereas no alterations were found in CG. VO2-peak increased significantly in both groups, being higher in the HIIT. Serum levels of MMP-2 decreased significantly in HIIT whereas no changes were detected in the CG. Significant improvements in test performance for HIIT. Significant correlations between VO2-peak and cognitive performance in some cognitive domains at t0 and at t1, whereas changes in VO2-peak showed no association with changes in cognitive performance. However, changes in VO2-peak indicated a negative association with serum MMP-2 levels.
Collett et al., 2017[30]	EDSS score NR, PwMS (n=14), HC (n=9), RRMS (n=5), SPMS (n=5), PPMS (n=1), Drop outs (n=6)	Recovery of: HR, Temp, RPEbr, RPEleg, MEPs 30 s post session then every 2 min till 10 min, then every 5 min till 45 min	CG performed significantly better on the exercise test achieving greater Wpeak, HR, and RPE. Perceived exertion in the legs did not differ between groups. Significant effect of the exercise on HR for all intensities, but no overall significant difference between groups at any intensity for either RPE legs or breathing. There were no significant differences in MEPs between groups or between exercise intensities in either group. No significant increase in temperature at 45% in the MS. Most perceived and physiological measure correlated during recovery for both groups across intensities. However, notably, correlations between temperature and RPE (RPEBre and RPEleg) were only found in the MS group.
Keytsman et al., 2019[42]	EDSS score 2.6 ± 0.2, PwMS (n=16), MS Types NR, Drop outs (n=0)	Body composition, BP, Resting HR, Cardiorespiratory functions (HR_{max}, VO_{2max}, RER, VE_{max}), OGTT, total Chol, fasting glucose, fasting TG, HDL, LDL, insulin sensitivity, W_{max}, peak lactate, to exhaustion, Isometric and isokinetic strength of legs ext and flex, PASID	Workload capacity, time to exhaustion, HRrest, insulin sensitivity, and expiratory volume, besides, isometric and isokinetic muscle strength of the quadriceps and hamstrings of both legs are significantly increased in the HIIT group. No change for body composition, BP, blood lipid profiles., CRP, HbA1c, fasting glucose, fasting insulin, 2h insulin after 12 weeks.
Zaenker et al., 2018[10]	EDSS score 0-5.0, PwMS (n=30), RRMS (n=22), SPMS (n=3), PPMS (n=1), Drop outs (n=4)	Cardiorespiratory functions (VO_{2max}, HR_{max}) Peak power, Peak lactate, Isokinetic strength quads and hams QoL: SEP 59 — T 0, 12 w	After 12 weeks of training women group showed significant improvements in VO_{2max}, MTP, LET and HR_{max}, VO_{2max} only in the men group tended to increase. Women significantly increased the quadriceps strength at each speed while men improved strength only at 180°/sec. In hamstrings, women showed significant improvement at 180°/sec and 240°/sec with a leg effect and men at 180°/sec without leg effect. Women significantly improved vitality, general well-being, and physical health composite score, but not men. Based on EDSS, significant improvement in VO_{2max}, LET, MTP, and HR_{max} in Group I (EDSS 0-3), but not in Group II (EDSS 3.5-5), and for increased muscle strength, within 90, 180 and 240°/sec in group I, however group II showed improvement only at 240°/sec, without leg effect. In EDSS groups only group I enhanced Vitality and General well-being. SEP-59 were significantly improved, physical health composite score of MSQOL-54 tended to significance.
Bansi et al., 2018[41]	EDSS score 1.0-6.5, PwMS (n=57), RRMS (n=33), SPMS (n=24), Drop outs (n=0)	5HT, Trp, Kyn, Kyn/Trp ratio, before and after CPET — T 3 w	SPMS showed significantly decreased serum Trp levels and a tendency for increased cardio-pulmonary fitness. Significant time effects for Trp, Kyn, reduction in Trp and increase in Kyn/Trp ratio only in RRMS. No differences between exercise interventions on Trp metabolites over time. Significant time effects were found for serum 5HT

(*continued on next page*)

Table 3 (*Continued*)

Author and Year	Criteria EDDS Score, Number of Patients, MS Phenotypes, Drop Out	Outcome Measures	Study Results
			(increase), Trp levels (decrease) and Kyn/Trp ratio (increase). Both training interventions increased VO_{2max} although the increase was more pronounced in HIIT. VO_{2max} negatively correlated with both Kyn levels and Kyn/Trp ratio only in RRMS.
Jorissen et al., 2018[32]	EDSS score 2.8 ± 0.4, PwMS (n=41) and HC (n=40), Drop outs (n=0)	Cardiorespiratory functions (HR, VO_{2max}), NMR Spectroscopy (HDL, LDL, VLDL) — T 0,12w	MIT reduced LDL-c, VLDL size and increase IDL particle count. HIIT had no effect on the measured lipoprotein profile parameters.
Guillamó et al., 2018[40]	EDSS score < 3, PwMS (n=29) (RRMS), Drop outs (n=6)	MFIS, HAD, FAMS, Cardiorespiratory functions (VO_{2max}, HR_{max}, RER, VCO_2, $VEqO_2$, $VEqCO_2$) — T 1 (0), (20), (40) (W); strength (30CST) and balance test (postural sway, TTD, RA, MLD, APD, COP) — T 0, 20w	No significance within or between group were observed throughout the intervention for the HAD, MFIS, and FAMS. A significant difference was observed for absolute VO2 mean values between t1 vs. t2 in the CFTFG, but not for peak values. Oxygen consumption decreased in the CG between the t1 and t3 assessments but increased in the CFTFG. In the 30-second sit to stand test, the CFTFG obtained a significant improvement. No significant intervention-related changes for balance were observed in the active groups. CG presented a slight deterioration, with higher TTD (Total Travel Distance) of the COP during the test with open eyes.
Wonneberger & Schmidt, 2019[35]	EDSS score < 3.5, PwMS (n=40) (RRMS), Drop outs (n=11)	Ramp Test (VO_{2max}), PPO, FSS, T25-FW) — T 0,8 w	A significant group-by-time effect of VO_{2max} was detectable in the HIIT group as opposed to the MT group. By contrast, there was no significant change of the FSS and T25FW in the entire cohort. Significant reduction of fatigue, but no effects on VO_{2max} and T25FW were demonstrated in the fatigue group. In the nonfatigue group, none of parameters changed.
Hubbard et al., 2019[33]	EDSS of 4.0–6.5, PwMS (n=20), RRMS (n=13), progressive MS (n=7), Drop outs (n=0)	Cardiorespiratory functions (VO_2, VCO_2, V_E, RER, W_{peak}), HR, C_{Temp}, Perceived tolerance (RPE)	For all cardiorespiratory outcomes showed statistically significant condition—time interactions. HIIT did not induce higher core temperature compared to the CG. CG rated their perceived exertion as higher during warm-up as compared to the HIIT warm-up.
Joisten, Proschinger, et al., 2021[34]	EDSS score 3.0-6.0, PwMS (n=68), RRMS (n=42), SPMS (n=26), Drop outs NR	Cardiorespiratory functions (VO_{2max}, HR_{max}, $Watt_{max}$, $Watt_{rel}$), Cellular inflammation markers (NLR, SII, PLR) To assess training effects: 0, post intervention; To immediate effects: post exercise, after 3 hours (recovery)	Significant time effects within HIIT group for both PLR, NLR, and SII from baseline to post intervention with a downregulation of NLR and SII, and PLR value improved in MCT compared to HIIT. Elevations from baseline to recovery and post exercise to recovery only within the HIIT group. Significant interaction effects were observed for both NLR and SII, with HIIT showing greater elevations at recovery than MCT.
Rademacher et al., 2020[8]	EDSS score 3.0– 6.0, PwMS (n=75), RRMS (n=45), SPMS (n=29), Drop outs (n=1)	Cardiopulmonary functions (VO_{2max}, watts, HR_{max}), BICAMS (SDMT, CVLMT-II, BVMT-R), FSMC — T 0,3 w	Both groups showed over time improvement for levels of VO_{2max} and Wattrel, HIIT group had significantly higher Wattrel than CG. For the outcome fatigue, no time or interaction effects could be observed. Significant time effects for SDMT, VLMT, and BVMT-R but no significant group x time (interaction) for HIIT and CG. Improvements of processing speed over time in both groups; for VLMT and BVMT-R, but no significant results were observed.
Rademacher et al., 2021[37]	EDSS score 1.0 - 6.5, 130 PwMS (n=130), RRMS (n=77), SPMS (n=53), Drop outs (n=4)	BICAMS — T 0,3 w	Cognitive performance outcomes revealed significant main time effects for SDMT, VLMT, and BVMT-R for HIIT compared to MCT. No significant change observed for visuospatial memory.
Joisten, Rademacher et al., 2021[21]	EDSS score 3.0 – 6.0, PwMS (n=69), RRMS (n=42), SPMS (n=27), Drop outs (n=0)	pNfL Levels, KYN Pathway, MetabolitesInterleukin-6 (IL-6) immediately before and after,3h after 1st session, after the training intervention; BICAMS 24 hours after baseline blood sample collection	HIIT resulted in a decrease in pNfL and an increase in the production of KA. The increase in KA and the decrease in the ratio of quinolinic acid to KA were positively correlated with the reduction in pNfL. HIIT had a greater impact than MCT. HIIT may activate the KYN pathway, leading to neuroprotection, compared to MCT.
Lea Schlagheck et al., 2021[39]	EDSS score 1.0 – 6.5, PwMS (n=131) -RCT_1 (n=57), RCT_2 (n=74)- MS_{HIIT} (n=65) -RRMS (n=39), SPMS(n=26)- MS_{MCT} (n=66) RRMS (n=39), SPMS (n=27)-, Drop out NR	FSMC, Cardiorespiratory functions (VO_{2max}, peak power output, HR_{rest}, HR_{max}) — T 0,3 w	VO2peak/kg improved over time in HIIT and MCT. HIIT group showed higher VO2peak/kg at t1 compared to MCT. HIIT participants rather than MCT, younger age and lower baseline fitness predict a greater absolute change in VO2peak/kg.
Keytsman et al., 2021[38]	EDSS score 2.3±1.3, PwMS (n=31), RRMS (n=29), PPMS (n=2), Drop out (n=0)	Exercise capacity (VO_2, VO_{2max}, HR_{max}, $HR_{recovery}$, VE, RER, W_{max}), Body composition (body fat mass and percentage, BMI, total and fat free mass), Isometric muscle strength (knee ext-flex)	In MSPER, VO2max, workload, time until exhaustion, BMI significantly increased following the periodized intervention, whilst HRmax, recovery heart rate, peak lactate, RER, weight, fat mass fat percentage, fat free mass and total mass did not. In MSCLA, workload and time until exhaustion significantly increased, fat mass and fat percentage significantly decreased following the classic endurance intervention, whilst VO2max, HRmax, recovery heart rate, peak lactate, RER, weight, BMI, fat free mass, and total mass did not. PRE-POST changes for VO2max, weight, BMI, fat mass, and total mass were significantly different between MSPER and MSCLA. Other parameters did not. Mean BORG RPE scores were significantly higher for HIIT sessions compared to endurance sessions in both MSPER and MSCLA.
Wolf et al., 2022[36]	EDSS score 1.0 – 6.5, PwMS (n=131), RRMS (n=78), SPMS (n=53), Drop outs (n=2)	HADS, FSMC, Cardiorespiratory functions (VO_{2max})	PwMS with severe fatigue at baseline, time effect for exercise training was statistically nonsignificant. HIIT did not show significant effect for FSMC and HADS.

Abbreviations: 30CST, 30 second sit to stand; 6minWC, 6-minute wheelchair-test; 9HPT, 9-hole peg test; APD, antero-posterior displacements; AUC, area under the curve; BP, blood pressure; BMI, body mass index; RPEbr, Borg scale of perceived exertion breathing; RPEleg, Borg scale of perceived exertion leg; BBT, box and block test; BDNF, brain derived neurotrophic factor; BICAMS, brief international cognitive assessment for multiple sclerosis; BVMT/BVMT-R, brief visuospatial memory test/revised; CVLMT-II, California verbal learning test-II; CPET, cardiopulmonary exercise test; COP, center of pressure; Chol, cholesterol; Conc, concentration; CG, control group; CTemp, core body temperature; CRP, C-reactive protein; VE, expiratory volume; FSS, Fatigue Severity Scale; HGT, handgrip power; HR, heart rate; HR_{rest}, heart rate at rest; HDL, high density lipoprotein; HADS, Hospital Anxiety and Depression Scale; IDL, intermediate density lipoprotein; Kyn/KYN, Kynurenine; LDL, low density lipoprotein; LET, lactates at the end of test; MDI, Major Depression Inventory; MMP, matrix metalloproteinases; VE_{max}, maximal expiratory volume; VO_{2max}, maximal volume of oxygen consumed; MLD, medio-lateral displacements; MEPs, motor evoked potentials; MIT, medium-intensity cardiovascular training; MWT-A: Multiple Choice Vocabulary Test Version A; MSIS-29, Multiple Sclerosis Impact Scale; NLR, neutrophil-to-lymphocyte ratio; NMR, Nuclear Magnetic Resonance; OGTT, Oral Glucose Tolerance Test; PPO/$Watt_{max}$/W_{max}, Peak power output; PA level, physical activity level; PASIPD, Physical Activity Scale for Individuals with Physical Disabilities; P MRS, phosphorous magnetic resonance spectroscopy; pNfL, plasma neurofilament light chain; PLR, platelet-to-lymphocyte ratio, Pri, primary outcome measure; QoL, quality of life; RA, radial area; $HR_{recovery}$, recovery heart rate; $Watt_{rel}$, relative peak power output; SC, satellite cell; SEP-59, Sclerose EnPlaque-59; Sec, secondary outcome measure; 5HT, Serotonin; SDMT, Symbol Digit Modalities Test; SII, systemic immune-inflammation index; Temp, temperature; TAP, Test Battery of Attention; T25-FW, Timed 25-Foot Walk Test; TTD, total travel distance; TMT, Trail-Making Test; TG, Triglyceride; Trp, Tryptophan; VCO_2, carbon dioxide production; VE, ventilation; $VEqCO_2$, ventilatory equivalent for CO2; $VEqO_2$, ventilatory equivalent for O2; VLMT, Verbal Learning and Memory Test; VLDL, very low-density lipoprotein; VO_2, volume of oxygen consumed.

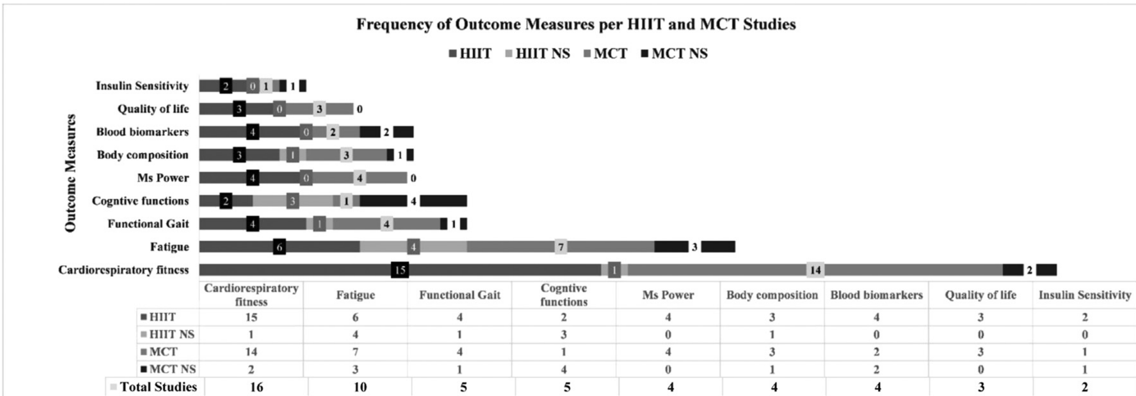

Fig 2 Number of studies considered each outcome measure, graph representing the frequency of HIIT or MCT protocols improvements. NS: Not significant

to the competitive season.[57] However, in the studies reviewed for this analysis, PwMS were not prepared for these high-intensity programs, as most of the study protocols started from a baseline level of physical activity. This critical oversight may explain why the anticipated outcomes were not achieved. As a result, it is recommended that future studies consider implementing a moderate-intensity training program before randomizing participants to the HIIT protocol. By incorporating this step, researchers can potentially optimize the effectiveness of the intervention for PwMS.

In the context of the safety and efficacy of HIIT, only one study, as reported,[47] documented adverse side effects. Consequently, establishing an aerobic base beforehand[57] for PwMS becomes imperative. This preliminary step aims to enhance their cardiorespiratory fitness, preparing them for the demands of high-intensity exercises. This proactive approach significantly reduces the likelihood of encountering adverse side effects during subsequent sessions of HIIT protocol.

According to our registered protocol, comparator interventions were specified to include either continuous moderate-intensity aerobic exercise alone or in combination with either stretching or resistance exercises. It is essential to emphasize that our main emphasis was on comparing HIIT using a bicycle ergometer or

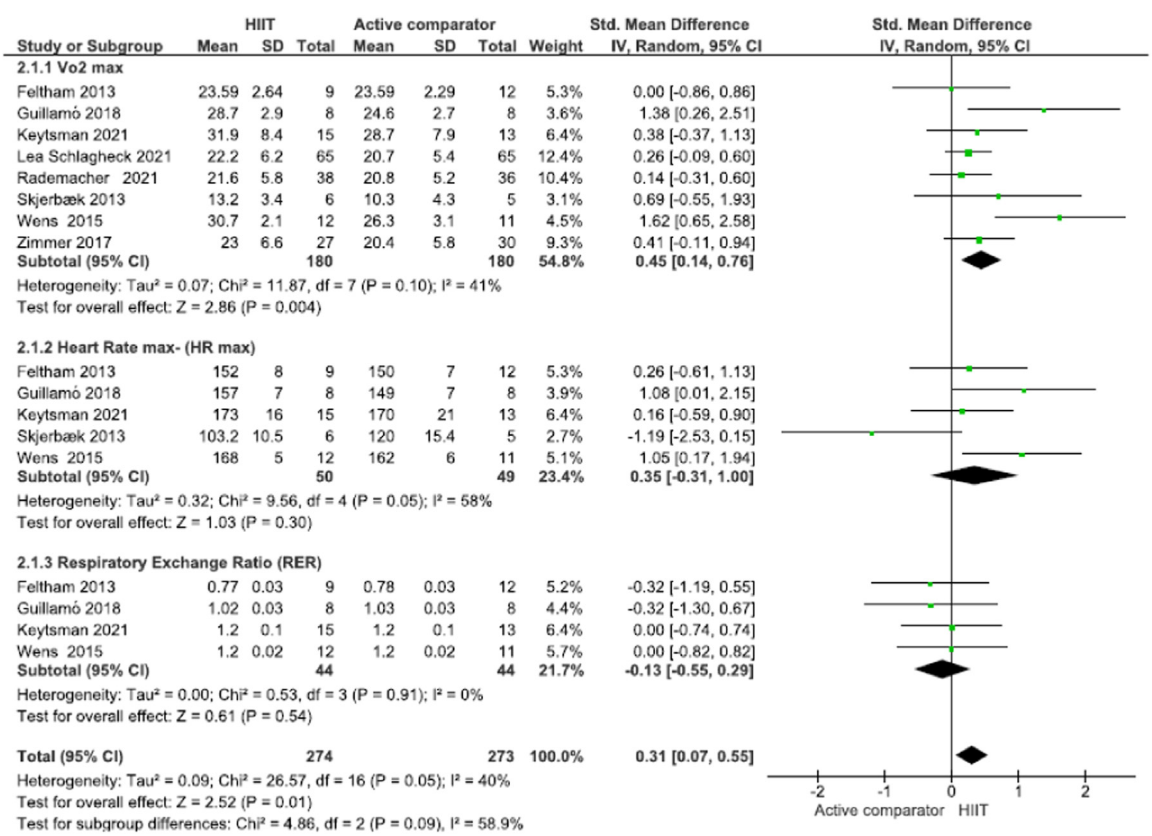

Fig 3 Meta-analysis effect of HIIT Versus MCT on cardiorespiratory fitness outcome.

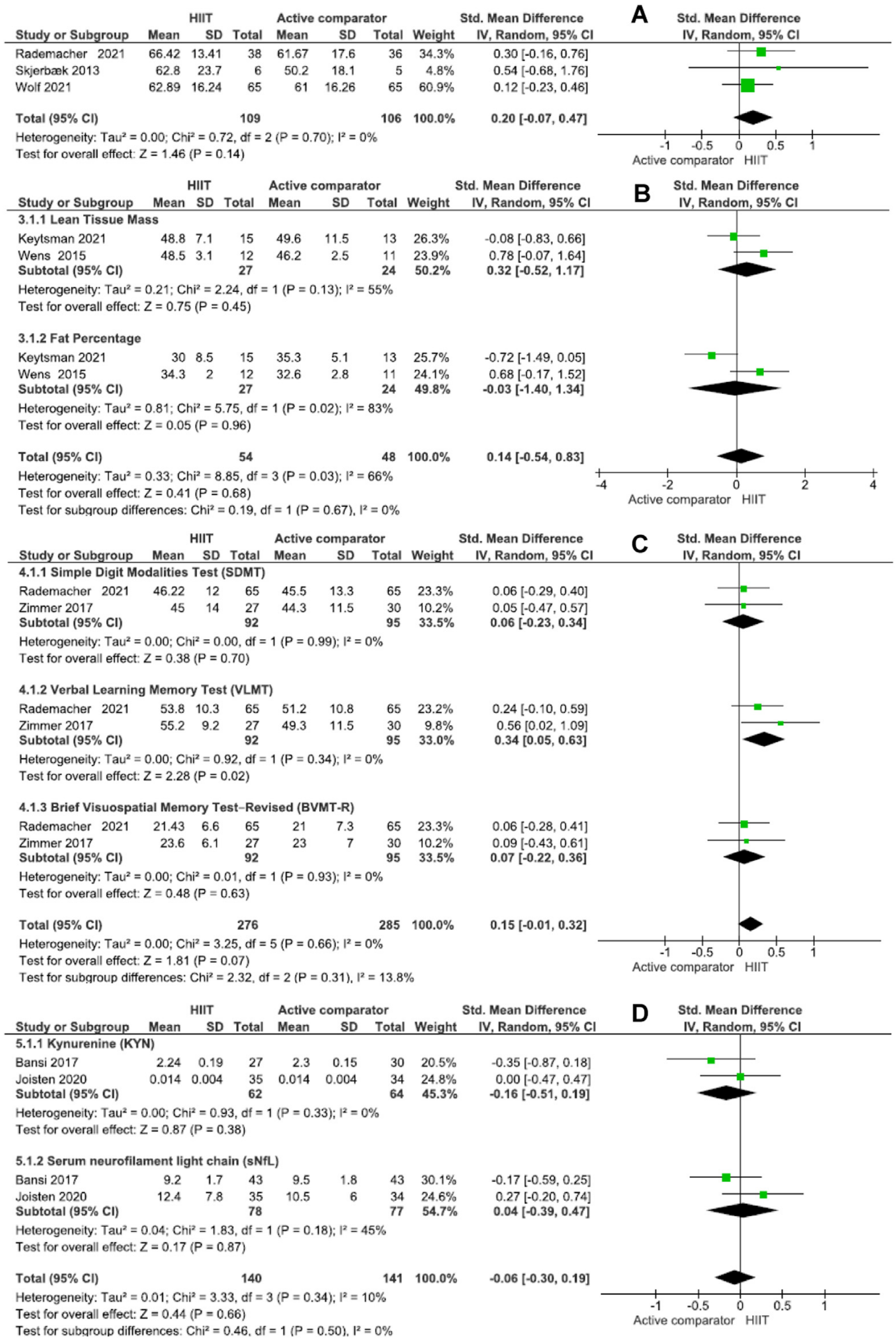

Fig 4 Meta-analysis effect of HIIT Versus MCT on (A) fatigue outcome, (B) body composition, (C) cognitive functions, and (D) blood biomarker, respectively.

recumbent stepper as the primary exercise modalities. This emphasis was maintained to ensure consistency in the type of exercise interventions under evaluation. Consequently, we excluded all studies that compared HIIT with other exercise modalities, such as stretching or resistance exercise, when presented as stand-alone modalities to maintain methodological homogeneity.

The registered protocol specified that anxiety and depression were intended outcome measures. Some of the included studies initially addressed anxiety and depression as outcome measures in the protocol submission. However, these studies were later removed from the analysis because they did not meet our inclusion criteria. This was a necessary step to maintain the methodological rigor of our review. As a result, we were unable to conduct a

Table 4 Quality assessment of articles through the utilization of the PEDro scale.

Author and Year	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	Total
Collett et al., 2011[47]	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8
Feltham et al., 2013[45]	Y	Y	Y	Y	N	N	Y	N	Y	Y	Y	7
Skjerbæk et al., 2014[44]	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	7
Wens et al., 2015[43]	Y	Y	Y	Y	N	N	N	N	Y	Y	Y	7
Farup et al., 2016[31]	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8
Wens et al., 2017[48]	Y	Y	Y	Y	N	N	N	N	Y	Y	Y	7
Zimmer et al., 2018[46]	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8
Collett et al., 2017[30]	Y	N	Y	Y	N	N	N	N	N	Y	Y	4
Keytsman et al., 2019[42]	Y	N	N	N	N	N	N	Y	Y	N	Y	4
Zaenker et al., 2018[10]	Y	N	N	N	N	N	N	Y	Y	N	Y	3
Bansi et al., 2018[41]	N	Y	Y	Y	N	N	N	Y	Y	Y	Y	7
Jorissen et al., 2018[32]	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	7
Guillamó et al., 2018[40]	Y	N	N	Y	N	N	N	Y	Y	Y	Y	5
Wonneberger & Schmidt, 2019[35]	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	7
Hubbard et al., 2019[33]	Y	Y	N	Y	N	N	N	Y	Y	Y	N	5
Joisten, Proschinger, et al., 2021[34]	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8
Rademacher et al., 2020[8]	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8
Rademacher et al., 2021[37]	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8
Joisten, Rademacher, et al., 2021[21]	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8
Lea Schlagheck et al., 2021[39]	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8
Keytsman et al., 2021[38]	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8
Wolf et al., 2022[36]	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8

meta-analysis because of the insufficient number of studies required to facilitate a robust and meaningful analysis.

Study limitations

The current review has significant strength points to be considered: (1) most of studies have included patients belonging to different phenotypes of MS, the total number of the participants for all studies could represent the actual distribution of the heterogeneity of MS population; (2) our meta-analysis was based on multiple objective measures to assess cardiorespiratory fitness, body composition, and blood biomarkers; and (3) overall, the included studies where of high quality and had relatively large sample sizes.

Our meta-analysis has multiple limitations: (1) several studies have combined different exercise modality within the same arm (e.g. HIIT + resistance training),[10,31,42,43] so potential carry-over effects in these studies may affect the overall results; (2) the exercise protocol and study designs showed heterogeneity between the studies, therefore, future reviews should include more homogenous HIIT protocols within the studies, and follow guidelines for exercise intervention; those appropriate details will help in the replication of the exercise protocols within the research studies by the clinicians[58]; (3) small number of studies included in this meta-analysis and the limited data available for a quantitative analysis, besides, all articles were included in the review regardless of PEDro score; (4) the studies could only be combined with regard to the short-term effects and failed to evaluate the differential effects based on HIIT protocol, interval intensities, number of cycles, total number of sessions, comparator groups, or intervention modality. Therefore, these results should be carefully considered; (5) it was not possible to conduct a subgroup analysis based on EDSS in the present study, and there isn't sufficient data to perform additional analyses; (6) the heterogeneity might be attributed to the differences between studies, such as study design, study region, age, sex ratio, and disease course of the participants; (7) the studies included in this meta-analysis had certain geographic characteristics, all the studies were in European countries, so the results of the study were somewhat biased; and (8) because of the strict eligibility criteria for study inclusion, only a limited number of studies were included in the analysis, focusing on outcomes such as cognitive functions, blood biomarkers, and fatigue. As a result, no definitive conclusions could be drawn from the available evidence.

Conclusion

Our findings suggest that HIIT is not superior to MCT in PwMS, both training modalities have similar effects, in terms of fatigue, body composition, and blood biomarkers for PwMS. However, only VO2max of cardiorespiratory functions, and memory domain of cognitive functions were in favor of HIIT protocol. Although the quality of evidence is limited due to heterogeneity in training characteristics of the HIIT and MCT protocols across studies. In other words, HIIT may attain similar therapeutic results with MCT in a shorter time.

Suppliers

a. Endnote software; Clarivate Inc

Keywords

Blood biomarkers; Cardiorespiratory fitness; Cognitive functions; Exercises; Fatigue; High intensity interval training; Multiple sclerosis

Corresponding author

Hussein Youssef, MSc, Koç University Hospital, Graduate School of Health Sciences, Davutpaşa Cad. No:4, Topkapı/Zeytinburnu, 34010, Istanbul, Turkey. *E-mail address:* husseinahmedyoussef@gmail.com.

References

1. Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. N Engl J Med 2000;343:938–52.
2. Feinstein A. Cognitive impairment in multiple sclerosis. The clinical neuropsychiatry of multiple sclerosis. Cambridge University Press; 2007. p. 115–44.
3. Amato MP, Goretti B. Pharmacological treatment for cognitive impairment in multiple sclerosis. In: DeLuca J, Sandroff BM, eds. Cognition and behavior in multiple sclerosis, Washington: American Psychological Association; 2018:245–64.
4. Motl RW, Sandroff BM, Kwakkel G, et al. Exercise in patients with multiple sclerosis. Lancet Neurol 2017;16:848–56.
5. Latimer-Cheung AE, et al. Development of evidence-informed physical activity guidelines for adults with multiple sclerosis. Arch Phys Med Rehabil 2013;94:1829–36.
6. Halabchi F, Alizadeh Z, Sahraian MA, Abolhasani M. Exercise prescription for patients with multiple sclerosis; potential benefits and practical recommendations. BMC Neurol 2017;17:185.
7. Campbell E, Coulter EH, Paul L. High intensity interval training for people with multiple sclerosis: a systematic review. Mult Scler Relat Disord 2018;24:55–63.
8. Rademacher A, et al. Cognitive impairment impacts exercise effects on cognition in multiple sclerosis. Front Neurol 2020;11:619500.
9. Valkenborghs SR, et al. Effect of high-intensity interval training on hippocampal metabolism in older adolescents. Psychophysiology 2022;59:e14090.
10. Zaenker P, Favret F, Lonsdorfer E, Muff G, de Seze J, Isner-Horobeti ME. High-intensity interval training combined with resistance training improves physiological capacities, strength and quality of life in multiple sclerosis patients: a pilot study. Eur J Phys Rehabil Med 2018;54:58–67.
11. Fleg JF. Salutary effects of high-intensity interval training in persons with elevated cardiovascular risk. F1000Res. 2016;5:F1000.
12. Bertapelli F. ACSM'S exercise management for persons with chronic diseases and disabilities. Adapted Physical Activity Quarterly 2017;34:201–2.
13. Gibson-Moore H. UK Chief Medical Officers' physical activity guidelines 2019: what's new and how can we get people more active? Nutr Bull 2019;44:320–8.
14. Wen D, et al. Effects of different protocols of high intensity interval training for VO2max improvements in adults: a meta-analysis of randomised controlled trials. J Sci Med Sport 2019;22:941–7.
15. Pilutti LA, et al. Physical fitness assessment across the disability spectrum in persons with multiple sclerosis: a comparison of testing modalities. J Neurol Phys Ther 2015;39:241–9.
16. Langeskov-Christensen M, Heine M, Kwakkel G, Dalgas U. Aerobic capacity in persons with multiple sclerosis: a systematic review and meta-analysis. Sports Med 2015;45:905–23.
17. Heine M, Hoogervorst ELJ, Hacking HGA, Verschuren O, Kwakkel G. Validity of maximal exercise testing in people with multiple sclerosis and low to moderate levels of disability. Phys Ther 2014;94:1168–75.
18. Valet M, Stoquart G, Glibert Y, Hakizimana JC, Lejeune T. Is fatigue associated with cardiorespiratory endurance among patients suffering from multiple sclerosis? Ann Phys Rehabil Med 2016;59S:e41.
19. Higgins JPT, ed. Cochrane handbook for systematic reviews of interventions, Version 6, Cochrane; 2019.
20. Orban A, et al. Effect of high-intensity exercise on multiple sclerosis function and phosphorous magnetic resonance spectroscopy outcomes. Med Sci Sports Exerc 2019;51:1380–6.
21. Joisten N, et al. Exercise diminishes plasma neurofilament light chain and reroutes the kynurenine pathway in multiple sclerosis. Neurol Neuroimmunol Neuroinflamm 2021;8.
22. Penner IK, Raselli C, Stöcklin M, Opwis K, Kappos L, Calabrese P. The Fatigue Scale for Motor and Cognitive Functions (FSMC): validation of a new instrument to assess multiple sclerosis-related fatigue. Mult Scler 2009;15:1509–17.
23. Langdon DW, et al. Recommendations for a brief international cognitive assessment for multiple sclerosis (BICAMS). Mult Scler 2012;18:891–8.
24. Symbol digit modalities test. In: Kreutzer JS, DeLuca J, Caplan B, eds. Encyclopedia of clinical neuropsychology, New York, NY: Springer New York; 2011. p. 2444.
25. Baños J. California Verbal Learning Test-Second Edition D Delis, J Kramer, E Kaplan, B Ober. San Antonio, TX. The Psychological Corporation, 2000. Arch Clin Neuropsychol 2002;17:509–12.
26. Benedict RHB, Schretlen D, Groninger L, Dobraski M, Shpritz B. Revision of the brief visuospatial memory test: studies of normal performance, reliability, and validity. Psychol Assess 1996;8:145–53.
27. de Morton NA. The PEDro scale is a valid measure of the methodological quality of clinical trials: a demographic study. Aust J Physiother 2009;55:129–33.
28. Cohen J. A power primer. Psychol Bull 1992;112:155–9.
29. Stewart LA, Tierney JF, Clarke M. Reviews of individual patient data, Cochrane Handbook for Systematic Reviews of Interventions. Chichester, UK: John Wiley & Sons, Ltd; 2011.
30. Collett J, Meaney A, Howells K, Dawes H. Acute recovery from exercise in people with multiple sclerosis: an exploratory study on the effect of exercise intensities. Disabil Rehabil 2017;39:551–8.
31. Farup J, Dalgas U, Keytsman C, Eijnde BO, Wens I. High intensity training may reverse the fiber type specific decline in myogenic stem cells in multiple sclerosis patients. Front Physiol 2016;7:193.
32. Jorissen W, et al. Twelve weeks of medium-intensity exercise therapy affects the lipoprotein profile of multiple sclerosis patients. Int J Mol Sci 2018;19.
33. Hubbard EA, Motl RW, Fernhall BO. Acute high-intensity interval exercise in multiple sclerosis with mobility disability. Med Sci Sports Exerc 2019;51:858–67.
34. Joisten N, et al. High-intensity interval training reduces neutrophil-to-lymphocyte ratio in persons with multiple sclerosis during inpatient rehabilitation. Mult Scler 2021;27:1136–9.
35. Wonneberger M, Schmidt S. High-intensity interval ergometer training improves aerobic capacity and fatigue in patients with multiple sclerosis. Sport Sci Health 2019: 1–9.
36. Wolf F, et al. The aerobic capacity - fatigue relationship in persons with Multiple Sclerosis is not reproducible in a pooled analysis of two randomized controlled trials. Mult Scler Relat Disord 2022;58:103476.
37. Rademacher A, et al. Do baseline cognitive status, participant specific characteristics and EDSS impact changes of cognitive performance following aerobic exercise intervention in multiple sclerosis? Mult Scler Relat Disord 2021;51:102905.
38. Keytsman C, Van Noten P, Verboven K, Van Asch P, Eijnde BO. Periodized versus classic exercise therapy in multiple sclerosis: a randomized controlled trial. Mult Scler Relat Disord 2021;49:102782.
39. Lea Schlagheck M, et al. VO2peak response heterogeneity in persons with multiple sclerosis: to HIIT or not to HIIT? Int J Sports Med 2021;42:1319–28.
40. Guillamó E, et al. Feasibility and effects of structured physical exercise interventions in adults with relapsing-remitting multiple sclerosis: a pilot study. J Sports Sci Med 2018;17:426–36.
41. Bansi J, et al. Persons with secondary progressive and relapsing remitting multiple sclerosis reveal different responses of tryptophan metabolism to acute endurance exercise and training. J Neuroimmunol 2018;314:101–5.

42. Keytsman C, Hansen D, Wens I, Eijnde BO. Impact of high-intensity concurrent training on cardiovascular risk factors in persons with multiple sclerosis - pilot study. Disabil Rehabil 2019;41:430–5.
43. Wens I, et al. High intensity exercise in multiple sclerosis: effects on muscle contractile characteristics and exercise capacity, a randomised controlled trial. PLoS ONE 2015;10:e0133697.
44. Skjerbæk AG, et al. Endurance training is feasible in severely disabled patients with progressive multiple sclerosis. Mult Scler 2014;20:627–30.
45. Feltham MG, et al. Cardiovascular adaptation in people with multiple sclerosis following a twelve week exercise programme suggest deconditioning rather than autonomic dysfunction caused by the disease. Results from a randomized controlled trial. Eur J Phys Rehabil Med 2013: 49-765-74.
46. Zimmer P, et al. High-intensity interval exercise improves cognitive performance and reduces matrix metalloproteinases-2 serum levels in persons with multiple sclerosis: a randomized controlled trial. Mult Scler 2018;24:1635–44.
47. Collett J, et al. Exercise for multiple sclerosis: a single-blind randomized trial comparing three exercise intensities. Mult Scler 2011;17:594–603.
48. Wens I, et al. High intensity aerobic and resistance exercise can improve glucose tolerance in persons with multiple sclerosis: a randomized controlled trial. Am J Phys Med Rehabil 2017;96:161–6.
49. Foster C, et al. The effects of high intensity interval training vs steady state training on aerobic and anaerobic capacity. J Sports Sci Med 2015;14:747–55.
50. Thum JS, Parsons G, Whittle T, Astorino TA. High-intensity interval training elicits higher enjoyment than moderate intensity continuous exercise. PLoS ONE 2017;12:e0166299.
51. Stern G, Psycharakis SG, Phillips SM. Effect of high-intensity interval training on functional movement in older adults: a systematic review and meta-analysis. Sports Med 2023;9:5.
52. Yu T, Zhang Z, Zhou D, Li C. Systematic review and meta-analysis on the rehabilitation effect of different intensity exercise on the patients with cardiovascular diseases. Comput Math Methods Med 2022;2022:1364985.
53. Liou K, Ho S, Fildes J, Ooi SY. High intensity interval versus moderate intensity continuous training in patients with coronary artery disease: a meta-analysis of physiological and clinical parameters. Heart Lung Circ 2016;25:166–74.
54. Anjos JM, et al. The impact of high-intensity interval training on functioning and health-related quality of life in post-stroke patients: a systematic review with meta-analysis. Clin Rehabil 2022;36:726–39.
55. Schlagheck ML, Bansi J, Langeskov-Christensen M, Zimmer P, Hvid LG. Cardiorespiratory fitness ($\dot{V}$O2peak) across the adult lifespan in persons with multiple sclerosis and matched healthy controls. J Sci Med Sport 2023;27. 10-5.
56. Hawley JA, Myburgh KH, Noakes TD, Dennis SC. Training techniques to improve fatigue resistance and enhance endurance performance. J Sports Sci 1997;15:325–33.
57. Laursen PB, Jenkins DG. The scientific basis for high-intensity interval training. Sports Medicine 2002;32:53–73.
58. Page P, Hoogenboom B, Voight M. Improving the reporting of therapeutic exercise interventions in rehabilitation research. Int J Sports Phys Ther 2017;12:297–304.