The Effect of High Intensity Interval Training in Multiple Sclerosis Patients: A Systematic Review and Meta-Analysis

Abeer A. Elwishy[1], Fatma Kh. Mohamed[2*], Nevin M Shalaby[3], Hossam Mohammed Alsaid[4].

1. Professor of Physical Therapy for Neurology and Neurosurgery, Faculty of Physical Therapy, Cairo University, Giza, Egypt. ORCID ID: 0000-0002-4772-2452
2. Department of Physical Therapy for Neurology, Faculty of Physical Therapy, Horus University-Egypt, New Damietta, Egypt. ORCID ID: 0009-0008-9479-4038
3. Professor of Neurology, Faculty of Medicine, Cairo University, Egypt. ORCID ID: 0000-0001-9925-8367
4. Lecturer of Physical Therapy for Neurology and Neurosurgery, Faculty of Physical Therapy, Cairo University, Giza, Egypt. ORCID ID: 0009-0002-2033-9549

*** Corresponding author: Fatma Kh. Mohamed** **Email: fabdelaziz@horus.edu.eg**

Abstract

Objective: This review investigates the effectiveness of high-intensity interval training (HIIT) on multiple sclerosis (MS) patients, focusing on cognitive functions, aerobic fitness, exercise capacity, and muscle strength. MS often leads to persistent physical symptoms that hinder daily activities and quality of life. **Methods:** The review analyzed studies from various databases, identifying randomized controlled trials comparing HIIT with either healthy individuals or other interventions, up to August 2023. **Results:** Four studies involving 186 patients were included. Key findings revealed that while HIIT did not significantly improve muscle strength compared to traditional training, it did enhance processing speed in cognitive functions. However, no significant improvements were noted in verbal learning, visuospatial memory, fatigue, or overall aerobic fitness and exercise capacity. A meta-analysis of exercise capacity outcomes indicated moderate heterogeneity among studies, but results were statistically insignificant across VO_2 max, workload, and maximum heart rate metrics. **Conclusion:** It could be concluded that while HIIT may positively influence cognitive processing speed in PwMS, it does not significantly impact other cognitive functions, muscle strength, fatigue, or aerobic fitness. The authors suggest that further randomized controlled trials are necessary to explore the broader effects of HIIT on these outcomes in MS patients, highlighting the need for continued research in this area to better understand the potential benefits of HIIT for improving the quality of life in individuals with MS.

Key words: Aerobic fitness, Cognitive functions, Exercise capacity, High intensity interval trainings, Multiple sclerosis.

Introduction

Multiple sclerosis (MS) is a highly debilitating autoimmune neuro-inflammatory disease with immune-pathological properties (1). It is a chronic neurodegenerative disorder of the central nervous system (CNS), causing motor, sensory and cognitive impairments. Such disability progression is in part driven by brain atrophy and focal lesions, which are quantifiable by magnetic resonance image (MRI) and the blood biomarker serum neuro-filament light chain, a promising marker reflecting neuro-axonal damage (2). Nearly one million people in the United States are affected by multiple sclerosis (3). The estimated prevalence of MS in Egypt was about 60-100/100.000 in different centers. MS attacks women more than men; the prevalence ratio reaches 3.2:1, respectively. MS is a leading cause of neurological disability in young adults. The social impact of the disability caused by MS is profound. It results in loss of employment and leads to dependency on care providers and social isolation (4). The most common symptoms of MS are muscle weakness, numbness and tingling, L-hermitte's sign , bladder problems, bowel problems, fatigue, dizziness and vertigo, sexual dysfunction, spasticity and muscle spasms, tremor, visual problems (double or blurred vision or a partial or total loss of vision) ,gait and mobility changes, emotional changes and depression, learning and memory problems. There is also a higher risk of urinary tract infections, reduced activity, and loss of mobility. These can impact a person's work and social life. In the later stages, people may experience changes in perception and thinking, as well as sensitivity to heat (5). Less common symptoms include Issues with speech (dysarthria, dysphonia, changes in speech pattern), Swallowing problems, Breathing problems and the 'MS hug', Tremors, body twitches, Seizures, Hearing loss, Pruritis & itching (6).

High Intensity Interval Training (HIIT) is a promising modality for people with Multiple Sclerosis (PwMS) (7). HIIT is an increasingly popular form of aerobic exercise which includes short bursts of exercise at very high intensity with either a complete or working rest in between bursts. Total time for training sessions typically last around 20 minutes, have 4-6 cycles of 80-95% of maximal effort for 1-4 minutes with a similar time of working recovery or rest. HIIT has been recommended as a possible effective intervention for PwMS as it can allow people to exercise at higher intensities while avoiding thermo-sensitive reactions and its effect on increasing muscle strength (8). The clinical benefits of HIIT in MS patients are improving fatigue, cognition and mobility (9). HIIT is a promising time efficient approach in MS leading to rapid improvement of aerobic fitness and fatigue (10). HIITs in PwMS provided positive evidence for improvements in multiple outcome measures relating to fitness but they were not the primary outcomes (8). So, here in our review we tended to search studies that included fitness and exercise capacity as primary measures and also cognitive functions measures as from neurological aspect respectively.

Materials And Methods

This study was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. In addition, this review protocol was registered at ClinicalTrials.gov PRS (Protocol Registration and Result System) (NCT 05954195).

Search strategies:

A comprehensive searching of the following electronic databases was done from the inception till August 2023: The Cochrane library, Pedro, Pubmed, The Web of Science, Google Scholar, Semantic Scholar and Science Direct. Searching was done using the following Mesh Terms: ("Multiple Sclerosis" OR "Disseminated Sclerosis" OR "MS" OR "Chronic Progressive Multiple Sclerosis" OR "Relapsing Remitting Multiple Sclerosis" OR "Acute Fulminating") AND ("High Intensity Interval Training" OR "High Intensity Intermittent Exercise" OR Sprint Interval Training"). After the literature search, the retrieved studies were downloaded and imported into Rayyan computer software for duplicate removal and then imported into an Excel sheet."

An electronic search was followed by a manual search of reference lists of identified trials. Studies were screened by two independent reviewers, first by title, then abstract and finally by reading the full text.

Inclusion Criteria:

Published full text of RCTs that assessed the effect of HIIT in PwMS were included, trials enrolled diagnosed patients with MS aged between (20-50) years old, irrespective of their gender, subtype of MS or onset of the disease, exercised by HIIT compared either with MS patients exercised by another trainings or healthy persons exercised with the same HIITs.

Outcome measures:

Primary Outcome measures: for Cognitive Functions, Symbol Digit Modalities Test (SDMT) for measuring processing speed, Verbal Learning Memory Test (VLMT) for measuring verbal learning and Brief Visuospatial Memory Test (BVMT-R) for measuring visuospatial learning and memory (2). For Muscle strength, Isometric muscle strength for quadriceps and hamstring for both legs using isokinetic device (8, 11). For Exercise capacity, (VO2 max) maximum oxygen consumption, (HR max) maximum heart rate and workload measured during exercising (11,12,13). For Aerobic fitness and Fatigue, Fatigue Scale for Motor and Cognitive functions (FSMC) is used (13,14). Secondary Outcome measures: The two studies included Body composition in their outcome measures they are measured by identification of body weight, body mass index (BMI), total mass, fat mass, fat percentage, and fat free mass (11,12). Submaximal cardiac and pulmonary function & Expression of genes involved in mitochondrial functions are considered secondary outcomes (15).

Exclusion criteria:

The studies were excluded when:1- Have designs other than randomized trials. 2- Published abstracts with no full text articles available. 3- If they targeted non adults (age younger than 20 or older than 50). 4- Populations other than multiple sclerosis.

Data Extraction:

Eligible studies for the inclusion criteria analyzed in details and the following items were extracted by two independent reviewers: into a standardized form: authors, date of publication, study design, sample size, disability level, length of intervention, frequency of training, type of training, number of intervals per session, target intensity ranges, total time spent in high intensity during the intervention, additional exercise training modalities employed, outcome measures and results. (16).

Methodological quality assessment:

Two review authors assessed the risk of bias of each included study independently. Disagreements were resolved by a third author. Risk of bias were assessed using the Cochrane Collaboration's tool for assessment of risk of bias'(17). Risk of bias criteria' was judged as 'low risk', 'high risk' or 'unclear risk' and individual bias items were evaluated as described in the Cochrane Handbook for Systematic Reviews of Interventions (18). The assessment reveals that all four studies (11,12,13,15) showed a low risk in most bias domains, including random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, and selective reporting. However, they exhibited a high risk in blinding of participants and personnel, which was often challenging in exercise-based interventions. The "Other Bias" category remained unclear across studies, indicating potential areas not fully addressed. The level of evidence in our systematic review was determined by the quality, quantity, and consistency of the included studies, according to assessment the risk of bias, and considered to be moderate to high due to the generally low risk of bias.

Data analysis:

Extracted data from included trials were illustrated in form of tables to document outcomes of each intervention comparison in an included review, as well as the number of studies and the number of participants included in the comparison, and (when available from the reviews) the mean difference (or standardized mean difference), 95% confidence intervals and I^2 statistic for heterogeneity.

Testing for Heterogeneity:

The homogeneity of the studies that differ in intervention, population, sample sizes, outcomes and study quality were determined. Each study was analyzed alone, and data was tabulated and Meta-analysis was produced using Review Manager (RevMan – version 5.4.1, The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark, 2021), and Microsoft Excel 2010 (Microsoft Corp., Redmond, WA, USA).In case of homogeneity, the Meta-analysis was used, a quantitative statistical analysis of several separate but similar experiments or studies, in order to test the pooled data for statistical significance. In case of heterogeneity, descriptive analysis was used. The following tests were used to test the heterogeneity of the estimates in the included studies in the meta-analysis: 1- Cochran Q Chi square test: A statistically significant test (p-value<0.1) denoting the heterogeneity between the studies. 2- I-square (I2) index which was interpreted as the following: I2 = 0% to 40%: Insignificant heterogeneity, I2 = 30% to 60%: Moderate heterogeneity, I2 = 50% to 90%: Substantial heterogeneity, I2 =75% to 100%: Considerable heterogeneity.

Results

The electronic search strategy revealed 7101 relevant RCTs and hand searching of relevant reference lists provided one additional article until August 2023 as illustrated in PRISMA flow chart **(Figure 1).**

After the removal of 125 duplicates by Rayyan computer software, and deleting of 5839 un-relating articles, the net studies became= 1137, screening by title and abstract. Then articles that screened by full text were 19 complete RCTs, which were identified for assessment of eligibility for full review. Of those studies, four studies were met the eligibility criteria and were subsequently included in this systematic review. The titles of these included studies were explained in **(Table 1).**

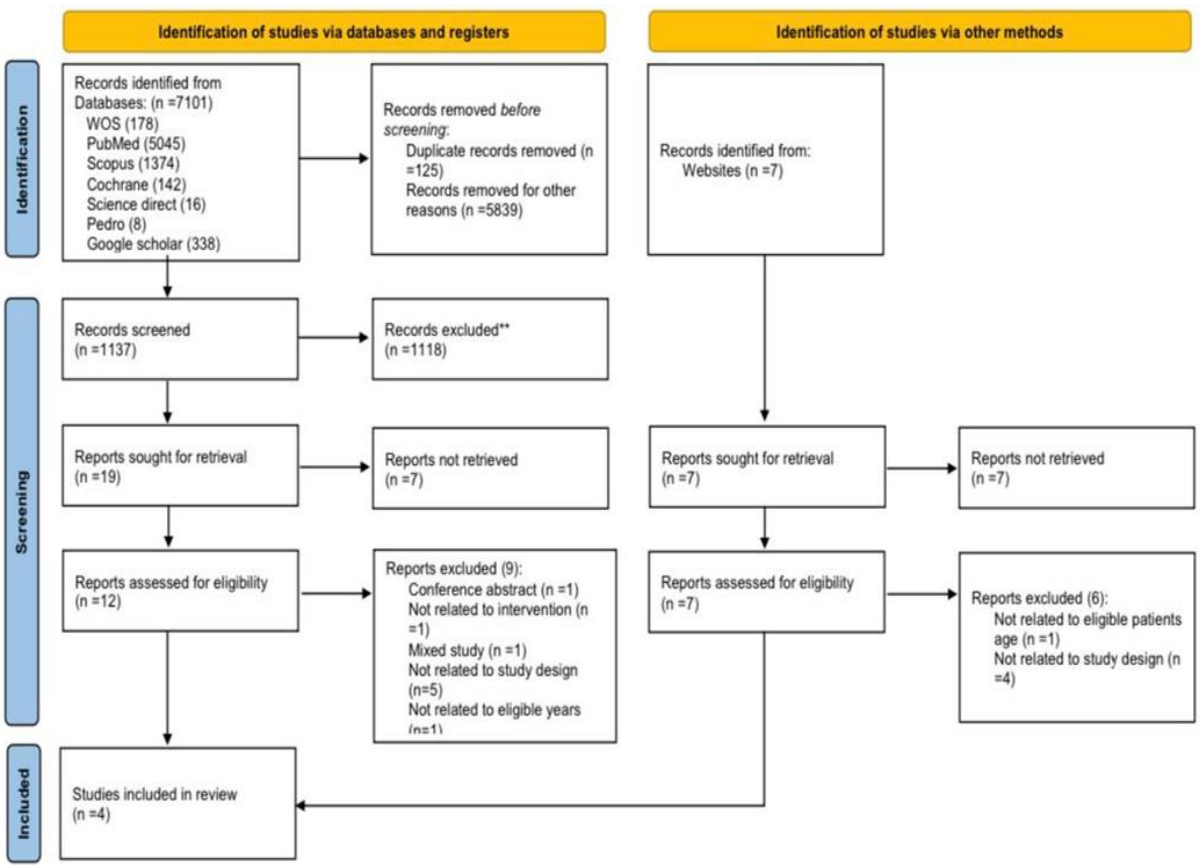

Figure (1): Prisma 2020 Flow Diagram for new SRs which included searches of databases, registers and other sources

Table (1): Included studies

Author (year)	Title
Spaas et al (2022)	Altered muscle oxidative phenotype impairs exercise tolerance but does not improve after exercise training in multiple sclerosis
Rademacher et al (2021)	Cognitive Impairment Impacts Exercise Effects on Cognition in Multiple Sclerosis
Keytsman et al (2021)	Periodized versus classic exercise therapy in Multiple Sclerosis: a randomized controlled trial
Keytsman et al (2019)	Periodized home-based training: A new strategy to improve high intensity exercise therapy adherence in mildly affected patients with Multiple Sclerosis

Study Characteristics:

The data extracted from the four studies are summarized in **(Table 2).**

Table (2): The data extracted from the four studies

Study	**Keytsman et al., 2019**	**Rademacher et al., 2021**	**Keytsman et al.,2021**	**Spaas et al., 2022**
Design	RCT	RCT	RCT	RCT
Sample size	37 (18 MS & 19 HC)	75 MS	31 MS	43 (23 MS & 20 HC)
Participants	aged >18y, mild MS, all types, EDSS 0→3.5,	>21y, all types, EDSS (3.0 - 6.0)	>18y, all types, EDSS (2.3+_1.3)	20 y, EDSS: 2.6 ± 1.5, PASIPD: (20.9 ± 13.4)
HIIT intervention regime	Cycling training using bicycle	Bicycle ergometer	Stationary bicycle	Braked cycle ergometer with a metabolic cart + Machine-based upper and lower body resistance exercises.
Intervention Duration, Frequency	6 months 3 times/week 1-1.5 hours/session	3 weeks 3 times/week 24 min./session	12 weeks 3 times/week 10 min./ session	12 weeks 5 sessions/ 2 weeks, session duration not mentioned
Control intervention	Same interventions	Moderate continuous training	Classic moderate endurance training	Same interventions

Outcomes	Exercise capacity, Body composition	Aerobic fitness, Fatigue, Cognitive performance	Exercise capacity, Isometric muscle strength for Quad. And Hamstring, Body composition	Exercise capacity, Intramuscular impairments, Submaximal cardiac and pulmonary function.
Outcome measures	VO2 max., HR max., Workload, BW, BMI, TM, FM, FP, FFM.	VO2 max., HR max., Workload, FSMC, SDMT, VLMT, BVMT-R	VO2 max., HR max., workload, knee extension and flexion peak torques, BMI, BW, FFM, FM, FP, TM.	VO2 max., Peak power output., lower gas exchange threshold, phosphocreatine stores, lactate accumulation (muscle metabolic response) and SDH activity (Succinate dehydrogenase), Expression of genes involved in mitochondrial functions.
Results	Significant improvements for all measures	Significant improvements for aerobic fitness and processing speed of cognitive performance. But no significant effect for fatigue, visuospatial and verbal learning outcomes.	Significant improvements for exercise capacity and BMI only. But the remaining measures for body composition didn't change and no significant improvement in muscle strength in both groups.	No significant improvements in cardiac, pulmonary nor intramuscular impairments after trainings in MS patients. MS patients have lower exercise capacity than healthy subjects and didn't differ after trainings **Except** VO2 max. improved by 23% in MS patients.

Intervention:

In studies, the exercise intensities differed as starting by warming up period at 40% of participants' heart rate maximum, cooling down period at the end of the session at 30% of participants' heart rate maximum and the interval high intensity period between 85-90% or 95-100% of participants' maximum heart rate. All studies included cyclic training as a high intensity interval training except (15) added resistive trainings for upper and lower limbs while doing cyclic training.

In conclusion, the included studies conducted supervised high intensity interval training using cycle ergometer for average of 12 weeks, with an average of 48 minutes per session for PWMS with all types and their EDSS score less than 6.

Outcome Measures:

Primary outcomes:

The included four studies differed in their considering primary outcomes as (12) assessed Therapy adherence by total training duration, total cycling Distance and caloric expenditure, Exercise capacity by VO2max, time until exhaustion, heart rate, lactate peak, Respiratory Exchange Ratio (RER) & (13) assessed Aerobic Fitness by Peak O2 consumption (VO2 max.), Workload max., Heart rate, Graded cardiopulmonary exercise Fatigue through the German version of the functional scale of motor and cognitive functions (FSMC) & (11) assessed Exercise capacity by VO2max, workload, time until exhaustion, maximal heart rate, recovery heart rate, peak lactate, Isometric muscle strength of the knee extensors and flexors (45◦ and 90◦ knee angle) was measured, using an isokinetic dynamometer by measuring the peak knee flexion and extension torques & (15) assessed Exercise capacity through VO2peak, peak power output, lower gas exchange threshold, respiratory compensation point, and higher peak RER, Intramuscular impairments through intramuscular phosphocreatine stores, lactate accumulation (muscle metabolic response) and SDH activity (Succinate dehydrogenase).

Secondary outcomes

The four included studies discussed different secondary outcomes as (12) assessed Body composition by body weight, body mass index (BMI), total mass, Fat mass, fat percentage and fat free mass & (13) assessed Cognitive performance with the Brief International Cognitive Assessment for MS (BICAMS) which included Processing speed measured by symbol digit modalities test (SDMT), verbal learning by verbal learning memory test (VLMT), visuospatial learning by brief visuospatial memory test revised (BVMT-R) & (11) assessed Body composition by BMI, weight, fat mass, fat percentage, fat free mass, total mass. & (15) assessed Submaximal cardiac and pulmonary function by maximal cardiopulmonary exercise testing, Expression of genes involved in mitochondrial functions intra muscles.

Follow-up:

Throughout both training programs, BORG RPE scores (a scale of 6- 20, representing ratings of perceived subjective fatigue of the training effort) were noted following every training session (endurance and HIIT) and eventually averaged. Furthermore, in order to compare total exercise commitment and efficiency between both training interventions, peak-effort training minutes were calculated using a previously published formula by (11).

Effect of interventions of included studies:

Meta-analysis

Exercise Capacity Results (VO2 max., HR max., Workload):

We analyzed data from the four included studies using Review Manager (RevMan – version 5.4.1, The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark, 2021), and Microsoft Excel 2010 (Microsoft Corp., Redmond, WA, USA). A formal meta-analysis was conducted for all outcomes if the data were sufficient. We expressed pooled continuous effect measures as the mean difference (MD) with 95%CI. We explored and quantified between-study statistical heterogeneity using the I2 test. By default, we used the fixed effect model in all analyses. If heterogeneity was statistically significant ($p < 0.05$) or I2 was > 50%, we used the Der Simonian and Laird random-effects model instead (20). We considered 2-sided statistical analysis testing setting the α-error level at 0.05.

For VO_2 max: Three studies assessed the maximum oxygen consumption of the participants during exerting the program of high intensity interval training using cycle ergometer and its affection on exercise capacity using maximum exercise testing for both intervention and control groups. There was moderate heterogeneity across the studies (n= 3 studies, n= 139 participants, P= 0.14; I2= 50%). The overall result is statistically insignificant (Z = 0.05; P= 0.96) **Figure (2).**

Study or Subgroup	Study Mean	Study SD	Study Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Keytsman et al., 2019	42.9	7.1	18	46.8	7.6	19	29.5%	-3.90 [-8.64, 0.84]
Keytsman et al., 2021	31.9	8.4	13	28.7	7.9	15	21.8%	3.20 [-2.87, 9.27]
Rademacher et al., 2021	21.58	5.84	38	20.84	5.2	36	48.8%	0.74 [-1.78, 3.26]
Total (95% CI)			**69**			**70**	**100.0%**	**-0.09 [-3.55, 3.37]**

Heterogeneity: Tau² = 4.74; Chi² = 3.99, df = 2 (P = 0.14); I² = 50%
Test for overall effect: Z = 0.05 (P = 0.96)

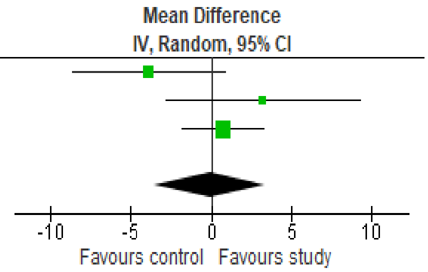

Figure (2): Forest plot of overall analysis of comparison: 1 Comparison between study and control groups, outcome: 1.1 VO_2max:

For workload: Two studies assessed the workload of the participants during exerting the program of high intensity interval training. There was significant heterogeneity across the studies (n= 2 studies, n=65 participants, P= 0.14; I2= 54%). The overall result is statistically insignificant (Z = 0.77; P = 0.44) **Figure (3).**

Study or Subgroup	Study Mean	Study SD	Study Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Keytsman et al., 2019	237.2	47.4	18	270.8	53.1	19	57.2%	-33.60 [-66.00, -1.20]
Keytsman et al., 2021	188	53.9	13	180	67	15	42.8%	8.00 [-36.81, 52.81]
Total (95% CI)			**31**			**34**	**100.0%**	**-15.80 [-56.14, 24.54]**

Heterogeneity: Tau² = 467.30; Chi² = 2.17, df = 1 (P = 0.14); I² = 54%
Test for overall effect: Z = 0.77 (P = 0.44)

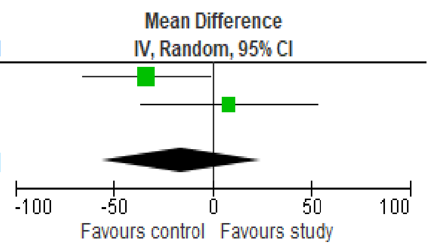

Figure (3): Forest plot of overall analysis of comparison: 1 Comparison between study and control groups, outcome: 1.2 Workload.

For HR max: Two studies assessed the maximum heart rate of the participants during exerting the program of high intensity interval training. There was not any heterogeneity across the studies (n= 2 studies, n=65 participants, P= 0.79; I2= 0%). The overall result is statistically insignificant (Z = 0.42; P = 0.67) **Figure (4).**

Study or Subgroup	Study Mean	Study SD	Study Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Keytsman et al., 2019	179.1	9.8	18	178.2	11.8	19	79.5%	0.90 [-6.07, 7.87]
Keytsman et al., 2021	173	16	13	170	21	15	20.5%	3.00 [-10.73, 16.73]
Total (95% CI)			**31**			**34**	**100.0%**	**1.33 [-4.89, 7.55]**

Heterogeneity: Chi² = 0.07, df = 1 (P = 0.79); I² = 0%
Test for overall effect: Z = 0.42 (P = 0.67)

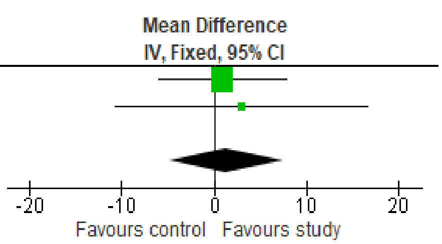

Figure (4): Forest plot of overall analysis of comparison: 1 Comparison between study and control groups, outcome: 1.3 HR max.

Safety Results:

The (12) study provided safety as this was the first time a HIT oriented periodized homebased training strategy was applied in MS patients, and for safety reasons, the present project only included mildly affected relatively fit persons with MS (EDSS: 1.8 ± 1.1). During the patients' participation in the program, Healthy controls were asked to accompany one MS patient throughout the challenge. Regarding the adverse events or injuries that happened during and after HIIT period, (11) reported no drop-outs, adverse events or side effects (e.g. fatigue, spasticity) due to the allocated interventions were reported during the course of the study. (13) reported that no adverse events occurred during Patients' participation in HIIT program. (12) also reported no injuries or adverse events (physical complications or exacerbations) occurred during the challenge, but five persons with MS and three HC dropped out. Reasons were musculoskeletal injuries not related to the intervention program (2 persons with MS, 1 HC), motivational issues (1 person with MS, 1 HC), one exacerbation in the MS group, and personal reasons (1 person with MS, 1 HC).

Discussion

The objective of our systematic review was to assess the effect of HIIT in PwMS and to investigate the strength of qualitative evidence that support HIIT effectiveness in PwMS and to determine the possible adverse events of HIIT on MS patients. Using HIIT in MS patients is still a challenge; due to the limitation of published randomized articles using HIIT in different types of MS patients and also due to the decreased published randomized articles about the effects of using HIIT in MS patients from neurological overview. Although there is a systematic review that had evaluated the effect of HIIT in people with MS (8) but it included only the cardiovascular effects after HIIT program in MS patients, so here we concerned with reporting the effects of HIIT on PwMS mainly from the neurological aspect (like mentioning cognitive functions, fatigue, aerobic fitness). In this review, the intensive electronic databases of PubMed, Web of Science, Scopus, the Cochrane library, Science direct, Google scholar and PEDro were searched. After finishing filtration steps, four studies were included. To obtain the highest level of evidence, this review included randomized control trails only. This review used Cochrane Collaboration's tool for Risk of Bias in RCTs to assess the score and quality of the included RCTs. The assessment revealed that all four studies showed a low risk in most bias domains. However, they exhibited a high risk in blinding of participants and personnel, which is often challenging in exercise-based interventions. The "Other Bias" category remained unclear across studies, indicating potential areas not fully addressed.

The level of evidence in a systematic review was moderate to high. We had done meta-analysis for the four studies for one outcome which is the exercise capacity, done for the three outcome measures (VO2 max, HR max and work load). For VO2 max, three studies assessed VO2 max for the participants during exerting the program of high intensity interval training using cycle ergometer using maximum exercise testing for both intervention and control groups. There was moderate heterogeneity across the studies (n= 3 studies, n= 139 participants, P= 0.14; I2= 50%). The overall result was statistically insignificant (Z = 0.05; P= 0.96). For HR max, two studies assessed HR max of the participants during exerting the program of high intensity interval training. There was not any heterogeneity across the studies (n= 2 studies, n=65 participants, P= 0.79; I2= 0%). The overall result was statistically insignificant (Z = 0.42; P = 0.67). For Workload, two studies assessed the workload of the participants during exerting the program of high intensity interval training. There was significant heterogeneity across the studies (n= 2 studies, n=65 participants, P= 0.14; I2= 54%). The overall result was statistically insignificant (Z = 0.77; P = 0.44).

From previous studies, the following reasons for recommending using HIIT in PWMS were that HIIT induced various beneficial and superior effects on MS impairments, mainly exercise capacity and muscle strength, compared to low or moderate exercise interventions which leaded to improved mobility, reduced disability and increased quality of life in these patients. The (11,13) studies mentioned that Exercise training especially became of particular interest as a non-pharmacological supportive treatment option in the last decade. Previous research had already shown associations between exercise training and improved cognitive performance in healthy and cognitively impaired older adults. Additionally, data also suggested exercise-induced neuro-protective effects in several neurological diseases, such as Alzheimer’s disease. (16) suggested that Concurrent resistance and high-intensity interval training is well-tolerated by patients with MS and is effective in improving certain cardiovascular risk factors and exercise capacity in this population. The efficacy of concurrent resistance and aerobic exercise training in this population therefore deserved further study. (12) thought that Exercise therapy and increased physical activity in persons with MS improved mobility, muscular strength, physical fitness and fatigue without increasing relapse rate. As such, physical activity and more particular exercise therapy had become an important complementary part of MS rehabilitation. In particular, high intensity interval training/rehabilitation (HIIT) in MS had gained much attention. Although and in contrast to lower intensity exercise that had shown good long-term therapy adherence, it appeared to be less effective to improve health-related variables such as body composition, blood pressure and blood lipid profiles. It substantially enhanced functionally (daily life) relevant variables such as exercise capacity (+22%) and muscle strength (+44%) however, and in this population it was also associated with improvements of various quality of life measures as well as cognitive performance (+8%). Because this exercise mode appeared to be safe and well-tolerated in MS, further optimization of high intense exercise therapy and especially its effective longer-term implementation in actual rehabilitation programs in this population, was highly warranted. Consequently, any HIIT-oriented exercise therapy strategy that improved longer-term compliance (therapy adherence) was worthwhile investigating. Periodized, home-based training within an awareness of increased physical activity in MS context could be such a strategy.

From all the previous studies, we tend to systematically review all data about HIIT in PwMS to collect all effects of HIIT in MS patients and how much safety and efficacy that type of training in patients with MS. So, after data collection and doing this systematic review and meta-analysis, we can say that HIIT has some benefits for PwMS as HIIT improves the exercise capacity for MS patients especially the maximum heart rate reached and measured before and after usage of HIIT. Also, HIIT improves the information processing speed of the patients. But it has no effect in muscular strength, aerobic fitness, exercise fatigue, changes in intramuscular impairments, verbal learning and visuospatial process of cognitive functions. May be, because some limitations founded and mentioned in each study. Generally, because of the limited articles published about using HIIT in MS patients and its effect on them from the neurological aspect. Specifically, (11) mentioned the limitations founded during his study as patients through course of training didn't keep their daily activities and dietary habits, not enough investigation about the effect of using HIIT on functional rehabilitation measures as gait and balance in PwMS, the study included only mild MS type not all types and the sample contained mostly MS with relapsing remitting and only two persons with secondary progressive MS. (13) informed some limitations too. Firstly, the study was a subgroup analysis and the division into PwMS with impaired and intact cognition was done afterwards, consequently leaving the original randomization out.

Moreover, the sample size calculation was based on the primary outcome of the original trial. However, it was relatively large compared to existing trials in that research context. Second, the study was conducted during inpatient rehabilitation, limiting the total time of the intervention period (3 weeks), consequently, potential neuronal adaptations might not fully develop in that relatively short period of time. Third, the cognitive functions measures were secondary outcome measures not primary. Finally, one intervention group consisted only of female participant since sex was no stratification factor during their randomization process. (15) explained the limitations as the sample size was lower for certain comparisons following the training intervention, the chosen concurrent resistance and high-intensity interval aerobic training intervention may have been suboptimal for eliciting clear improvements in aerobic and mitochondrial function. (12) also informed the limitation in using relatively fit mild MS patients in their study.

Conclusions:

According to the results of this study, high intensity interval training appears to have a positive effect on information processing speed and maximum heart rate after exercising and safe in the management of multiple sclerosis patients. However, more future randomized articles are still needed to cover the effect of using HIIT in all MS types and also discuss the effect of using HIIT in different aspects of MS neurological symptoms as cognition, physical performance, balance, depression and their sensory impairments so cover this issue.

Recommendations:

1-Well- designed, randomized controlled trials on the effectiveness of using HIIT in Different MS types on cognition alone, sensory impairments alone, physical performance alone, depression alone, activities of daily living alone and quality of life alone as considering each point of the mentioned above as a primary measures in the future searches.

2- Accompanying the future studies with a motivational long term goal after finishing the program as that promising motivational goal will encourage them overcome their symptoms their fatigue.

3- Long-term follow up studies with a larger population of subjects must be performed to determine the effects of using HIIT in PWMS.

4- Further RCTs on the effectiveness of HIITs in people with progressive multiple sclerosis who have a severe level of impairment are also required, as most available studies include patients with relapsing remitting MS only.

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