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| **CRITICALLY APPRAISED TOPIC** |

**FOCUSED CLINICAL QUESTION**

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| Is High Intensity Interval Training (HIIT) more effective than typical activity recommendations at reducing fatigue and improving activity tolerance in a 28-year-old woman with Relapsing-Remitting Multiple Sclerosis and an Expanded Disability Status Scale (EDSS) of 6? |

**AUTHOR**

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**CLINICAL SCENARIO**

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| I worked with a 28-year-old woman with Relapsing-Remitting Multiple Sclerosis (RRMS) who was motivated to be as independent as possible in her self-care and the care of her young daughter. She reliably performed her home exercise program and was eager to progress her exercises in therapy. This patient was able to ambulate a short distance with standby assist, and able to ambulate >100m at a time using her rollator. She was educated in energy conservation strategies and encouraged to engage in increased physical activity in addition to physical therapy; however, her progress was limited due to frequent and severe fatigue and inability to tolerate activity for more than about 7-8 minutes at a time. In my experience working with patients with MS, I and other clinicians often give advice about energy conservation, including encouraging the patient to accomplish more over a longer period by incorporating rest breaks rather than trying to accomplish everything without rest and becoming fatigued for the remainder of the day.Over the past 20 years, exercise has transitioned from being considered controversial and potentially dangerous to those with MS to being a vital aspect of rehabilitation and wellness.1 Moderate intensity exercise is now recommended for improving fitness in those with MS; however, it has not been until recent years that high intensity exercise has been considered for people with MS.2 High intensity interval training (HIIT) has been shown to be more efficient at improving VO2max and reducing cardiovascular risk factors than continuous moderate training in healthy individuals, and has recently been shown to be beneficial for patients with other neurologic diagnoses such as stroke survivors or those with Parkinson’s Disease.2 It is speculated that HIIT may be particularly beneficial for patients with MS due its incorporation of intervals (comparable to energy-conserving rest breaks) which may allow for increased intensity of work without thermosensitive responses which may trigger brief symptom exacerbation.2 HIIT may be an effective intervention for patients with RRMS who would benefit from additional physical activity but struggle due to symptoms such as fatigue. |

**SUMMARY OF SEARCH**

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| Eight studies including one systematic review, two RCTs, one randomized controlled trial, three non-randomized trials, and one repeated-measures design met the inclusion and exclusion criteria used in this literature search.* A systematic review examining the safety and efficacy of HIIT demonstrated that HIIT via cycle ergometry can improve VO2peak and VO2max, HRMax, peak power, muscle strength, and MMP-2 levels in those with MS who have low to moderate levels of disability. It also suggests that these improvements may be significant compared to moderate continuous exercise and may be achieved in a more efficient manner.2
* Many of the available studies have combined HIIT with other exercise training such as continuous aerobic exercise or resistance training, so it is not yet clear if improvements would be maintained with HIIT intervention alone.2
* There is no evidence for reduction of fatigue severity with HIIT compared to continuous training; however, both seem to reduce fatigue in a sub-group of participants with severe fatigue as assessed by the Fatigue Severity Scale (FSS).8
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**CLINICAL BOTTOM LINE**

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| There is insufficient evidence available to determine if HIIT is more effective than typical recommendations at reducing fatigue and improving activity tolerance in a young woman with RRMS and an EDSS of 6.0; however, there seems to be evidence that HIIT is at least as effective and more efficient than moderate continuous training at improving fitness in similar patients with RRMS and lower levels of disability.2 There is also evidence indicating that aerobic training can reduce fatigue in those with severe levels of fatigue.8 |

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| ***This critically appraised topic has been individually prepared as part of a course requirement and has been peer-reviewed by one other independent course instructor*** |

*The above information should fit onto the first page of your CAT*

**SEARCH STRATEGY**

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| **Terms used to guide the search strategy** |
| **P**atient/Client Group | **I**ntervention (or Assessment) | **C**omparison | **O**utcome(s) |
| Multiple sclerosisMSRelapsing-RemittingRRMS | High Intensity Interval TrainingHIITHITHigh intensity interval exerciseHIIESprint interval trainingSIT | Typical activity | FatigueActivity tolerance |

**Final search strategy (history):**

1. Multiple sclerosis OR RRMS
2. High intensity interval training OR HIIT OR HIT
3. High intensity interval exercise OR HIIE
4. Sprint interval training
5. Fatigue
6. Activity tolerance
7. Exercise tolerance
8. Endurance
9. Physical activity
10. **#1 AND (#2 OR #3 OR #4) AND (#5 OR #6 OR #7 OR #8 OR #9)**

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| **Databases and Sites Searched** | **Number of results** | **Limits applied, revised number of results (if applicable)** |
| **PubMed** | **20** | **N/A** |
| **PEDro** | **4** | **N/A** |
| **Cochrane** | **1 Review,****17 Trials** | **N/A** |

## INCLUSION and EXCLUSION CRITERIA

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| **Inclusion Criteria** |
| * Patient population with Multiple Sclerosis
* High intensity exercise intervention
* Outcome measures to assess fatigue, activity tolerance, or function
* Randomized controlled trials, cohort studies, and randomized crossover trials
* Systematic Reviews and Meta-Analyses
* Standardized training of researchers
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| **Exclusion Criteria** |
| * Not published in English
* Narrative review articles
* Published prior to 2005
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**RESULTS OF SEARCH**

**Summary of articles retrieved that met inclusion and exclusion criteria**

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| **Author (Year)** | **Risk of bias (quality score)\*** | **Level of Evidence\*\*** | **Relevance** | **Study design** |
| Guillamo E, et al. (2018)1 | Downs and Black: 16/29 | 2b | Low | Non-randomized pilot study |
| Wens I, et al. (2015)3 | PEDro score: 6/10 | 1b | Moderate | RCT |
| Zaenker P, et al. (2018)4 | Downs and Black: 15/29 | 2b | Low | Non-randomized pilot study |
| Campbell E, et al. (2018)2 | AMSTAR 2:Low quality review | 1a | Moderate | Systematic review |
| Keytsman C, et al. (2018)5 | Downs and Black: 15/29 | 2b | Low | Non-randomized controlled trial |
| Hubbard EA, et al. (2019)6 | Downs and Black:20/29 | 2b | Moderate | Repeated measures design |
| Wonneberger M, et al. (2019)7 | PEDro score: 4 /10 | 1b | Moderate | Randomized cohort study |
| Keytsman C, et al. (2019)8 | PEDro score: 5/10 | 2b | Low | RCT |

\*Indicate tool name and score

\*\*Use Portney & Watkins Table 16.1 (2009); if downgraded, indicate reason why

**BEST EVIDENCE**

The following 2 studies were identified as the ‘best’ evidence and selected for critical appraisal. Rationale for selecting these studies were:

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| * 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.

This is the highest quality evidence available in this selection for examining the effects of HIIT for patients with MS. Unfortunately, the outcome measures examined most thoroughly are related to physical fitness rather than fatigue and activity tolerance; however, I believe information related to these outcome measures can be deduced from available information on endurance, perceived exertion, and secondary outcome measures such as the fatigue severity scale and physical activity scale which are included in at least one of the studies in the review.* Wonneberger M, Schmidt S. High-intensity interval ergometer training improves aerobic capacity and fatigue in patients with multiple sclerosis. *Sport Sciences for Health.* 2019.

Although this article is an unblinded, randomized cohort study and is thus not the highest level of evidence available, it is the article that appears to be most directly relevant to my clinical question. This randomized cohort study is examining the efficacy of high-intensity interval training on aerobic capacity and fatigue for patients with relapsing-remitting MS, which is very similar to the population, intervention, and outcome in my clinical question. |

**SUMMARY OF BEST EVIDENCE**

**(1) Description and appraisal of “High intensity interval training for people with multiple sclerosis: a systematic review” by Campbell E, Coulter EH, Paul L; 2018.**

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| **Aim/Objective of the Study/Systematic Review:** |
| The objective of this systematic review was to examine the safety and efficacy of high intensity interval training (HIIT) in people with multiple sclerosis (MS).  |
| **Study Design** |
| Campbell E et al. is a systematic review of clinical trials including HIIT for participants with MS.**Search Strategy**: A literature search of EMBASE, MEDline, PEDro, CENTRAL, and Web of Science Core Collections was conducted in September 2017. There were no limits on year of publication. The search terms for each of these were included in a table in the review. As an example, the search strategy for CENTRAL was: (((multiple sclerosis) OR (relapsing remitting) OR (chronic progressive) or (secondary progressive) OR (primary progressive)) OR (MeSH descriptor: [multiple sclerosis] explode all trees)) AND (((High intensity interval training) OR (interval training) or (High intensity interval exercises) OR (interval exercise) OR (aerobic interval training) OR (high intensity) OR (high-intensity) OR (exercise intensity) or (HIIT) or (HIT))). All included articles’ reference lists were also searched.**Selection Criteria**: Inclusion eligibility: Clinical trials consisting of aerobic intervention of HIIT either alone or in combination with other exercises. HIIT was defined as an intensity of 80% or more of maximal effort in intervals of 5 min or less. Trials included participants with MS, with the data for people with MS presented separately if in a mixed population. Only articles published in English were included.Exclusion criteria: Non-human studies, case studies, or abstracts. Articles focusing only on resistance, balance, or core training.**Data Collection:** The following data was collected from each article: authors, publication date, study design, sample size, adverse events, number of drop-outs, type of MS, level of disability, number of intervals per session, target intensity, total time in high intensity training, any additional exercise training modalities, outcome measures, and results.**Quality Assessment**: The PEDro scale was used to methodologically rate the studies, which is a valid and reliable method that can be used for both randomized controlled trials (RCTs) and cohort studies. At least two reviewers assessed each included article, and any disagreement was settled through discussion. |
| **Setting** |
| This review was part of first author Evan Campbell’s PhD which was funded through scholarship from NHS Ayrshire and Arran, United Kingdom. All authors are associated with universities in Glasgow, UK. |
| **Participants** |
| * This review included 11 articles describing 7 studies. Of these studies, 4 were RCTs, 1 was a randomized crossover trial, and 2 were cohort studies. The lowest number of participants in a study was 11, the highest was 61, and the total number of participants included in all the studies of the systematic review was 249.
* Many of the studies included participants with several types of MS; however, relapsing-remitting (RR) MS was the most common. Secondary Progressive (SP), and Primary Progressive (PP) MS were also included. The studies used participants with a range of disability levels, but most studies had participants with a mean EDSS between 2 and 2.7. One study included participants with progressive, severe disability (EDSS 6.0-8.0).
* Number of drop-outs varied amongst studies: three studies had 0 drop-outs, one had 1, one had 3, one had 4, and one had 6
* PEDro scores for included articles ranged from three to eight out of ten. Eight articles received scores of seven or eight and were considered “high quality”, the remaining three articles received scores of three, four, and five. None of the articles received points for blinding of subjects or therapists.
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| **Intervention Investigated** |
| *Control* |
| * Two of the studies were cohort studies and did not have control groups.
* One study was a randomized crossover trial, each participant did a single session of each type of intervention (two moderate continuous exercise sessions, one HIIT)
* Of the four RCTS, the following controls were used:
	+ Moderate continuous exercise: 45% peak power for 20 minutes over 24 sessions
	+ Sedentary (no intervention); continuous exercise (80-100% HRMax) + resistance training (leg presses, curls, extensions, lateral pull downs, arm curls, chest presses 1x 10 reps max progressing to 2x 20 reps max) for 12 weeks
	+ High intensity continuous exercise: 70% HRMax minimum, 5x/week for 3 weeks
	+ In-patient rehabilitation only: 10 sessions over 4 weeks
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| *Experimental* |
| The following HIIT interventions were used in the studies in this review. Cycle ergometry was used for HIIT unless stated otherwise:* **HIIT** at 90% peak power; 30 seconds on, 30 seconds off over 20 minutes; 2x/week for 12 weeks
	+ Same training, but over only one session
* **HIIT** for 5x 1 min at 80-90% HRMax for 6 weeks, 5x 2 min 90-100% HRMax for 6 weeks **+ Resistance training** (leg presses, curls extensions, lateral pull downs, arm curls, chest presses 1x 10 reps max load, progressing to 2 x 20 reps max load)
* **HIIT** for 5x 1 min at 90-110% peak power, with warm-up, 3 min working rest, and warm down **+ resistance** bodyweight exercises + 30-45 minutes of **continuous moderate aerobic exercise** (cycling, swimming, or walking)
* **HIIT** 3x/week for 3 weeks; 5x 3 min intervals at 85-90% HRMax with 1.5 min of working rest at 50-60% HRMax for 20 total minutes
* **HIIT upper limb ergometer training** of 6x 3 min intervals with 2 min at 65-75% VO2max and 30-60 sec sprint at 100% max effort + **in-patient rehabilitation**
* **HIIT** starting with 5x 1 min at 85-90% HR max with 1 min rest, progressing to 5x 2 min at 100% HRMax with 1 min rest **+ resistance training** (leg presses, curls, extensions lateral pull downs, arm curls, chest presses starting at 1x 10 reps max load, progressing to 2x 20 reps max load)
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| **Outcome Measures** |
| * There was a total of 60 different outcome measures used in the studies in this review, with fitness being measured most commonly (five of the six studies); however, fitness measures were not the primary outcomes in any of the studies.
* Six of the 11 articles did not separate primary and secondary outcome measures. Of the five articles that did clarify, the primary outcome measures were: 2 min walk test, muscle fiber CSA and proportion, oral glucose tolerance test, satellite cells type I and type II fibre myonuclei and central nuclei analysis, and the brief international cognitive assessment for MS (BICAMS)
* Common secondary (or not separated) outcome measures were: VO2max, HRMax, peak power, respiratory exchange ratio (RER), short form 36 (SF36), fatigue severity scale (FSS), multiple sclerosis impact scale (MSIS-29), and 6 min wheelchair test
* One study assessed serum levels of brain derived neurotrophic factor (BDNF), matrix metalloproteinases (iex-2 and MMP-9), and serotonin (5HT)
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| **Main Findings** |
| There was significant heterogeneity among interventions, participants, and outcome measures included in the studies in this review; however, the following are the results of common measures assessed in the studies:* **VO2Max or VO2peak** was measured in 6 studies, with improvement after HIIT in 5/6 studies: 2 cohort studies report improvement in VO2peak (+13.5%, p< 0.001) and VO2max (+5.9 ml/min/kg, p < 0.05); 2 RCTs report improvement in VO2max  for both HIIT (95% CI (-4.096; -2.002) p <0.001) and continuous training (95% CI (-2.394; -0.426) p = 0.006) groups; 1 RCT reports VO2max improvement in HIIT group compared to continuous or sedentary groups (+17%, p<0.01); 1 RCT (Skjerbaek et al., 2014) reports no change in VO2peak
* **HRMax** was measured in 5 studies, with improvement after HIIT in 2/5 studies: 3 did not report changes after HIIT; two report significant within group increases with HIIT (+3.73%, p=0.012; +6.2%, p=0.05)
* **Peak power** was measured in 4 studies, with improvement after HIIT in 4/4 studies: 2 cohort studies report increase in peak power (+9.4%, p<0.0001; +25 W (CI -34, -16) p<0.05); 1 RCT report increase in peak power after HIIT compared to continuous and sedentary groups (+21% (SD 4), p<0.01); 1 RCT reports increase in peak power only in participants completing more than 8 sessions of HIIT (p=0.05)
* **Muscle strength** was measured in 4 studies, with improvement after HIIT in 4/4 studies: 2 cohort studies report stronger isokinetic and isometric hamstring and quadriceps contractions (p<0.05); 1 study reports increase in isometric hamstring strength only in the HIIT group (range +13% to +20% Nm, p=0.006), and between-group differences in both quadriceps and hamstring strength in both HIIT (range 24% to 44% Nm, p=0.006) and high-intensity continuous ( range +19% to +33%, p=0.006) groups; 2 articles report improvement in isometric leg extension power but this is not maintained at 12-week follow-up (12 weeks: +15.9 W, 24 weeks: -10.9 W, p<0.01)
* **Neurochemicals** related to MS were measured in one study (2 articles): levels of MMP-2 improved in the HIIT group only, despite equal energy expenditure in all training groups (p=0.009), there were no reported changes in serotonin, BDNF, or tryptophan metabolism
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| **Original Authors’ Conclusions** |
| The authors conclude that cycle ergometry HIIT is safe and effective to improve fitness in those with MS. They note that, when compared with moderate continuous training, HIIT requires fewer and shorter sessions to achieve similar results. Finally, the authors call for additional research on this subject with specific focus on those with progressive MS or higher levels of disability, and to examine benefits other than fitness. |
| **Critical Appraisal** |
| **Validity** |
| **AMSTAR** score 7/11: a priori design provided: no; duplicate study selection and data extraction: yes; comprehensive literature search performed: yes; status of publication used as an inclusion criteria: yes; list of studies provided: no; characteristics of included studies provided: yes; scientific quality of included studies assessed: yes; scientific quality used appropriately in forming conclusions: no; methods used to combine findings appropriate: n/a; likelihood of publication bias assessed: yes; conflict of interest included: yes**AMSTAR 2** results: Moderate quality reviewOverall, this systematic review provides moderate quality evidence given the limited quantity and quality of available literature examining HIIT for those with MS. **Strengths:*** Investigators did not include studies of lesser quality than cohort studies, such as case series or abstracts.
* Investigators performed a fairly thorough search (although they included only English articles) and included a broad variety of articles when considering quality, participants, interventions, and outcome measures, which is a strength in that it is a comprehensive review of current available literature, but a possible weakness in its heterogeneity.
* Investigators combatted selection bias by having two independent members of the research team determine eligibility of articles for inclusion and quality assessment of included articles.
* Quality of studies was assessed and reported using the PEDro scale.
* Good overall discussion of common results of the included studies, with confidence intervals and p-values clearly noted, and acknowledgement and consideration of differences among the studies and some limitations of the review.

**Weaknesses:*** Quality and quantity of included studies. This review included 11 articles describing only seven studies with 249 total participants. These are low numbers for a systematic review, especially when considering that only four of these studies were RCTs. Three of the seven studies were not high quality, and only three were large enough to be powered.
* Heterogeneity of the studies. Due to substantial differences in interventions, participants, and outcome measures, there is limited generalizability of the results of this review.
* Authors did not report on funding or conflicts of interest for individual studies.
* Only one of the studies conducted any follow-up, and this study did not demonstrate retention of positive results.
* Table presentation of study data was poorly organized and difficult to follow, particularly when examining outcome measures.
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| **Interpretation of Results** |
| Overall, this systematic review provides limited, moderate quality evidence for the safety and efficacy of HIIT via cycle ergometry in improving physical fitness in participants with MS. As noted in previous sections, the quantity and quality of the studies included in this review are limited; however, the authors of this review demonstrated efforts to reduce bias, discuss relevant results, and acknowledge limitations of the included studies.This review provides limited evidence that HIIT can improve VO2peak and VO2max, HRMax, peak power, muscle strength, and MMP-2 levels in those with MS who have low to moderate levels of disability. The evidence suggests that HIIT produces similar and sometimes better results compared to moderate continuous exercise for participants with MS. Moreover, the studies report high adherence to HIIT. The majority of the participants in studies in this review had relapsing remitting MS with a moderate to low level of disability (EDSS of 4 or less), which causes me to consider these results to be generalizable to primarily those in this population. This review provides clear, positive evidence of the effects of HIIT on cardiovascular fitness and muscle strength in participants with MS; however, there is limited evidence for the effects of HIIT on other domains. As the authors note in their limitations, it is also difficult to ascertain whether these benefits are indeed due to HIIT. Many of the included studies incorporate HIIT in combination with another form of exercise, such as continuous moderate training or resistance training. The one included study which did have participants with progressive MS and more severe levels of disability also differed from the other studies in that the intervention used upper extremity ergometry, included a lower time of exercising at high intensity, and the study was underpowered. I will be interested to see future larger studies using cycle ergometry and increased time of high intensity exercise with participants with progressive MS and/or more severe levels of disability to determine if this approach may be safe and effective for those patients.  |
| **Applicability of Study Results** |
| This review is only tangentially relevant to my clinical question due to my question being specific to a patient of a higher level of disability (EDSS of 6) and focused on outcome measures related to fatigue and activity tolerance. This review instead included primarily patients with lower levels of disability (although still the relapsing-remitting disease type) and results focused on aerobic fitness and muscle strength. Specific fatigue measures were used in two of the included studies, but these were not discussed in this review. Activity tolerance may be assessed through functional measures such as the 2 min walk test or 6 min wheelchair test which were also included but not discussed, or activity tolerance and fatigue may be deduced through their correlations with cardiovascular fitness. As fitness increases, disability and fatigue decrease.4 Thus, it is possible that, although not directly addressed in this review, the improved cardiovascular and muscular fitness which many participants with MS experienced may also be associated with improvements in fatigue or activity tolerance which were not assessed. Incorporating HIIT via cycle ergometry is certainly feasible not only as an intervention within the clinic but also for potential physical activity outside of the clinic once safety and efficacy has been established with the individual patient. Due to the demonstrated improvements in fitness and the apparent adherence of participants to this type of exercise, this may be a practical strategy to incorporate as part of a rehabilitation or fitness plan for those with MS. However, due to the lack of evidence in this review indicating efficacy for patients with MS of higher levels of disability, HIIT would not be a priority intervention consideration for the patient in my clinical question. Given the efficacy of the intervention on similar patients with lower levels of disability, my knowledge of the patient’s physical and self-monitoring ability, and the low quality of the study which incorporated patients of higher levels of disability, I would consider HIIT if other, more evidence-based approaches have been ineffective. |

**(2) Description and appraisal of “High-intensity interval ergometer training improves aerobic capacity and fatigue in patients with multiple sclerosis” by Wonneberger M, Schmidt S; 2019.**

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| **Aim/Objective of the Study/Systematic Review:** |
| The objective of this study is to examine the effects of HIIT on aerobic capacity and fatigue in patients with MS. |
| **Study Design** |
| This study is a prospective, unblinded, randomized cohort study in which 40 participants with RRMS were simply randomized to either a moderate endurance training (MT) or high intensity interval training (HIIT) group for eight weeks.Outcomes were measured at baseline and immediately following eight weeks of training intervention. There were no additional follow-up measures recorded.**Inclusion criteria:** diagnosis of RRMS according to the revised McDonald criteria, EDSS of < or equal to 3.5, and age between 18 and 55 years. **Exclusion criteria**: pregnancy, patients with progressive MS or a temperature-sensitive form of MS, history of cardiovascular or pulmonary disease |
| **Setting** |
| Participants were recruited from “Neurologische Gemeinschaftspraxis Bonn”, an outpatient MS center in Germany. |
| **Participants** |
| * N=40 participants with relapsing-remitting MS (31 females, nine males)
* Participants recruited from an outpatient MS center in Germany
* Participants have mean age of 42.1 years (SD 9.3), mean years since diagnosis of 10.9 (SD 7.7), and mean EDSS of 2.24 (SD 0.85)
* Baseline demographics and characteristics were comparable between intervention groups (height, BMI, years since diagnosis, body weight, age, fatigue severity scale (FSS), Timed 25-Foot Walk (T25-FW), EDSS, and peak power output (PPO)) except for VO2 peak which was higher at baseline in the moderate training (MT) group than the HIIT group.
* Dropout rate of 27.5% over the 8 week intervention period. Five participants from the HIIT group and six from the MT group discontinued the study prematurely. Reasons for discontinuation include: relapse (n=1), fall (1), back pain (1), time (4), or no reasons provided (4).
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| **Intervention Investigated** |
| *Control* |
| There was no control group. |
| *Experimental* |
| Two intervention groups:Group I (Moderate continuous training=MT) exercised continuously at 50% peak power outputGroup II (HIIT) performed a 7.5 minute warm-up at 40-50% peak power output; eight intervals of 60 seconds at 70% peak power output alternating with 60 seconds at 50% peak power output; and a 7.5 minutes cool down at 40-50% peak power outputBoth groups exercised on a stationary bicycle ergometer for a total of 30 minutes, three times per week for eight weeks. Participants exercised in a fitness center near their residence with supervision by personal coaches. |
| **Outcome Measures** |
| * The primary outcome measure was **change in VO2peak** which was assessed using ramp protocols on a cycle ergometer. Although the ramp VO2peaktest is detailed in this paper and elsewhere, it is not clear who administered this test and where it was administered in this study. The wattage at which VO2 plateaued was defined as peak power output for each individual, and this was used to determine exercise intensity for that individual. This article reports that there is not yet consensus on how much change in VO2peak is necessary for clinical significance; however, one study reports a relative increased of approximately 3.5 ml/min/kg results in 13% reduction of mortality and 15% reduction of cardiovascular disease.
* Secondary outcome measures were changes in fatigue and walking speed
	+ Fatigue was measured using the **Fatigue Severity Scale** (FSS), which can detect change over time, but this article reports there is not a clear minimal clinically important difference. The FSS is a 9-item questionnaire which can be scored with a maximum score of 63 or with a maximum score of 7 in which the score is the mean of the scores of the 9 items.10 A higher score indicates higher severity of fatigue. A 2013 article suggests that a change in FSS score of 1.9 points would be clinically important.10 A cut-off score designating severe fatigue is 36/63 or 4/7.8,10
	+ Changes in walking speed were measured using the **Timed 25-Foot Walk Test** (T25-FW). A clinically significant change in gait velocity is generally a 20% improvement.8
 |
| **Main Findings** |
| After 8 weeks, there was a significant increase in VO2peak in the HIIT group, but not in the MT group* Mean change of 3.0 ml/min/kg, 95% CI (1.3; 4.6); p=0.04

After 8 weeks, no significant changes were noted in FSS score; however, total sub-group analysis of participants with high baseline fatigue (FSS > or equal to 4) demonstrated significant reduction of FSS score.* Mean change of -0.3, 95% CI (-0.6; -0.03), P=0.03

No significant changes in either group in T25-FW |
| **Original Authors’ Conclusions** |
| The authors conclude that HIIT on a stationary bicycle ergometer may be safe and effective exercise training for patients with RRMS to improve aerobic fitness and to decrease fatigue in those patients with elevated baseline fatigue. They call for additional research related to tailoring HIIT exercise plans to individuals with MS to further assess the impact of this training on fatigue. |
| **Critical Appraisal** |
| **Validity** |
| **PEDro Scale 4/10**: eligibility criteria specified: yes; subjects randomly allocated: yes; allocation concealed: no; groups similar at baseline: no; blinding of subjects: no; blinding of therapists: no; blinding of assessors: no; measures obtained from 85% of subject: no; intention-to-treat: yes; between-group comparisons: yes; point measures and measures of variability: yesStrengths:* The authors performed intention-to-treat (ITT) analysis to preserve sample size and randomization.
* This article presented the collected data and results in an organized manner including means, standard deviations, confidence intervals, and p-values.
* Intervention groups engaged in the same standardized duration and frequency of exercise, and participants were randomly allocated to the intervention groups.

Weaknesses:* Subjects were all selected from the same MS clinic and were thus not randomly selected which may impact external validity
* This study lacked blinding and concealment
* The baseline VO2peak values were significantly different between groups, despite the authors’ main conclusion that HIIT may be an efficient way to improve VO2peak. Because the MT group had a higher baseline VO2peak, there may have been a possible ceiling effect which could have limited change in VO2peak in the MT group compared to the HIIT group.
* The purpose of this study was to examine the effects of HIIT; however, the highest intensity goal was 70% of peak power which, when compared to comparable articles such as the previously examined Campbell E et al. systematic review, is a relatively moderate level of intensity.
* Although clinical significance is briefly discussed for each of the outcome measures, the statistical significance of the improvements in FSS (in the high fatigue sub-group) and VO2peak are not necessarily clinically meaningful changes for those participants.
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| **Interpretation of Results** |
| Overall, this is a low-quality randomized cohort study that provides limited evidence for the safety and potential efficacy of HIIT on improving aerobic capacity in patients with RRMS. This study provides evidence that HIIT may improve VO2peak in patients with RRMS when compared to moderate training; however, the reliability of this evidence is questionable due to significant baseline differences in VO2peak between these groups. It is also unclear whether the demonstrated mean improvement in VO2peak is clinically important. At the least, this study does demonstrate that HIIT may have comparable if not increased effects on VO2peak in participants with RRMS when compared with moderate training. This study did not demonstrate any significant changes in T25-FW or FSS; however, statistically significant changes were shown in both groups in sub-group analysis or participants with severe fatigue. This may indicate that aerobic exercise is beneficial in reducing fatigue in this population, but clinical importance is again a question.Overall, this is an adequate initial study in considering the effects of HIIT and demonstrates that this intervention is at least safe and comparable to moderate-intensity training. |
| **Applicability of Study Results** |
| This study is very relevant to my clinical question and scenario, as it addressed the diagnosis of the participant in my scenario, my proposed intervention, and my desired outcomes. The participants in this study had low levels of disability (mean EDSS of 2.4) compared to the patient in my clinical question (EDSS of 6.0), so results of this study are not necessarily generalizable to my clinical scenario. This intervention would be practical to incorporate either in the clinic or into the patient’s home program due to limited need for equipment or supervision. HIIT is an intervention I would consider due to its demonstrated safety and potential for improved aerobic capacity; however, there is not yet adequate evidence based solely on this study that HIIT is a better choice for my clinical scenario than moderate continuous training. |

**SYNTHESIS AND CLINICAL IMPLICATIONS**

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| High-intensity interval training has been shown to be a safe and effective intervention for patients with relapsing-remitting MS of low levels of disability.2 Based on the Campbell E et al. systematic review and the Wonneberger M et al. cohort study, HIIT can result in improvements in aerobic fitness, muscle strength, MMP-2, and potentially fatigue in individuals with severe baseline fatigue.2,8 Although there is evidence that HIIT can result in these improvements when compared with continuous moderate intensity training, it is not clear whether these differences are clinically meaningful. However, because HIIT is safe and has a comparable (Wonneberger)8 or improved (Campbell)2 rate of adherence compared to continuous training, this may be the preferred intervention option for those patients who were represented well in these studies. Because the patient in my clinical scenario has a higher level of disability than was represented in either of these articles, I would be hesitant to incorporate HIIT unless other, more evidence-based approaches had been ineffective.As demonstrated in my search results and the quality of the articles selected, there is limited evidence available related to HIIT for individuals with MS. This is a new topic (the earliest applicable article was published in 2015) and the current available evidence does not provide much more information than indicating that HIIT is safe and potentially at least as effective as continuous training for patients with MS.2 The highest quality of evidence available, the Campbell et al. systematic review, is a low to moderate quality review including only 249 total participants and demonstrating substantial heterogeneity among the included studies.2 Most of the remaining studies on this topic are either randomized cohort studies or non-randomized pilot studies. In my search, I also discovered many recent conference abstracts related to this subject. Due to these results, I am confident there will be an increase in the evidence available on this topic in the coming years. Future research should include assessment of the impact of HIIT (at peak power of at least 80%) on fatigue severity and quality of life in individuals with MS, and the efficacy of HIIT compared to moderate continuous exercise for patients with progressive MS and/or higher levels of disability. |

**REFERENCES**

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| 1. Dalgas U, Langeskov-Christensen M, Stenager E, Riemenschneider M, Hvid LG. Exercise as medicine in Multiple Sclerosis—time for a paradigm shift: preventive, symptomatic, and disease-modifying aspects and perspectives. *Curr Neurol Neurosci Rep*. 2019; 19(88).
2. 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.
3. Guillamo E, Cobo-Calvo A, Oviedo GR, Travier N, Alamo J, Nino-Mendez OA, Martinez-Yelamos A, Martinez-Yelamos S, Javierre C. Feasibility and effects of structure physical exercise intervention in adults with relapsing-remitting multiple sclerosis: a pilot study. *J Sports Sci Med.* 2018;17(3):426-436.
4. Wens I, Dalgas U, Vandenabeele F, et al. High intensity exercise in multiple sclerosis: effects on muscle contractile characteristics and exercise capacity, a randomised controlled trial. *PLoS ONE*. 2015;10(9):e0133697. doi:10.1371/journal.pone.0133697
5. 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(1):58-67.
6. Keytsman C, Van Noten P, Spaas J, Nieste I, Van Asch P, Eijnde BO. Periodized home-based training: A new strategy to improve high intensity exercise therapy adherence in mildly affected patients with Multiple Sclerosis. *Mult Scler Relat Disord*. 2019;28:91-97. doi:10.1016/j.msard.2018.12.018
7. Hubbard EA, Motl RW, Fernhall BO. Acute High-Intensity Interval Exercise in Multiple Sclerosis with Mobility Disability. *Med Sci Sports Exerc*. 2019;51(5):858-867. doi:10.1249/MSS.0000000000001866
8. Wonneberger M, Schmidt S. High-intensity interval ergometer training improves aerobic capacity and fatigue in patients with multiple sclerosis. *Sport Sciences for Health.* 2019.
9. Keytsman C, Van Noten P, Verboven K, Bogaers A, Eijnde BO. Periodization principles in the rehabilitation of multiple sclerosis. *Multiple Sclerosis Journal*. 2019;25(7).
10. Shirely Ryan Ability Lab. Fatigue Severity Scale. https://www.sralab.org/rehabilitation-measures/fatigue-severity-scale. Accessed December 3, 2019.
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