Title: High intensity interval training for people with Multiple Sclerosis: a systematic review.

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Abstract

Background: Aerobic High Intensity Interval Training (HIIT) is safe in the general population and more efficient in improving fitness than continuous moderate intensity training. The body of literature examining HIIT in Multiple Sclerosis (MS) is expanding but to date a systematic review has not been conducted. The aim of this review was to investigate the efficacy and safety of HIIT in people with MS.

Methods: A systematic search was carried out in September 2017 in EMBASE, MEDline, PEDro, CENTRAL and Web of Science Core collections using appropriate keywords and MeSH descriptors. Reference lists of relevant articles were also searched. Articles were eligible for inclusion if they were published in English, used HIIT, and included participants with MS. Quality was assessed using the PEDro scale. The following data were extracted using a standardised form: study design and characteristics, outcome measures, significant results, drop-outs, and adverse events.

Results: Seven studies (described by 11 articles) were identified: four randomised controlled trials, one randomised cross-over trial and two cohort studies. PEDro scores ranged from 3-8. Included participants (n=249) were predominantly mildly disabled; one study included only people with progressive MS. Six studies used cycle ergometry and one used arm ergometry to deliver HIIT. One study reported six adverse events, four which could be attributed to the intervention. The other six reported that there were no adverse events. Six studies reported improvements in at least one outcome measure, however there were 60 different outcome measures in the seven studies. The most commonly measured domain was fitness, which improved in five of the six studies measuring aspects of fitness. The only trial not to report positive results included people with progressive and a more severe level of disability (Extended Disability Status Scale 6.0-8.0).

Conclusion: HIIT appears to be safe and effective in increasing fitness in people with MS and low levels of disability. Further research is required to explore the effectiveness of HIIT in people with progressive MS and in those with higher levels of disability.

1 Introduction

Exercise is a safe and feasible intervention for people with Multiple Sclerosis (MS) (Heine et al., 2015) and is recommended for increasing cardiovascular fitness and muscular strength (Latimer-Cheung et al., 2013). Cardiovascular fitness in people with MS is lower compared to healthy individuals (Langeskov-Christensen et al., 2015) and is inversely correlated with disease severity and impairment, with fitness decreasing as disability and fatigue rise (Heine et al., 2014; Heine et al., 2016; Kuspinar et al., 2010; Marrie and Horwitz, 2010; Motl and Fernhall, 2012; Valet et al., 2016). Reviews of trials evaluating the effects of exercise in people with MS have indicated that exercise training is beneficial for increasing and maintaining cardiovascular fitness (Dalgas et al., 2008; Rietberg et al., 2005).

Traditionally, continuous moderate intensity training programmes, to increase fitness and reduce cardiovascular disease risk factors in healthy adults, last 30-60 minutes at 40-85% of maximal intensity, with higher intensities producing a greater increase in fitness (Garber et al., 2011). High Intensity Interval Training (HIIT), however, involves 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 (Cassidy et al., 2017; Kessler et al., 2012).

Compared to continuous moderate intensity training, HIIT is more efficient in improving VO_2 max in healthy individuals (Milanovic et al., 2015), people with coronary artery disease (Elliott et al., 2015), increased cardio-metabolic risk (Weston et al., 2014), and heart failure (Haykowsky et al., 2013; Ismail et al., 2013; Smart et al., 2013; Wisloff et al., 2007). HIIT also produces greater or equal effects, to continuous moderate intensity training, in improving cardiovascular risk factors such as high blood pressure and altered glucose metabolism (Fleg, 2016). The main advantage of HIIT over continuous moderate intensity training is the shorter time required to achieve similar energy expenditure, and comparable, or greater benefits (Fleg, 2016). This is due to an increase in oxygen consumption after acute strenuous exercise known as Excess Post-exercise Oxygen Consumption (Gaesser and Brooks, 1984). Furthermore,

shorter exercise intervals of 2 minutes or less have been found to be more enjoyable than continuous moderate intensity training by participants due to the shorter duration of each burst at high intensity (Cassidy et al., 2017).

Previous work examining the effect of HIIT in people with Parkinson's found an increase in Brain Derived Neurotrophic Factor (BDNF) production, decrease parkinsonian rigidity and muscle tone (Marusiak et al., 2015), improved gait parameters (Pohl et al., 2003) and cognitive performance (Alves et al., 2014). In addition there is limited but positive evidence for using HIIT to improve walking endurance in stroke survivors (Boyne et al., 2015; Boyne et al., 2016). However, given that only one of five studies compared HIIT to another form of aerobic exercise (Boyne et al., 2016) indicates that HIIT is an emerging modality in these conditions.

High intensity interval training has been recommended as a possible effective intervention for people with MS as it can allow people to exercise at higher intensities while avoiding thermosensitive reactions (Dalgas et al., 2008). Over the past several years there has been increasing interest in HIIT in MS and several interventional trials published; however no systematic review of HIIT in people with MS has been undertaken. Therefore the aim of this review was to establish the efficacy and safety of HIIT in people with MS.

2 Methods

An electronic search was undertaken of the following databases in September 2017: EMBASE, MEDline, PEDro, CENTRAL and Web of Science Core collections. The search terms used can be seen in Table 1. The Boolean operators 'AND' and 'OR' were used to combine searches as appropriate. No limits were placed on time of publication. The reference lists of included articles were also searched.

Articles were eligible for inclusion if they were clinical trials that consisted of an aerobic intervention of HIIT alone or in combination with another type of exercise training (HIIT was defined as intervals of exercise of 5 minutes or less reaching an intensity of 80% or more of maximal effort in each interval (Fleg, 2016)), included participants with MS, or if in a mixed population, data for people with MS were presented separately, and published in English. Articles were excluded if they were non-human studies, case studies, conference

abstracts or focused solely on resistance, core or balance training. To ensure relevant articles were included, if the abstract or title did not provide the exercise intensity, the methods of the articles were read.

Table 1. Search strategy.

Database	Search terms
Medline	((exp Multiple Sclerosis/) OR ((Multiple Sclerosis or relapsing remitting OR chronic progressive OR secondary progressive OR primary progressive).mp.)) 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).mp.)
Embase	((multiple sclerosis/) OR ((Multiple Sclerosis or relapsing remitting OR chronic progressive OR secondary progressive or primary progressive).mp.)) 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).mp.)
Web of Science core collections	(TS=("Multiple sclerosis" OR "MS" OR "relapsing remitting" OR "chronic progressive" OR "secondary progressive" OR "primary progressive")) AND (TS=("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 "HIIT" OR "HIT"))
PEDro	High intensity multiple sclerosis
CENTRAL	(((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 exercise) OR (interval exercise) OR (aerobic interval training) OR (high intensity) OR (high-intensity) OR (exercise intensity) or (HIIT) or (HIT)))

Abbreviations: exp: explode; mp: multi-purpose keyword search; TS: Topic Search

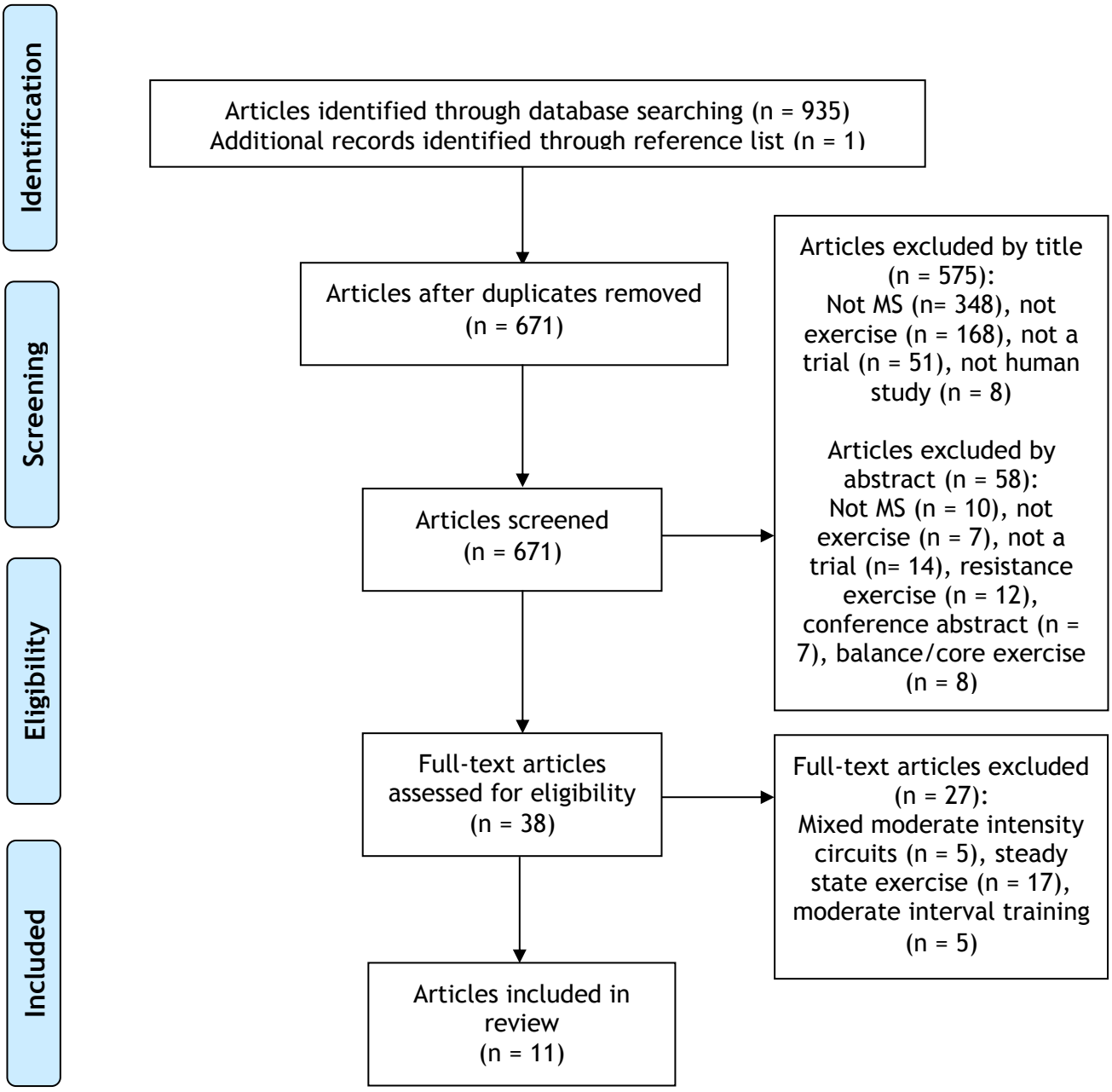
Quality assessment was carried out using the PEDro scale which is valid and reliable in methodological rating of studies (de Morton, 2009; Maher et al., 2003). The PEDro scale has 11 criteria but produces a score out of ten as no point is awarded for listing of exclusion and inclusion criteria. Included articles were assessed by at least two reviewers (EC, EHC, LP). Where there was disagreement between reviewers this was settled by discussion. Although primarily for Randomised Controlled Trials (RCTs), the PEDro scale can be used for cohort studies, with points deducted due to lack of randomisation. This has

been done in previous systematic reviews of multiple sclerosis interventions (Kjolhede et al., 2012; Martin-Valero et al., 2014).

The following data were extracted from each article into a standardised form: authors, date of publication, study design, sample size, type of MS, disability level, number of drop-outs, adverse events, 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.

3 Results

The electronic search identified 935 potential articles and hand searching of relevant reference lists provided one additional article. After the removal of 264 duplicates, the remaining 671 articles were screened by title and abstract. From titles alone, 575 were excluded. Following this, another 58 were excluded by abstract. The full text of 38 articles were read for eligibility by at least two members of the research team and 27 were subsequently excluded (Figure 1). Eleven articles, which described seven studies, were included in this review.



Abbreviations: n: number, MS: multiple sclerosis

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of screening and inclusion process for review (Moher et al., 2009).

Of the included articles four were RCTs) (described by seven articles) (Bansi et al., 2017; Collett et al., 2011; Farup et al., 2016; Feltham et al., 2013; Skjerbæk et al., 2014; Wens et al., 2015; Wens et al., 2017; Zimmer et al., 2017), one was a randomised crossover trial (Collett et al., 2017) and two were cohort studies (Keytsman et al., 2017; Zaenker et al., 2016).

PEDro scores ranged from three to eight out of ten (Table 2). Eight articles were regarded to be of high quality with a score of seven (Bansi et al., 2017; Feltham et al., 2013; Skjerbæk et al., 2014; Wens et al., 2015; Wens et al., 2017) or eight (Collett et al., 2011; Farup et al., 2016; Zimmer et al., 2017). Points were commonly lost due to a lack of blinding of participants and therapists. All articles were included in the review regardless of PEDro score.

Table 2. Quality assessment of articles using the PEDro scale.

Lead author, year	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	Total
Collet, 2011	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8
Feltham, 2013	Y	Y	Y	Y	N	N	Y	N	Y	Y	Y	7
Collet, 2017	Y	N	Y	Y	N	N	N	N	N	Y	Y	4
Wens, 2015	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	7
Farup, 2016	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8
Wens, 2017	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	7
Skjerbaek, 2014	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	7
Zaenker, 2017	Y	N	N	N	N	N	N	Y	Y	N	Y	3
Zimmer, 2017	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8
Bansi, 2017	N	Y	Y	Y	N	N	N	Y	Y	Y	Y	7
Keytsman, 2017	Y	N	N	N	N	N	N	Y	Y	N	Y	3

C1: specification of inclusion criteria; C2: randomisation of participants; C3: concealment of allocation; C4: groups similar at baseline; C5: blinding of subjects; C6: blinding of therapists; C7: blinding of assessors; C8: one key outcome measure taken for at least 85% of sample; C9: intention to treat analysis if appropriate; C10: between group statistical analysis; C11: point measures and measures of variability

Three of the studies, reported by seven articles, provided a power calculation and had a sample size large enough to be powered (Collett et al., 2011; Farup et al., 2016; Feltham et al., 2013; Wens et al., 2015; Wens et al., 2017; Zimmer et al., 2017). The other four studies did not report on power (Bansi et al., 2017; Collett et al., 2017; Keytsman et al., 2017; Skjerbæk et al., 2014; Zaenker et al., 2016). Only one study had a follow up period, which was 12 weeks after completion of the intervention (Collett et al., 2011) (Table 3).

Sample sizes ranged from 11 (Skjerbæk et al., 2014) to 61 (Collett et al., 2011) with a total number of 249 participants. Five studies included participants that were predominantly mildly disabled (EDSS < 4.0) (Collett et al., 2011; Collett et

al., 2017; Farup et al., 2016; Feltham et al., 2013; Keytsman et al., 2017; Wens et al., 2015; Wens et al., 2017; Zaenker et al., 2016) one study recruited a predominantly moderately disabled group (EDSS 4.0-6.0) (Bansi et al., 2017; Zimmer et al., 2017) and one study recruited participants who were more severely disabled (EDSS 6.0-8.0) (Skjerbæk et al., 2014) (Table 3). Five studies included participants with both relapsing remitting MS and progressive MS (Bansi et al., 2017; Collett et al., 2011; Collett et al., 2017; Farup et al., 2016; Feltham et al., 2013; Wens et al., 2015; Wens et al., 2017; Zimmer et al., 2017), one study only included participants with progressive MS (Skjerbæk et al., 2014), and one study did not report on MS type (Keytsman et al., 2017). A total of 60 different outcome measures were used across the seven studies.

All studies conducted HIIT, in a supervised setting, on a cycle ergometer apart from Skjerbæk et al. (2014) who used upper limb ergometry. Four studies (eight articles) compared HIIT to a form of continuous training (Bansi et al., 2017; Collett et al., 2011; Collett et al., 2017; Farup et al., 2016; Feltham et al., 2013; Wens et al., 2015; Wens et al., 2017; Zimmer et al., 2017), one study compared HIIT and in-patient rehabilitation to just in-patient rehabilitation (Skjerbæk et al., 2014), and two studies did not have a comparator group (Keytsman et al., 2017; Zaenker et al., 2016) (Table 3). Inclusion and exclusion criteria of all studies were standard compared to other exercise interventions in MS.

Four studies (eight articles) combined HIIT with another form of exercise training; two with resistance training (Farup et al., 2016; Keytsman et al., 2017; Wens et al., 2015; Wens et al., 2017), one with continuous moderate intensity training (Collett et al., 2011; Feltham et al., 2013), and one with both resistance training and continuous moderate intensity training (Zaenker et al., 2016) (Table 3).

In terms of exercise dose, the number of training sessions ranged from 1 to 30 and length of intervention ranged from 3 weeks (Bansi et al., 2017; Zimmer et al., 2017) to 12 weeks (Collett et al., 2011; Farup et al., 2016; Feltham et al., 2013; Keytsman et al., 2017; Wens et al., 2015; Wens et al., 2017; Zaenker et al., 2016). Length of exercise interval ranged from 30 seconds (Collett et al., 2011; Collett et al., 2017; Feltham et al., 2013) to 2 minutes (Farup et al., 2016;

Keytsman et al., 2017; Wens et al., 2015; Wens et al., 2017). One study had intervals of 3 minutes but only 30-60 seconds of each was spent at a high intensity (Skjerbæk et al., 2014). Total time spent in high intensity exercise, over the whole intervention, ranged from 10 minutes (Collett et al., 2017) to 225 minutes (Farup et al., 2016; Keytsman et al., 2017; Wens et al., 2015; Wens et al., 2017) (Table 3).

Table 3 Summary of studies included in review and statistically significant results

Author, Year, Design	n, Drop-outs, Powered	MS type, Disability	Intervention	Outcome Measures, Time points	Statistically significant results (mean (SD))
Collett et al. 2011 RCT 3 arm	n=61 Drop out: 6 Pow: Y	RR: 22 SP: 25 PP: 7 Unknown: 1 Barthel index: 19 Able to walk 2 min with or without aid	HIIT vs CONT vs COMB 12 wks, 2/wk Total: 24 sessions CONT (n=20): 45% peak power, 20 min HIIT (n=18): 90% peak power 30sec on 30 sec off, 20 min COMB (n=17): 10 min CONT a/a followed by 10 HIIT a/a	Pri: 2 min walk Sec: TUG Leg ext power Peak power Barthel Index SF36 FSS 0, 6, 12, 24 wks	2 min walk (WG) (p<0.01) 6 wks: HIIT: +12.94m (4.71), CONT: +4.71m (4.24), COMB: +3.22m (4.60). Improvements maintained at 24 wks TUG (WG) (p<0.05) 6wks: HIIT: -2.5s (1.8), CONT: -3.5s (1.7), COMB: -0.9s (1.9). Improvements maintained at 12 wks but not 24 Leg power (ALL) (p<0.01) 6 wks: +19.4W (4.1), 12 wks: +15.9W (4.1), 24 wks: -10.9W (3.1) Peak power (ALL) (p<0.05) 24 wks: -29W (5) SF36: (p<0.05), 12 wks: -4.5 (1.6) maintained at 24 wks
Feltham et al. 2013 RCT	Sub-analysis of Collett et al. 2011	RR: 9 SP: 9 PP: 3	CONT a/a n=12 HIIT a/a n=9	†BP RER Peak power VO_2 max	VO_2 peak (ALL) (p =0.05): increase from med 8.05ml/kg (2.23) to med 9.2ml/kg (3.72)

	n=21	Barthel index: 19 Drop out: 0		VO_2 norm HRMax 0, 6, 12 wks	Peak power (ALL) (p =0.05): increase from med 112W (58) to med = 113W (55)
Collett et al. 2017 RXT	n=23 14 with MS 9 HC Drop out: 4 (3 MS, 1 control) Pow: N	RR: 5 SP:5 PP:1 Barthel index: 19 (1) Able to use ergometer safely	CONT1 vs CONT2 vs HIIT 3 weeks, 1 session/week Each participant did as single CONT1, CONT2 and HIIT session CONT1: 20 min 45% peak power CONT2: 20 min 60% peak power HIIT: 20 min 90% peak power (30 sec intervals with 30 sec rest)	†Recovery of: HR, Temp, RPEbr, RPEleg, MEPs 30 sec post session then every 2 min till 10min, then every 5 min till 45 min	Return to resting HR: CONT1: MS in 15 min vs control 4 min CONT2: both groups not down to rest HR in 45 min HIIT: both MS and control return in 30 min Recovery to baseline RPEleg CONT1: MS 6 min vs control 0.5 min CONT2: MS 15 min vs control 6 min HIIT: MS 35 min vs control 4 min RPEbr: CONT1: MS 8 min vs control 0.5 min CONT2: MS 6 min vs control 2 min HIIT: MS 6 min vs control 6 min MEP: Return to baseline levels; CONT1: both groups in 15 min CONT2: MS 15 min vs control 25 min HIIT: MS MEP not significantly decreased and control recovered in 4 min

					Temp: CONT1: no change CONT2: MS group returned to baseline in 35 min, no change in control HIIT: MS group returned baseline in 25 min, control in 8 min.
Wens et al. 2015 RCT 3 arm	n=34 Drop out: 0 Pow: Y	RR: 26 Progressive: 8 (type of progressive NR) EDSS range 1.0-6.0 Mean EDSS 2.7	SED vs HIIT+RES vs CONT+RES 12 wks, 5 session/2 wks SED, n=11: no intervention HIIT+RES, n=12: 5 x 1 min peak power (80-90%HRMax) for 6 weeks 5 x 2 min 100-120% peak power (90-100% HRMax) 6 weeks CONT+RES, n=11: 6 min at 80-90% HRMax for first 6 weeks For second 6 weeks progressed to 2 x 10 min at 90-100% HRMax RES for both ex groups: leg presses, curls,	Pri: Muscle fibre CSA and proportion Sec: Isometric muscle strength Endurance capacity: RER VO_2max HRMax Test duration Body composition PA level; PASIPD	BG compared to SED: Mean CSA muscle fibres HIIT: +21% (7) (p<0.05) CONT: +23% (5) (p<0.01) Muscle fibre type I CSA: CONT: +29.8% (5.5) (p=0.003) Muscle fibre type IIa CSA: HIIT: 22.8% (6.2) (p<0.05) BG compared to SED: Strength knee flex + ext weak leg: HIIT: range +24% (13) to +44% (20) (p= 0.01 to p=0.006) CONT: range +19% (9) to 33% (17) (p= 0.01 to p=0.006) Hams strong leg HIIT: range +13% (7) to +20% (7) (p=0.006)

			extensions, lateral pull downs, arm curls, chest presses. Intensity 1 x 10 reps max load, progressed to 2 x 20 reps max load	0, 12 wks	BG compared to SED and CONT: Peak power +21% (4) (p = 0.0001) Time to exhaustion +24% (5) (p=0.00008) VO_2max +17% (5) (p=0.001) Lean tissue mass (WG): HIIT + 1.4% (0.5) (p = 0.01) Body fat percentage (WG) HIIT: -3.9% (2) (p = 0.04) CONT: -2.5% (1.2) (p = 0.02) HRMax (WG) CONT: +3.7% SD1.5 HIIT: +6.2% SD 2.2 PASID (BG vs SED) HIIT: 86% (27) (p = 0.004) CONT: 73% (19) (p = 0.003)
Wens et al. 2017 Same as Wens et al. 2015	Same as Wens et al. 2015	Same as Wens et al. 2015	Same as Wens et al. 2015	Pri: AUC from OGTT Fasting glucose conc Sec:GLUT4 content vastus lateralis	All WG: Fasting glucose conc HIIT: -7.3% (6.8) (p< 0.05) CONT: - 9.0% (6.2) (p< 0.05) Glucose clearance (AUC) HIIT: -6.9% (6.2) (p< 0.05) CONT: -11.0% (7.7) (p< 0.05)

					Insulin (AUC) CONT: -12.3% (14.7) (p< 0.05) Muscle GLUT4 content: HIIT: +6.6% (4.5) (p< 0.05)
Farup et al. 2016 Same as Wens et al. 2015	Same as Wens et al. 2015 but no SED group HC n=18 Pow: Y	MS mixed no SED group	Combined exercise groups as Wens et al 2015 No SED group	Pri: SC/type I fibre SC/type II fibre, SC/ mm^2 type I and II fibre Myonuclei, and central nuclei analysis Sec: Muscle tissue fibrosis and lipid content	MS(WG): SC/type II fibre: +165% (68) (p<0.05) SC/mm2 type II fibre: +135% (63) (p< 0.05) Lipid content BG MS vs HC MS: +117% (37) (p < 0.05).
Zaenker et al. 2017 Cohort study	n=26 Drop out: 0 Pow: N	MS mix RR 22 SP 3 PP 1 EDSS med 2.0 (0-5)	HIIT+RES+CONT 12 wks Wks 1-4: 1 x HIIT and 1x RES session/wk Wks 5-12: a/a + unsupervised CONT or RES session HIIT: 10 min warm up, 5 x 1	†VO_2 peak Peak power Peak lactate HRMax Isokinetic strength quads and hams	ALL WG as cohort study VO2peak +13.5% (p<0.0001) Peak power +9.4% (p<.0001) Peak lactate +31% (p<0.001) HRMax +3.73% (p=0.0120) Inc strength quads and hams at all torques (p<0.05) (size of change not provided)

			min 90-110% peak power, 3 min working rest, 5 min warm down RES: body weight exercises, 2 x hams + 2 x quads. Start 4 x 10 reps prog to 5 x 15 reps CONT: 30-45 min CONT of pt choice such as cycling, swimming or walking	QoL: SEP 59 0, 12 wks	SEP 59: Improvement in vitality (p= 0.0012), emotional well-being (p= 0.0378), and general well-being (p= 0.0052) size of change not reported.
Zimmer et al. 2017 RCT	n=57 Dropout: 3 Pow: Y	MS mix RR (30) and SP (27) EDSS range 1.0-6.5 Mean 4.37	HIIT vs CONT 3 Weeks, HIIT 3 x week, CONT: 5 x week HIIT: 20 min, 5x 3 min intervals at 85-90% of HRMax, with 1.5 min working rest at 50-60% HRMax CONT: min 70% HRMax	Pri: BICAMS: TMT, TAP test (errors and speed), SDMT, VLMT, BVMT Sec: Serum levels of serotonin, BDNF, MMP-2, MMP-9, VO_2peak 0, 3 wks	Time effects SDMT TMT TAP errors Time x group effect Serum MMP-2 in HIIT: decreased p=0.009 CI (5.336; 36.587) VO2 peak in both groups HIIT: p<0.001 CI (-4.096; -2.002) CONT: p=0.006 CI (-2.394; -0.426) VLMT HIIT: improvement p=0.046 (CI) (-6.319; -

					0.51)) TAP errors HIIT improved *p*=0.001 CI (0.508; 1.789)
Bansi et al. 2017 Same as Zimmer et al. 2017	Same as Zimmer et al. 2017	Same as Zimmer et al. 2017	Same as Zimmer et al. 2017	†HIIT vs CONT: within RRMS and SPMS 5HT,Trp, Kyn, Kyn/Trp ratio	RRMS training groups (no diff between HIIT or CONT): Reduction in Trp (*p*=0.02) Increase in Trp/Kyn ratio (*p*=0.002)
Skjerbaek et al. 2014 RCT	n=11 Drop out: 1 Pow: N	PP (n=3) SP (n=8) EDSS 6.5-8.0	HIIT + in-pt rehab vs in-pt rehab 10 sessions over 4 wks, UL ergometer HIIT training 6x 3 min intervals: 2 min at 65-75%VO2max followed by 30-60 sec sprint of 100% max effort	†VO_2 peak, HRMax, 6minWC, FSMC, MDI, MSIS-29, 9HPT, HGT, BBT 0, 4 wks	Nil
Keytsman et al. 2017 Cohort study	n=16 Drop out: 0 Pow: N	MS type: NR EDSS mean 2.6	HIIT+RES 12 wks, 5 session per 2 wks HIIT Wks 1-6: 5 x 1min 85-90% HRmax, 1 min rest Wks 7-12: 5 x 2 min 100% HRmax, 1 min rest RES: leg presses, curls, extensions, lateral pull downs, arm curls, chest presses. Intensity 1 x 10 reps	†Body composition, resting HR, BP, OGTT, total chol, fasting glucose, fasting TG, HDL, LDL, insulin	All *p*<0.05 Resting HR: -6% (bpm) 2 hr glucose conc: -13% (mmol/l) Insulin sensitivity: -24% WMax; +25 W (CI -34, -16) t to exhaustion: +2 min (CI-3,-1) VEmax: 15 l/min (CI-23,-7) Isometric and isokinetic strength increased in both legs

			max load, progressed to 2 x 20 reps max load after 6 wks	sensitivity, Wmax, HRMax, VO_2max, RER, peak lactate, t to exhaustion, VEmax Isometric and isokinetic strength of legs ext and flex, PASID	Peak lactate +2.1 mmol/l RER: -0.04 VO_2max: +5.9 ml/min/kg

† Outcome measures in these studies were not separated into primary and secondary outcome measures

Abbreviations: RCT: randomised controlled trial; RXT: randomised crossover trial; n: number of participants; Pow: statistically powered; a/a: as above; HC: healthy controls; RR; relapsing remitting; SP: secondary progressive; PP: primary progressive; Pri: primary outcome measure; Sec: Secondary outcome measure; min: minute; NR: not reported; EDSS: expanded disability status scale; HIIT: high intensity interval training; SED: sedentary; med: median; CONT: continuous moderate intensity training; COMB: combination; wk: week; sec: second; RES: resistance training; HRMax: maximal heart rate; VO_2max: maximal volume oxygen consumed VO_2: volume of oxygen consumed; TUG: timed up and go test; ext: extension; SF36: short form 36; FSS: fatigue severity scale; BP: blood pressure; RER: respiratory exchange ratio; HR: heart rate; temp: temperature; RPEbr: borg scale of perceived exertion breathing; RPEleg: borg scale of perceived exertion legs; MEPs: motor evoked potentials; CSA: cross sectional area; PASIPD; Physical Activity Scale for Individuals with Physical Disabilities; OGTT: oral glucose tolerance test; conc: concentration; SC: satellite cells; quads: quadriceps; hams: hamstrings; SEP: Sclerose En Plaques-59; BICAMS: brief international cognitive assessment for MS; TMT: trail making test; TAP: Test of Attentional Performance; SDMT: symbol digit modalities test; VLMT: California verbal learning memory test; BVMT: Brief visuospatial memory test-revised; BDNF: brain derived neurotrophic factor; MMP: matrix metalloproteinases; 6minWC: 6 minute wheelchair test; 5HT: serotonin; Trp; tryptophan; Kyn; kynurenine; FSMC: fatigue scale of motor and cognitive function; MDI: major depression inventory; MSIS-29: multiple sclerosis impact scale; 9HPT: 9 hole peg test; HGT: hand grip test; BBT: box and block test; HDL: high density lipoprotein; LDL: low density lipoprotein; TG: triglyceride; chol: cholesterol; VEmax: maximal expiratory volume W: watts; WG: within group analysis; BG: between group analysis: CI: confidence interval

One study reported six adverse events (Collett et al., 2011; Feltham et al., 2013). Four were knee or leg pain while cycling, which were deemed to be possibly related to the intervention. Two of the adverse events were, deemed by the researchers as, unrelated to the intervention (one exacerbation of symptoms and one loss of consciousness). The other six studies reported that there were no adverse events in either their intervention or control groups (Bansi et al., 2017; Collett et al., 2017; Farup et al., 2016; Keytsman et al., 2017; Skjerbæk et al., 2014; Wens et al., 2015; Wens et al., 2017; Zaenker et al., 2016; Zimmer et al., 2017).

The retention of participants within the studies was high; one study had a drop out of greater than 10% (Collett et al., 2017), two studies less than 10% (Bansi et al., 2017; Collett et al., 2011; Feltham et al., 2013; Zimmer et al., 2017), while four studies had no drop outs (Farup et al., 2016; Keytsman et al., 2017; Skjerbæk et al., 2014; Wens et al., 2015; Wens et al., 2017; Zaenker et al., 2016) (Table 3). Details of all statistically significant changes in outcomes measures are presented in Table 3.

Six studies measured either VO_2peak or VO_2max (Bansi et al., 2017; Collett et al., 2011; Farup et al., 2016; Feltham et al., 2013; Keytsman et al., 2017; Skjerbæk et al., 2014; Wens et al., 2015; Wens et al., 2017; Zaenker et al., 2016; Zimmer et al., 2017). One of the RCTs reported an improvement, compared to both the sedentary and continuous training groups, in VO_2max in their HIIT group (+17% (SD) 5, p<0.01) (Farup et al., 2016; Wens et al., 2015; Wens et al., 2017). Two RCTs reported an improvement of VO_2peak in both their HIIT and continuous training groups ((median 8.05 ml/kg - 9.2 ml/kg (Collett et al., 2011; Feltham et al., 2013)), (HIIT (95% CI (–4.096; –2.002) p<0.001), continuous (95% CI (–2.394; –0.426) p=0.006) (Bansi et al., 2017; Zimmer et al., 2017)). The two cohort studies found improvements, one in VO_2peak (+13.5% (p<0.0001) (Zaenker et al., 2016), and the other in VO_2max (+5.9 ml/min/kg (p<0.05 (Keytsman et al., 2017)). Conversely, one RCT reported no change in the VO_2peak of their HIIT group (Skjerbæk et al., 2014) (Table 3).

Two of the five studies which measured HRMax found significant within group increases in their HIIT group, indicating a probable learning effect of exercising to greater intensities (Whyte et al., 2008); (+3.73%, p=0.012 (Zaenker et al., 2016), +6.2%, p=0.05 (Farup et al., 2016; Wens et al., 2015; Wens et al., 2017)). The other three studies which measured HRMax did not find changes after their HIIT intervention (Collett et al., 2011; Feltham et al., 2013; Keytsman et al., 2017; Skjerbæk et al., 2014) (Table 3).

Peak power, was measured in four studies (Collett et al., 2011; Farup et al., 2016; Feltham et al., 2013; Keytsman et al., 2017; Wens et al., 2015; Wens et al., 2017; Zaenker et al., 2016). One RCT reported an increase, compared to their sedentary and continuous training groups, in peak power after the intervention (+21% (SD 4) (p<0.01) (Farup et al., 2016; Wens et al., 2015; Wens et al., 2017)) and the two cohort studies also reported an increase in peak power (+9.4%, p<0.0001, (Zaenker et al., 2016), +25 W (CI -34, -16), p<0.05 (Keytsman et al., 2017)). The RCT by Collett et al. (2011) initially found no differences in peak power post intervention, however, subsequent analysis demonstrated that peak power was increased in participants who completed more than 8 sessions, (median 112 W to median 113 W, p=0.05) (Feltham et al., 2013) (Table 3).

All four studies that examined muscle strength reported improvements following the intervention (Collett et al., 2011; Farup et al., 2016; Feltham et al., 2013; Keytsman et al., 2017; Wens et al., 2015; Wens et al., 2017; Zaenker et al., 2016). Collett et al. (2011) and Feltham et al. (2013) reported improvements in isometric leg extension power at the end of the intervention but this was not maintained at a 12 week follow up (12 weeks: +15.9W SD 4.1, 24 weeks: -10.9W SD 3.1, p<0.01). One study found an increase in isometric hamstring strength in the HIIT group only (range +13% Nm, (SE 7) to +20% (SE 7), p=0.006) and between group differences in the quadriceps and hamstring of the weak leg in both the HIIT (range +24% Nm, SE 13, p=0.01, to +44% Nm, SE 20 p=0.006) and high intensity continuous groups (range +19% Nm, SE 9 p= 0.01, to 33% Nm, SE 17 p=0.006) (Wens et al., 2015). Both cohort studies found improvements in muscle strength (Keytsman et al., 2017; Zaenker et al., 2016). Keytsman et al. (2017) reported stronger isometric hamstring contractions in the stronger leg at 90 degrees, in quadriceps at 45

degrees, and both muscle groups in maximal isokinetic contractions. In the weaker leg stronger isometric hamstring and quadriceps contractions were found at both 45 and 90 degrees along with stronger hamstring isokinetic contractions (p<0.05). Zaenker et al. (2016) reported increases in the strength of quadriceps and hamstrings of both legs at three different torques of 90, 180 and 240 degrees per second (p<0.05) (Table 3).

4 Discussion

This was the first systematic review for the use of HIIT in MS. Overall, the seven studies included in the review provided positive evidence for the use of HIIT in people with MS. All studies except one (Skjerbæk et al., 2014) found improvements in multiple outcome measures. Predominantly improvements were observed in outcome measures relating to fitness. It should however, be noted that fitness outcome measures were not primary outcomes in any of the studies included. High intensity interval training was well tolerated with adverse events only occurring in one study (Collett et al., 2011; Feltham et al., 2013). Previous research has shown that HIIT is safe in healthy individuals (Milanovic et al., 2015), people with chronic heart failure (Smart et al., 2013), coronary artery disease (Elliott et al., 2015), and increased cardio-metabolic risk (Weston et al., 2014). Due to the low incidence of adverse events, this review suggests that HIIT is also safe in people with MS.

The evidence in this review is positive for the use of HIIT in increasing cardiovascular fitness in people with MS. Five of the six studies that measured cardiovascular fitness reported improvements in at least one outcome measure (Bansi et al., 2017; Collett et al., 2011; Farup et al., 2016; Feltham et al., 2013; Keytsman et al., 2017; Wens et al., 2015; Wens et al., 2017; Zaenker et al., 2016; Zimmer et al., 2017). Skjerbæk et al. (2014), who measured both VO_2peak and HRMax, did not find statistically significant changes, although a trend towards statistical significance for VO_2peak was reported (p=0.06, data not in Table 3. This study however differed from the others as the participants had progressive MS and

were the most disabled and deconditioned. Furthermore, the study was underpowered and had one of the lowest time exercising at high intensity over the whole intervention (60 minutes). A similar low time at high intensity was used by Zaenker et al. (2016), but with the addition of continuous and resistance training elements to the intervention.

Skjerbæk et al. (2014) was also the only study to use arm ergometry, whereas the other studies used cycle ergometry. Arm ergometry is a practical modality of exercise for those with mobility problems but engages smaller muscles than leg cycling ergometry, resulting in lower energy expenditure and thus creating less demand on the cardiorespiratory system. Indeed, a previous study comparing arm ergometry, leg cycling and rowing at a moderate intensity in people with progressive MS, found that the leg cycling group increased their VO_2max while no changes were found in the arm ergometry and rowing groups (Briken et al. 2014). Further research is warranted to investigate the efficacy of using upper limb ergometry for delivering HIIT for people with higher levels of disability/progressive MS.

Previous research comparing HIIT to continuous moderate intensity training in other conditions has quantified the effectiveness via meta-analyses. For example, in healthy individuals HIIT is more effective than continuous moderate intensity training in increasing VO_2max by 4.5 ml/kg/min (Milanovic et al., 2015) and in people with increased cardiometabolic risk, HIIT is more effective in increasing VO_2peak by 3.03 ml/kg/min (Weston et al., 2014). While the evidence for HIIT in people with MS is positive, due to the heterogeneity of outcome measures and the lack of control groups in two of the studies, a meta-analysis was not possible or appropriate. This makes comparison of the effect of HIIT between MS and other conditions difficult.

All four studies that measured muscle strength reported improvements (Collett et al., 2011; Farup et al., 2016; Feltham et al., 2013; Keytsman et al., 2017; Wens et al., 2015; Wens et al., 2017; Zaenker et al., 2016). One of these did not specifically include a resistance training element (Collett et al., 2011; Feltham et al., 2013), but still reported an increase in isometric muscle strength. This may

indicate that aerobic HIIT could be effective in increasing leg muscle strength. This is in line with HIIT research in healthy populations which demonstrated an increase in muscle strength following a HIIT cycling intervention (Herbert et al., 2017; Wright et al., 2016). As working muscles at a higher intensity produces greater increases in strength (Garber et al., 2011), the increase in strength from HIIT is likely induced from cycling at a higher workrate during the high intensity intervals, compared to continuous moderate intensity training.

Only one study (published over two articles) examined the effect of HIIT on neurochemicals related to MS, exploring the effects of HIIT on levels of serotonin, BDNF, metalloproteinase 2 and 9, and tryptophan metabolism (Bansi et al., 2017; Zimmer et al., 2017). The researchers reported, that compared to the continuous training group, the HIIT group improved their level of matrix metalloproteinase 2. As the intervention and control undertook an exercise programme of equal energy expenditure this suggests that higher intensity of exercise could have a more beneficial effect on neurological markers. The cohort study by Keytsman et al. (2017) measured the effect of HIIT on lipid profiles but did not report any significant changes (Keytsman et al. (2017). This trial was however, underpowered and had no control group. Both of these areas of research warrant further investigation, particularly since a previous review concluded that the evidence was inconclusive for the effect of aerobic exercise on BDNF in people with neurological conditions (Mackay et al., 2017) and a previous work on the effect of exercise on blood lipids in people with MS is also inconclusive (Wens et al., 2013).

4.1 Limitations

The heterogeneity of the outcome measures used across the seven studies limited comparison with previous reviews of HIIT in other conditions and prevented a meta-analysis. The lack of power calculations in some studies also limited the applicability of results in this patient population. Lastly, four of the seven studies combined HIIT with another form of exercise training, thus making it difficult to draw conclusions on the specific effect of HIIT.

5 Conclusion

The evidence presented in this review suggests that HIIT, via cycle ergometry, is a safe and effective way of improving fitness in people with MS and requires fewer, shorter training sessions compared to a moderate intensity, continuous training mode to gain benefits. Further investigation of HIIT is required in people with progressive MS and/or those with a moderate and severe level of disability. In addition, future research should examine the possible benefits of HIIT in people with MS, beyond cardiovascular fitness and muscle strength.

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