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Review article

Evaluating functional electrical stimulation (FES) cycling on cardiovascular, musculoskeletal and functional outcomes in adults with multiple sclerosis and mobility impairment: A systematic review

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ABSTRACT

Background: People with Multiple Sclerosis (PwMS) are at an increased risk of diseases associated with low levels of physical activity (PA). Deconditioning may lead to an acceleration in the development of secondary complications from MS, impairing physical function and exacerbating disease progression. Functional Electrical Stimulation (FES) Cycling may provide a suitable lower limb exercise intervention for PwMS with mobility impairment. The effects of FES cycling on cardiovascular, musculoskeletal and functional outcomes for PwMS with mobility impairment are yet to be investigated to date.

Objective: The objective of this review was to systematically examine the outcomes of PwMS with mobility impairment following FES cycling intervention.

Methods: A systematic search of four electronic databases (MEDLINE, Web of Science, CINAHL and PEDro) from their inception to 8th January 2019 was performed. Inclusion criteria was (1) include human participants with definite diagnosis of MS (2) participants had to be aged 18 years or older (3) include participants with mobility impairment (determined as an average participant EDSS $\geq$ 6.0) (4) evaluate FES cycling as an intervention study.

Results: Initial searches found 1163 studies. 9 of which met the full inclusion criteria: 5 pre-post studies with no control group, 2 randomised controlled trials (RCTs), 1 retrospective study and 1 case study. Two studies had the same participant group and intervention but reported different outcomes. Outcome data was available for $n = =76$ unique participants, with $n = =82$ completing a FES cycling intervention. Of the $n = =4$ papers with clear dropout rates, pooled dropout rate was 25.81%. Two papers reported non-significant improvements in aerobic capacity following a FES cycling intervention. Four papers reported no change in lower limb strength and two papers reported significant reductions in spasticity post training. Four studies failed to provide information regarding adverse events with the other studies reporting $n = =10$ adverse events across 36 participants.

Conclusion: Findings suggest FES cycle training may reduce CVD risk alongside trends for a reduction in spasticity post training, however the low quality of the literature precludes any definitive conclusions. FES cycle training appears to be well tolerated in PwMS with mobility impairment, with no serious adverse events.

1. Introduction

Multiple Sclerosis (MS) is a chronic autoimmune disease affecting the Central Nervous System (CNS) and is characterised by inflammation and neurodegeneration of the myelin sheath, axons and grey and white matter (Kierkegaard et al., 2016; Motl et al., 2017; Motl, 2013; Klaren et al., 2013; Wens et al., 2016). MS presents as symptoms of fatigue and impairment of both autonomic and somatic systems which have a deleterious impact on walking performance (and other types of physical activity), overall health, quality of life and ability to complete activities of daily living (ADLs) (Motl et al., 2017; Motl, 2013).

In line with these limitations, people with MS (PwMS) frequently fail to engage in the recommended amounts of moderate-to-vigorous physical activity (MVPA) necessary to accrue health benefits

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(Klaren et al., 2013). Moreover, studies of PwMS also report that they experience both real and perceived barriers to engaging in physical activity (PA), which when combined with reductions in physical function, may promote an inactive lifestyle resulting in physical deconditioning (Wens et al., 2016; Stroud et al., 2009).

The consequences of insufficient PA and deconditioning may be particularly problematic in this cohort. PwMS are not immune to the increased risk of cardiovascular disease (CVD) occurring as a result of low levels of PA (Heine et al., 2016; Marrie et al., 2015; Jadidi et al., 2013). Indeed, deaths from secondary chronic conditions such as hypertension, increased cholesterol and diabetes are common, and the mortality rate in PwMS is estimated as being between 1.7 to 3.5 times greater than that of the general population (Lalmohamed et al., 2012; Jick et al., 2014). In addition, deconditioning may lead to an acceleration in the development of secondary complications from MS in an interdependent manner. Deconditioning has been suggested to impair physical function and exacerbate disease progression, resulting in further reductions in levels of PA, and an associated cycle of decline in health (Wens et al., 2016; Sandroff et al., 2013; Sandroff et al., 2015). Indeed, disease progression has been significantly correlated to reductions in aerobic capacity, muscular strength and walking performance (Heine et al., 2016; Sandroff et al., 2013; Pilutti et al., 2015; Motl and Learmonth, 2014).

Disease progression in MS is monitored and assessed utilising the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983). The scale describes different levels of impairment and ranges from 0 to 10, with 0 representing no symptoms and 10 representing death (Kurtzke, 1983). An EDSS score of 6.0 is an identifiable milestone on the scale, whereby the individual can walk a maximum of 100 m without stopping, even with the support of a unilateral assistive device (Confavreux and Vukusic, 2006). As EDSS increases, PwMS are likely to participate in reduced amount of PA in comparison to those with lower EDSS, thus PwMS of disability levels of EDSS $\geq$ 6.0 are less likely to meet MVPA guidelines and have a greater risk of experiencing CV comorbidities (Beckerman et al., 2010). For example, vascular comorbidities have been significantly correlated to an increased risk of mobility impairment and speed of disability progression (Marrie et al., 2010). Furthermore, whilst there is evidence that exercise has a multitude of health benefits for PwMS (Latimer-Cheung et al., 2013; Platta et al., 2016; Ewanchuk et al., 2018), few intervention studies have evaluated the effects of PA in persons with greater levels of impairment (e.g. EDSS of 6.0 and above).

Sensorimotor impairments in MS typically impact on the lower limbs, with up to 75% of PwMS experiencing a gait impairment (Lee et al., 2017). This can make the use of upper body exercise appealing (Skjerbæk et al., 2014). Whilst both upper body and lower body exercises may have the potential to elicit cardiovascular adaptions in PwMS, it is important to note that the peripheral adaptation and conditioning of the lower limbs remain vital for PwMS's mobility and contribute to their ability to complete personal and instrumental ADLs (Paltamaa et al., 2012). Lower body function is of particular importance in enabling PwMS to remain independent since it supports the completion of personal ADLs such as self-care, transfer and locomotion (Månsson and Lexell, 2004).

Functional Electrical Stimulation (FES) cycling is a suggested lower limb exercise intervention for individuals who have higher levels of impairment (Davis et al., 2008). FES cycling can be used where individuals are unable to propel a cycle ergometer independently due to reduced physical function (Davis et al., 2008). The intervention applies electrical stimulation to the lower limb muscles, which is appropriately timed to generate cyclical contractions to propel the cycle ergometer (Duffell et al., 2008). This intervention has reported to benefit other neurological conditions, such as persons with incomplete or complete spinal cord injury (SCI), including increased lower limb skeletal muscle mass, muscular strength, and endurance whilst also improving aerobic capacity, and glucose metabolism (Davis et al., 2008; Thrasher et al., 2013; Griffin et al., 2009). In PwMS, FES cycling may support higher exercise intensities, enabling greater engagement with the level of MVPA than would be otherwise possible with passive leg cycling; increasing the potential for cardiovascular conditioning (Edwards et al., 2018a). This methodology therefore, may be a feasible option for reducing comorbid CVD risk.

Over the last decade, FES cycling has attracted an increased number of investigations due to the potential benefit this intervention has for PwMS, both in terms of supporting their physical functioning, and reducing CVD risk. To date, the evidence remains unclear as to the efficacy of FES cycling to support PwMS in maintaining cardiorespiratory and musculoskeletal health, and preventing the development of further comorbidities. No systematic evaluation has been conducted in this group. Given that FES cycling is a more appropriate intervention for those with higher levels of mobility impairment, the aim of this review is to systematically examine cardiovascular, musculoskeletal and functional outcomes in PwMS with mobility impairment following a FES cycling intervention.

2. Methodology

2.1. Search strategy

This systematic review was conducted was in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIMSA) statement (Moher et al., 2009). A comprehensive literature search was performed in order to examine the effect of FES cycling on cardiovascular, musculoskeletal and functional outcomes in PwMS. Four electronic databases (MEDLINE, Web of Science, CINAHL and PEDro) were searched from their inception to 8th January 2019. Search terms used were as follows: ("Multiple Sclerosis" OR "Progressive MS" OR "Relapsing Remitting MS") AND ("NMES" OR "FES" OR "ESAC" OR "neuromuscular stimulation" OR "electrical stimulation" OR "stimulation-assisted cycl*" OR "assisted cycl*"). Table 1 provides an example of the search strategy. Filters were applied so that only research articles and articles that were peer-reviewed would be retrieved.

2.2. Description of the intervention

FES cycling utilises a commercially available motorised ergometer (e.g. RT300, Restorative Therapies Inc, Baltimore, MD, USA), typically accessed from a seated position (Thrasher et al., 2013). This enables the user to remain on their wheelchair, reducing the requirement for transferring (Backus et al., 2017). Stimulation electrodes are placed on the skin, typically above the quadriceps, hamstrings and glutei and a bilateral current is delivered to the muscles providing timed and cyclical stimulation necessary to produce a cycling motion (Duffell et al., 2008; Fornusek and Davis, 2008). A target cadence is predetermined on the ergometer with suitable software amending the electrical stimulation and ergometer's resistance based on muscle fibre recruitment and

Table 1
Sample search strategy.

#1	"Multiple Sclerosis" OR "Progressive MS" OR "Relapsing Remitting MS" [all fields]
#2	"NMES" OR "FES" OR "ESAC" OR "neuromuscular stimulation" OR "electrical stimulation" OR "stimulation-assisted cycl*" OR "assisted cycl*" [all fields]
#3	#1 AND #2

NMES = =Neuromuscular Electrical Stimulation, FES = =Functional Electrical Stimulation, ESAC = =Electrical Stimulation-Assisted Cycling.

fatigability (Griffin et al., 2009). Where a participant has leg function, their individual volitional efforts will contribute to attaining the target cadence (Backus et al., 2017).

2.3. Inclusion criteria

To be included in this review, the study had to (1) include human participants with definite diagnosis of MS (2) participants had to be aged 18 years and over (3) include participants with an average EDSS 6.0 or above, or an equivalent mobility impairment (4) evaluate FES cycling as an intervention study. Since the number of qualifying studies was anticipated to be small, no restrictions were placed on the type of study included in this review, and all qualifying studies were included regardless of study quality.

2.4. Study selection

Following searches of the relevant databases, results were imported into bibliographic software (Zotero: V 5.0.60, Fairfax, VA, USA). Subsequently, articles were screened to remove duplicates. Two authors (JS and NS) independently conducted a literature search and screened the title and abstracts of relevant papers to remove studies which clearly did not meet the inclusion criteria. Where it was not clear in the title or abstract if the study was suitable for inclusion, the full text was read. Using the inclusion criteria, both authors independently generated a list of eligible studies.

2.5. Data extraction

In addition to bibliographic data, the following information was extracted from each article by JS and verified by NS: (i) participant data (Table 2) (ii) intervention protocols (Table 3) (iii) intervention outcomes (Table 4).

2.6. Study quality assessment

Study quality was appraised using four different tools based on study type. The majority of studies were evaluated using the tools designed by the National Heart, Lung and Blood Institute (NHLBI), specifically cohort studies (Quality Assessment for Before-After (Pre-Post) Studies With No Control Group [Internet] 2014) and RCTs (Quality Assessment of Controlled Intervention Studies [Internet] 2014). Case studies were evaluated using the tools developed by Murad et al. (2018) and retrospective studies using the Newcastle-Ottawa Scale (Wells et al., 2019).

3. Results

Fig. 1 denotes the literature search and screening process undertaken. The initial search found 1162 potential articles supplemented with 1 study from an external source; with 9 of these meeting the inclusion criteria. Of these, 5 were pre-post studies with no control group (Backus et al., 2017; Fornusek and Hoang, 2014; Ratchford et al., 2010; Reynolds et al., 2015; Szecsi et al., 2009), two were Randomised Controlled Trials (RCTs) (Edwards et al., 2018b; Pilutti et al., 2018), one was a retrospective study (Hammond et al., 2015) and one was a case study (Krause et al., 2007). Two papers reported different outcomes on the same participant group following the same intervention (Edwards et al., 2018b; Pilutti et al., 2018). As a result, there was a total of 9 papers which underwent quality assessment, however these 9 papers describe 8 different interventions. For clarity, the remainder of this review will refer to papers, not interventions.

3.1. Demographic information

The mean participant EDSS in each study was ≥6.0. Of the 9 selected papers, four did not exclusively feature participants with EDSS ≥ 6.0 (Szecsi et al., 2009; Edwards et al., 2018b; Pilutti et al., 2018; Hammond et al., 2015). Two papers did not report participant EDSS however their inclusion criteria approximately equated to that of participants with mobility impairment and EDSS ≥ 6.0 (Backus et al., 2017; Reynolds et al., 2015). The highest level of impairment reported in participants was EDSS 8.5 (Fornusek and Hoang, 2014). Six papers utilised participants with both progressive and relapsing remitting MS (Backus et al., 2017; Ratchford et al., 2010; Reynolds et al., 2015; Edwards et al., 2018b; Pilutti et al., 2018; Hammond et al., 2015). Three exclusively recruited participants with progressive MS (Fornusek and Hoang, 2014; Szecsi et al., 2009; Krause et al., 2007). One study only provided age range therefore from the other 8 papers with extractable data, the mean participant age was 50.77 ± 10.21 years and disease duration 17.14 ± 8.35 years. Two papers, which reported on the same participants reported body height and mass (Edwards et al., 2018b; Pilutti et al., 2018). Three papers reported BMI in kg/m^2 (Reynolds et al., 2015; Edwards et al., 2018b; Pilutti et al., 2018).

In three papers, data were only provided for participants who completed the FES cycling intervention (Backus et al., 2017; Reynolds et al., 2015; Hammond et al., 2015). The same three papers failed to identify the number of participants recruited and drop outs (Backus et al., 2017; Reynolds et al., 2015; Hammond et al., 2015). Whilst one of the remaining papers was a case study, the other 5 papers reported dropout rates (Fornusek and Hoang, 2014; Ratchford et al., 2010; Szecsi et al., 2009; Edwards et al., 2018b; Pilutti et al., 2018). Two of these papers failed to provide demographic data for participants who withdrew (Edwards et al., 2018b; Pilutti et al., 2018). In the four remaining papers a total of 23 out of 31 participants who started the FES cycling protocol completed and 8 dropped out; resulting in a pooled dropout rate of 25.81% (Fornusek and Hoang, 2014; Ratchford et al., 2010; Szecsi et al., 2009; Edwards et al., 2018b).

One paper only provided demographic information for those participants where the main outcome, muscle oxygen consumption (mVO_2), was successfully measured (Reynolds et al., 2015). Resting and Peak Heart Rate (HR) was provided in one paper, however these were from baseline assessments and not measured pre and post intervention (Fornusek and Hoang, 2014).

3.2. Protocols

Intervention duration ranged between 2 and 24 weeks. Eight papers were completed under supervision in a clinical exercise setting (Backus et al., 2017; Fornusek and Hoang, 2014; Reynolds et al., 2015; Szecsi et al., 2009; Edwards et al., 2018b; Pilutti et al., 2018; Hammond et al., 2015; Krause et al., 2007) and the remaining paper was undertaken unsupervised at home (Ratchford et al., 2010). Seven papers conducted 2/3 sessions per week for a range of 2–24 weeks (Backus et al., 2017; Fornusek and Hoang, 2014; Ratchford et al., 2010; Reynolds et al., 2015; Szecsi et al., 2009; Edwards et al., 2018b; Pilutti et al., 2018). The other two papers were once every week for 2 weeks (Krause et al., 2007) or completed in two blocks of 4 weeks (Hammond et al., 2015).

In two papers, the protocol was unclear (Ratchford et al., 2010; Hammond et al., 2015). The protocol of five papers was to cycle continuously for a minimum of 10–60 min utilising FES (Backus et al., 2017; Fornusek and Hoang, 2014; Reynolds et al., 2015; Edwards et al., 2018b; Pilutti et al., 2018). Of these, the protocol for four papers was to reach a point where a participant could complete 30 min of FES cycling at a target cadence of 35–50 rpm (Backus et al., 2017; Reynolds et al., 2015; Edwards et al., 2018b; Pilutti et al., 2018). Two papers utilised periods of stimulation interspersed with periods of rest (Szecsi et al., 2009; Krause et al., 2007).

Table 2
Summary of papers' participant data.

Study	Study design	n	Drop out	Participant characteristics		MS Related measures				Anthropometric measures		
				Sex	Age (Years)	EDSS Range	Mean EDSS	Disease duration (Years)	Type of MS	Height (cm)	Body mass (kg)	Body mass index (kg m^{-2})
Backus et al. (2017)	Pre-Post No Control	14	NR	$F = =7$ $M = =7$	55.28 ± 10.98	NR	NR	15.29 ± 7.35	PP = =2 SP = =7 RR = =5	NR		
Edwards et al. (2018b) and Pilutti et al. (2018)[15]	RCT	CON = =5, FES = =6	CON = =1, FES = =2	CON: $F = =4$, FES: $F = =3$ $M = =1$	CON: 48.5 ± 7.7, FES: 57.3 ± 6.0	5.5–6.5	CON: 6.3 ± 0.9, FES: 6.3 ± 0.5	CON: 20.8 ± 8.5, FES: 22.3 ± 5.3	CON: $P = =2$ RR = 2, FES: $P = =2$ RR = 2	CON: 160.5 ± 9.2, FES: 161.1 ± 10.4	CON: 85.8 ± 46.0, FES: 70.6 ± 19.5	CON: 32.1 ± 13.9, FES: 27.2 ± 7.4
Fornusek and Hoang (2014)	Pre-Post No Control	8	1	$F = =8$	39 ± 14	6.5–8.5	7.3 ± 0.7	NR	SP = =8	NR		
Hammond et al. (2015)[2]	Retrospective	CON = =10, FES = =30	NR	$F = =27$ $M = =13$	54.7 ± 12	2.5–7.5	6.0 ± 1.4	16.8 ± 12.7	PP = =12 SP = =14 RR = =14	NR		
Krause et al. (2007)	Case Study	1	NR	$M = =1$	46	–	7.5	NR	SP = =1	NR		
Ratchford et al. (2010)	Pre-Post No Control	5	1	$F = =2$ $M = =3$	50 (median) (range 46–60)	6.0–6.5	6.5 (median)	13 (median) (range 6–21)	PP = =2 SP = =3	NR		
Reynolds et al. (2015)[3]	Pre-Post No Control	14	NR	$F = =1$ $M = =7$	54.5 ± 13.9	NR	NR	16.8 ± 6.9	PP = =2 SP = =4 RR = =2	NR	NR	24.7 ± 3.3
Szecsi et al. (2009)[4]	Pre-Post No Control	12	4	$F = =1$ $M = =11$	50.9 ± 6.9	4.0–8.0	6.5 ± 1.1	15.3 ± 8.2	$P = =8$	NR		

Inclusion criteria of all papers equated to mean EDSS ≥ 6.0. 1, demographic data only given for those that completed the intervention; 2, demographic data not split by control and intervention; 3, demographic data only given for those for those with measurable mVO_2; 4, EDSS unknown for $n = =1$; 5; two papers appear to be same participants and same intervention and have been grouped to prevent double counting; F, female; M, male; PP, Primary Progressive; RR, Relapsing Remitting; SP, Secondary Progressive; P, Progressive; Con, Control Group; FES, FES Cycling Group; NR, Not Reported. Data are mean ± SD unless otherwise stated.

Table 3
Summary of papers' intervention protocols.

Study	Study design	Apparatus	Muscles stimulated	Target cadence (rpm)	Stimulation settings	Session duration (mins)	Frequency	Study duration (weeks)	Total number of sessions	Total training volume (mins)	Continuous stimulation (C)/Intervals of stimulation (I)	Progression	Setting	Supervised (Y/N)	Notes
Backus et al. (2017)	Pre-Post No Control	RT300	Quadriceps, Hamstrings & Gluteals	35–50	PW = -=200 μs; *F* = 50 Hz	30	3 x a week	4	12	360	C	↑ 0.14 Nm Increments (if 3 sessions for 30 mins continuously)	Clinical	Y	If participant was unable to cycling for 30-mins, the cycle entered a passive mode for remainder of session
Edwards et al. (2018-b) and Pilutti et al.-(2018)[1]	RCT	RT300	Quadriceps, Hamstrings & Gluteals	40–50	PW = -=250 μs; *F* = 50 Hz	10 → 30	3 x a week	24	72	1800	C	↑10 min after 4 weeks (until 30 min reached)	Clinical	Y	CON completed on same apparatus.
Fornusek and Hoang (2014)	Pre-Post No Control	Motomed Viva 1.5 & Custom Muscle Stimulator	Quadriceps, Hamstrings & Gluteals	10	PW = -=300 μs; *F* = 35 Hz; Initial SA = =30-=mA	40	≈ 1.8 x a week	≈ 10	18	720	C	↑ SA at constant rate to reach predetermined level at 20 min. Then 20 mins at SA	Clinical	Y	Participants instructed not to push voluntarily during the training.
Hammond et al. (2015)	Retrospective	RT300, MotoMed FES Ergometer, Portable Neuromuscular Electrical Stimulation Units 300PV & SWISS Stim among others	NR	NR	NR	≥60	≈ 4.4 h total ABRT a month	≈ 8	≈ 16	≈ 960	NR	NR	Clinical	Y	Part of wider ABRT program. The average prescribed 12-month ABRT consisted of two 3-hour sessions per week administered in two blocks of 4 weeks each.
Krause et al. (2007)	Case Study	Constant Current 8-channel Stimulator	Quadriceps, Gluteals & Femoral Biceps	NR	SA: 30 → 90 mA	≥30	1 x a week	2	2	≈ 60	I	Stimulation increased with tolerance	Clinical	Y	Short breaks of 3–5 mins
Ratchford et al. (2010)	Pre-Post No Control	RT300	Quadriceps, Hamstrings & Gluteals	NR	Initial PD = -=250 ± -25% = %μ-s; Initial *F* = 33–45 -=Hz	≥60	≈ 3.8 x a week	24	NR	≈ 5472	NR	NR	Home	N	Asked to use at least 3 times per week for at least an hour per session
Reynolds et al. (2015)	Pre-Post No Control	RT300		40–50	NR	30	≈ 3 x a week	4–5	12	360	C	↑ 0.14 Nm	Clinical	Y	Stimulation gradually

(*continued on next page*)

Table 3 (*continued*)

Study	Study design	Apparatus	Muscles stimulated	Target cadence (rpm)	Stimulation settings	Session duration (mins)	Frequency	Study duration (weeks)	Total number of sessions	Total training volume (mins)	Continuous stimulation (C)/Intervals of stimulation (I)	Progressi-on	Setting	Supervised (Y/N)	Notes
			Quadriceps, Hamstrings & Gluteals									Increment-s (if 3 sessions for 30 mins continu-ously)			increased to cause cycling at 50 rpm. If participant was unable to cycling for 30-mins, the cycle entered a passive mode for remainder of session
Szecsi et al. (2009)	Pre-Post No Control	Theravital Cycle Ergometer & Constant Current 8-channel Stimulator	Quadriceps & Hamstrings	NR	*F* = 20 Hz; Max SA =- =127 mA, Constant PW =- =300 μs	12–18	3 x a week	2	6	72–108	I	NR	Clinical	Y	*n* = =11 received conventional physiotherapy 5 times a week, and outpatient *n* = =1 attended conventional physiotherapy sessions twice a week. Highest cycling resistance was selected that would allow the subject to tolerate well 12–18 min of active ergometric pedalling (with and without stimulation), but at the same time not become too exhausted.

1, two papers appear to be same participants and same intervention and have been grouped to prevent double counting; F, frequency; PW, pulse width; PD, phase duration; SA, stimulation amplitude; NR, not reported; ABRT, Activity Based Restorative Therapy; RT300, Restorative Therapies Inc, Baltimore, MD, USA; Motomed Viva 1.5, Reck Medixintechnik GmBH, Betzenweiller, Germany; Motomed FES Ergometer, Reck Medixintechnik GmBH, Betzenweiller, Germany; Portable Neuromuscular Electrical Stimulation Units 300PV, Empi, St Paul, MN, USA; SWISS Stim, Valmed, Sion, Swizerland; Constant Current 8-channel Stimulator, Krauth + Timmermann, Germany; Theravital, Medica-Medizintechnik Ltd, Hochdorf, Germany.

3.3. Cardiorespiratory performance

One paper investigated mVO_2 and reported no improvement following a FES cycling intervention (Reynolds et al., 2015). One paper measured peak aerobic capacity (VO_{2peak}) across control and intervention groups and measured no change (Edwards et al., 2018b). Peak work rate (WR_{peak}) was measured in one paper, with no improvement following the intervention (Edwards et al., 2018b). Two papers measured power generation during FES cycling across the duration of the intervention, reporting no change (Backus et al., 2017; Szecsi et al., 2009). In two papers, where participants could cycle continuously for 30 min, the resistance at which they could cycle significantly increased (Backus et al., 2017; Reynolds et al., 2015). Conversely, in the same two papers, where participants were unable to cycle continuously for 30 min, active cycling time significantly increased (Backus et al., 2017; Reynolds et al., 2015).

3.4. Functional performance

Walking performance was measured in three papers in a variety of tests; 2-min walk test (2MW) (Ratchford et al., 2010; Edwards et al., 2018b), timed 25-foot walk test (T25FW) (Ratchford et al., 2010; Edwards et al., 2018b), 10 m Walk Test (10MWT) (Szecsi et al., 2009) and 12-item MS Walking Scale (MSWS-12) (Edwards et al., 2018b). All three papers reported insignificant changes (Ratchford et al., 2010; Szecsi et al., 2009; Edwards et al., 2018b). Timed Up-and-Go (TUG) performance was measured in two papers; with no change post FES cycling (Ratchford et al., 2010; Edwards et al., 2018b).

3.5. Musculoskeletal outcomes

Lower body strength was commonly measured in the Knee Extensors (KE), Knee Flexors (KF), Hip Extensors, Hip Flexors and/or Dorsiflexors or in combined tests (Backus et al., 2017; Ratchford et al., 2010; Szecsi et al., 2009; Edwards et al., 2018b). Three papers found no improvement in either KE or KF strength (Ratchford et al., 2010; Szecsi et al., 2009; Edwards et al., 2018b). Combined strength testing of the Hip Flexors, KE, KF & Dorsiflexors did not change (Backus et al., 2017). One study, that observed a significant increase in thigh volume failed to measure changes in muscle mass or fat free mass in order to ascertain the cause of such increase (Fornusek and Hoang, 2014).

The most frequently measured parameter was spasticity (Backus et al., 2017; Fornusek and Hoang, 2014; Ratchford et al., 2010; Szecsi et al., 2009; Krause et al., 2007). Three papers utilised the Modified Ashworth Scale (MAS) (Backus et al., 2017; Szecsi et al., 2009; Krause et al., 2007). One study utilised the Lower Limb Spasticity Measurement System (LLSMS) (Ratchford et al., 2010). One study used self-reporting (Fornusek and Hoang, 2014). Three papers reported a reduction in spasticity post FES cycling; two papers described significant improvements in spasticity directly post FES cycling (Szecsi et al., 2009; Krause et al., 2007) and one paper described self-evaluated measures on an unspecified time frame (Fornusek and Hoang, 2014). Four papers reported no longer term improvements when measures were taken on different days (Backus et al., 2017; Ratchford et al., 2010; Szecsi et al., 2009; Krause et al., 2007).

3.6. Psychological outcomes

Two papers evaluated mental health finding no change utilising the Mental Health Inventory (MHI) and Symptom Checklist-90 accordingly (Backus et al., 2017; Ratchford et al., 2010). Quality of Life was measured in three papers with no significant change post FES cycling (Backus et al., 2017; Ratchford et al., 2010; Pilutti et al., 2018).

3.7. Adverse events

Four papers did not explicitly report any information regarding adverse events (Fornusek and Hoang, 2014; Szecsi et al., 2009; Hammond et al., 2015; Krause et al., 2007). Of the five remaining papers, a total of 36 participants reported 10 adverse events; none of which were described as serious (Backus et al., 2017; Ratchford et al., 2010; Reynolds et al., 2015; Edwards et al., 2018b; Pilutti et al., 2018). Only two papers specifically discuss MS-related adverse events and in both cases, none were reported (Backus et al., 2017; Reynolds et al., 2015). Two papers reported 8 minor events which included skin irritation, increased spasticity, bowel dysfunction and fatigue (Ratchford et al., 2010; Edwards et al., 2018b). Two papers both reported a moderate adverse event which caused a participant to drop out; both of which were falls noted by researchers as unrelated to the intervention (Ratchford et al., 2010; Edwards et al., 2018b).

3.8. Study quality

The study quality assessment tools indicated that papers consistently had unclear or insufficient sample sizes to provide confidence in the findings (Tables 5–8). The largest sample size was that of a retrospective study, which contained 40 participants (Hammond et al., 2015). Of the 8 other papers, sample size ranged from 1 to 14 (Backus et al., 2017; Fornusek and Hoang, 2014; Ratchford et al., 2010; Reynolds et al., 2015; Szecsi et al., 2009; Edwards et al., 2018b; Pilutti et al., 2018; Krause et al., 2007). Across all nine papers, 82 participants were reported to complete a FES cycling intervention, but outcome data was only provided for 76 (Backus et al., 2017; Fornusek and Hoang, 2014; Ratchford et al., 2010; Reynolds et al., 2015; Szecsi et al., 2009; Edwards et al., 2018b; Pilutti et al., 2018; Hammond et al., 2015; Krause et al., 2007). Only two papers had a blinded assessment of outcome measures (Edwards et al., 2018b; Pilutti et al., 2018). Across the 7 papers with cohort study designs (Backus et al., 2017; Fornusek and Hoang, 2014; Ratchford et al., 2010; Reynolds et al., 2015; Szecsi et al., 2009; Edwards et al., 2018b; Pilutti et al., 2018), only 2 reported a dropout rate $\leq 20\%$ (Fornusek and Hoang, 2014; Ratchford et al., 2010). None of the papers included in this review recorded outcome measures multiple times following a FES cycling intervention (Backus et al., 2017; Fornusek and Hoang, 2014; Ratchford et al., 2010; Reynolds et al., 2015; Szecsi et al., 2009; Edwards et al., 2018b; Pilutti et al., 2018; Hammond et al., 2015; Krause et al., 2007).

4. Discussion

The aim of this systematic review was to conduct a comprehensive literature search examining the effect of FES cycle training on cardiovascular, musculoskeletal and functional outcomes in PwMS and EDSS $\geq$ 6.0. The heterogeneity in outcome measures across the nine papers prevented a meta-analysis. The low quality of the literature base precludes any definitive conclusions regarding the efficacy of FES cycle training in improving cardiovascular health in PwMS and higher EDSS scores. In the present review, one of the main findings is that FES cycle training appears to be well tolerated in PwMS with mobility impairment, with no serious adverse events.

4.1. Cardiorespiratory performance

Aerobic capacity is a strong indicator of cardiovascular fitness and associated CVD risk in PwMS (Heine et al., 2016). CVD is of particular risk for PwMS, with papers demonstrating that PwMS are more likely to have CVD in comparison to healthy controls (Wens et al., 2016; Mincu et al., 2018). Although definitive data is lacking, it is plausible that those with the greatest level of mobility impairment are subject to an increased risk of CVD, with a significant correlation between disease

Table 4
Summary of papers' objective outcome measures.

Study	Outcome Measures Pre-Post Intervention	Adverse Events	Type of Adverse Events Reported
Backus et al. (2017)	↑ Resistance or Time during FESC ↔ Power during FESC, Lower Limb Strength (Combined MMT of Bilateral HF, KF, KE and AD), Spasticity (MAS), Fatigue (MFIS), Pain (MOS PES), Mental Health (MHI), QOL (MSQLI)	0	–
Edwards et al. (2018b) and Pilutti et al. (2018)[1]	↔ T25FW, MSWS-12, 2MW, TUG, VO_{2peak}, WR_{peak}, KE Strength, KF Strength, Leg FFM, Leg FM, Leg % Fat, Leg BMD, Cognition (SDMT), Fatigue (FSS, MFIS), Pain (SF-MPQ), QOL (MSIS-29)	7 (6 Min, 1 Mod)	Min (n = =6): Skin Irritation/Redness n = =3, Non-Debilitating Fatigue n = =2, Increased Muscle Spasticity n = =1 Mod (n = =1): Fall Outside of Training
Fornusek and Hoang (2014)	↑ Left and Right Thigh Circumference	NR	NR
Hammond et al. (2015)	↑ Lower Extremity Motor (ISNCSCI) ↔ Upper Extremity Motor (ISNCSCI), Light Touch (ISNCSCI), Pin Prick (ISNCSCI)	NR	NR
Krause et al. (2007)	↓ Spasticity (MAS)	NR	NR
Ratchford et al. (2010)	↑ GDNF, IFNγ, IL-8, MIP-1α, MCP-1↔ EDSS, 2MW, T25FW, 9HPT, PASAT, TUG, KE Strength, KF Strength, HE Strength, HF Strength, FD Strength, Lower Limb Sensation, Spasticity (LLSMS), Gait, QOL (SF-36), Mental Health (SCL-90), Other cytokines, chemokines and growth factors	3 (2 Min, 1 Mod)	Min (n = =2): Bowel Incontinence n = =1, Increased Muscle Spasticity n = =1 Mod (n = =1): Fall Outside of Training
Reynolds et al. (2015)	↑ Resistance or Time during FESC, mVO_2	0	–
Szecsi et al. (2009)	↔ Power during FESC, Smoothness during FESC, 10MWT (ST & LT), KE Strength, KF Strength, Spasticity (MAS, LT) ↓ Spasticity (MAS; ST)	NR	NR

↑, significant increase ($p \leq 0.05$); ↔, no significant change; ↓, significant decrease ($p \leq 0.05$); 1, two papers appear to be same participants and same intervention and have been grouped to prevent double counting; Min, minor adverse event; Mod, moderate adverse event; FESC, functional electrical stimulation cycling; HE, hip extensor; HF, hip flexor; KF, knee flexor; KE, knee extensor; AD, ankle dorsiflexor; FD, foot dorsiflexor; MMT, manual muscle test; MAS, modified ashworth scale; MFIS, modified fatigue impact scale; SDMT, symbol digit modalities test; SF-MPQ, short-form McGill pain questionnaire; MOS PES, medical outcomes study pain effects scale; MHI, mental health inventory; QOL, quality of life; MSQLI, multiple sclerosis quality of life index; SF-36 = =short-form 36; SCL-90, symptom checklist-90; FSS, fatigue severity scale; T25FW, timed 25-foot walk test; 2MW, 2-minute walk; MSWS-12, 12-item multiple sclerosis walking scale; TUG, timed up-and-go; FFM, fat-free mass; FM, fat mass; BMD, bone mineral density; MSIS-29, 29-item multiple sclerosis impact scale; ISNCSCI, international standards for neurological classification of spinal cord injury; 9HPT, 9-hole peg test; PASAT, paced auditory serial addition test; LLSMS, lower limb spasticity measurement system; GDNF, glial cell-derived neurotrophic factor; IFNγ, interferongamma; IL-8, interleukin-8; MIP-α, macrophage inflammatory protein-1 alpha; MCP-1, monocyte chemotactic protein-1; 10MWT, 10 m Walk Test; ST, Short-Term; LT, Long-Term.

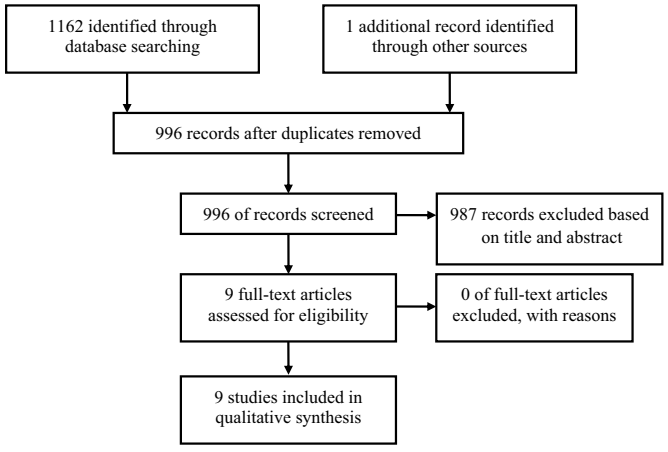

Fig. 1. PRISMA flow diagram of literature search and review process.

progression and aerobic capacity (Heine et al., 2016; Pilutti et al., 2015). Whilst aerobic training has been demonstrated to reduce this CVD in PwMS (Howe and Gomperts, 2019); the majority of this work has been in those with EDSS < 6.0, whereas those with higher mobility impairment (e.g. EDSS ≥ 6.0) have been poorly researched in the literature (Howe and Gomperts, 2019). FES cycling has the potential to increase the dose of exercise attainable in PwMS with higher mobility impairment, and could therefore increase aerobic capacity and PA (Edwards et al., 2018a; Dolbow et al., 2013). However, despite this potential, from the evidence of this review, the effectiveness of FES cycling in improving aerobic capacity is equivocal. Only two papers recorded valid objective measures of aerobic capacity (Reynolds et al., 2015; Edwards et al., 2018b). One paper found a significant increase in peripheral oxygen consumption (mVO_2) following 360 min of FES cycle training across 4 weeks while the other study reported trends for improvement in VO_{2peak} that fell short of statistical significance (Wells et al., 2019; Szecsi et al., 2009). In both cases, the samples were small ($n \leq 8$) and the studies were underpowered, making it difficult to draw definitive conclusions.

Walking tests are associated with aerobic capacity in PwMS (Sandroff et al., 2013). In the present review, walking performance was the most frequently utilised functional test (Ratchford et al., 2010; Szecsi et al., 2009; Edwards et al., 2018b) however no papers reported any improvements. This apparent limited effectiveness may be due to the lack of specificity since walking performance is also reliant on balance and lower limb strength asymmetries (Sandroff et al., 2013). Moreover, whether different doses of exercises would be more effective (e.g. longer duration or higher intensity) remain to be determined. Indeed, the high level of variability within the FES cycling interventions makes it difficult to attribute any changes to a specific protocol. While four of the nine papers had similar protocols (Backus et al., 2017; Reynolds et al., 2015; Edwards et al., 2018b; Pilutti et al., 2018), only two had matched training volumes and outcome measures in both papers had a high level of variability (Backus et al., 2017; Fornusek and Hoang, 2014).

4.2. Cardiovascular risk factors

Obesity, typically measured utilising BMI, is a well-accepted and independent risk factor for CVD (Poirier et al., 2006). Given the increased risk of CVD in PwMS compared to the general population, it is surprising that only two papers provided BMI data (Reynolds et al., 2015; Edwards et al., 2018b). One paper gave baseline measures for BMI (Reynolds et al., 2015). The other paper provided more nuanced assessment of fat free mass, fat mass and bone density (measured utilising a bone densitometer) and reported no change following FES cycle training (Edwards et al., 2018b). The overall poor reporting of BMI and

small sample size in Edwards et al. (2018b) makes it difficult to assess the role of FES cycle training in preventing obesity as a CVD risk factor.

However, the accuracy of standard BMI thresholds for persons with lower limb impairment have been questioned since BMI does not distinguish between muscle and fat compartments (Bandini et al., 2015). Consequently, in persons with reduced lower limb muscle tone and bone density, BMI thresholds designed for able bodied persons may underestimate the risk of increased body fat (Bandini et al., 2015). Notably, in this regard FES cycling has been reported to improve body composition including increase in lean tissue in persons with SCI (Frotzler et al., 2008). However, the potential of FES cycling to produce similar effects in PwMS is yet to be investigated.

4.3. Spasticity

Spasticity is a common and debilitating symptom for persons with MS (Haas, 2011; Pozzilli, 2014). In particular, this is important for PwMS since disease progression and duration are both strongly correlated with spasticity and reductions in mobility (Pozzilli, 2014; Tintoré, 2015). Alongside a reduction in mobility and associated independence, spasticity can also be a direct source of MS-related pain (Truini et al., 2013). FES cycling has been suggested as a possible support mechanism for spasticity since it is associated with a reduction in spastic muscle tone in persons with SCI (Jain et al., 2010) but the degree to which this is the case with PwMS remains to be determined.

Spasticity was the most commonly recorded measure, and FES cycle training appears to acutely improve symptoms of spasticity but this does not appear to translate into medium term effects (defined as approximately 48 h after training) (Szecsi et al., 2009; Krause et al., 2007). No papers evaluated longer term effects of FES cycling and thus the effect of FES cycle training in reducing spasticity > 48 h remains unclear. The MAS was the most frequently utilised measurement within this review and is commonly used to measure spasticity in persons with MS (Tintoré, 2015). That being said, a number of limitations are reported with the MAS related to inter-rater reliability, sensitivity to change and insufficient guidelines regarding its use (Frotzler et al., 2008; Pozzilli, 2014). Future studies should look to use more robust measures of spasticity with less subjectivity.

4.4. Lower limb muscular strength

Lower Limb Muscular Strength is correlated to walking performance in PwMS and is important in enabling PwMS to complete personal and instrumental ADLs (Månsson and Lexell, 2004; Kjølhede et al., 2012). Clearly, one aim of FES cycling is to stimulate the musculature of the lower limbs thus aiming to increase strength, reduce the rate of decline and preserve function in the lower body; with the potential to support PwMS's ability to maintain ADLs. Moreover when this lower limb function is lost, this in turn translates into greater loads being placed on the upper body and a higher risk of chronic upper body injury (Jain et al., 2010; Haubert et al., 2006). Four papers assessed this outcome, however no improvements in lower body muscular strength following FES cycle training were found within the present review (Backus et al., 2017; Ratchford et al., 2010; Szecsi et al., 2009; Edwards et al., 2018b).

Clearly, cycling is generally considered to be aerobic in nature and may be considered to produce modest increases in muscular strength. Indeed, to elicit skeletal muscle hypertrophy in healthy populations using aerobic exercise, the optimum exercise intensity is suggested as a minimum of 70% HR reserve (HRR), 4 times a week for 30 min (Konopka and Harber, 2014). Given that none of the papers included in this review had sufficient exercise volume to equate to this, nor was % HRR or $\%VO_{2peak}$ set as a target within the interventions, it is perhaps not surprising that no changes in strength were noted. Moreover, FES cycling can be considered as a dynamic training modality with moderate speeds of muscle contraction. However, in all cases, strength was

Table 5
NHLBI quality qssessment tool for before-after (Pre-Post) studies with no control group.

Study	Research question clear?	Participant eligibility criteria clear?	Participants representative of clinical population of interest?	Were all eligible participants enrolled?	Was sample size sufficiently large to provide confidence in the findings?	Was the intervention clearly described and delivered consistently?	Outcome measures prespecified, clear, valid and reliable? Assessed consistently?	Blinded assessment of outcomes?	Loss to follow-up after baseline ≤20%	Did the statistical method examine changes pre and post intervention? p values provided?	Outcome measures taken multiple times pre and post intervention?
Backus et al. (2017)	Y	Y	Y	Y	UC	Y	Y	N	NR	Y	N
Fornusek and Hoang (2014)	Y	Y	Y	Y	UC	Y	N	N	Y	N	N
Ratchford et al. (2010)	Y	Y	Y	Y	N	Y	Y	N	Y	N	N
Reynolds et al. (2015)	Y	Y	Y	Y	UC	Y	Y	N	NR	Y	N
Szecsi et al. (2009)	Y	Y	Y	Y	UC	Y	Y	N	N	Y	N

Y, yes; N, no; UC, unclear; NR, not reported.

Table 6
Quality assessment of case reports and case series.

Study	Domain Selection Patient represent whole experience of the investigator or is the selection method unclear to the extent that other patients with similar presentation may not have been reported?	Ascertainment Exposure adequately ascertained?	Outcome adequately ascertained?	Causality Other alternative causes that may explain the observation ruled out?	Challenge/ rechallenge phenomenon?	Dose–response effect?	Follow-up long enough for outcomes to occur?	Reporting Case described with sufficient details to allow other investigators to replicate the research or to allow practitioners make inferences related to their own practice?
Krause et al. (2007)	UC	Y	Y	N	N	N	Y	Y

Y, yes; N, no; UC, unclear.

Table 7
NHLBI quality qssessment for controlled intervention studies.

Study	Study described as RCT?	Method of randomisation adequate?	Treatment allocation concealed?	Study participants and providers blinded to treatment group assignment?	Outcome assessors blinded to participants' group assignments?	Groups similar at baseline on important characteristics that could affect outcomes?	Drop out rate at endpoint ≤20% or lower of number allocated to treatment?	Differential drop-out rate at endpoint ≤15%	High adherence to intervention protocols for each treatment group?	Were other interventions avoided or similar in the groups?	Were outcomes assessed using valid and reliable measures, implemented consistently across all participants?	Sample size sufficiently large to detect difference in main outcome between groups with ≥80% power?	Outcomes reported or subgroups analysed prespecified?	All randomised participants analysed in group to which they were originally assigned?
Edwards et al. (2018b) and Pilutti et al. (2018)[1]	Y	Y	Y	N	Y	Y	N	Y	Y	NR	Y	N	Y	N

Y, yes; N, no; NR, not reported; 1, two papers appear to be same participants and same intervention and have been grouped to prevent double counting.

Table 8
Newcastle-Ottawa quality assessment scale for case control studies.

Study	Domain Selection	Comparability	Outcome					
	Case Definition Adequate?	Representativeness of cases	Selection of controls	Definition of controls	Comparability of cases and controls on basis of design or analysis	Ascertainment of exposure	Same ascertainment for cases and controls	Non-response rate
Hammond et al. (2015)	⋆	⋆				⋆	⋆	

⋆ one star.

assessed isometrically using semi-quantitative (Backus et al., 2017; Szecsi et al., 2009), static (Hammond et al., 2015) or isokinetic (Edwards et al., 2018b) methods. It is well established that changes in strength are specific to the speed and type of contraction used in training, and outcome measures should reflect the training mode (Baker et al., 1994). Indeed, strong correlations only existed between isometric and dynamic strength using large forces, or explosive power as anticipated (Juneja et al., 2010), which was not the case in the interventions used in the papers.

Consequently, the conclusion that FES cycling does not improve strength in PwMS with EDSS ≥ 6.0 should be viewed with caution, and must be re-evaluated with more appropriate protocols, given the mismatch between training stimulus and outcome assessment. Evidence has shown that PwMS and mobility impairment can reach higher % HR_{peak} during an acute bout of FES cycling in comparison to passive leg cycling (76.4%HR_{peak} vs 55.5%HR_{peak}) (Edwards et al., 2018a). This supports the theory that FES cycling protocols have the potential to provide increases in strength. A further limitation is that of the papers in this review, only two interventions were longer than 10 weeks and in both cases, sample sizes were too small to make meaningful interpretations ($n = =4$ completed in both cases) (Ratchford et al., 2010; Edwards et al., 2018b; Pilutti et al., 2018). Another consideration for those papers that measured muscular strength, is that the majority had no control group. As disease progression is correlated to reductions in lower limb muscular strength, future research should look to determine if maintenance of muscular strength is clinically meaningful over time in comparison to controlled counterparts (Sandroff et al., 2013).

4.5. Adverse events & adherence

Accurate reporting of adverse events is particularly important in this group since there are few intervention papers evaluating the benefits of PA in persons with EDSS ≥ 6.0 (Latimer-Cheung et al., 2013; Platta et al., 2016; Ewanchuk et al., 2018). In general, previous studies have indicated exercise to be safe in PwMS, with one systematic review of RCT's reporting no increased risk of relapse (Pilutti et al., 2014). However, a notable limitation is that, in that review, only one of the papers included participants with a mean EDSS ≥ 6.0 and none included participants with an EDSS > 6.5 (Pilutti et al., 2014). One systematic review has reported on exercise interventions for PwMS and EDSS ≥ 6.0 but did not come to any meaningful conclusions regarding exercise safety, in part due to the small number of research papers evaluating this population (Edwards and Pilutti, 2017). This present review extends these findings, by identifying consistent, if limited evidence that FES cycle training in PwMS who have an EDSS ≥ 6.0 appears to be well tolerated with no serious adverse events. Moreover, while there are clear differences in aetiology, this finding is in broad agreement with substantial evidence regarding the reported benefits of FES cycling and safety in persons with SCI (Arnold et al., 1992).

Whilst encouraging, it is important to note that reporting of adverse events was generally poor, making more detailed recommendations in PwMS and higher EDSS scores difficult. Moreover, PwMS and EDSS ≥ 6.0 are relatively poorly represented in the MS literature regarding exercise interventions, with little information in regards to adherence to exercise interventions, and potential barriers to participation they experience. Future FES cycling studies should seek to explicitly provide adverse event data in this population.

This review also found poor reporting of participant recruitment and dropout rates thus impacting on the conclusions which can be drawn regarding attrition. By only reporting the outcomes of those completing an intervention, investigators risk attrition bias which, hampers the understanding of exercise adherence and the capacity of this population to sustain FES cycling at prescribed training volumes (Dumville et al., 2006). Understanding exercise adherence and how to increase participation in persons with MS is an important area for future research (Motl et al., 2017).

4.6. Quality of the literature

Nine papers of varying study design were considered in this review. Most papers had small sample sizes that lacked justification, and therefore had underpowered statistical analysis. For example, the sample sizes across all the pre-post cohort studies were relatively small. Moreover, two papers attempted to overcome sample size limitations by calculating effect sizes for all insignificant outcomes (Edwards et al., 2018b; Pilutti et al., 2018). While this is understandable, it is important that insignificant improvements aren't assumed to be type 2 errors, as underpowered studies may also artificially inflate the effect size (Button et al., 2013). Studies must seek to increase their sample sizes or provide statistical justification for their sample size use if any meaningful conclusions regarding the effect of FES cycling in persons with MS are to be assessed. The only study to have sufficient sample size for statistical power was the retrospective paper by Hammond et al. (2015). However, in this case, participation allocation into either FES cycling or control groups was decided for clinical reasons, suggesting that finding may be affected by allocation bias (Gluud, 2006).

Of concern is the preponderance of subjective outcome measures in certain papers (Fornusek and Hoang, 2014). This study reported significant improvements in several self-evaluated outcomes including increases in circulation, strength, balance and muscle mass and reductions in pain, cramp and spasticity (self-reported measures with no statistical testing were not included in Table 4). This is of concern given the use of an intervention group and no control; with clear risk of response bias and the potential for treatment effect (Rosenman et al., 2011). The study provided resting and peak HR, however, this was poorly reported with resting and HR_{MAX} values only assessed pre intervention, making interpretation difficult (Fornusek and Hoang, 2014).

Whilst the present review affirms the requirement for evaluating cardiorespiratory performance and FES cycle training in PwMS and EDSS $\geq$ 6.0, the lack of consistent measures of cardiorespiratory performance or other measures of CVD risk, mean it is difficult to draw conclusions regarding the effect on their cardiovascular health and CVD risk. Future research should accurately monitor cardiorespiratory performance and CVD risk factors before and after FES cycle training in PwMS and EDSS $\geq$ 6.0.

Two interventions would not be replicable based on the information provided within the papers reviewed (Ratchford et al., 2010; Hammond et al., 2015). If the quality of evidence regarding FES cycling in PwMS is to improve, there is a clear requirement for statistically justifiable sample sizes and a consistency in intervention protocols/testing parameters to enable a future quantitative analysis. None of the papers included in this review had a follow up and so it remains unclear if there are any long lasting changes in outcome measures following a FES cycling intervention. In particular, this is important for PwMS based on the degenerative nature of the condition; where no change over time may represent a net clinical benefit.

The use of functional tests was typically favoured in the present review in place of direct measures (Table 4). Whilst maintaining and/or improving function is of clear priority for PwMS when participating in exercise; it is important to note that the underlying mechanisms for conditioning and preservation of this function in PwMS and FES cycling are not understood at present. As such, isolating the underlying reasons for changes in functional tests and hence, the use of direct measures remains of important when evaluating FES cycling in PwMS.

Most FES Cycling research has been in persons with complete SCI and the transfer of this exercise modality to PwMS is justifiable. However, future research must appreciate that PwMS will require different protocols which will need to be fully reported. In particular, PwMS may still have some lower limb function making it more difficult to differentiate between the work provided by the individual (i.e. via central command) versus that provided by the stimulation. It would be beneficial if researchers clearly stated if participants were instructed and/or encouraged to cycle volitionally, and to what level/effort. For example, one paper in the present review instructed participants not to cycle volitionally, as the aim of their research was to isolate the effect of the electrical stimulation (Fornusek and Hoang, 2014). Volitional effort being encouraged or discouraged is not clearly reported across all the papers within this review. Where participants are asked to actively cycle, the variance in stimulation and WR across the session could provide insight regarding participant fatigability.

5. Conclusion

The current systematic review suggests that FES cycle training appears to be well tolerated in PwMS with mobility impairment. Findings suggest that FES cycle training may reduce CVD risk in some persons alongside trends suggesting reductions in spasticity post training. However, the low quality of the literature base precludes any definitive conclusions regarding the efficacy of FES cycle training in improving cardiovascular, musculoskeletal and functional outcomes in PwMS and higher EDSS scores. Future research should examine the use of FES cycle training in PwMS and mobility impairment using larger sample sizes, with correct statistical power, consistent cycle protocols and utilising direct objective measurable outcomes.

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