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 ≥ 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.

Keywords
Multiple Sclerosis; Mobility Impairment; Functional Electrical Stimulation; Functional Electrical Stimulation Cycling; High EDSS
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 [1–5]. 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) [2,3].

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 [4]. 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 [5,6].

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 [7–9]. 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 [10,11]. 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 [5,12,13]. Indeed, disease progression has been significantly correlated to reductions in aerobic capacity, muscular strength and walking performance [7,12,14,15].

Disease progression in MS is monitored and assessed utilising the Expanded
Disability Status Scale (EDSS) [16]. The scale describes different levels of impairment and ranges from 0 to 10, with 0 representing no symptoms and 10 representing death [16]. An EDSS score of 6.0 is an identifiable milestone on the scale, whereby the individual can walk a maximum of 100m without stopping, even with the support of a unilateral assistive device [17]. 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 ≥ 6.0 are less likely to meet MVPA guidelines and have a greater risk of experiencing CV comorbidities [18]. For example, vascular comorbidities have been significantly correlated to an increased risk of mobility impairment and speed of disability progression [19]. Furthermore, whilst there is evidence that exercise has a multitude of health benefits for PwMS [20–22], 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 [23]. This can make the use of upper body exercise appealing [24]. Whilst both upper body and lower body exercises may have the potential to elicit cardiovascular adaptations 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 [25]. 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 [26].

Functional Electrical Stimulation (FES) cycling is a suggested lower limb exercise intervention for individuals who have higher levels of impairment [27]. FES cycling can be used where individuals are unable to propel a cycle ergometer independently due to reduced physical function [27]. The intervention applies electrical stimulation to the lower limb muscles, which is appropriately timed to generate cyclical contractions to propel the cycle ergometer [28]. 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 [27,29,30]. 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 [31]. 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 [32]. 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.

### Table 1: Sample Search Strategy

<table>
<thead>
<tr>
<th>#1</th>
<th>“Multiple Sclerosis” OR “Progressive MS” OR “Relapsing Remitting MS” [all fields]</th>
</tr>
</thead>
<tbody>
<tr>
<td>#2</td>
<td>“NMES” OR “FES” OR “ESAC” OR “neuromuscular stimulation” OR “electrical stimulation” OR “stimulation-assisted cycl*” OR “assisted cycl*” [all fields]</td>
</tr>
<tr>
<td>#3</td>
<td>#1 AND #2</td>
</tr>
</tbody>
</table>

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

#### 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 [29]. This enables the user to remain on their wheelchair, reducing the requirement for transferring [33]. 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 [28,34]. 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 fatigability [30]. Where a participant has leg function, their individual volitional efforts will contribute to attaining the target cadence [33].

#### 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 (ii) intervention protocols (iii)
intervention outcomes.

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 [35] and RCTs [36].
Case studies were evaluated using the tools developed by Murad et al. [37] and
retrospective studies using the Newcastle-Ottawa Scale [38].
3. Results

Figure 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 [33,39–42], two were Randomised Controlled Trials (RCTs) [43,44], one was a retrospective study [45] and one was a case study [46]. Two papers reported different outcomes on the same participant group following the same intervention [43,44]. 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.
1162 identified through database searching
1 additional record identified through other sources

996 records after duplicates removed

996 of records screened

9 full-text articles assessed for eligibility

9 studies included in qualitative synthesis

987 records excluded based on title and abstract

0 of full-text articles excluded, with reasons

Figure 1: PRISMA flow diagram of literature search and review process
Table 2: Summary of Papers’ Participant Data
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.
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 [42–45]. Two papers did not report participant EDSS however their inclusion criteria approximately equated to that of participants with mobility impairment and EDSS ≥ 6.0 [33,41]. The highest level of impairment reported in participants was EDSS 8.5 [39]. Six papers utilised participants with both progressive and relapsing remitting MS [33,40,41,43–45]. Three exclusively recruited participants with progressive MS [39,42,46]. 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 [43,44]. Three papers reported BMI in kg/m² [41,43,44].

In three papers, data were only provided for participants who completed the FES cycling intervention [33,41,45]. The same three papers failed to identify the number of participants recruited and drop outs [33,41,45]. Whilst one of the remaining papers was a case study, the other 5 papers reported dropout rates [39,40,42–44]. Two of these papers failed to provide demographic data for participants who withdrew [43,44]. 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% [39,40,42,43].

One paper only provided demographic information for those participants where the main outcome, muscle oxygen consumption (mVO₂), was successfully measured [41]. Resting and Peak Heart Rate (HR) was provided in one paper, however these were from baseline assessments and not measured pre and post intervention [39].
<table>
<thead>
<tr>
<th>Study [Citation]</th>
<th>Study Design</th>
<th>Apparatus</th>
<th>Muscles Stimulated</th>
<th>Target Cadence (rpm)</th>
<th>Stimulation Settings</th>
<th>Session Duration (mins)</th>
<th>Frequency</th>
<th>Study Duration (weeks)</th>
<th>Total Number of Sessions</th>
<th>Total Training Volume (mins)</th>
<th>Continuous Stimulation (C) / Intervals of Stimulation (I)</th>
<th>Progression Setting</th>
<th>Supervised (Y/N)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Backus et al. [33]</td>
<td>Pre-Post No Control</td>
<td>RT300</td>
<td>Quadriceps, Hamstrings &amp; Gluteals</td>
<td>35 - 50</td>
<td>PW = 200 μs; F = 50 Hz</td>
<td>30</td>
<td>3 x a week</td>
<td>4</td>
<td>12</td>
<td>360</td>
<td>C ↑ 0.14 Nm Increments (if 3 sessions for 30 mins continuously)</td>
<td>Clinical</td>
<td>Y</td>
<td>If participant was unable to cycling for 30 mins, the cycle entered a passive mode for remainder of session</td>
</tr>
<tr>
<td>Edwards et al. / Pilutti et al. [43][44]</td>
<td>RCT</td>
<td>RT300</td>
<td>Quadriceps, Hamstrings &amp; Gluteals</td>
<td>40 - 50</td>
<td>PW = 250 μs; F = 50 Hz</td>
<td>10 → 30</td>
<td>3 x a week</td>
<td>24</td>
<td>72</td>
<td>1800</td>
<td>C ↑ 10 min after 4 weeks (until 30 min reached)</td>
<td>Clinical</td>
<td>Y</td>
<td>CON completed on same apparatus</td>
</tr>
<tr>
<td>Fornusek &amp; Hoang [39]</td>
<td>Pre-Post No Control</td>
<td>Motomed Viva 1.5 &amp; Custom Muscle Stimulator</td>
<td>Quadriceps, Hamstrings &amp; Gluteals</td>
<td>10</td>
<td>PW = 300 μs; F = 25 Hz; Initial SA = 30 mA</td>
<td>40</td>
<td>≈ 1.8 x a week</td>
<td>≈ 10</td>
<td>18</td>
<td>720</td>
<td>C ↑ SA at constant rate to reach predetermined level at 20 minutes. Then 20 mins at SA</td>
<td>Clinical</td>
<td>Y</td>
<td>Participants instructed not to push voluntarily during the training</td>
</tr>
<tr>
<td>Hammond et al. [45]</td>
<td>Retrospective</td>
<td>RT300, Motomed FES Engometer, Portable Neuromuscular Electrical Stimulation Units 300PV &amp; SWISS Stim among others</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>≥ 60</td>
<td>≈ 4.4 hours total ABRT a month</td>
<td>≈ 8</td>
<td>≈ 16</td>
<td>≈ 960</td>
<td>NR</td>
<td>Clinical</td>
<td>Y</td>
<td>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.</td>
</tr>
<tr>
<td>Krause et al. [46]</td>
<td>Case Study</td>
<td>Constant Current 8-channel Stimulator</td>
<td>Quadriceps, Glusteals &amp; Femoral Biceps</td>
<td>NR</td>
<td>SA: 30 → 90 mA</td>
<td>≥ 30</td>
<td>1 x a week</td>
<td>2</td>
<td>2</td>
<td>≈ 60</td>
<td>I Stimulation increased with tolerance</td>
<td>Clinical</td>
<td>Y</td>
<td>Short breaks of 3-5 mins</td>
</tr>
<tr>
<td>Study</td>
<td>Participants</td>
<td>Intervention</td>
<td>Muscle Groups</td>
<td>Initial PD (μs), Initial F (Hz)</td>
<td>Frequency</td>
<td>Duration</td>
<td>Max SA (mA)</td>
<td>Constant PW (μs)</td>
<td>Initial Resistance (Nm)</td>
<td>Incremental Res.</td>
<td>Stimulation Details</td>
<td>Outcome</td>
<td></td>
<td></td>
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<tr>
<td>Ratchford et al. [40]</td>
<td>Pre-Post No Control</td>
<td>RT300</td>
<td>Quadriceps, Hamstrings &amp; Gluteals</td>
<td>≥ 60</td>
<td>3.8 x a week</td>
<td>24</td>
<td>NR</td>
<td>5472</td>
<td>60</td>
<td>3.8</td>
<td></td>
<td>Activity Based Restorative Therapy (ABRT)</td>
<td>Clinical</td>
<td></td>
</tr>
<tr>
<td>Reynolds et al. [41]</td>
<td>Pre-Post No Control</td>
<td>RT300</td>
<td>Quadriceps, Hamstrings &amp; Gluteals</td>
<td>30</td>
<td>3 x a week</td>
<td>4 - 5</td>
<td>12</td>
<td>360</td>
<td>C</td>
<td>1.4</td>
<td></td>
<td>Home</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Szecsi et al. [42]</td>
<td>Pre-Post No Control</td>
<td>Theravel Cycle Ergometer &amp; Constant Current 8-channel Stimulator</td>
<td>Quadriceps &amp; Hamstrings</td>
<td>12 - 18</td>
<td>3 x a week</td>
<td>2</td>
<td>6</td>
<td>72 - 108</td>
<td>I</td>
<td>NR</td>
<td></td>
<td>Clinical</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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, Switzerland; Constant Current 8-channel Stimulator, Krauth + Timmermann, Germany; Theravital, Medica-Medizintechnik Ltd, Hochdorf, Germany.
3.2. Protocols

Intervention duration ranged between 2 and 24 weeks. Eight papers were completed under supervision in a clinical exercise setting [33,39,41–46] and the remaining paper was undertaken unsupervised at home [40]. Seven papers conducted 2/3 sessions per week for a range of 2 – 24 weeks [33,39–44]. The other two papers were once every week for 2 weeks [46] or completed in two blocks of 4 weeks [45].

In two papers, the protocol was unclear [40,45]. The protocol of five papers was to cycle continuously for a minimum of 10 - 60 minutes utilising FES [33,39,41,43,44]. Of these, the protocol for four papers was to reach a point where a participant could complete 30 minutes of FES cycling at a target cadence of 35 – 50 rpm [33,41,43,44]. Two papers utilised periods of stimulation interspersed with periods of rest [42,46].
### Table 4: Summary of Papers’ Objective Outcome Measures

<table>
<thead>
<tr>
<th>Study [Citation]</th>
<th>Outcome Measures Pre-Post Intervention</th>
<th>Adverse Events</th>
<th>Type of Adverse Events Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Backus et al. [33]</td>
<td>† Resistance or Time during FESC ↔ Power during FESC, Lower Limb Strength (Combined MMT of Bilateral HF, KE and AD), Spasticity (MAS), Fatigue (MFIS), Pain (MOS PES), Mental Health (MHI), QOL (MSQLI)</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Edwards et al. / Pilutti et al. [43] [44]</td>
<td>↔ T25FW, MSWS-12, 2MW, TUG, VO_{peak}, 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)</td>
<td>7 (6 Min, 1 Mod)</td>
<td>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</td>
</tr>
<tr>
<td>Fornusek &amp; Hoang [39]</td>
<td>↑ Left and Right Thigh Circumference</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Hammond et al. [45]</td>
<td>↑ Lower Extremity Motor (ISNCSCI) ↔ Upper Extremity Motor (ISNCSCI), Light Touch (ISNCSCI), Pin Prick (ISNCSCI)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Krause et al. [46]</td>
<td>↓ Spasticity (MAS)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Ratchford et al. [40]</td>
<td>† 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</td>
<td>3 (2 Min, 1 Mod)</td>
<td>Min (n=2): Bowel Incontinence n=1, Increased Muscle Spasticity n=1 Mod (n=1): Fall Outside of Training</td>
</tr>
<tr>
<td>Reynolds et al. [41]</td>
<td>↑ Resistance or Time during FESC, mVO_{2}</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Szecsi et al. [42]</td>
<td>↔ Power during FESC, Smoothness during FESC, 10MWT (ST &amp; LT), KE Strength, KF Strength, Spasticity (MAS, LT) ↓ Spasticity (MAS; ST)</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

†, significant increase (p ≤ 0.05); ↔, no significant change; ↓, significant decrease (p ≤ 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.
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, 10m Walk Test; ST, Short-Term; LT, Long-Term.
3.3. Cardiorespiratory Performance

One paper investigated mVO₂ and reported no improvement following a FES cycling intervention [41]. One paper measured peak aerobic capacity (VO₂peak) across control and intervention groups and measured no change [43]. Peak work rate (WRpeak) was measured in one paper, with no improvement following the intervention [43]. Two papers measured power generation during FES cycling across the duration of the intervention, reporting no change [33,42]. In two papers, where participants could cycle continuously for 30 minutes, the resistance at which they could cycle significantly increased [33,41]. Conversely, in the same two papers, where participants were unable to cycle continuously for 30 minutes, active cycling time significantly increased [33,41].

3.4. Functional Performance

Walking performance was measured in three papers in a variety of tests; 2-minute walk test (2MW) [40,43], timed 25-foot walk test (T25FW) [40,43], 10m Walk Test (10MWT) [42] and 12-item MS Walking Scale (MSWS-12) [43]. All three papers reported insignificant changes [40,42,43]. Timed Up-and-Go (TUG) performance was measured in two papers; with no change post FES cycling [40,43].

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 [33,40,42,43]. Three papers found no improvement in either KE or KF strength [40,42,43]. Combined strength testing of the Hip Flexors, KE, KF & Dorsiflexors did not change [33]. 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 [39].

The most frequently measured parameter was spasticity [33,39,40,42,46]. Three papers utilised the Modified Ashworth Scale (MAS) [33,42,46]. One study utilised the
Lower Limb Spasticity Measurement System (LLSMS) [40]. One study used self-reporting [39]. Three papers reported a reduction in spasticity post FES cycling; two papers described significant improvements in spasticity directly post FES cycling [42,46] and one paper described self-evaluated measures on an unspecified time frame [39]. Four papers reported no longer term improvements when measures were taken on different days [33,40,42,46].

3.6. Psychological Outcomes

Two papers evaluated mental health finding no change utilising the Mental Health Inventory (MHI) and Symptom Checklist-90 accordingly [33,40]. Quality of Life was measured in three papers with no significant change post FES cycling [33,40,44].

3.7. Adverse Events

Four papers did not explicitly report any information regarding adverse events [39,42,45,46]. Of the five remaining papers, a total of 36 participants reported 10 adverse events; none of which were described as serious [33,40,41,43,44]. Only two papers specifically discuss MS-related adverse events and in both cases, none were reported [33,41]. Two papers reported 8 minor events which included skin irritation, increased spasticity, bowel dysfunction and fatigue [40,43]. 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 [40,43].
Table 5: NHLBI Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group

<table>
<thead>
<tr>
<th>Study [Citation]</th>
<th>Research question clear?</th>
<th>Participant eligibility criteria clear?</th>
<th>Participants representative of clinical population of interest?</th>
<th>Were all eligible participants enrolled?</th>
<th>Was sample size sufficiently large to provide confidence in the findings?</th>
<th>Was the intervention clearly described and delivered consistently?</th>
<th>Outcome measures prespecified, clear, valid and reliable? Assessed consistently?</th>
<th>Blinded assessment of outcomes?</th>
<th>Loss to follow-up after baseline ≤20%</th>
<th>Did the statistical method examine changes pre and post intervention? p values provided?</th>
<th>Outcome measures taken multiple times pre and post intervention?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Backus et al. [33]</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>UC</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Fornusek &amp; Hoang [39]</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>UC</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Ratchford et al. [40]</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Reynolds et al. [41]</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>UC</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Szecsi et al. [42]</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>UC</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study [Citation]</th>
<th>Selection</th>
<th>Ascertainment</th>
<th>Causality</th>
<th>Reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krause et al. [46]</td>
<td>UC</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
</tr>
</tbody>
</table>

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 to make inferences related to their own practice?
### Table 6: Quality Assessment of Case Reports and Case Series

<table>
<thead>
<tr>
<th>Study Citation</th>
<th>Study described as RCT?</th>
<th>Method of randomisation adequate?</th>
<th>Treatment allocation concealed?</th>
<th>Study participants and providers blinded to treatment group assignment?</th>
<th>Outcome assessors blinded to participants' group assignments?</th>
<th>Groups similar at baseline on important characteristics that could affect outcomes?</th>
<th>Drop out rate at endpoint ≤20% or lower of number allocated to treatment?</th>
<th>Differential drop-out rate at endpoint ≤15%</th>
<th>High adherence to intervention protocols for each treatment group?</th>
<th>Were other interventions avoided or similar in the groups?</th>
<th>Were outcomes assessed using valid and reliable measures, implemented consistently across all participants?</th>
<th>Sample size sufficiently large to detect difference in main outcome between groups with ≥80% power?</th>
<th>Outcomes reported or subgroups analysed prespecified?</th>
<th>Did all randomised participants included in group to which they were originally assigned?</th>
</tr>
</thead>
</table>

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

### Table 7: NHLBI Quality Assessment for Controlled Intervention Studies
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

<table>
<thead>
<tr>
<th>Study Citation</th>
<th>Domain</th>
<th>Selection</th>
<th>Comparability</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Case Definition</td>
<td>Adequate?</td>
<td>Representativeness of cases</td>
<td>Same ascertainment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Selection of controls</td>
<td>Selection of controls</td>
<td>for cases and controls</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Definition of controls</td>
<td>Comparability of cases and controls on basis of</td>
<td>Ascertainment of exposure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>of design or analysis</td>
</tr>
<tr>
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</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hammond et al.</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
</tr>
<tr>
<td>[46]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

★, one star.
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. The largest sample size was that of a retrospective study, which contained 40 participants [45]. Of the 8 other papers, sample size ranged from 1 to 14 [33,39–44,46]. Across all nine papers, 82 participants were reported to complete a FES cycling intervention, but outcome data was only provided for 76 [33,39–46]. Only two papers had a blinded assessment of outcome measures [43,44]. Across the 7 papers with cohort study designs [33,39–44], only 2 reported a dropout rate ≤20% [39,40]. None of the papers included in this review recorded outcome measures multiple times following a FES cycling intervention [33,39–46].

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 ≥ 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 [7]. CVD is of particular risk for PwMS, with papers demonstrating that PwMS are more likely to have CVD in comparison to healthy controls [5,47]. 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 progression and aerobic capacity [7,14]. Whilst aerobic training has been demonstrated to reduce this CVD in PwMS [48]; 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 [48]. 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 [31,49]. 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 [41,43]. One paper found a significant increase in peripheral oxygen consumption (mVO₂) following 360 minutes of FES cycle training across 4 weeks while the other study reported trends for improvement in VO₂peak that fell short of statistical significance [38,42]. In both cases, the samples were small (n≤8) and the studies were underpowered, making it difficult to draw definitive conclusions.

Walking tests are associated with aerobic capacity in PwMS [12]. In the present review, walking performance was the most frequently utilised functional test [40,42,43] 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 [12]. 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 [33,41,43,44], only two had matched training volumes and outcome measures in both papers had a high level of variability [33,39].

4.2. Cardiovascular Risk Factors

Obesity, typically measured utilising BMI, is a well-accepted and independent risk factor for CVD [50]. Given the increased risk of CVD in PwMS compared to the general population, it is surprising that only two papers provided BMI data [41,43]. One paper gave baseline measures for BMI [41]. 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 [43]. The overall poor reporting of BMI and small sample size in Edwards et al. [43] 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 [51]. 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 [51]. Notably, in this regard FES cycling has been reported to improve body composition including increase in lean tissue in persons with SCI [52]. 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 [53,54]. In particular, this is important for PwMS since disease progression and duration are both strongly correlated with spasticity and reductions in mobility [54,55]. Alongside a reduction in mobility and associated independence, spasticity can also be a direct source of MS-related pain [56]. 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 [58] 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 hours after training) [42,46]. No papers evaluated longer term effects of FES cycling and thus the effect of FES cycle training in reducing spasticity > 48 hours remains unclear. The MAS was the most frequently utilised measurement within this review and is commonly used to measure spasticity in persons with MS [55]. 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 [52,54]. 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 [26,57]. 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 [58,59]. Four papers assessed this outcome, however no improvements in lower body muscular strength following FES cycle training were found within the present review [33,40,42,43].

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 minutes [60]. Given that none of the papers included in this review had sufficient exercise volume to equate to this, nor was %HRR or %VO2peak 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 assessed isometrically using semi-quantitative [33,42], static [45] or isokinetic [43] 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 [61]. Indeed, strong correlations only existed between isometric and dynamic strength using large forces, or explosive power as anticipated [62], 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\textsubscript{peak} during an acute bout of FES cycling in comparison to passive leg cycling (76.4\%HR\textsubscript{peak} vs 55.5\%HR\textsubscript{peak}) [31]. 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) [40,43,44]. 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 [12].

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 [20–22]. 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 [63]. 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 [63]. 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 [64]. 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 [65].

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 [66]. Understanding exercise adherence and how to increase participation in persons with MS is an important area for future research [2].

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 [43,44]. 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 [67]. 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. [45]. 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 [68].

Of concern is the preponderance of subjective outcome measures in certain papers [39]. 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 [69]. The study provided resting and peak HR, however, this was poorly reported with resting and HR\textsubscript{MAX} values only assessed pre intervention, making interpretation difficult [39].

Whilst the present review affirms the requirement for evaluating cardiorespiratory performance and FES cycle training in PwMS and EDSS ≥ 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 ≥ 6.0.

Two interventions would not be replicable based on the information provided within the papers reviewed [40,45]. 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 [39]. 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 suggest 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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Declaration of Conflicting Interests

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References


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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