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Rooney, Scott; Albalawi, Hani; Paul, Lorna

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Exercise in the management of Multiple Sclerosis relapses: current evidence and future perspectives

Abstract

Relapses are a common feature of Multiple Sclerosis (MS); however, recovery from relapses is often incomplete, with up to half of people experiencing residual disabilities post-relapse. Therefore, treatments are required to promote recovery of function and reduce the extent of residual disabilities post-relapse. Accordingly, this perspectives article explores the role of exercise in relapse management. Current evidence from two studies suggests that exercise in combination with steroid therapy improves disability and quality of life post-relapse, and may be more beneficial in promoting relapse recovery than steroid therapy alone. However, given the small number of studies and methodological limitations, further studies are required to understand the effects of exercise in relapse management and the mechanism through which exercise influences relapse recovery.

Keywords: Multiple Sclerosis; relapse; exercise; rehabilitation

Introduction

Multiple Sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the central nervous system (CNS) which manifests in demyelination and axonal loss, and ultimately leads to impaired neural function and disability [1]. It is estimated that, with a prevalence of 50–300 per 100,000 people, approximately 2.3 million people are living with MS globally – most of whom are diagnosed between the ages of 30-50 [2]. The course of MS is highly variable, but can be classified according to two main, differing clinical phenotypes: relapsing-remitting MS (RRMS) and progressive MS [3]. RRMS is the most common form of MS accounting for 80% of the population [4], and is characterised by transient episodes of neurological disability known as relapses [3].

Relapses, defined as “an increase in patient-reported symptoms or objectively observed signs typical of an acute inflammatory demyelinating event lasting at least 24 hours” [3], are caused by a localised auto-inflammatory response within the CNS which targets the myelin sheath and results in demyelination [1]. The process of demyelination is initiated by the breakdown of the blood-brain barrier, enabling auto-reactive lymphocytes to migrate into the CNS [5]. This is followed by amplification of cell-mediated immunity initiating an auto-immune response within the CNS [6]. As lymphocytes accumulate in the CNS, release of pro-inflammatory cytokines by T-cells recruit microglia which phagocytise the oligodendrocyte-myelin unit resulting in demyelination [7]. Demyelination interrupts the propagation of action potentials along affected axons, leading to conduction failure of neural pathways and the development of the signs and symptoms of the relapse [8]. The clinical presentation of MS relapses are heterogeneous and dependent upon the location of the demyelinating lesion within the CNS, but can include impaired motor or sensory function, visual disturbances, or cognitive dysfunction [1].

Relapses are an important prognostic factor in determining the severity and progression of MS, as a higher relapse rate earlier in the disease course is associated with greater accumulation of disability as the disease progresses [9-11]. Furthermore, the extent of recovery following relapses is also strongly associated with long-term disability outcomes, with incomplete recovery following relapses leading to higher levels of disability [12]. Therefore, the management of MS relapses is important to the preservation of long-term

physical function [13]. Current clinical management of acute relapses involves the prescription of corticosteroids to attenuate the immune response associated with the relapse; however, recovery of function following relapses is often incomplete with over one third of MS patients experiencing residual disabilities post-relapse [12, 13]. Accordingly, additional therapeutic strategies are required to promote relapse recovery and minimise the extent of residual impairment following relapses.

Rehabilitation interventions have been proposed as treatment strategies to facilitate relapse recovery [14]. Exercise therapy is one of the most commonly prescribed and extensively researched rehabilitation interventions in MS populations, and has been demonstrated to have a role in the maintenance of function and long-term symptom management [15]. In addition, exercise may have a role in reducing the number of relapses [16] and preventing the onset and progression of disability in people with MS [17]. Therefore, exercise may have the potential to facilitate relapse recovery and reduce long-term disability following relapses. However few studies have considered the effects of exercise on the acute recovery of function following relapses; consequently, the role of exercise in relapse management remains unclear. Accordingly, this perspectives article aims to: 1) outline the evidence relating to relapse recovery and prognosis; 2) identify and summarise the existing literature on the use of exercise interventions in relapse recovery in people with MS; 3) discuss future perspectives for research evaluating the effect of exercise during or after relapses.

Relapse rates, recovery and prognosis

Relapse rates

Relapses are a frequent and defining feature of MS. Despite the use of disease modifying therapies to reduce the number of relapses, annualised relapse rates in MS populations range from 0.27 to 1.66 relapses per year [18]; thus, people with RRMS may experience at least one relapse every three years. Although the clinical presentation of MS relapses is varied depending upon the location of active demyelination within the CNS, relapses typically involve altered motor, visual and sensory function [1]. In a sample of 34,858 relapses from the MSBase cohort, the majority of relapses (68%) were monosymptomatic indicating impairment in a single functional domain, and the most common relapse phenotypes included

sensory (50%) and pyramidal symptoms (42%), followed by brainstem (16%), visual (14%), and cerebellar symptoms (10%) [19]. Similarly in a study population of 1424 people with MS, Cossburn et al. [20] reported that relapses most commonly affected the pyramidal tracts (47%), and that upper and lower limb motor dysfunction were the most common clinical presentation during relapses. It has also been found that relapses involving bowel/bladder or pyramidal tract impairments are associated with the greatest increase in Expanded Disability Status Scale (EDSS) score [19], and have the greatest impact on activities of daily living [21]. Therefore, relapses involving motor function through pyramidal tract lesions are among the most prevalent and have the greatest impact on disability.

Recovery and prognosis

Recovery from MS relapses is often incomplete, as residual disability is recorded in one third to half of all relapses [22-26]. It is estimated that 42-49% of people with MS experience a residual disability defined by a ≥ 0.5 point increase in EDSS score following relapses, whereas 28-48% experience an increase in EDSS score of ≥ 1.0 points [22, 23, 25]. Residual disability following relapse is associated with poorer long-term disability outcomes, as incomplete recovery after the first relapse is predictive of shorter duration to reach EDSS milestones when compared to people with complete relapse recovery [10, 28]. In addition, incomplete relapse recovery predicts incomplete remission and higher EDSS scores during subsequent relapses [29, 30]. Therefore, promoting relapse recovery is key to improving prognosis and long-term disability outcomes.

Several factors influence the likelihood of relapse recovery and these factors may inform the design of therapeutic interventions involved in relapse management. For example, relapse phenotype is associated with recovery and prognosis, as relapses which impact on sphincter or pyramidal function have a higher probability of incomplete recovery and are associated with higher long-term EDSS scores after relapses – more so than relapses involving visual, sensory, and cerebellar function [19, 24, 31]. Accordingly, the recovery of motor and sphincteric function is an important factor influencing relapse prognosis and should be a key target of relapse management interventions. In addition to MS phenotype, modifiable factors such as longer relapse duration and higher relapse severity and non-modifiable factors such

as polysymptomatic relapses and older age at relapse onset are also associated with higher levels of residual disability post-relapse [19, 24, 26].

The largest improvements in function following relapse are recorded within the first 2-3 months [26, 32]. Although recovery may be recorded after 6 months post-relapse, this occurs in a small proportion of patients and the magnitude of recovery is significantly smaller compared to that recorded within the first 6 months [26, 32]. The rate of recovery following relapse has been demonstrated to influence relapse prognosis, For example, incomplete recovery at 30-60 days post-relapse was found to be associated with long-term residual disability [24, 25]. Conversely, Leone et al. [24] reported that 59% of relapses involving pyramidal tract function which reached peak symptom severity within 0-14 days had no residual disability following resolution of the relapse. Therefore, treatment strategies should promote early recovery of function post-relapse to improve long-term prognosis.

Exercise and relapse management

The aim of relapse management is to accelerate and enhance clinical recovery in order to improve prognosis and long-term disability outcomes [13]. Current clinical guidelines recommend the prescription of oral or intravenous corticosteroids in the management of acute relapses [33], as treatment with methylprednisolone reduces the severity and duration of relapses [34, 35]. In addition, treatment with corticosteroids decreases the number of gadolinium enhancing lesions indicating restoration of the blood brain barrier and reduction in inflammatory activity within the CNS [36, 37]. However, while corticosteroids attenuate the immune response that triggers MS relapses [38], they have limited effect on remyelination or recovery of neural pathways following the initial inflammatory damage. Therefore, a large proportion experience incomplete recovery and residual disability post-relapse.

Exercise, defined as “planned, structured and repetitive bodily movement with a purpose of improving or maintaining one or more components of physical fitness” [39], is a commonly prescribed treatment that is recommended for people with MS [40]. Exercise encompasses a broad spectrum of interventions including endurance, resistance, and task-specific training –

all of which have been demonstrated to be safe in people with MS [16]. The effects of exercise have been extensively evaluated in MS populations, and exercise has been shown to improve a range of outcomes including mobility [41], depression [42], fitness [43], and fatigue [44]. Therefore, considering that impaired motor function and increased mobility disability are common features of MS relapses, exercise may have the potential to augment routine pharmacological treatment to facilitate improved relapse recovery and reduce long-term disability. The potential effect of exercise on relapse recovery is outlined in the conceptual Figure 1.

Figure 1 near here

Current evidence: systematic literature search

As part of this perspectives article, a systematic literature search was conducted in order to identify the current evidence relating to the effects of exercise on relapse recovery. Searches were conducted on the following databases: Medline (via Ovid), CINAHL (via EBSCOhost), Web of Science Core Collections, and Physiotherapy Evidence Database (PEDro) from inception to September 2019. Keywords relating to ‘Multiple Sclerosis’ and ‘relapse’ were combined with ‘exercise’ or ‘rehabilitation’. Reference lists of the included studies and other systematic reviews in the field were also scanned to identify relevant articles. To be included, studies had to: 1) include adults with a definite diagnosis of RRMS who were experiencing or recovering from a relapse as confirmed by confirmed by medical assessment; 2) evaluate the effects of exercise on relapse recovery either as a standalone intervention or as part of a rehabilitation programme; 3) use a randomised controlled trial (RCT) or longitudinal observational study design. Due to the heterogeneous presentation of relapses, relapse recovery was not defined by improvement in a pre-specified outcome measure; instead recovery was determined as improvement in at least one clinical feature that is associated with relapse onset (e.g. disability, fatigue, depression) [12]. No specific time post-relapse was defined in the eligibility criteria in order to identify studies at various stages of recovery and elucidate whether the timing of exercise post-relapse influenced the intervention effect. Studies which evaluated the effect of exercise on relapse incidence alone were excluded; however, no other restrictions were placed on the outcome measurements used in studies. Only full-text articles published in English were included.

The search retrieved 1,163 potential related publications, of which 973 were exported to Rayyan systematic review software after duplicates were removed. One researcher (HA) initially screened titles and abstracts against the eligibility criteria, and 925 articles were excluded. The full texts of the 48 remaining articles were then screened by two researchers (HA, SR) for eligibility, and 42 articles were excluded mainly as they did not involve participants experiencing or recovering from a relapse. In addition two studies examining the impact of ‘multidisciplinary rehabilitation’ interventions in people with MS were excluded despite reporting distinct results for participants experiencing a relapse as it was not clear whether the rehabilitation intervention involved an exercise component [45, 46]. Accordingly, three studies, published over four articles, met the inclusion criteria (Table 1) [47-50].

Table 1 near here

Two of these studies were RCTs [48-50], and one study used a non-RCT design (controlled pre-post test design) which delivered a single exercise session [47]. The methodological quality of the included studies was assessed by two researchers (HA, SR) using either the PEDro scale for RCTs due to the multidisciplinary nature of the interventions that were delivered [51], or the Joanna Briggs Institute checklist for quasi-experimental studies [52]. In addition, each study was classified using the Spinal Cord Injury Rehabilitation Evidence (SCIRE) system to evaluate the overall quality of the study; this system has been used frequently in other reviews examining the effect of exercise in people with MS [53-55]. Both RCTs scored 5 on the Pedro scale and were regarded to be of level two evidence alongside the non-RCT (Table 2).

Table 2 near here

Current evidence: findings from studies investigating the effects of exercise on relapse recovery

Both RCTs evaluated the effect of exercise as part of a multidisciplinary rehabilitation intervention rather than as a standalone intervention [48-50]; however, exercise was reported to be the main component of both rehabilitation programmes. Craig et al. [50] highlighted that exercise was the most frequently prescribed rehabilitation intervention, and that participants spent the most time taking part in exercise therapy sessions compared with other components of rehabilitation such as occupational therapy and bladder management. The intervention prescribed in the study by Craig et al. [50] involved different types of exercise targeting muscle strength, balance, posture, gait and fitness; however, the paper did not provide enough detail regarding other exercise dose variables (i.e. intensity, frequency, and duration). Similarly Nedeljkovic et al. [48, 49] reported that the exercise programme comprised of aerobic, resistance and balance exercise and was performed for one hour, five times a week, for three weeks – although the specific mode and intensity of exercise were unclear. Importantly, neither study reported whether any adverse events occurred and, if so, if they were associated with the prescribed interventions; therefore, the safety of performing exercise during relapses is unknown.

In the study by Craig et al. [50], 41 participants with RRMS were recruited and randomly assigned to either an intervention group that received a personalised rehabilitation programme alongside steroid therapy or a control group that received only steroid therapy. The length and content of the rehabilitation programme varied between participants depending on their needs, and included treatments other than exercise such as health promotion advice or bladder management techniques if required. The mean number of days from relapse to commencing rehabilitation was 45.95. The authors found that disability and physical function improved one month post-intervention for those in the intervention group (as measured by changes on Amended Motor Club Assessment (AMCA), Guy's Neurological Disability Scale (GNDS), and Barthel Index (BI)). Furthermore, this increase in function was sustained at three months post-intervention and was significantly greater in the group that received rehabilitation compared to the group that received steroid treatment alone. However, while the intervention group showed significant improvement in the majority of Short-form

36 Item Health Survey (SF-36) subscales, this change was not significantly greater than the control group.

In the other RCT by Nedeljkovic et al. [48, 49], 49 participants with MS who were currently receiving steroid therapy for a relapse were recruited. Similar to the study by Craig et al. [50], participants were randomly assigned to receive a three-week multidisciplinary rehabilitation intervention alongside steroid therapy or steroid therapy alone. Outcome measures relating to disability (EDSS), functioning (Functional Independence Measure), depression (Beck Depression Inventory), fatigue (Fatigue Severity Scale), quality of life (MS Quality of Life-54), and self-efficacy (MS Self-Efficacy Scale) were measured one and three months post-intervention. The results of this study showed that all the outcomes improved significantly in the rehabilitation group one month after the intervention, and the improvements were maintained at three months. The effect sizes were also higher in the intervention group as compared to the control group, though the differences between the groups were not statistically significant. However, the study did not report sample calculations and may have been underpowered to detect such differences. In addition, the authors did not report the time between relapse onset and treatment commencement in the rehabilitation or control group.

The final study was a non-RCT exploring the acute effects of a single session of aerobic, interval exercise on cytokines and adipokines during the relapse phase of MS [47]. In this study, 15 participants with MS in the relapse phase were compared to 15 participants in remitting (non-relapse) phase, 5 participants in a relapsing control group (who did not take part in the exercise intervention), and 20 healthy volunteers. All participants, except the 5 relapsing controls, performed a single session of aerobic exercise consisting of four sets of five-minute intervals at 60-70% maximal heart rate intensity using an upper and lower limb cycle ergometer. The results of this study showed that, in contrast to participants in the remitting group and healthy controls, pro-inflammatory cytokine TNF- α levels significantly decreased following exercise in the relapse group, whereas levels of the pro-inflammatory cytokine, IL-6 significantly increased; however, these changes were not maintained 6-hours post-exercise. Levels of leptin, another pro-inflammatory cytokine, also decreased significantly in all groups except the relapsing control. Based on these results, the authors

concluded that a single dose of aerobic exercise does not induce an inflammatory cytokine response in people with MS in relapsing phase.

Mechanisms contributing to recovery of function

The recovery of function following relapse involves resolution of the inflammatory response to limit the extent of demyelination and axonal damage, which is often followed by remyelination and neural re-organisation [56]. Remyelination is initiated by the migration of oligodendrocyte-precursor cells (OPCs) to the sclerotic lesion followed by the differentiation of OPCs into myelin producing oligodendrocyte cells to repair the lesion and restore nerve conduction [57]. In addition, re-organisation of cortical networks may contribute to the recovery of function by compensating for irreversible tissue damage sustained during relapses [58]. Although this article has identified that the role of exercise in relapse recovery remains unclear, evidence suggests that exercise may have a short term anti-inflammatory effect and, in the longer term, modify the structure and function of the CNS in people with MS [59]. Therefore, several physiological mechanisms may augment natural recovery of function and support the use of exercise post-relapse (Figure 2).

Figure 2 near here

For instance, exercise may induce an anti-inflammatory effect to alter the immune response associated with MS relapses [60]; thus, exercise may augment corticosteroid treatment and reduce the duration and severity of relapses through minimising the extent of demyelination and axonal damage. Several RCTs have investigated the levels of pro-inflammatory cytokines following exercise in MS populations, with some studies reporting a reduction in pro-inflammatory cytokines IL-6 and TNF- α following multiple bouts of aerobic and resistance training [61-63]. In addition, Majdinasab et al. demonstrated a transient reduction in TNF- α levels immediately following a single bout of exercise in people currently undergoing a relapse [47]. However, results remain equivocal due to inconsistent effect of exercise on cytokine levels between studies [64]. Furthermore, no study has yet investigated the long-term effects of exercise on inflammatory biomarkers during an active MS relapse, and it is unclear whether changes in cytokine levels following exercise have any impact on functional

outcomes. Therefore, further studies are required to explore the possible anti-inflammatory effect of exercise in relapse recovery.

Exercise may also have a long-term role in the remyelination of axons to promote the recovery of neural function following MS relapses. A key phase of remyelination is the differentiation of OPCs into remyelinating oligodendrocytes, and several mechanisms can either inhibit or promote this process – one of which being axonal electrical activity [57, 65]. Conduction of action potentials along axons promotes oligodendrocyte development and myelination [66, 67], and electrical stimulation of demyelinated axons in animal models has resulted in increased myelination and recovery of neural function [68]. Therefore, the activation of demyelinated neural pathways – particularly those of the pyramidal tract involved in upper and lower limb movement – through exercise could have a potential role in the recovery of function following relapse. As identified through the literature search, no studies have yet investigated the effect of active exercise on remyelination following acute demyelination; however, an RCT investigating the effects of trans-orbital electrical stimulation on myelin repair in MS patients with optic neuritis is currently being conducted (NCT04042363). Accordingly, future studies might investigate whether activation of demyelinated neural pathways through active exercise has a similar impact on remyelination following relapse compared to extrinsic electrical stimulation of the CNS.

Exercise may also contribute to the long-term recovery of function following relapses by promoting neuroplasticity after resolution of the initial demyelinating event. Neuroplasticity refers to the ability of the CNS to structurally and functionally adapt in response to damage (i.e. MS relapses) [69], and can therefore contribute to the recovery of CNS function in people with MS after a relapse by facilitating re-organisation of neural networks [70, 71]. As plasticity of the CNS is task-dependent [72], any changes in the CNS that occur following exercise are more likely to occur in neural pathways involved in the planning and execution of movement. A recently published review of studies investigating neuroplasticity in people with MS has outlined the effect of exercise on neuroplastic changes to the CNS in people with MS [72]. For example, studies have shown that the neurotrophin brain-derived neurotrophic-factor (BDNF) - which promotes growth and differentiation of new neurons and synapses – increases in response to exercise in people with MS [73-75]; although, it

remains unclear whether the increase in neurotrophic factors recorded in exercise studies leads to structural CNS changes [76]. Another RCT has demonstrated that exercise may promote structural CNS changes in MS, as increased cortical thickness was recorded across four regions (anterior cingulate gyrus, temporal pole, orbital sulcus and inferior temporal sulcus) following 24 weeks of resistance training [77]. In addition, studies investigating functional CNS changes using f-MRI have demonstrated increased connectivity of frontal lobe regions and primary sensori-motor cortex following 12 weeks of resistance and endurance based exercise [78, 79]. However, while some evidence supports the role of exercise in promoting neuroplasticity in MS, overall findings are inconsistent and there is limited knowledge of the length of time or volume of exercise required to induce these potential neuroplastic effects particularly in people following acute relapses [72]. In addition, it is not yet clear whether these potential changes in CNS structure and function result in clinically meaningful improvements in disability or physical function following relapse.

Finally, people with MS have reduced levels of physical activity in comparison to healthy controls [80]. Moreover, physical function is reduced in people with MS [81, 82], and lower levels of physical activity are shown to be negatively associated with physical function independent of disability [83]. Therefore, physical inactivity may contribute to a decline in physical function independent of MS pathology, and this loss of function secondary to inactivity may be reversed through exercise to compensate for the loss of function following relapses. Indeed RCTs have demonstrated increased muscle cross-sectional area and proportion of type II fibres following resistance training indicating that peripheral mechanisms not directly associated with MS pathology contribute to changes in muscle function with exercise [84, 85]. In addition, there is consistent evidence that exercise improves walking speed and endurance in patients with mild to moderate MS [86]. Consequently, exercise may facilitate recovery post-relapse by reversing the negative effects of physical inactivity and deconditioning to compensate for the loss of neural function.

Future perspectives

The evidence presented in this article highlights the potential role of exercise in relapse management through promoting relapse recovery and reducing the risk of long-term disability post-relapse. Currently, evidence from two underpowered studies suggests that

delivering exercise as a part of a short-term multidisciplinary rehabilitation programme, in addition to steroid therapy, improves functional outcomes and quality of life following MS relapses [48-50]. Additionally, exercise in conjunction with steroid therapy may be more beneficial than steroid therapy alone in promoting relapse recovery [50]. However, despite the potential beneficial effects of exercise, there is a lack of studies that have investigated the role of exercise in the acute recovery of function following an MS relapse, as many exercise studies exclude participants who have recently been diagnosed with a relapse. Considering that up to 50% of people may experience residual disabilities following relapse [12], there is a need for further research to explore the role of therapeutic strategies – such as exercise – in relapse recovery.

As discussed, the clinical presentations of relapses are heterogeneous and dependent on the location of the demyelinating lesion within the CNS [1]. Due to the influence of exercise on physical function, exercise may have the greatest impact on relapses involving the pyramidal tracts by promoting the recovery of upper and/or lower limb function – this is important considering that relapses involving the pyramidal tracts have been shown to be one of the most common types of relapse and have a high risk of incomplete recovery [12, 13]. However, no study has yet reported the effects of exercise on relapse recovery when stratified by relapse phenotype. Accordingly, future studies should clearly outline the specific relapse phenotype within the inclusion criteria in order to recruit a homogeneous population that will likely respond to treatment. Furthermore, studies should tailor the exercise prescription to the specific impairments associated with the target relapse phenotype.

Given the variability in MS relapses, future studies should also consider using a comprehensive assessment to measure recovery across different aspects of function. While the primary outcome measures used by the studies primarily assessed changes in disability and physical function (e.g. EDSS, BI, FIM, GNDS) [48-50], it is important to consider other secondary outcomes such as fatigue, depression, and quality of life that may also be affected following MS relapse [87]. In addition, future studies should include outcome measures related to primary disease activity in order to determine the mechanisms accounting for the potential beneficial impact of exercise on relapse recovery. For example, diffusion tensor imaging or positron emission tomography can be used to quantify the extent of remyelination

following relapse [88]. Motor evoked potentials can also be used to determine the extent of remyelination by assessing the conduction of affected neural pathways [89]. Additionally, functional neuroimaging techniques such as fMRI or fNIRS can quantify neural activity and provide data to determine whether neural re-organisation is contributing to the recovery of function independent of remyelination [90].

As evidence suggests that relapse recovery is time dependent (with the largest increase in function typically occurring within 6-months of relapse onset) [12, 13], it is important to establish the optimal timing of exercise post-relapse in order to maximise recovery of function within this time-frame. Of the studies identified in this article, only one reported the mean 45.95 days number of days from relapse onset to treatment commencement, with this study reporting improvements in disability and physical function post-intervention [50]. However, considering that the greatest recovery of function is recorded 2-3 months post-relapse [26], it is unclear what effect earlier intervention would have on recovery. For example, people who experience a similar acute loss of neurological function as a result of stroke are recommended to commence rehabilitation within days of the stroke in order to maximise the long-term recovery of function [91]. In addition, it is unclear whether the time delay between corticosteroid treatment and exercise prescription influences the effects of treatment. Only two RCTs have evaluated the effects of exercise and corticosteroid treatment compared with corticosteroid treatment alone, and both studies prescribed exercise and corticosteroids concurrently [48-50]. Therefore, future studies should explore the safety and timing of exercise prescription with regards to relapse onset and corticosteroid treatment.

Future studies should also determine the optimum type and dose of exercise required to elicit beneficial effects on relapse recovery. Recommendations regarding exercise prescription cannot be inferred from the evidence identified in this article due to the limited number of studies and details of the specific type, frequency, duration, and intensity of exercise were not fully reported. Furthermore, most studies delivered exercise as a component of a multidisciplinary rehabilitation programme; consequently, it was not possible to identify the specific effect of exercise when delivered as part of rehabilitation.

Lastly, while exercise has been demonstrated to be safe and not associated with increased risk of relapse in people with MS [16], no studies have yet reported the safety of exercise specifically in people experiencing an acute relapse. Although the studies did not report any long-term worsening of function in the exercise intervention groups, the safety of exercise – particularly during the acute inflammatory phase of relapses – remains unclear as adverse events were not reported. Evidence suggests that people with MS may experience a transient increase in symptoms following exercise attributed to a rise in body temperature and slowed axonal conduction, and this increase in symptoms following exercise may be further exacerbated during relapses due to the already impaired conduction of demyelinated axons [92]. Accordingly, future studies should establish the safety of exercise as a treatment in relapse recovery and determine whether exercise acutely exacerbates the signs and symptoms of relapses.

Conclusions

In summary, there is a need for therapeutic strategies to promote recovery following MS relapses in order to reduce the extent of residual disabilities and promote long-term function. Exercise may have the potential to enhance relapse recovery, as evidence from a small number of studies suggests that prescribing exercise alongside standard steroid therapy has a beneficial effect on both disability and quality of life following relapse. However, due to the limited available evidence, further studies are required explore the effects of exercise therapy on relapse recovery in order to inform relapse management strategies and improve the care of people with MS. In addition, future studies should also determine the mechanisms through which exercise influences relapse recovery to support the role of exercise in relapse management.

Practice points

- Relapses are a frequent and defining feature of MS characterised by transient increase in neurological disability.
- Between one third and half of people with MS who are diagnosed with a relapse will experience incomplete recovery and residual disability, highlighting the need for treatments to promote relapse recovery.

- Evidence from a small number of underpowered studies indicates that exercise improves physical function and disability following relapse, suggesting that exercise may have a role in relapse recovery.
- However, further investigation is needed to determine the effectiveness of exercise in the management of acute MS relapses.
- Future studies should also investigate the mechanisms underlying the effect of exercise in relapse recovery (e.g. inflammation, remyelination, and/or neuroplasticity).

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Figure 1 Conceptual diagram highlighting the potential beneficial effect of exercise on relapse recovery through reducing relapse severity and duration, and decreasing the level of residual disability.

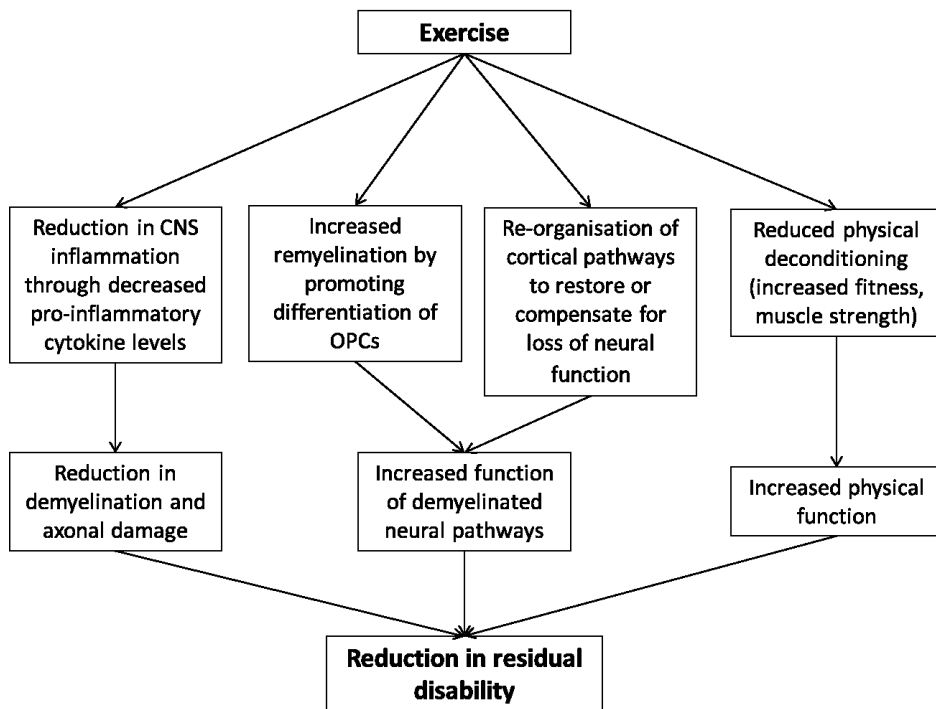


Figure 2 Possible mechanisms which may account for the positive effect of exercise on relapse recovery

Table 1 Evidence table

Author, date, design	Sample details	Intervention	Control	Main outcomes	Main findings
Majdinasab et al. 2018 [47]; Non-RCT Iran JBI checklist = 8	N= 50 (15 relapsing; 15 remitting (non-relapsing); 15 healthy controls; 5 relapsing controls) Sex (m/f), n: 0/50 EDSS, mean ± SD = 2.11±0.76 MS duration (years), mean ± SD = 3±1 Dropout: NA	Single bout of aerobic exercise: 4 sets of five minutes of upper/lower limb cycling at 60-70% maximum heart rate interspersed with 2 minutes rest	NA	TNF-a, IL-6, IL-10, adiponectin, leptin Before exercise ; immediately after, 1 hour, and 6 hours post-exercise	<u>Relapsing group</u> TNF-a: ↓ immediately after exercise, ↑ 1 hour post-exercise, no change 6 hours post-exercise IL-6: ↑ immediately after exercise, no change at 1 or 6 hours post-exercise IL-10: ↓ immediately after exercise, no change at 1 or 6 hours post-exercise Adiponectin: no change immediately after, 1 hour or 6 hours post-exercise Leptin: ↓ immediately after, 1 hour and 6 hours post-exercise <u>Between groups</u> Leptin: ↓ in relapsing group 1 hour post-exercise
Nedeljkovic et al. 2016 [48, 49]; RCT Serbia PEDro = 5	N = 49 Sex (m/f), n:13/26 EDSS, mean ± SD: I = 4.4±1.3; C = 4.2±0.7 MS duration (months) median: I = 96; C = 60 Dropout, n (%) = 12 (25%)	3-week multi-disciplinary rehabilitation programme and intravenous steroid therapy Rehabilitation included: physiotherapy, occupational therapy, psychology, social services Exercise component: 1 hour, 5x per week Included: aerobic exercise, stretching, strengthening, balance and gait training	Usual care: IVMP	EDSS, BDI, FIM motor/cognitive, FSS, MSQoL-54 0, 1, 3 months	<u>Within groups</u> EDSS: I, ↓ at month 1 and 3 months; C, ↓ at month 1 and 3 months FIM motor: I, ↑ at month 1 and 3 months; C, ↑ at month 1 and 3 months FIM cognitive: I, no change; C, no change BDI: I, ↓ at month 1 and 3 months; C, no change FSS: I, no change; C, no change MSQoL-54: I, ↑ only at 3 months; C, no change <u>Between groups at 1 and 3 months</u> EDSS: no change

Author, date, design	Sample details	Intervention	Control	Main outcomes	Main findings
					FIM motor: no change FIM cognitive: no change BDI: no change FSS: no change
Craig et al. 2003 [50]; RCT UK PEDro = 5	N = 40 Sex (m/f), n: 13/27 EDSS, mean = 5.25 MS duration (years) mean = 6.4 Dropout, n (%) = 1 (2%)	Personalised multi-disciplinary rehabilitation programme and intravenous steroid therapy Rehabilitation included: physiotherapy, occupational therapy, MS nurse specialist, orthoptist Included exercise component for balance, stability, posture, and fitness	Usual care: IVMP and referral to out-patients physiotherapy occupational therapy as appropriate	GNDS, AMCA, BI, SF-36 0, 1, 3 months	<u>Between groups at 3 months</u> GNDS: ↓ in favour the intervention AMCA: ↑ in favour the intervention BI: ↑ in favour the intervention SF-36: no change
Abbreviations: AMCA, Amended Motor Club Assessment; BDI, Beck's Depression Inventory; BI, Barthel Index; C, control group EDSS, Expanded Disability Status Scale; FIM, Functional Independence Measure; FSS, Fatigue Severity Scale; GNDS, Guy's Neurological Disability Scale; I, intervention group; IVMP, intravenous methylprednisolone; JBI, Joanna Briggs Institute; MS, Multiple Sclerosis; MSQoL-54, Multiple Sclerosis Quality of Life-54; RCT, randomised controlled trial; SF-36, Short Form 36 Health Survey ↑ significant increase (p<0.05); ↓ significant decrease (p<0.05)					

Table 2 Level of evidence of each article was identified using the Spinal Cord Injury Rehabilitation Evidence (SCIRE) system

Level of evidence	Number of studies	Criteria
Level one	0	<ul style="list-style-type: none"> ▪ RCT: PEDro Score > 6. Includes cross over design with randomized experimental conditions and within-subjects comparison
Level two	3: Majdinasab et al. [47]; Nedeljkovic et al. [48, 49]; Craig et al. [50]	<ul style="list-style-type: none"> ▪ RCT: PEDro Score ≤ 6 ▪ Prospective controlled trial: non-randomized. ▪ Cohort: longitudinal study using two (minimally) similar groups with one group being exposed to a condition
Level three	0	<ul style="list-style-type: none"> ▪ Case-control studies: retrospective study comparing controls conditions
Level four	0	<ul style="list-style-type: none"> ▪ Pre-post: trial with a baseline measure, intervention and a post-test using a single group of subjects ▪ Post-test: post-test with 2 or more groups using a single group (intervention followed by a post-test with no retest or baseline assessment)
Level five	0	<ul style="list-style-type: none"> ▪ Observational: study using cross sectional analysis to interpret relations