Effectiveness of fatigue management interventions in reducing severity and impact of fatigue in people with progressive multiple sclerosis: a systematic review

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Title: Effectiveness of fatigue management interventions in reducing the severity and impact of fatigue in people with progressive Multiple Sclerosis: A systematic review

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Practice Points

- Exercise, behavioural interventions, and rehabilitation demonstrate potential to manage fatigue in progressive MS populations.
- Evidence in this review suggests that aerobic exercise can improve fatigue in people with progressive MS; however, the optimal dose was not determined.
- Further evidence is required to determine the effectiveness of these interventions in studies that use fatigue as the primary outcome and recruit people who are experiencing high levels of fatigue.

Abstract

Background: Rehabilitation interventions are recommended to manage Multiple Sclerosis (MS) related fatigue. However, existing research has largely been generalised to those with relapsing-remitting MS, making it difficult to determine the effectiveness of these interventions amongst people with progressive MS. Therefore, this study aimed to systematically review the evidence related to the effectiveness of fatigue management interventions in reducing the severity and/or impact of fatigue in people with progressive MS.

Methods: Six electronic databases (CINAHL, Cochrane Library, MEDLINE, PEDro, ProQuest, and Web of Science Core Collections) were searched for relevant articles up until November 2017. Randomised controlled trials and quasi-experimental studies that examined the effects of exercise, behavioural interventions, and rehabilitation on fatigue in people with progressive MS using self-reported fatigue outcome measures were included in this review.

Results: Eight exercise, two rehabilitation and two behavioural interventions were investigated by the 13 articles included in this review. Heterogeneous effects were reported between studies with only two exercise, one behavioural, and two rehabilitation interventions recording significant improvements in fatigue severity or impact post-intervention. However, most studies were underpowered, only two studies used fatigue as the primary outcome, and only one specifically recruited participants with pre-defined levels of fatigue.

Conclusion: Evidence from this review is inconclusive regarding the effectiveness of non-pharmacological interventions in reducing the impact and severity of fatigue in progressive MS populations. Adequately powered randomised controlled trials are required to evaluate fatigue management interventions in people with progressive MS experiencing high levels of fatigue and using fatigue as the primary outcome.

Key Words: Progressive Multiple Sclerosis; Fatigue; Review

Abbreviations: CNS, central nervous system; EDSS, Expanded Disability Status Scale; FIS, Fatigue Impact Scale; FSMC, Fatigue Scale for Motor and Cognitive functions; FSS, Fatigue Severity Scale; MCID, minimal clinically important difference; MFIS, Modified Fatigue Impact Scale; MS, Multiple Sclerosis; MS QoL, Multiple Sclerosis Quality of Life Scale; RCT, randomised controlled trial; RRMS, relapsing remitting multiple sclerosis; SF-36, Medical Outcomes Study 36-Item Short Form Survey

Introduction

Fatigue is a common symptom of Multiple Sclerosis (MS) reported in over 70% of the population.[1-3] MS-related fatigue is often perceived as the most debilitating symptom, which significantly impacts upon activities of daily living, social participation and quality of life, [4-5] and is associated with changes to employment.[6] Fatigue is a highly complex and multifactorial symptom that may be defined as "a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities".[7] Subjectively, this may be described as exhaustion, a lack of energy, or overwhelming tiredness which is pervasive and can occur at rest.[8]

Although fatigue can be experienced throughout the course of MS, it has a higher prevalence amongst people with progressive forms of the disease.[1, 9-10] Primary pathological disease processes involving structural and functional central nervous system (CNS) changes, and secondary factors independent of MS pathology are associated with fatigue pathogenesis.[11-13] However, as the pathophysiological mechanisms underlying fatigue in MS are not well understood,[11-13] current treatment strategies are focused on symptom management through non-pharmacological interventions.[14]

Rehabilitation interventions are recommended to manage MS-related fatigue,[14] and several studies have demonstrated that interventions such as exercise, energy conservation management, and cognitive behavioural therapy have moderate, positive short-term effects on fatigue outcomes.[15-18] However, results have largely been generalised to those with relapsing remitting MS (RRMS), with few studies making a distinction between RRMS and progressive MS populations. Therefore, in line with The International Progressive MS Alliance research priorities,[19] there is a need to determine the effectiveness of fatigue management interventions in people with progressive MS due to the high prevalence and impact of fatigue amongst this population. Hence, the aim of this work was to systematically

review the evidence related to the effectiveness of fatigue management interventions in reducing the severity and/or impact of fatigue in people with progressive MS. To achieve this aim the following objectives were met: (i) to summarise the details of fatigue management interventions for people with progressive MS; (ii) to critically evaluate the effectiveness of fatigue management interventions in reducing the severity and/or impact of fatigue in people with progressive MS; (iii) to identify limitations of the current evidence to inform the direction of future study.

Methods

Systematic review protocol and registration

A review protocol was developed and registered with the PROSPERO database in December 2017 (PROSPERO ID: CRD42017082203).

Search Strategy

Searches of the following databases were conducted from inception to November 2017: CINAHL (via EBSCOhost), Cochrane Library, MEDLINE (via Ovid), PEDro, ProQuest (Health & Medical Collection, Nursing & Allied Health Database, PsycINFO), and Web of Science Core Collections. Search strategies included a combination of keywords and subject headings related to multiple sclerosis, exercise, behavioural therapy, rehabilitation and fatigue, and were adapted for use in each different database (Supplementary table 1). Reference lists of relevant review articles were also hand searched to identify any additional articles. After each database was searched, results were exported to Covidence systematic review software (2017, Veritas Health Innovation, Melbourne, Australia) and duplicates were

removed prior to screening. The primary reviewer (SR) initially screened all articles by title and then by abstract against the inclusion and exclusion criteria. Subsequently, two reviewers (SR and LP) independently screened full texts of the remaining articles for eligibility. Disagreements were resolved through consensus in consultation with a third reviewer (FM) if required.

Inclusion and exclusion criteria

To be included in this review studies had to have: (i) recruited adults with a definite diagnosis of MS and a progressive form of the disease (secondary or primary progressive); (ii) evaluated non-pharmacological interventions in accordance with the definitions provided in Table 1; (iii) used a self -reported measure of fatigue impact or severity as either a primary or secondary outcome (including sub-scales of questionnaires); (iv) used a randomised controlled trial or quasi-experimental design; (v) been published in English. Studies that included a combination of types of MS were only included when specific results for those with progressive MS could be identified. Non-human studies, pharmacological studies, and conference proceedings and abstracts were excluded from this review.

Table 1 Near here

Data extraction

Data extraction was completed independently by one reviewer (SR) using a standardised data extraction form. The data extraction form was developed based on the CONSORT and TIDieR guidelines.[22-23]

Quality assessment

Quality of evidence was assessed using the Downs and Black checklist – a 32- point scale developed for quality assessment of both randomised controlled trials (RCTs) and non-RCTs.[24-25] An initial quality assessment was conducted where each of the three reviewers independently scored an article to ensure consistency in assessment between reviewers. Following this quality assessment, question 27 of the checklist was modified such that an article was assigned 1 point for including a sample size calculation and zero if the article did not, resulting in a total possible score of 28. This modification was implemented in keeping with two systematic reviews of exercise interventions in MS.[26-27] Quality assessment was completed independently by two reviewers. When discrepancy arose, agreement was reached through consensus in consultation with a third reviewer.

Data synthesis

Due to the inclusion of quasi-experimental studies and heterogeneity in study design, it was not feasible to conduct a meta-analysis; therefore, results were generated through narrative synthesis. Preliminary synthesis involved a descriptive summary of key information extracted from all articles. Individual study estimates of treatment effects were presented under each mode of intervention and explored within and between studies considering moderator variables to explain differences in results. Where available, results for the relevant fatigue outcome measures were compared to minimal clinically important difference (MCID).

Results

Results of the search

Through searching the selected electronic databases, 560 articles were identified, and an additional 4 articles were added from references lists of relevant studies (Figure 1). After removing duplicates, 463 articles remained for title and abstract screening of which 308 were excluded by title and 97 by abstract. The remaining 58 articles were included for full-text screening. After screening full-texts, 45 articles were excluded as the results of those with progressive MS were not identifiable in 41 studies (either MS type was not reported, or results for those with progressive MS were not presented separately), 3 studies did not include participants with progressive MS, and 1 study did not include a fatigue outcome measure. Two articles described the same study but reported different outcome measures;[29-30] therefore, 13 articles from 12 studies were included (Table 2).

Figure 1 Near here

Table 2 Near here

Study design

From the included articles, six were RCTs,[31-32, 36-37, 39, 41] and seven were quasi-experimental studies (pre/post-test design (n=4),[34-35, 38, 40] non-randomised controlled trial design (n=2),[29-30] and non-randomised cross-over trial design (n=1)[33]). All but one RCT included two trial arms (control and intervention) – the study by Briken et al involved three intervention conditions in addition to the control group.[36] The length of intervention period

171 ranged from 4-52 weeks; however, most studies delivered interventions for ≤ 12 weeks
172 (n=11), with one rehabilitation intervention lasting 52 weeks.[29-30] Four articles reported
173 follow-up outcome assessments which were conducted at four,[32, 39] six,[41] or eight weeks post-
174 intervention.[33]

175

176 ***Quality assessment***

177 Total quality assessment scores ranged from 15-25 (Table 3), and no study was
178 excluded based on the results of the quality assessment. Only seven articles reported adverse
179 events,[31, 33-34, 37-38, 40-41] six adjusted for confounding variables and loss to follow-up,[29-30, 35-37,
180 [39, 41] six reported compliance with interventions,[35-40] and one included a power calculation to
181 determine sample size.[41] Due to the nature of the interventions, none of the studies blinded
182 participants to treatment allocation.

183

184 **Table 3 Near here**

185

186 ***Sample characteristics***

187 Study sample sizes ranged from 6-111 participants, and overall 474 participants were
188 included, 325 of which were allocated to receive an intervention, and 149 to a control
189 condition. Expanded Disability Status Scale (EDSS) scores of study samples ranged from
190 1.5-9, and 12 articles reported participants with EDSS > 6.[29-35, 37-41] Only one study used a
191 pre-defined level for moderate-severe fatigue (Fatigue Severity Scale (FSS) ≥4) as an
192 inclusion criterion for participant recruitment.[33]

193

Outcome measures

There were seven self-reported outcome measures used across the included articles to measure the impact and/or severity of fatigue – the most commonly used were the FSS (n=4),[32, 38-39, 41] and the Modified Fatigue Impact Scale (MFIS) (n=4).[34-36, 40] In addition, studies also used the Fatigue Impact Scale (FIS),[31, 33] MS-Related Symptom Checklist (fatigue subscale),[30] Fatigue Scale for Motor and Cognitive functions (FSMC),[37] Medical Outcomes Study 36-Item Short Form Survey (SF-36) vitality subscale,[29, 41] and MS Quality of Life 54 (MS QoL-54) energy subscale.[35] Of the 13 included articles, 2 stated that fatigue was the primary outcome of investigation,[30, 33] and in the remaining 11 fatigue was a secondary outcome where the primary outcomes were quality of life,[29, 31, 34] aerobic fitness,[36-37] global measures of physical function,[35] distress,[39] temporal measures of gait,[41] lung function,[32] exercise safety,[40] or sitting balance.[38]

Interventions

In accordance with the definitions of interventions for this review, eight exercise,[32, 34-38, 40-41] two rehabilitation,[29-31] and two behavioural interventions[33, 39] were described by the 13 included articles.

Of the eight exercise interventions, four were classified as aerobic exercise,[35-37, 40] one as combined exercise,[34] one as task-orientated exercise,[41] and two as other exercise.[32, 38] Various modes of exercise were used across the four trials of aerobic exercise: one used arm ergometry;[37] two used body-weight supported treadmill training;[35, 40] one used recumbent stepping;[40] and Briken et al used arm ergometry, cycling, and rowing.[36] Most interventions were performed at moderate intensity, and were progressed through increasing the duration of training; however, the study by Skjerbaek et al implemented a high intensity interval training

protocol involving three minute intervals working at a heart rate corresponding to 65-75% VO_{2peak}.[37] In addition to aerobic exercise, the combined exercise intervention described by Roehrs and Karst incorporated elements of upper and lower limb resistance exercises, and was delivered in a pool by physical therapy students.[34]

The study by Straudi et al was characterised as task-orientated exercise, as the intervention aimed to improve temporal gait parameters by using a robotic assisted gait orthosis in conjunction with body-weight supported treadmill training.[41] The two other exercise interventions involved seated Pilates,[38] and inspiratory muscle training.[32] The seated Pilates intervention was delivered by a qualified Pilates instructor, and incorporated elements of core and upper limb strengthening with a daily home exercise program.[38] Inspiratory muscle training followed a self-management program of inspiratory muscle resistance exercises which consisted of three sets of 10 loaded inspirations using a threshold inspiratory muscle training device.[32]

The two behavioural intervention studies involved mindfulness,[39] and energy conservation management.[33] The mindfulness intervention was delivered, via a group-based video conference, by a health psychologist. The content involved components of the Mindfulness-based Stress Reduction programme with additional cognitive therapy exercises and 'homework' tasks. The energy conservation intervention was delivered face-to-face in a group by occupational therapists, and involved education regarding optimum energy use to minimise the impact of fatigue through re-structuring or altering activities of daily living following Packer's energy conservation course.

Rehabilitation interventions were delivered by a multidisciplinary team consisting of physiotherapists, occupational therapists, and support services in an outpatient setting, and treatments were individualised to each participant.[29-31] In the study by Di Fabio et al.,

participants received five hours of rehabilitation one day per week which consisted of physiotherapy (gait, transfer and balance training, endurance training, range of movement exercises), occupational therapy to maintain upper limb use during activities of daily living and enhance communication skills, and support services (support groups, social work, recreation activities, falls prevention programmes, seating clinics, and nutritional information).[29-30] The intervention delivered by Patti et al. consisted of one hour of physiotherapy treatment five days per week, 30 minutes of occupational therapy and speech therapy twice per week, and support sessions on symptom self-management and goal setting.[31] In addition to outpatient rehabilitation, Patti et al. included the prescription of a daily home-exercise programme.[31]

Effectiveness of exercise interventions

Of the studies investigating aerobic exercise interventions, Skjerbaek et al. reported that, although FSMC scores improved in the exercise group post-intervention (mean difference = -2.2 ± 8.7), there was no significant difference between the exercise and control groups over time.[37] Similarly, Pilutti et al. and Pilutti et al. reported non-significant improvements in MFIS scores post-intervention (effect size -0.93, and -1.04 respectively).[35, 40] However, Pilutti et al. found statistically significant changes in MSQoL-54 energy subscale post-intervention (p=0.01).[35] The studies by Pilutti et al., Skjerbaek et al., and Pilutti et al. had small samples (n=6-12) and included participants with severe disability (EDSS: 5.5-8).[35, 37, 40] In contrast, Briken et al. investigated three aerobic exercise interventions in a larger population (n=47) of participants with moderate disability (EDSS: 4-6), and reported that exercise significantly improved fatigue from baseline (p=0.019); however, only arm

ergometry demonstrated significant improvements in comparison to the control group ($p=0.013$).[36]

Of the remaining exercise interventions, no significant changes were noted in fatigue following combined exercise,[34] pilates,[38] or inspiratory muscle training.[32] In addition, there were no significant improvements in FSS post-intervention or at six week follow-up for those receiving task-orientated exercise interventions; however, SF-36 vitality subscale scores improved post-intervention for the group receiving robot-assisted gait training ($p<0.01$), but returned to baseline at six week follow-up.[41]

Effectiveness of behavioural interventions

In a non-randomised cross-over trial, Vanage et al. investigated the use of an energy conservation course and reported a significant improvement in FIS total and subscale scores post-intervention (effect size 0.89, $p<0.01$) which was maintained at eight week follow-up.[33] However, Bogosian et al. reported no significant difference in fatigue scores post-intervention and at six week follow-up between the group receiving a mindfulness intervention and a wait-list control.[39] In addition to the mode of intervention, differences in results between studies may be explained by study design as Vanage et al. recruited participants with clinically significant level of fatigue and used fatigue as a primary outcome,[33] whereas Bogoian et al did neither.[39]

Effectiveness of rehabilitation interventions

Di Fabio et al. reported that fatigue scores (MS-Related Symptom Checklist) for those receiving 52-weeks multidisciplinary rehabilitation were significantly different post-

intervention in comparison to wait-list controls (effect sizes 0.46 and -0.2 for the intervention and control group respectively).[30] From the same study, Di Fabio et al. also reported that SF-36 vitality subscales scores improved post-intervention for the group receiving rehabilitation (effect size 0.3), and that fatigue in the wait-list control group increased in severity (effect size -0.39).[29] In Patti et al., those receiving 12-weeks outpatient rehabilitation demonstrated a statistically significant improvement in post-intervention fatigue scores ($p<0.001$).[31]

Clinical significance of changes in fatigue

Of the outcome measures reported, MCID has only been determined for the FIS within MS populations. When anchored to measures of health-related quality of life, FIS demonstrates a MCID of 10-20 points.[42] Of the two included studies that used the FIS, both reported statistically significant improvements in fatigue post-intervention (mean difference of 18.8 ± 14.3 ($p<0.001$)[31] and mean difference of 15.7 ± 25 ($p<0.01$)[33]). The mean change in FIS scores recorded by both studies is within the range of MCID reported for the FIS; however, both studies reported large standard deviations suggesting that these interventions may be clinically significant for only some participants.

Discussion

Overall, the evidence presented in this review is inconclusive regarding the use of exercise, behavioural, and rehabilitation interventions to manage the severity and impact of fatigue in progressive MS populations. However, the quality of evidence is generally weak due to the small number of under-powered studies with limited methodological designs.

Exercise interventions

The evidence is inconclusive regarding the effectiveness of exercise as an intervention to reduce the severity and impact of fatigue in people with progressive MS. However, of the four studies that investigated aerobic exercise, all demonstrated improvement in fatigue impact post-intervention;[35-37, 40] although, only Briken et al reported that changes in fatigue impact were statistically significant.[36] The result of this review including studies of people with progressive MS is comparable with a similar review which reported that aerobic exercise improves fatigue in those with RRMS.[17] However, the studies included in this current review had small sample sizes, and were underpowered to detect significant changes in fatigue. In addition, three of the studies included participants with high-levels of disability (EDSS≥6) which may have further influenced results as, to date, the positive evidence for the effect of exercise on fatigue has only been demonstrated in those with mild-moderate disability (EDSS≤5.5),[17, 43] whereas varied effects are reported in those with higher levels of disability.[27]

Comparing the effectiveness of aerobic exercise with other modes of exercise is limited by the small number of heterogeneous studies. Only four studies investigated forms of exercise other than aerobic – including aquatic therapy[34] and inspiratory muscle training[32] – and the evidence generally does not support the effectiveness of these interventions for reducing fatigue in progressive MS populations. Furthermore, none of the included studies investigated the use of resistance training – which has been demonstrated to improve fatigue in people with RRMS.[43] Consequently, although this review highlights the potential effectiveness of aerobic exercise in fatigue management for people with progressive MS, there is insufficient evidence to determine whether this is the most effective mode of exercise.

335 The mechanisms through which exercise may attenuate fatigue symptoms are
336 unknown. It is hypothesised that exercise may have a neuroprotective and neuroregenerative
337 benefit through increasing neural growth factors which modulate structural and functional
338 CNS changes associated with primary MS-related fatigue.[13] In addition, exercise training can
339 influence secondary fatigue mechanisms caused by deconditioning, sleep disorders, and
340 depression through increasing aerobic capacity, improving sleep quality, and managing
341 depression.[13] Immunological biomarkers interferon-γ, tumour necrosis factor α, and
342 interleukin-1 have also been associated with fatigue in MS,[44] but may have limited relevance
343 to those with progressive MS due to the absence of a marked inflammatory response.[45]

344 Of the aerobic exercise interventions included, three were performed at moderate
345 intensity for durations of between 30-45 minutes, 2-3 times per week.[35-36, 40] While this dose
346 of exercise is recommended for people with mild-moderate MS,[46] there was no evidence of a
347 dose-response relationship to suggest that this prescription is most effective in managing
348 fatigue – particularly in progressive MS populations. Indeed, one trial investigated shorter
349 duration, high-intensity aerobic exercise,[37] which may hold potential in fatigue management
350 through inducing greater improvements in aerobic capacity over a shorter time.[47] Therefore,
351 no conclusions regarding the optimum dose of exercise to manage fatigue in people with
352 progressive MS can be generated from the evidence in this review.

353 There is also limited evidence for the long-term effectiveness of exercise
354 interventions. Only two studies conducted follow-up measurement, neither of which reported
355 a significant long-term change in fatigue severity in comparison to the baseline assessment.[32,
356 41] Consequently, there is a need to evaluate the long-term effectiveness of exercise
357 interventions to determine if improvements in fatigue are sustained after the intervention
358 period.

Despite the limited evidence for the effectiveness of exercise intervention, most studies reported low attrition rates indicating acceptability of exercise interventions in progressive MS populations. In addition, some studies confirmed that exercise interventions were feasible in populations with higher levels of disability associated with progressive MS, which is in line with evidence from previously published reviews.[27]

Behavioural interventions

As only two studies of behavioural interventions were included in this review it is not possible to reach any conclusion regarding their effectiveness in reducing the severity or impact of fatigue. Both studies investigated different forms of behavioural therapy interventions, and reported contrasting results regarding short and long term effectiveness. Vanage et al. reported that an 8-week energy conservation course significantly reduced fatigue impact immediately after the intervention period and at 8 week follow-up,[33] which is comparable with previous evidence from predominantly RRMS populations.[15]

In contrast, Bogosian et al. reported no significant difference in fatigue severity post-intervention or at 4 weeks follow-up between those receiving a mindfulness intervention and a waitlist control.[39] Mindfulness is used in MS to manage somatic symptoms and improve health-related quality of life,[48] and is recommended in the NICE guidelines as a strategy to manage fatigue.[14] However, the mindfulness intervention implemented by Bogosian et al. was designed to manage distress not fatigue.[39] Therefore, despite the association between mood disorders and fatigue,[9, 49-51] the applicability of these findings to fatigue management is limited. In addition, the mindfulness sessions were delivered via video conference which, while accommodating those with severe mobility disabilities, may limit the social benefits reported during group based interventions delivered face-to-face.[33, 52]

Rehabilitation interventions

Although evidence from this review is positive regarding the effects rehabilitation on fatigue only 2 studies of rehabilitation interventions were included. Generally, rehabilitation interventions were individualised to each participant, goal-orientated, addressed functional performance, and were delivered by a multidisciplinary team. In both articles, changes in fatigue severity after 52-weeks of multidisciplinary rehabilitation were statistically significant, with moderate effect sizes reported for those receiving rehabilitation and worsening fatigue in the wait-list control group.[29-30] However, as this study only included two points of outcome assessment (baseline and 52 weeks), the rate at which improvements in fatigue were accumulated cannot be observed. Patti et al. implemented a shorter duration, higher intensity intervention which demonstrated clinically significant improvements in fatigue impact for some participants post-intervention.[31] Therefore, there is a need to determine the most effective duration of rehabilitation interventions.

It is acknowledged that exercise and/or behavioural interventions can be delivered as components of rehabilitation. However, the rehabilitation interventions included in this review were multidisciplinary, and were differentiated from exercise and behavioural interventions alone as they contained additional treatment strategies – such as physiotherapy and occupational therapy to maintain physical function. Consequently, it was not possible to identify the effectiveness of each component part of rehabilitation – for example, the effectiveness of exercise delivered as part of rehabilitation. This information is essential to constructing rehabilitation programmes that are best designed to manage fatigue.

Limitations of the evidence

There were several important limitations which impact upon the overall quality of evidence. Firstly, only two studies used fatigue as a primary outcome measure,[30, 33] and of these studies, only one recruited participants with clinically significant levels of fatigue (FSS≥4).[33] Therefore, there is limited evidence of the effect of interventions specifically designed to manage fatigue in people with clinically significant levels of fatigue.

In addition, seven different fatigue outcome measures were used in this review, limiting the ability to directly compare results between studies. Although a meta-analysis of exercise interventions demonstrated that the selection of fatigue outcome measure did not moderate the effect of interventions,[17] there is a need for core fatigue outcome measures to enable pooling of statistical data for meta-analysis and comparison of effects between studies. In addition, MCID has only been determined for the FIS. Therefore, the MCID of the MFIS and FSS should be determined to establish the clinical significance of changes in both fatigue severity and impact.

Finally, most studies were under-powered to detect significant changes in fatigue. In addition, due to the inclusion of quasi-experimental studies, several studies were unable to control for confounding variables which may have accounted for the heterogeneous treatment response reported within and between studies. Furthermore, adverse events and compliance to interventions were poorly reported across studies, limiting the ability to determine the safety and efficacy of interventions in clinical practice.

Limitations of the review

There were many other studies that investigated the effectiveness of fatigue management interventions in people with progressive MS; however, these studies were

excluded as the results for those with progressive MS could not be specifically identified. In addition, the overall quality of evidence in this review is limited by the inclusion of quasi-experimental studies, which are less methodologically rigorous and introduce risk of selection bias. Furthermore, due to the inclusion of quasi-experimental studies and heterogeneity in outcome measures and interventions used between studies, it was not feasible to conduct a meta-analysis and results were generated by narrative synthesis.

Conclusion

There is insufficient evidence regarding the effectiveness of non-pharmacological interventions in reducing the impact and severity of fatigue in people with progressive MS. This review suggests that exercise, behavioural interventions, and rehabilitation may have the potential to manage fatigue. However future, adequately powered, rigorous trials of interventions to manage fatigue in populations with severe levels of fatigue are required. In addition, future studies should clearly identify the specific results for people with progressive MS due to the limited available evidence for this population.

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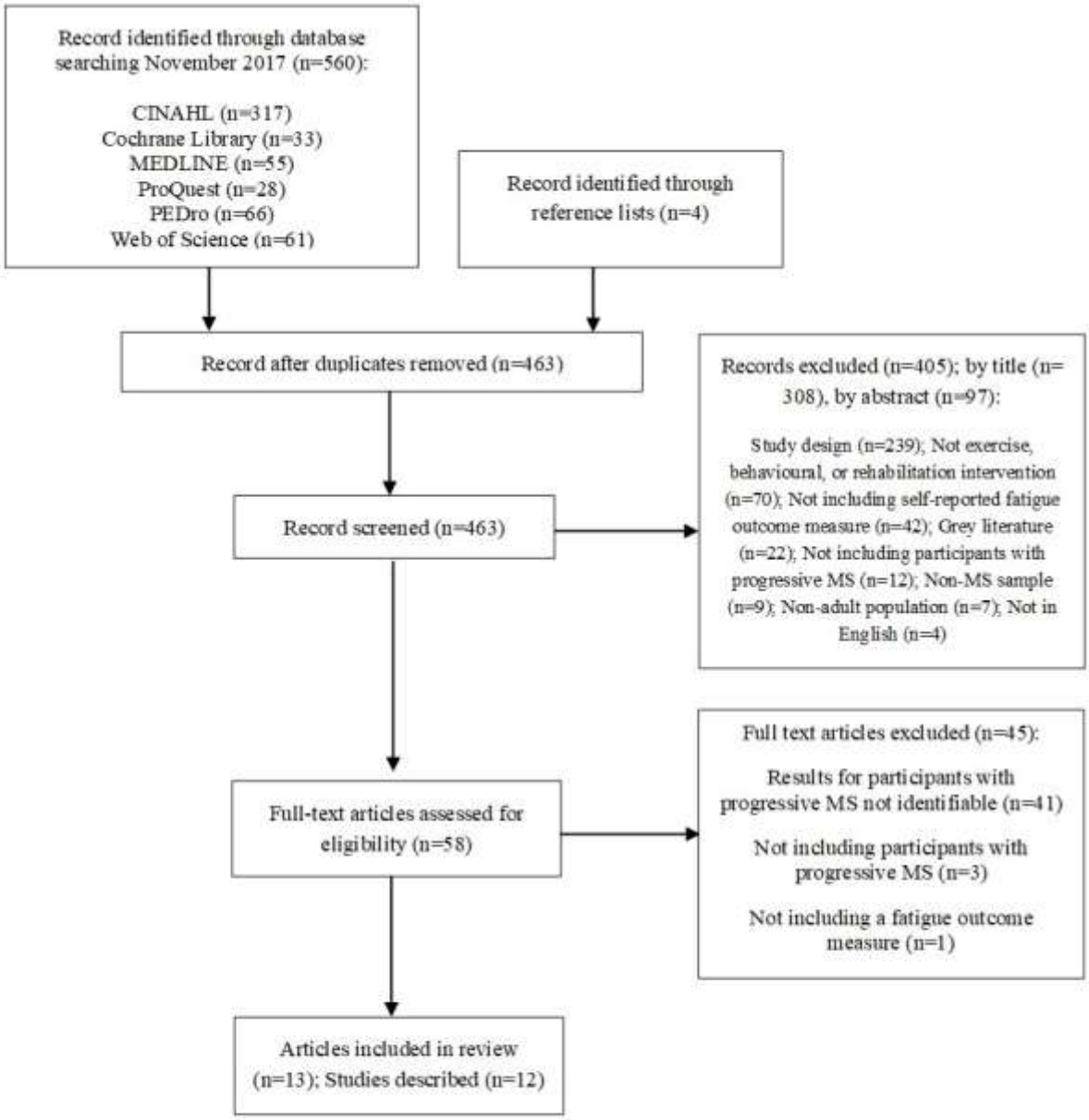
Figure Legend

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.[28]



607 **Table 1** Definition of included interventions

Intervention	Definition
Exercise	Exercise was defined as "planned, structured and repetitive bodily movement carried out to improve or maintain one or more components of physical fitness" – this definition included conventional aerobic and/or resistance based exercise, task orientated exercise, and alternative exercise methods.[20]
Behavioural	For behavioural interventions, studies must state or describe a behavioural therapy intervention which aimed to facilitate behavioural or attitudinal changes. Common behavioural interventions are cognitive behavioural therapy, mindfulness, or interventions aimed at modifying behaviour specifically in relation to energy conservation or symptom self-management.[14]
Rehabilitation	Rehabilitation interventions included treatment strategies that aimed to maintain or improve current level of function, or prevent the loss of function, and were delivered in a hospital (in-patient or out-patient) or community based setting by a multi-disciplinary team of relevant health-care professionals.[21] Exercise and/or behavioural interventions were classified as rehabilitation interventions if additional treatment components were delivered alongside these interventions.

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Table 2 Study, participant, intervention, and outcome details, and main findings from included articles

Author, date, and design	Sample details	Intervention type, mode of delivery, duration, frequency, duration	Fatigue outcome measure (Primary/ secondary), time-points	Main findings*	
Di Fabio et al.,[29] 1997, Quasi-experimental (non-randomised controlled trial) Rehabilitation	N= 44 (all progressive MS) SPMS, n (%): NR PPMS, n (%): NR EDSS range, 5-8 Sex (m/f), n: 6/25 Dropout, n (%): 13 (30%)	Outpatient rehabilitation program (n=19): delivered in a MS treatment centre by physical therapists, occupational therapists, and supportive services Waiting list control (n=25) 52 weeks, 1 day/week, 5 hours	SF-36 vitality subscale (secondary) 0, 52 weeks	<u>SF-36 (vitality subscale)</u> Within group (effect size): I=0.3; C=-0.39	
Di Fabio et al.,[30] 1998, Quasi-experimental (non-randomised controlled trial) Rehabilitation	N= 46 (all progressive MS) SPMS, n (%): NR PPMS, n (%): NR EDSS range, 5-8 Sex (m/f), n: 12/34 Dropout, n (%): 13 (28%)	Outpatient rehabilitation program (n=20): delivered in a MS treatment centre by physical therapists, occupational therapists, and supportive services Waiting list control (n=26) 52 weeks, 1 day/week, 5 hours	MS-Related Symptom Checklist fatigue subscale (Primary) 0, 52 weeks	<u>MS-Related Symptom Checklist fatigue subscale</u> Baseline†: I=2.9 (0.32); C=3.2 (0.25) Within group (effect size): I=0.46; C=-0.20 Between groups: P=0.004	
Patti et al.,[31] 2002, RCT Rehabilitation	N= 111 (all progressive MS) SPMS, n (%): NR PPMS, n (%): NR EDSS range, 4-8 Sex (m/f), n: 47/64 Dropout, n (%): 13 (12%)	Outpatient rehabilitation program (n=58): 6 weeks, 6 days/week, followed by 6 weeks home-exercise. Rehabilitation included physiotherapy, occupational therapy, speech therapy, supportive treatments, group physiotherapy Home-exercise control (n=53): 12 weeks of home-exercise program	FIS (secondary) 0, 6, 12 weeks	<u>FIS</u> Baseline: I= 116.8±40.9, C=127±36 12 weeks (MD): I=-18.8±14.3, P<0.001; C=0.6±0.9, P>0.05 Between groups: P <0.001	
Klefbeck et al.,[32] 2003, RCT Exercise – other	N= 16 (all progressive MS) SPMS, n (%): NR PPMS, n (%): NR EDSS range, 6.5-9.5 Sex (m/f), n: 9/6 Dropout, n (%): 1 (6%)	Inspiratory muscle training (n=8): 10 weeks, 10 minutes training twice every other day consisting of 3 sets of 10 loaded inspirations using Threshold IMT device with 1 minute rest between sets. Control (n=8): Usual physiotherapy care	FSS (secondary) 0, 10, 14 weeks	<u>FSS</u> Baseline: I= 5±1.3, C=4.5±1.3 Between groups (10 weeks): P>0.05	
Vanage et al.,[33] 2003, Quasi-experimental (Non-randomised cross-over trial) Behavioural	N= 37 (all progressive MS) SPMS, n (%): NR PPMS, n (%): NR EDSS, ≥5 Sex (m/f), n: 8/29 Dropout, n (%): 9 (24%)	Group based (3-8 participants per group) energy conservation course modified for those with increased disability, delivered by occupational therapists in a rehabilitation centre Group A: intervention followed by control (n=21), Group B: control followed by intervention (n=16) Control: chaplaincy led support group	FIS (primary) Pre-intervention, post-intervention, 8 week follow-up	<u>FIS (total)</u> Pre/post-intervention: MD= 15.7±25, Effect size=0.89, P<0.01 Post-intervention, 8 week follow-up: MD=2.1±23.7, Effect	<u>FIS (cognitive)</u> Pre/post-intervention: MD=4±6.8, Effect size=0.82, P<0.01 Post-intervention, 8 week follow-up: MD=-0.4±7.2, Effect

		8 weeks, 1 session/week, 60 minutes		size=0.13, P>0.05 FIS (physical) Pre/post-intervention: MD=4.2±7.9, Effect size=0.75, P<0.01 Post-intervention, 8 week follow-up: MD: 1±8.1, Effect size: 0.17, P>0.05	size=-0.08, P>0.05 FIS (psychosocial) Pre/post-intervention: MD=7.5±12.7, Effect size=0.83, P<0.01 Post-intervention, 8 week follow-up: MD=1±13.3, Effect size=-0.11, P>0.05
Roehers & Karst,[34] 2004, Quasi-experimental (Pre/post-test) Exercise – combined	N= 31 (all progressive MS) SPMS, n (%): NR PPMS, n (%): NR EDSS range, 1.5-8 Sex (m/f), n: 7/12 Dropout, n (%): 12 (39%)	Aquatic exercise intervention (n=31): endurance, strengthening, and balance exercises delivered in a pool by physical therapy students, exercises modified depending upon functional ability 12 weeks, 2 session/week, 60 minutes	MFIS (secondary) 0, 12 weeks	MFIS Baseline: 48.7±12.1 Post-intervention (final value): 43.5±15 Pre/post-intervention: P=0.035	
Pilutti et al.,[35] 2011, Quasi-experimental (Pre/post-test) Exercise – aerobic	N= 6 SPMS, n (%): 1 (17%) PPMS, n (%): 5 (83%) EDSS range, 5.5-8 Sex (m/f), n: 2/4 Dropout, n (%): 0 (0%)	Body-weight supported treadmill training (n=6) Percentage body weight support and treadmill speed individualised to each participant in relation to posture and comfort when walking Training progressed initially by increasing treadmill speed followed by reducing body weight support 12 weeks, 3 sessions/week, 30 minutes	MFIS (Secondary), MSQoL-54 energy subscale (secondary) 0,12 weeks	MFIS (total) Baseline: 43.5±12.26 Pre/post-test: MD=-13.3±20.96, Effect size (95% CI)=-0.93 (-30.11, 3.44), P=0.22 MFIS (physical subscale) Baseline: 24.3±5.8 Pre/post-test: MD=-5.9±9.27, Effect size (95% CI)=-0.8 (-13.33, 1.5), P=0.22 MFIS (cognitive subscale) Baseline: 14.6±8.92	Pre/post-test: MD=-6.8±9.46, Effect size (95% CI)=-0.78 (-14.32, 0.82), P=0.14 MFIS (psychosocial subscale) Baseline: 4.7±2.58 Pre/post-test: MD=-0.7±3.08, Effect size (95% CI)=-0.28 (-3.13, 1.8), P=0.62 MSQoL-54 (energy subscale) Baseline: 32±19.64 Pre/post-test: MD=19.3±12.56, Effect size (95% CI)=0.93 (9.28, 29.39), P=0.01
Briken et al.,[36]	N=47	Aerobic exercise, 4 trial arms: arm ergometry (n=12),	MFIS	MFIS	

2014, RCT Exercise – aerobic	SPMS, n (%): 31 (74%) PPMS, n (%): 11 (26%) EDSS range, 4-6 Sex (m/f), n: 18/24 Dropout, n (%): 5 (11%)	rowing (n=12), cycling (n=12), wait-list control (n=11) Intervention delivered in a medical centre by a physiotherapist. Training intensity tailored to each participant depending upon performance during submaximal aerobic fitness assessment 8-10 weeks, 2-3 sessions/week , 15-45 minutes	(Secondary) 0, 10 weeks	Baseline: Arm ergometry: 45.00±14.73, Rowing: 35.27±13.86, Cycling: 35.27±13.86, C: 38.00±15.15 Between group: Arm ergometry vs C: (P=0.013), Rowing vs C: (P>0.05), Cycling vs C: (P>0.05), All interventions vs C: (P=0.019)	
Skjerbaek et al.,[37] 2014, RCT Exercise – aerobic	N= 11 SPMS, n (%): 8 (73%) PPMS, n (%): 3 (27%) EDSS range, 6.5-8 Sex (m/f), n: 3/8 Dropout, n (%): 1 (9%)	Upper body endurance training (n=6): Standard care plus 10 sessions of upper limb arm ergometry over 4 weeks, consisting of 6 x 3 minute intervals at target heart rate corresponding to 65-75% of VO_{2peak}Control (n=5): 4 weeks of individualised multi-disciplinary inpatient rehabilitation delivered in a MS hospital.	FSMC (Secondary) 0, 4 weeks	<u>FSMC (total)</u> Baseline: I=65±18.5, C= 53±16.3 Within group (MD): I=-2.2±8.7, C=-2.6±7.9 Between groups: P=0.94 <u>FSMC (motor subscale)</u> Baseline: I=36±7.9, C=29±8	Within group (MD): I=-2.8±5.6, C=-2±5.3 Between groups: P=0.82 <u>FSMC (cognitive subscale)</u> Baseline: I=29±10.9, C=23.8±9.1 Within group (MD): I=0.6±3.6, C=-0.6±2.7 Between groups: P=0.57
van der Linden et al.,[38] 2014, Quasi-experimental (Pre/post-test) Exercise – other	N= 15 (all progressive MS) SPMS, n (%): NR PPMS, n (%): NR EDSS range, 7-8 Sex (m/f), n: 7/8 Dropout, n (%): 1 (7%)	Seated Pilates (n=15) exercises focused on core strengthening, with elements of upper limb strengthening exercises and a home-exercise program to be performed 15 minutes daily Delivered by a qualified Pilates instructor at 2 community centres Weeks 1-6: 2 session/week, 60 minutes Weeks 7-12: 1 session/week, 60 minutes	FSS (secondary) 0, 6, 12 weeks	<u>FSS</u> Baseline: 5.2±1.3 Week 6 (final value)=4.7±1.6 Week 12 (final value)=4.9±1.7 Baseline, week 6: P=0.132 Baseline, week 12: P=0.295	
Bogosian et al.,[39] 2015, RCT Behavioural	N= 40 SPMS, n (%): 23 (58%) PPMS, n (%): 17 (42%) EDSS mean (SD), 6.5 (1.5) Sex (m/f), n: 18/22 Dropout, n (%): 7 (18%)	Mindfulness intervention to manage distress Group-based video conference adapted from Mindfulness-Based Cognitive Therapy course book (n=19), wait-list control (n=21) Intervention delivered to groups of 5 people by health psychologist with training in delivering mindfulness sessions. 8 weeks, 1 session/week, 60 minutes	FSS (Secondary) 0, 8, 12 weeks	<u>FSS</u> Baseline: I: 39.91±14.45, C: 48.29±12.24 Between groups post-test: MD=-4.20, Effect size (95% CI)=-0.3 (-9.84, 1.45), P=0.145 Between groups 3-months: MD=-4.07, Effect size (95% CI)=-0.29 (-10.69, 2.56), P=0.302	
Pilutti et al.,[40] 2016, Quasi-experimental (Pre/post-test) Exercise – aerobic	N= 12 SPMS, n (%): 8 (66%) PPMS, n (%): 4 (33%) EDSS range, 6-8 Sex (m/f), n: 6/6 Dropout, n (%): 2 (17%)	Total-body recumbent stepper training (TBRST) (n=6), Body-weight supported treadmill training (BWSTT) (n=6) Participants instructed to exercise at 3-5 Borg rating of perceived effort (10-point scale) 12 weeks, 3 sessions/week, 30 minutes	MFIS (Secondary) 0,12 weeks	<u>MFIS (total)</u> Baseline: TBRST=35.6±9.21, BWSTT=54.2±9.71 Within groups (effect size): TBRST=-1.04, BWSTT=-1.23	<u>MFIS (cognitive subscale)</u> Baseline: TBRST=9.2±6.72, BWSTT=22.4±7.08 Within groups (effect size): TBRST= -0.59,

				Pre/post-test (groups combined): P>0.05 <u>MFIS (physical subscale)</u> Baseline: TBRST=22.8±5.03, BWSTT=27±1.66 Within groups (effect size): TBRST=-1.05, BWSTT=-1.58 Pre/post-test (groups combined): P≤0.05	BWSTT=-0.8 Pre/post-test (groups combined): P>0.05 <u>MFIS (psychosocial subscale)</u> Baseline: TBRST=3.6±1.47, BWSTT=4.8±1.44 Within groups (effect size):TBRST= -0.46, BWSTT=-1.03 Pre/post-test (groups combined): P≤0.05
Straudi et al.,[41] 2016, RCT Exercise – task orientated	N= 58 SPMS, n (%): 36 (69%) PPMS, n (%): 16 (31%) EDSS range, 6-7 Sex (m/f), n: 18/34 Dropout, n (%): 9 (16%)	Robot-assisted gait training (n=30): body-weight supported treadmill training with robotic-driven gait orthosis, starting with 100% guidance from orthosis and 50% body weight support, and 10% adjustments were made to both settings as training progressed. Treadmill speed varied between 0.1-3 km/h Conventional walking therapy (n=28): lower limb muscle stretching and strengthening, motor co-ordination, gait, and balance exercises 6 weeks, 2 sessions/week, 60 minutes	FSS (Secondary), SF-36 vitality sub-scale (Secondary) 0, 3, 6, 12 weeks	<u>FSS</u> Baseline: RAGT=5.78±1.11, CWT=5.69±1.27 MD (vs baseline): Week 3: RAGT= -0.13±0.83, P>0.05; CWT=-0.04±1.36, P>0.05 Week 6: RAGT=-0.23±1.05, P>0.05; CWT=0.01±1.15, P>0.05 Week 12: RAGT=0.18±0.87, P>0.05; CWT=0.18±1.16, P>0.05	<u>SF-36 Vitality</u> Baseline: RAGT: 45.37±17.92, CWT:44.20±20.45 MD (vs baseline): Week 3: RAGT=0.93±10.29, P>0.05; CWT=-3.20±18.98 P>0.05 Week 6: RAGT=7.41±13.40, P<0.01; CWT=2.20±16.40, P>0.05 Week 12: RAGT=-1.78±19.58, P>0.05; CWT=0.20±19.23, P>0.05

Abbreviations: C, Control group; EDSS, Expanded Disability Status Scale; FIS, Fatigue Impact Scale; FSS, Fatigue Severity Scale; FSMC, Fatigue Scale for Motor and Cognitive functions; I, Intervention group; MD, Mean difference; MFIS, Modified Fatigue Impact Scale; MS, Multiple Sclerosis; MS QoL, Multiple Sclerosis Quality of Life Scale; NR, not reported; PPMS, primary progressive multiple sclerosis; RCT, randomised controlled trial; SF-36, Medical Outcomes Study 36-Item Short Form Survey; SPMS, secondary progressive multiple sclerosis; VO_2peak, peak oxygen uptake

* Descriptive baseline and final values presented as mean ± SD unless stated otherwise

† Values presented as mean ± standard error

Table 3 Downs and Black Checklist scores for included studies

Authors	Downs & Black Checklist item*																											Total
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	(0-28)
Di Fabio et al.[29]	1	1	0	1	1	1	0	0	1	1	1	0	1	0	0	1	1	1	0	1	1	0	0	0	1	1	0	16
Di Fabio et al.[30]	1	1	0	1	1	1	1	0	1	1	1	0	1	0	0	1	1	1	0	1	1	0	0	0	1	1	0	17
Patti et al.[31]	1	1	1	1	0	1	1	1	1	0	1	1	1	0	1	1	1	1	0	1	1	1	1	0	0	0	0	19
Klefbeck et al.[32]	1	1	1	1	0	1	1	0	0	1	1	1	1	0	0	1	1	1	0	1	1	0	1	0	0	0	0	16
Vanage et al.[33]	1	1	1	1	2	1	1	1	0	0	1	1	1	0	0	1	0	1	0	1	1	1	0	0	0	0	0	17
Roehrs & Karst.[34]	1	1	1	1	0	1	1	1	1	1	0	0	1	0	0	1	1	1	0	1	1	0	0	0	0	0	0	15
Pilutti et al.[35]	1	1	1	1	0	1	1	0	1	1	0	0	1	0	0	1	1	1	1	1	1	0	0	0	0	1	0	16
Briken et al.[36]	1	1	1	1	1	1	0	0	1	1	1	1	1	0	0	1	0	1	1	1	1	0	1	0	1	1	0	19
Skjerbaek et al.[37]	1	1	1	1	2	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	0	1	1	1	0	0	23
van der Linden et al.[38]	1	1	1	1	0	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	0	0	0	0	0	0	18
Bogosian et al.[39]	1	1	1	1	1	1	1	0	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	0	24
Pilutti et al.[40]	1	1	1	1	2	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	0	1	0	0	0	0	21
Straudi et al.[41]	1	1	1	1	2	1	1	1	1	1	1	1	1	0	1	1	1	1	0	1	1	0	1	1	1	1	1	25

Notes: 2, criterion fully met (item 5); 1, criterion met or partially met (item 5); 0, criterion not met

*Abbreviated Downs and Black checklist item description: 1, hypothesis/aims/objectives reported; 2, main outcome measures reported; 3, participant characteristics reported; 4, intervention details reported; 5, principal confounders reported; 6, main findings reported; 7, variability in main outcomes reported; 8, adverse events reported; 9, loss to follow-up reported; 10, probability values reported; 11, source population representative of entire population; 12, study population representative of source population; 13, study setting representative of usual care; 14, participants blinded to intervention; 15, outcome assessors blinded; 16, no retrospective sub-group analysis; 17, analysis adjusts for different lengths of follow-up of participants; 18, statistical tests are appropriate; 19, reliable compliance with intervention; 20, outcome measures are valid and reliable; 21, recruitment of study groups from same population; 22, recruitment of participants over

same time period; 23, randomisation of participants; 24, allocation concealment; 25, adjustment for confounding variables in main analysis; 26, adjustment for loss to follow-up in main analysis; 27, inclusion of sample size calculation.

Supplementary table 1 Search strategies for electronic databases

Database	Search Terms
CINAHL (via EBSCOhost)	1. ("Multiple sclerosis" or MS) 2. (MH "Exercise+") or (MH "Resistance Training") or (MH "Therapeutic Exercise+") or (MH "Exercise Positions+") or (MH "Group Exercise") or (MH "Aerobic Exercises+") 3. (Exercise or "Resistance Training" or "Therapeutic Exercise" or "Exercise Position*" or "Group Exercise" or "Aerobic Exercise*") 4. (MH "Cognitive Therapy+") or (MH "Behavior Therapy+") 5. ("cognitive therap*" or "behav* therap*" or "cognitive behavio?ral therapy" or CBT or "psychotherapeutic treatment*" or mindfulness) 6. ("energy manag*" or "energy conserv*" or "energy saving" or "fatigue manag*" or "managing fatigue" or pacing) 7. (MH "Rehabilitation+") or (MH "Rehabilitation Centers+") or rehab* 8. (MH "Fatigue+") or (fatigue or "physical fatigue" or "mental fatigue" or "central fatigue" or "fatigue impact") 9. 2 or 3 or 4 or 5 or 6 or 7 10. 1 and 8 and 9
Cochrane Library	1. (("Multiple sclerosis" or MS) near/2 progressive) 2. (MeSH descriptor: [Exercise] explode all trees)or (MeSh descriptor: [Exercise therapy] explode all trees) or (Mesh descriptor: [Resistance training] explode all trees) or (MeSH descriptor: [Exercise movement techniques] explode all trees) or (MeSH descriptor: [Plyometric exercise] explode all trees) 3. (exercise or "exercise therap*" or "exercise movement technique*" or "resistance training" or "aerobic exercise*") 4. ("energy manag*" or "energy conserv*" or "energy saving" or "fatigue manag*" or "managing fatigue" or pacing) 5. (MeSH descriptor: [behavior therapy] explode all trees) or (MeSH descriptor: [cognitive therapy] explode all trees) 6. ("cognitive therap*" or "behav* therap*" or "cognitive behavio?ral therapy" or CBT or "psychotherapeutic treatment*" or mindfulness) 7. (MeSH descriptor: [Rehabilitation] explode all trees) or (MeSH descriptor: [Rehabilitation Centers] explode all trees) or rehab* 8. (fatigue or "physical fatigue" or "mental fatigue" or "central fatigue" or "fatigue impact") 9. 2 or 3 or 4 or 5 or 6 or 7 10. 1 and 8 and 9
MEDLINE (via Ovid)	1. (("Multiple sclerosis" or MS) adj2 progressive).mp. 2. exp Exercise/ or exp Exercise therapy/ or exp Resistance training/ or exp Exercise movement techniques/ or exp Plyometric exercise 3. (exercise or "exercise therap*" or "exercise movement technique*" or "resistance training" or "aerobic exercise*").mp. 4. ("energy manag*" or "energy conserv*" or "energy saving" or "fatigue manag*" or "managing fatigue" or pacing).mp. 5. exp behavior therapy/ or exp cognitive therapy/

	6. ("cognitive therap*" or "behav* therap*" or "cognitive behavio?ral therapy" or CBT or "psychotherapeutic treatment*" or mindfulness).mp. 7. exp Rehabilitation/ or rehab*.mp. or exp Rehabilitation Centers/ 8. (fatigue or "physical fatigue" or "mental fatigue" or "central fatigue" or "fatigue impact").mp. 9. 2 or 3 or 4 or 5 or 6 or 7 10. 1 and 8 and 9
PEDro	1. Progressive AND multiple AND sclerosis
ProQuest (Health & Medical Collection, Nursing & Allied Health Database, PsycINFO)	1. (("Multiple sclerosis" or MS) NEAR/2 progressive) 2. (exercise or "exercise therap*" or "exercise movement technique*" or "resistance training" or "aerobic exercise*") 3. ("energy manag*" or "energy conserv*" or "energy saving" or "fatigue manag*" or "managing fatigue" or pacing) 4. ("cognitive therap*" or "behav* therap*" or "cognitive behavio?ral therapy" or CBT or "psychotherapeutic treatment*" or mindfulness) 5. (Rehab* or "rehabilitation centres") 6. (fatigue or "physical fatigue" or "mental fatigue" or "central fatigue" or "fatigue impact") 7. 2 or 3 or 4 or 5 8. 1 and 6 and 7
Web of Science Core Collections	1. (("Multiple sclerosis" or MS) Near/2 progressive) 2. (exercise or "exercise therap*" or "exercise movement technique*" or "resistance training" or "aerobic exercise*") 3. ("energy manag*" or "energy conserv*" or "energy saving" or "fatigue manag*" or "managing fatigue" or pacing) 4. ("cognitive therap*" or "behav* therap*" or "cognitive behavio?ral therapy" or CBT or "psychotherapeutic treatment*" or mindfulness) 5. (Rehab* or "rehabilitation centres") 6. (fatigue or "physical fatigue" or "mental fatigue" or "central fatigue" or "fatigue impact") 7. 2 or 3 or 4 or 5 8. 1 and 6 and 7