

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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1 **Running Head:** Fatigue management in progressive MS

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

4

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12

13 **Practice Points**

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

21

22 **Abstract**

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

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

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

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

45

46 **Key Words:** Progressive Multiple Sclerosis; Fatigue; Review

47

48 **Abbreviations:** CNS, central nervous system; EDSS, Expanded Disability Status Scale; FIS,

49 Fatigue Impact Scale; FSMC, Fatigue Scale for Motor and Cognitive functions; FSS, Fatigue

50 Severity Scale; MCID, minimal clinically important difference; MFIS, Modified Fatigue

51 Impact Scale; MS, Multiple Sclerosis; MS QoL, Multiple Sclerosis Quality of Life Scale;

52 RCT, randomised controlled trial; RRMS, relapsing remitting multiple sclerosis; SF-36,

53 Medical Outcomes Study 36-Item Short Form Survey

Introduction

54
55 Fatigue is a common symptom of Multiple Sclerosis (MS) reported in over 70% of the
56 population.¹⁻³ MS-related fatigue is often perceived as the most debilitating symptom, which
57 significantly impacts upon activities of daily living, social participation and quality of life,⁴⁻⁵
58 and is associated with changes to employment.⁶ Fatigue is a highly complex and
59 multifactorial symptom that may be defined as “a subjective lack of physical and/or mental
60 energy that is perceived by the individual or caregiver to interfere with usual and desired
61 activities”.⁷ Subjectively, this may be described as exhaustion, a lack of energy, or
62 overwhelming tiredness which is pervasive and can occur at rest.⁸

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

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

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

86

87 **Methods**

88 *Systematic review protocol and registration*

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

91

92 *Search Strategy*

93 Searches of the following databases were conducted from inception to November
94 2017: CINAHL (via EBSCOhost), Cochrane Library, MEDLINE (via Ovid), PEDro,
95 ProQuest (Health & Medical Collection, Nursing & Allied Health Database, PsycINFO), and
96 Web of Science Core Collections. Search strategies included a combination of keywords and
97 subject headings related to multiple sclerosis, exercise, behavioural therapy, rehabilitation
98 and fatigue, and were adapted for use in each different database (Supplementary table 1).
99 Reference lists of relevant review articles were also hand searched to identify any additional
100 articles. After each database was searched, results were exported to Covidence systematic
101 review software (2017, Veritas Health Innovation, Melbourne, Australia) and duplicates were

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

107

108 ***Inclusion and exclusion criteria***

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

118

119 **Table 1 Near here**

120

121 ***Data extraction***

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

125

126 ***Quality assessment***

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

137

138 ***Data synthesis***

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

147

148

Results

149 *Results of the search*

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

160

161

Figure 1 Near here

162

163

Table 2 Near here

164

165 *Study design*

166 From the included articles, six were RCTs,^{31-32, 36-37, 39, 41} and seven were quasi-
167 experimental studies (pre/post-test design (n=4),^{34-35, 38, 40} non-randomised controlled trial
168 design (n=2),²⁹⁻³⁰ and non-randomised cross-over trial design (n=1)³³). All but one RCT
169 included two trial arms (control and intervention) – the study by Briken et al involved three
170 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

194 **Outcome measures**

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

206

207 **Interventions**

208 In accordance with the definitions of interventions for this review, eight exercise,^{32, 34-}
209 ^{38, 40-41} two rehabilitation,²⁹⁻³¹ and two behavioural interventions^{33, 39} were described by the 13
210 included articles.

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

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

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

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

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

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

252

253 *Effectiveness of exercise interventions*

254 Of the studies investigating aerobic exercise interventions, Skjerbaek et al. reported
255 that, although FSMC scores improved in the exercise group post-intervention (mean
256 difference = -2.2 ± 8.7), there was no significant difference between the exercise and control
257 groups over time.³⁷ Similarly, Pilutti et al. and Pilutti et al. reported non-significant
258 improvements in MFIS scores post-intervention (effect size -0.93 , and -1.04 respectively).^{35,}
259 ⁴⁰ However, Pilutti et al. found statistically significant changes in MSQoL-54 energy subscale
260 post-intervention ($p=0.01$).³⁵ The studies by Pilutti et al., Skjerbaek et al., and Pilutti et al.
261 had small samples ($n=6-12$) and included participants with severe disability (EDSS: 5.5-8).^{35,}
262 ^{37, 40} In contrast, Briken et al. investigated three aerobic exercise interventions in a larger
263 population ($n=47$) of participants with moderate disability (EDSS: 4-6), and reported that
264 exercise significantly improved fatigue from baseline ($p=0.019$); however, only arm

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

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

273

274 ***Effectiveness of behavioural interventions***

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

284

285 ***Effectiveness of rehabilitation interventions***

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

288 intervention in comparison to wait-list controls (effect sizes 0.46 and -0.2 for the intervention
289 and control group respectively).³⁰ From the same study, Di Fabio et al. also reported that SF-
290 36 vitality subscales scores improved post-intervention for the group receiving rehabilitation
291 (effect size 0.3), and that fatigue in the wait-list control group increased in severity (effect
292 size -0.39).²⁹ In Patti et al., those receiving 12-weeks outpatient rehabilitation demonstrated a
293 statistically significant improvement in post-intervention fatigue scores ($p < 0.001$).³¹

294

295 *Clinical significance of changes in fatigue*

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

304

305

305 **Discussion**

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

310

311 *Exercise interventions*

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

325 Comparing the effectiveness of aerobic exercise with other modes of exercise is
326 limited by the small number of heterogeneous studies. Only four studies investigated forms of
327 exercise other than aerobic – including aquatic therapy³⁴ and inspiratory muscle training³² –
328 and the evidence generally does not support the effectiveness of these interventions for
329 reducing fatigue in progressive MS populations. Furthermore, none of the included studies
330 investigated the use of resistance training – which has been demonstrated to improve fatigue
331 in people with RRMS.⁴³ Consequently, although this review highlights the potential
332 effectiveness of aerobic exercise in fatigue management for people with progressive MS,
333 there is insufficient evidence to determine whether this is the most effective mode of
334 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.

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

364

365 ***Behavioural interventions***

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

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

383

384 ***Rehabilitation interventions***

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

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

405

406 ***Limitations of the evidence***

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

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

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

426

427 ***Limitations of the review***

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

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

436

437

Conclusion

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

445

446 **Conflict of Interest:** None

447 **Financial Support:** This research did not receive any specific grant from funding agencies

448

449 **References**

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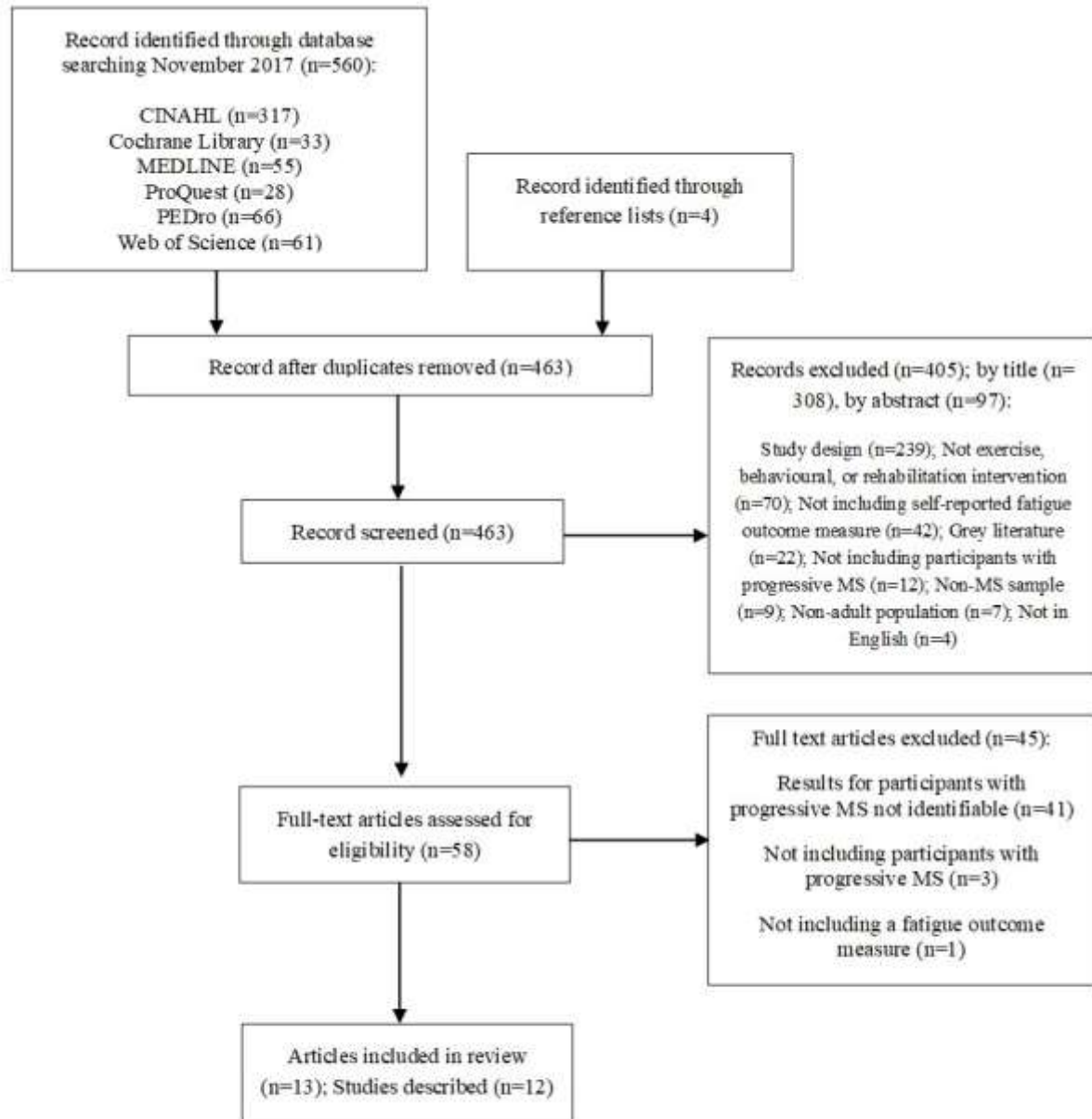
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602 **Figure Legend**

603 **Figure 1.** PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)
604 flow diagram.²⁸



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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	size=-0.08, P>0.05
				<u>FIS (physical)</u> 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	<u>FIS (psychosocial)</u> 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	<u>MFIS</u> 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	<u>MFIS (total)</u> 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 <u>MFIS (physical subscale)</u> 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 <u>MFIS (cognitive subscale)</u> 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 <u>MFIS (psychosocial subscale)</u> 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 <u>MSQoL-54 (energy subscale)</u> 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	<u>MFIS</u>	

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 <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	BWSTT=-0.8 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	<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; VO₂peak, 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 (0-28)
	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	
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	1	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)	<ol style="list-style-type: none"> 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 behavior?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	<ol style="list-style-type: none"> 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 behavior?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)	<ol style="list-style-type: none"> 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
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