REVIEW ARTICLE

The effect of exercise on depressive symptoms in multiple sclerosis based on a meta-analysis and critical review of the literature

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Background and purpose: The purpose of this study was to perform a systematic review of the literature on the effects of exercise on depressive symptoms in patients with multiple sclerosis (MS), as well as to apply meta-analytical procedures to the results.

Methods: A systematic search covering eight databases was conducted. The included studies were randomized controlled trials applied to people with definite MS who completed a structured exercise intervention which were compared to any comparator, including other forms of exercise. The outcomes included a primary measure of depression/depressive symptoms or an instrument with a clearly defined depression subscale.

Results: Fifteen randomized controlled trial studies were identified including a total of 331 exercising subjects and 260 controls. The average Physiotherapy Evidence Database (PEDro) score was 5.6 ± 1.3 points. Only one study applied depressive symptoms as the primary outcome. Four studies showed positive effects of exercise on depressive symptoms. An in-depth analysis of the studies revealed that the baseline level of depressive symptoms, patient disability level, choice of depression instrument and exercise intensity may influence the results. The meta-analysis included 12 studies reflecting a total of 476 subjects. The standardized mean difference across studies was $g = -0.37$, 95% confidence interval (−0.56; −0.17), and the null hypothesis of homogeneity within the sample could not be rejected ($Q = 12.05$, df = 11, $P = 0.36$).

Discussion: Exercise may be a potential treatment to prevent or reduce depressive symptoms in individuals with MS, but existing studies do not allow solid conclusions. Future well-designed studies evaluating the effects of exercise on depressive symptoms and major depression disorder in MS are highly warranted.

Introduction

Multiple sclerosis (MS) is a chronic neurodegenerative disorder, characterized by an unpredictable disease course, heterogeneous symptoms and usually with progressive deficits resulting in functional impairment, disability and frequent mood disorders occurring at disease onset or during life with MS [1,2]. Moreover, major depressive disorder (MDD) according to the Diagnostic and Statistical Manual of Mental Disorders IV diagnostic criteria [3] and depressive symptoms [4] occur frequently in persons with MS. Fatigue and cognitive dysfunction are included to a varying extent in the diagnostic criteria for MDD and are also frequent symptoms in MS. The lifetime risk of MDD is between 23% and 54%, whilst the point prevalence of MDD is 27%–54% in people with MS [4]. A 12-month period prevalence of 15.7% has been reported in persons with MS, which is nearly double the

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prevalence in persons without MS (7.4%) [4]. Also, the lifetime frequency of MDD is considerably lower in the general population [5] and in other comparable disorders with similar levels of functional impairment, including other neurological conditions [6–8]. Population-based MS studies show that 46.9% have significant depressive symptoms [9] and in any 2-week period about one-quarter of community residents with MS experience considerable levels of depressive symptoms [10].

The consequences of MDD are substantial in MS, given that MDD is associated with impaired cognition [11], lower compliance with disease-modifying drugs [12], suicidal attempts [13], risk of suicide [14,15] and increased strain on family and job [16]. Furthermore, MDD may not always be discovered in the MS clinic and, when it is, the medical treatment may be inadequate [16]. Moreover, a Cochrane review concluded that paroxetine and desipramine at best offer modest effects, and that the side-effects are often substantial [17]. Other interventions such as cognitive therapy have also been evaluated and have shown some promising results [18,19].

As an alternative to pharmacological treatment or cognitive therapy, a non-pharmacological intervention, exercise, has attracted attention and proven effective in otherwise healthy patients with MDD or depressive symptoms [20–22]. A meta-analysis of 90 studies involving patients with a chronic illness further found that exercise had a small reducing effect on depressive symptoms, but only six studies on MS were included [23].

However, studies in MS patients have shown that depressive symptoms represent a barrier towards participation in exercise programs [24]. Nonetheless, cross-sectional studies have provided evidence of an association between physical activity and depressive symptoms in persons with MS [25–29]. Consequently, data from longitudinal studies evaluating the effects of exercise on MDD and depressive symptoms in MS patients are of potentially high clinical value. Recently, a topical review was published on exercise and depression in MS, identifying 11 randomized controlled trials (RCTs) on the topic [30]. The review concluded that the findings of the literature were equivocal, probably due to methodological flaws such as depression only being a secondary outcome measure, and also none of the identified studies evaluated the effects of exercise in a sample of MS patients with diagnosed MDD. However, the topical review was not based on a systematic literature search since the search only covered one database (PubMed). Furthermore, the topical review did not make an in-depth analysis of the impact of exercise modality, volume and intensity, and also no meta-analytical procedures were applied. Consequently, our aim was to conduct a systematic review and meta-analysis of the existing literature on the effects of exercise therapy on depressive symptoms in people with MS. In addition, this review seeks to identify the potential importance of (i) the applied instrument measuring depressive symptoms, (ii) the baseline status of the patients, (iii) disability level, (iv) concurrent effects on primary outcome or fatigue and (v) the exercise modality, volume and intensity.

Methods

The present systematic review follows the PRISMA guidelines on systematic reviews of RCTs. No predefined review protocol was published. The study is based on a systematic literature search of eight databases (Bibliotek.dk, SveMed+, PubMed, Embase, Cochrane Library, PEDro, CINAHL and Sport Discus) that was performed to identify studies on depressive symptoms/depression and exercise therapy in people with MS published before 16 October 2013. Specifically the following PICO question [31] was formulated: 'Amongst people with MS, to what extent do structured exercise interventions (according to the definition of Caspersen *et al*. [32]), in comparison to non-training controls, active controls or to another exercise intervention, reduce the level of depressive symptoms (according to the definition of Eng and Reime [33]) evaluated by depression specific scales'. During the search the following MeSH terms were applied: 'exercise' or 'exercise therapy' in combination with 'depression' or 'mood' and 'multiple sclerosis'. In databases without a thesaurus free text searches were performed (Table 1).

As presented in Fig. 1 the search yielded 337 hits and after removal of duplicates 258 publications remained.

To be included in the systematic review the study had to (i) be based on a RCT design; (ii) enrol participants with definite MS according to the McDonald criteria [34]; (iii) evaluate an exercise intervention that was compared with either non-training controls, active controls or another exercise intervention; (iv) include a primary validated measure of depressive symptoms or depression or an instrument with a clearly defined depression subscale such as the Profile of Mood States (POMS); and (v) be available in English.

Exercise was defined according to the definition of Caspersen *et al*., stating that 'exercise is a subset of physical activity that is planned, structured and repetitive and has as a final or an intermediate objective the improvement or maintenance of physical fitness' [32].

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Table 1 Detailed list of retrieved articles and applied search terms in seven different databases

Database	Articles retrieved	Search terms (MeSH etc.)
Bibliotek.dk	0	('dissemineret sklerose' OR 'sklerose') AND ('styrketræning' OR 'træning')
SveMed+	0	'Multiple Sclerosis' AND ('Depression' OR 'Mood') AND ('Exercise' OR 'Exercise Therapy')
PubMed	106	'Multiple Sclerosis' AND ('Depression' OR 'Mood') AND ('Exercise' OR 'Exercise Therapy') Free text search: 'Multiple Sclerosis' AND ('Depression' OR 'Mood') AND ('Exercise' OR 'Exercise Therapy')
Embase	155	'Multiple Sclerosis' AND ('Depression' OR 'Mood') AND ('Kinesiotherapy' OR 'Exercise')
Cochrane	0	'Multiple Sclerosis' AND ('Depression' OR 'Mood') AND ('Exercise' OR 'Exercise Therapy')
SPORTDiscus	23	'Multiple Sclerosis' AND ('Depression' OR 'Mood') AND ('Exercise' OR 'Exercise Therapy')
PEDro	14	Abstract and title search: 'Multiple Sclerosis' AND ('Depression' or 'Mood') and 'Exercise'
CINAHL	39	'Multiple Sclerosis' AND ('Depression' OR 'Mood') AND ('Exercise' OR 'Exercise Therapy')

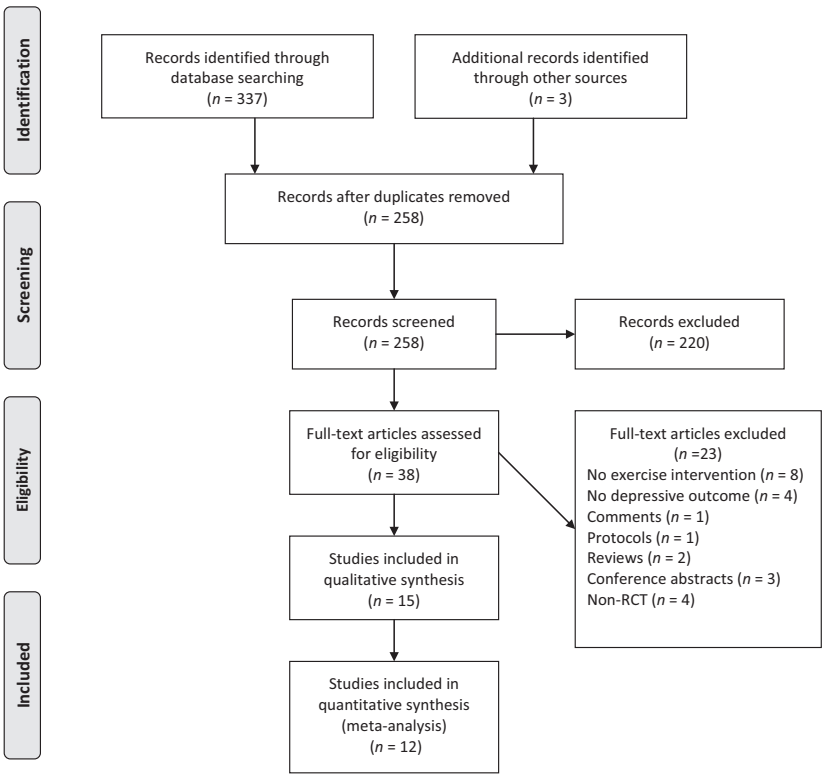


Figure 1 Flowchart depicting the selection of literature.

Depressive symptoms were defined as a range of symptoms detected by a validated scale of depressive symptoms used in established mental health research [33].

A total of 12 studies [35–46] that fulfilled the inclusion criteria were identified. The reference lists of these 12 publications as well as the authors' personal databases were checked for further relevant publications that were not captured by the search. This identified three further studies [47–49] and a total of 15 included studies (for details see Fig. 1). The identified studies were further classified according to the exercise intervention: (i) as resistance training [50], (ii) as endurance training [51], (iii) as combined training (i.e. resistance training + endurance training) or (iv) as other exercise modalities.

PEDro scoring

The methodological quality of the studies was evaluated using the original 11-item Physiotherapy Evidence Database (PEDro) scale, which is described in detail elsewhere [52]. Originally, a PEDro cut-off of 6 was set to distinguish between high and low quality trials, but a less strict cut-off of 5 is now most often applied [52]. Full results of the PEDro scoring are reported in Table S1.

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Meta-analysis

Meta-analytical procedures in accordance with the Meta-Analysis of Observational Studies in Epidemiology framework [53] were applied to further evaluate possible effects of exercise on scores of depressive symptoms in people with MS. Only studies including an exercise group and a non-exercising control group ($n = 11$) or a sham exercise group ($n = 1$) were included. In the case of several exercise interventions in an included study [43,47], the mean effect size (ES) of all study interventions was calculated to avoid bias from the same study being counted several times. In three cases [42,44,45] authors were contacted for additional data to the meta-analysis, and this was provided in two cases [44,45]. The standardized mean difference (SMD) was computed as the mean change from before to after the intervention of the exercise group subtracted from the mean change of the control group divided by the pre-intervention pooled standard deviation and adjusted for sample size. A negative SMD indicates a beneficial improvement in overall score of depressive symptoms in the exercise group compared with the control group. The SMD was computed using a random effects model and is reported as Hedges' g, which adjusts for sample size differences across studies. The underlying assumption of the random effects model is that samples are drawn from populations with different ESs and that the true effect differs between studies. Furthermore, based on the assumption of random effects, a 95% confidence interval around the SMD was computed and heterogeneity of the studies included in the meta-analysis was tested. Heterogeneity is present if the Q statistic, computed as the sum of the squares of each ES about the SMD, is significant ($P < 0.05$). The strength of the SMD was interpreted as small, moderate or large, referring to 0.2 to <0.5, ≥0.5 to <0.8, and >0.80, respectively [54].

Sub-analysis of influencing factors

The low number of heterogeneous studies that were identified made us decide not to do a further meta-analytic moderator analysis, due to the high risk of making non-valid conclusions. Instead it was decided to do a comparative in-depth analysis of the individual studies reporting significant effects on depressive symptoms and those studies that did not find any effects.

Results

Study characteristics

Tables 3 and 4 present a total of 15 RCT studies [35–49] that were identified from the literature search. The average PEDro score was 5.6 ± 1.3 points and three studies [39,47,49] were categorized as pilot studies by the authors. Study samples ranged from 11 to 95 participants, including a total of 331 exercising subjects and 260 controls. The exercise interventions lasted from 3 to 26 weeks and evaluated endurance training [36,39,40,42,43,45–47,49], resistance training [39,41], combined training [37,44] or other exercise modalities including sports climbing [38], yoga [38,43] and water activities [35,48]. Three studies evaluated several exercise interventions [38,39,43]. Exercise was compared with a non-training control group [36,37,40,41,43–49], an active/sham control group [35,40,42] or to another exercise intervention in studies without a non-training control group [38,39]. All studies reported that exercise was supervised (or partly supervised [44]). Nine studies [35,37,39–41,43,45,47,49] reported that exercise was performed in a group setting, one study applied combined group and individual sessions [44], whilst the remaining five studies [36,38,42,46,48] did not present information on this. Six studies reported data from blinded assessment [35–37,40,43,49], and four studies applied intention-to-treat analysis [36,37,44,48]. None of the included studies reported on or controlled for depressive medication, and two studies excluded subjects with MDD [40,42].

Effects of exercise on depressive symptoms

Of the 15 identified RCT studies four [35,40,41,47] reported improved depressive symptoms after the exercise intervention, whilst Petajan *et al*. [46] reported a temporary improvement after 5 and 10 weeks of intervention but not after 15 weeks. The study of Dalgas *et al*. [41] was not able to reproduce the reported improvement when the control group was subjected to the same resistance training intervention during the follow-up period. The study of Hebert *et al*. [36] showed a time effect on depression score in the exercise group, but no time × group interaction. All remaining studies [37–39,43–45,48,49] did not report any significant changes in depressive symptoms after exercise except for the study of Dettmers *et al*. [42], who reported a positive indication in an incomplete data set on depressive symptoms that had not undergone full statistical evaluation.

In summary, heterogeneous findings on the effects of exercise on depressive symptoms exist, with most studies showing no effects and one-third of the studies showing minor positive effects.

Findings from meta-analysis

The meta-analysis included 12 ESs from the 12 included studies reflecting a total of 476 subjects. As

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seen in Fig. 2 and Table 2, 11 ESs were negative and two out of the 12 individual ESs were statistically significant ($P < 0.05$). The SMD across studies was $g = -0.37$, 95% confidence interval (−0.56; −0.17), which differed statistically from zero. To test whether the results of the studies were sufficiently similar to warrant aggregation into an overall result, homogeneity of the sample was tested, showing that the null hypothesis of homogeneity could not be rejected ($Q = 12.05$, df = 11, $P = 0.36$). No correlation was found between the ES and the PEDro score (Spearman's rho = 0.09, $P = 0.78$). In summary the meta-analysis indicated a small beneficial effect of exercise on depressive symptoms in people with MS.

Level of depressive symptoms at baseline

In studies applying depression scales with defined cut-off scores, participants of five studies [35–37,40,45] showed average baseline depression scores above a level indicating mild depression. Of these studies two showed positive effects of exercise on depression score [35,40], one showed a time effect but no time × group interaction [36] and two showed no effects [37,45].

In summary, no clear effect of the baseline level of depressive symptoms can be seen. However, most of the studies that show positive effects of exercise on depressive symptoms have investigated participants with an average baseline depression score that is

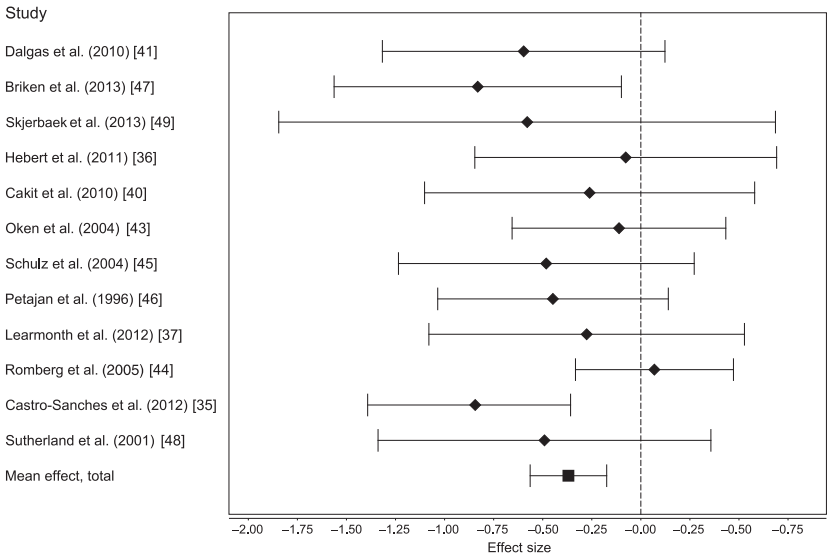


Figure 2 Forest plot of the effect sizes and 95% confidence intervals of the changes in depression score following different exercise interventions in people with multiple sclerosis.

Table 2 Effect sizes of studies evaluating the effects of exercise on depressive symptoms in people with MS

Study	Sample size	Effect size		95% confidence interval	
		Hedges' *g*	Standard error	Lower limit	Upper limit
Dalgas *et al.* (2010) [41]	31	−0.597	0.367	−1.317	0.123
Briken *et al.* (2013) [47]	42	−0.831	0.373	−1.563	−0.099
Skjerbæk *et al.* (2013) [49]	10	−0.579	0.646	−1.845	0.686
Hebert *et al.* (2011) [36]	26	−0.077	0.392	−0.846	0.692
Cakit *et al.* (2010) [40]	23	−0.261	0.429	−1.102	0.580
Oken *et al.* (2004) [43]	57	−0.111	0.278	−0.656	0.433
Schulz *et al.* (2004) [45]	28	−0.482	0.384	−1.235	0.272
Petajan *et al.* (1996) [46]	46	−0.448	0.300	−1.035	0.140
Learmonth *et al.* (2012) [37]	25	−0.276	0.410	−1.080	0.528
Romberg *et al.* (2005) [44]	95	0.069	0.205	−0.333	0.472
Castro-Sanchez *et al.* (2012) [35]	71	−0.844	0.245	−1.392	−0.358
Sutherland *et al.* (2001) [48]	22	−0.491	0.433	−1.339	0.357
Mean effect, total		−0.369	0.099	−0.564	−0.174

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above the cut-off score (indicative of mild depression) of the applied depression instrument, indicating a possible effect of the baseline level of depressive symptoms.

Influence of disability level, type of MS and age

Not all studies report the Expanded Disability Status Scale (EDSS) level of the participants [36,38,39,48] or they report only the EDSS range [40,49] making conclusions on the effects of EDSS difficult. However, in studies showing improved depressive symptoms after exercise the average EDSS level is generally moderate to high (3.7–6.3) [35,41,47], whereas it is generally lower (2.0–3.8) in studies reporting no effects on EDSS except in the study of Learmonth *et al*. (6.1) [37]. Most studies either include mixed MS populations with no sub-analyses on MS type [35,36,38–40,42,44,45,47,49] or do not report on this [37,43,46,48]. Only one study included only one type of MS patients (relapsing–remitting MS) and showed positive effects [41], but no conclusions can be made on the possible effect of MS type from the existing studies. The effects of exercise on depressive symptoms do not seem to be influenced by the age of the participants.

In summary, disability level but not age and MS type may impact the effects of exercise on depressive symptoms, but data are too limited to allow conclusions.

Influence of depression instrument

As presented in Table 3, the studies showing positive effects of exercise on depressive symptoms applied the Beck Depression Inventory (BDI) [35,40], the Major Depression Inventory [41] and the Inventory of Depressive Symptomatology [47], respectively. Studies showing no effects of exercise on the BDI [36,39] and Major Depression Inventory [49] were also present. No studies applying the Hospital Anxiety and Depression Scale (HADS), POMS or Center for Epidemiologic Studies Depression Scale showed any effects of exercise. A full list detailing the applied depression instruments can be found in Table S2.

In summary, especially instruments sensitive to somatic complaints may be more responsive to changes induced by exercise but the limited and heterogeneous results prohibit conclusions.

Influence of primary outcome and fatigue

Only one of the RCT studies applied depressive symptoms as the primary outcome [48], but found no effects of 10 weeks of water aerobics. In the four studies showing a positive effect of exercise on depressive symptoms [35,40,41,47], a concomitant significant effect was seen on the primary outcome as well as in a measure of MS fatigue. In all other studies that clearly stated the primary outcome [36,37,39,43] no effects of exercise were seen on the primary outcome or on depressive symptoms except in the study of Romberg *et al*. [44] showing a minor effect on walking speed but no effect on depressive symptoms. In studies showing no effects on depressive symptoms most studies also showed no effects on fatigue [36–39,44,46,49], but exceptions were found [43,45,48].

In summary, studies showing improved depressive symptoms after exercise also show a concomitant improvement in the primary outcome of the study and in fatigue, which contrasts with most studies showing no effects of exercise on depressive symptoms.

Influence of exercise modality, volume, duration and intensity

Only one study [41] evaluated the effects of resistance training on depressive symptoms against a non-training control group and reported improvements. However, the findings could not be reproduced in the control group when exposed to the same exercise protocol after the trial. Two endurance training studies [40,47] reported improved depressive symptoms, one found a temporary increase [46], one found indications of an improvement in an incomplete data set [42], whilst four studies showed no effects [36,43,45,49]. A head to head study evaluating resistance training and endurance training showed neither time nor a time × group effect on depressive symptoms [39]. None of the studies evaluating combined training showed any improvements in depressive symptoms [37,44]. In studies categorized as 'other training modalities', water Ai-Chi [35], but not water aerobics [48], yoga [38,43] and sports climbing [38], showed a positive effect on depressive symptoms. When comparing studies that show an effect of exercise on depressive symptoms with studies that report no effects, no apparent effect of exercise frequency (2.3 ± 0.5 sessions/week vs. 2.5 ± 1.0 sessions/week), total number of exercise sessions (26 ± 10 sessions/week vs. 31 ± 38 sessions/week) or duration of the exercise intervention (12 ± 5 weeks vs.12 ± 8 weeks) was observed. Exercise intensity (and progression) is generally poorly described in the included studies. Amongst the studies that report sufficiently on intensity [36,40,41,45–47,49], the studies reporting positive effects of exercise on depressive symptoms [40,41,47]

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Table 3 Characteristics of the studies evaluating the effects on depressive symptoms in people with multiple sclerosis: protocol description

Study	Exercise modality	Design	Sample size and age	Drop-outs, adherence and adverse events	Disability level, MS type and medication	Duration (weeks)/ frequency (days/week)	Training regime
Dalgas *et al.* (2010) [41]	RT	RCT with follow-up RT vs. CON (waitlist CON)	*n* = 38 RT 19, Con 19 47.7 ± 10.4 years	Total DO 7/38 (18%) RT DO 5/19 (13%) Adherence 99% No adverse events	EDSS range 3–5.5 Mean EDSS 3.7 Type RR Medication NR	12 weeks + 12 weeks follow-up 2 sessions/week Total 24 sessions	5 leg exercises 3–4 sets × 8–12 repetitions at 8–15 RM Supervised group sessions
Sabapathy *et al.* (2010) [39]	RT and ET	RCT (crossover with 8 week washout) RT vs. ET	*n* = 21 RT 15, ET 6 55 years (47–66 years)	Total DO 5/21 (24%) RT DO 1/21 (5%) ET DO 4/21 (19%) Adherence: RT 99%, ET 83% No adverse events	EDSS 1–3 Type RR, SP, PP Medication NR	2 × 8 weeks (crossover) 2 sessions/week Total 16 sessions	RT: 8 exercises (3 leg) 2–3 sets × 6–10 repetitions ET: circuit of 8 exercise stations, 5 min/station; intensity increased throughout the program Supervised group sessions
Briken *et al.* (2013) [47]	ET: ET1 cycling, ET2 arm-ergometry, ET3 rowing	RCT ET1, ET2, ET3 vs. CON (waitlist CON)	*n* = 47 ET1 12, ET2 11, ET3, 12, CON 11 48.8 ± 6.8 years	Total DO: 5/47 (10.5%) ET1 DO 1/12 (8.6%) ET2 DO 2/11 (17%) ET3 DO 1/12 (8.6%) CON DO 1/11 (10%) Adherence ≈100% No adverse events	EDSS 4–6 Mean EDSS 4.7–5.2 Type SP, PP Medication NR	8–10 weeks 2–3 sessions/week Total 16–30 sessions	ET1: cycling ET2: arm-ergometry ET3: rowing Duration 15−45 min Intensity 100%–130% of aerobic threshold Supervised group sessions
Skjerbæk *et al.* (2013) [49]	ET	RCT ET vs. CON	*n* = 11 ET 6, CON 5 62.0 ± 5.9 years	Total DO 1/11 (9%) ET DO 1/6 (17%) Adherence 96% No adverse events	EDSS 6.5–8 Type SP, PP Medication NR	4 weeks 3 sessions/week Total 10 sessions	ET: upper body ergometry Duration 6 × 3 min Intensity 65%–75% of VO_2-peak Supervised group sessions
Hebert *et al.* (2011) [36]	ET and balance	RCT ET and balance vs. CON (waitlist CON)	*n* = 38 ET 13, balance 12, CON 13 46.8 ± 10.5 years	Total DO 1/38 (3%) ET DO 0/13 (0%) Balance DO 0/12 (0%) CON DO 1/13 (8%) Adherence NR Adverse events 1	EDSS NR Type RR, SP Medication NR MDD excluded	6 weeks + 4 weeks follow-up 2 sessions/week Total 12 sessions	ET: bicycling. Duration 2 × 15 min Intensity 65%–75% of HR max Stretching Supervised
Cakit *et al.* (2010) [40]	ET	RCT ET vs. A-CON and CON	*n* = 45 ET 14, A-CON 10, CON 9 36.4 ± 10.5 years	Total DO 12/45 (27%) ET DO 1/15 (7%) A-CON DO 5/15 (33%) CON DO 6/15 (40%) Adherence NR No adverse events	EDSS ≤ 6.0 Type RR, SP Medication NR MDD excluded	8 weeks 2 sessions/week Total 16 sessions	ET: ergometer bicycling with increasing load. 15 sets of 2 min. Initially 40% of tolerated max. workload. 20–25 min walking, stretching, balance A-CON: home-based walking, stretching, balance Supervised group sessions

(continued)

Table 3 *(Continued)*

Study	Exercise modality	Design	Sample size and age	Drop-outs, adherence and adverse events	Disability level, MS type and medication	Duration (weeks)/ frequency (days/week)	Training regime
Dettmers *et al.* (2009) [42]	ET	RCT ET vs. A-CON	*n* = 31 ET 16, A-CON 15 45.8 ± 7.9 years	Total DO 1/31 (3%) ET DO 1/16 (6%) CON DO 0/15 (0%) Adherence NR Adverse events NR	EDSS < 4.5 Mean EDSS 2.6 All complained about fatigue Type RR, SP, PP Medication NR	3 weeks 3 sessions/week lasting 45 min Total 9 sessions	ET: Repetitive walking with distractive elements. Training at own comfortable speed. HR below 140 b/min. Supervised A-CON: sensory, balance, coordination training, stretching and relaxation.
Oken *et al.* (2004) [43]	ET and YT	RCT ET vs. YT, CON	*n* = 69 ET 21, YT 26, CON 22 48.8 ± 10.4 years	Total DO 12/69 (17%) ET DO 6/21 (29%) YT DO 4/26 (15%) CON DO 2/22 (9%) Adherence: ET 65%, YT 68% Six adverse events	EDSS < 6 Mean EDSS 2.9–3.2 Type NR Medication NR	26 weeks 1 session/week (and encouraged to exercise at home) Total 26 sessions	Ergometer bicycling and Swiss ball training Duration: Until fatigue or until reaching personal goal Intensity: Details NR Supervised group sessions
Schulz *et al.* (2004) [45]	ET	RCT ET vs. CON, HC (waitlist CON)	*n* = 39 ET 23, CON 16, HC 20 39 ± 9 years	Total DO NR ET DO NR CON DO NR Adherence NR Adverse events NR	EDSS < 5 Mean EDSS 2.5 Type RR, PP, SP Medication NR	8 weeks 2 sessions/week Total 16 sessions	Interval ergometer bicycling Duration 30 min Intensity 60% of VO_2 max Supervised group sessions
Petajan *et al.* (1996) [46]	ET	RCT ET vs. CON (waitlist CON)	*n* = 46 ET 21, CON 25 41.1 ± 2 years	Total DO 8/54 (15%) ET DO 6/27 (22%) CON DO 2/27 (7%) Adherence ≈97% 7 adverse events, 2 serious adverse events	EDSS < 6 Mean EDSS 3.8 Type NR Medication NR	15 weeks 3 sessions/week Total 45 sessions	Arm and leg ergometry Duration 40 min Intensity 60% of VO_2 max Supervised
Learmonth *et al.* (2012) [37]	CT	RCT CT vs. CON	*n* = 32 CT 20, CON 12 51.4 ± 8.0 years	Total DO 4/32 (12.5%) CT DO 3/20 (15%) CON DO 1/12 (8%) Adherence CT 71% No adverse events	EDSS range 5–6.5 Mean EDSS 6.1 Type NR Medication NR	12 weeks 2 sessions/week Total 24 sessions	CT: 30–40 min circuit exercises (8–12 exercises) targeting aerobic endurance, resistance and balance. 1 min work/1 min rest. 5 levels of progression. Self-regulated pace Supervised group session
Romberg *et al.* (2005) [44]	CT	RCT CT vs. CON		Total DO 4/95 (4%) CT DO 2/47 (4%)	EDSS range 1–5.5 Mean EDSS 2.0		Week 1–3: inpatient program

(continued)

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Table 3 *(Continued)*

Study	Exercise modality	Design	Sample size and age	Drop-outs, adherence and adverse events	Disability level, MS type and medication	Duration (weeks)/ frequency (days/week)	Training regime
			n = 95 CT 47, CON 48 43.8 ± 6.3 years	CON DO 2/48 (4%) Adherence 93% (RT 59%, ET 185%) No adverse events	Type All Medication NR	26 weeks CT 3–5 sessions/week Total 118–140 sessions	Week 4–26: home-based CT: circuit training, 10 exercises for whole body, 2 sets, 10–15 repetitions. Aquatic training/ preferred mode of ET Intensity: details NR Supervised group sessions/individual non-supervised
Castro-Sanchez *et al.* (2012) [35]	HT	RCT with follow-up HT vs. A-CON (A-CON sham exercise)	*n* = 73 HT 36, CON 37 46 years	Total DO 2/73 (3%) HT DO 0/36 (0%) CON DO 2/37 (5%) Adherence NR Adverse events NR	EDSS ≤ 7.5 Mean EDSS 6.3 Type SP and PP Medication NR	20 weeks + 10 weeks of follow-up 2 sessions/week Total 40 sessions	HT: Ai-Chi in swimming pool consisting of 16 exercises targeting arms, legs and the torso A-CON: abdominal breathing and contraction−relaxation exercises Supervised group sessions
Velikonja *et al.* (2010) [38]	SC and YT	RCT pre vs. post	*n* = 20 SC NR, YT NR 42 years (26–50 years)	DO NR Adherence NR Adverse events NR	EDSS ≤ 6 Type RR, SP, PP Medication NR	10 weeks 1 session/week Total 10 sessions	Details NR Supervised
Sutherland *et al.* (2001) [48]	WA	RCT ET vs. CON	*n* = 22 ET 11, CON 11 47.1 ± 4.8 years	Total DO 0/22 (0%) ET DO 5/18 (27%) CON DO 5/18 (27%) Adherence NR Adverse events NR	EDSS NR Type NR Medication NR	10 weeks 3 sessions/week Total 30 sessions	Water aerobics Duration NR Intensity NR Supervised

A-CON, active control; CON, control; CT, combined training; DO, drop-outs; EDSS, Expanded Disability Status Scale; ET, endurance training; HC, healthy controls; HR, heart rate; HT, hydrotherapy; MDD, major depression disease; NR, not reported; PP, primary progressive; RCT, randomized controlled trial; RM, repetition maximum; RR, relapsing−remitting; RT, resistance training; SC, sports climbing; SP, secondary progressive; WA, water aerobics; YT, yoga training.

are also the studies applying the highest relative exercise intensities.

In summary, it is not clear from the literature whether certain exercise modalities are superior to others, whether a certain training frequency is optimal or whether a certain exercise duration/volume is required to positively influence depressive symptoms. Exercise intensity may be an important factor (Table 4).

Discussion

The main finding of the present systematic review is that exercise therapy poses the potential to reduce depressive symptoms in patients with MS, but significant improvements were only found in approximately a third of the identified studies. In support of a potential beneficial effect were the results of the meta-analysis showing a small but positive effect of exercise on depressive symptoms across the included studies. Despite the overall acceptable methodological quality of the included studies (5.6 ± 1.3, cut-off high quality trials 5 [55]), interpretation of the identified studies should be performed cautiously. Moreover the included studies have generally not been designed to evaluate the effect of exercise on depressive symptoms, and these are characterized by great heterogeneity in terms of the applied exercise intervention (modality, duration, volume and intensity), choice of depression instrument, baseline level of depressive symptoms and patient disability level, of which some at least may influence the results. Furthermore, the results may be influenced by concomitant improvements in typical MS-related symptoms such as fatigue, which explain at least some of the improvements in depressive symptoms.

Effects of exercise on depressive symptoms

Our cautious conclusion that exercise poses the potential to reduce depressive symptoms in MS is in line with a recent topical review that identified 11 RCT studies on exercise and depression in MS [30]. However, the present systematic review adds a thorough literature search and in-depth analysis of potential factors that may have influenced the results, as well as a meta-analysis confirming the potential positive effect of exercise. Our findings are in agreement with a previous meta-analysis evaluating the impact of physical activity interventions on depressive symptoms in people without MDD, reporting a small negative SMD of −0.37 amongst 38 supervised exercise studies and −0.52 amongst 22 non-supervised exercise studies [21]. Our findings are also in agreement with findings from other related clinical populations. A recent systematic review and meta-analysis in stroke patients including 13 studies (n = 1022) showed a small but significant SMD of −0.13 in favour of a beneficial effect of exercise on depressive symptoms, but the effect was not retained at follow-up [33]. In people with MDD the most recent Cochrane review included 35 trials (1356 participants) comparing exercise with no treatment or a control intervention and reported the SMD for the primary outcome of MDD at the end of treatment to be −0.62, indicating a moderate clinical effect. Interestingly, when only the six trials (464 participants) with adequate allocation concealment, intention-to-treat analysis and blinded outcome assessment were included, the SMD was not statistically significant, −0.18 [56]. Although this Cochrane review included patients with MDD, this strongly suggests that high quality studies are needed before solid conclusions can be made on the effects of exercise on depressive symptoms and MDD in MS. In addition to long-term training effects exercise may also induce acute effects on depressive symptoms. Moreover, Petruzzello *et al.* [57] reported that a single session of moderate intensity cycling exercise was associated with acute reductions in depressive symptoms when measured 5, 20 and 60 min after exercise, suggesting a role for exercise in the immediate treatment of depressive symptoms.

Level of depressive symptoms at baseline

No clear effect of the baseline level of depressive symptoms was found on the effects of exercise, but most studies showing positive effects of exercise have participants with average baseline levels above the cut-off score of the applied depression instrument, indicative of more severe depressive symptoms or mild depression. Nevertheless, a major limitation of the existing literature is that no studies have evaluated MS patients with a clinically confirmed diagnosis of MDD. A similar limitation was seen in studies evaluating the effects of exercise on depression in stroke patients [33]. Our findings of a potential effect of the baseline level of depressive symptoms are somewhat supported by a meta-analysis of Sjösten and Kivelä who, based on studies on elderly people, reported that exercise was effective in treating depression, especially in individuals with higher depressive baseline levels [58]. Taken together, the existing literature provides preliminary evidence suggesting that exercise may prevent or reduce depressive symptoms in the more affected subjects, whereas no studies exist on the treatment effects of exercise on MDD in people with MS.

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Table 4 Characteristics of the studies evaluating the effects on depressive symptoms in people with multiple sclerosis: quality assessment, outcome and exposure description

Study	Outcome level and primary outcome	Depression instrument and cut-off	Baseline score depression	Post value depression score	Time effects on depression score	Time × group interaction on depression score	Effects of training	PEDro score (0–10)
Dalgas *et al.* (2010) [41]	Secondary PO strength	MDI Cut-off 20	RT 10.3 ± 5.9 CON 8.8 ± 4.5 Follow-up: RT 7.9 ± 4.9 CON 9.9 ± 4.8	RT 7.9 ± 4.9 CON 9.9 ± 4.8 Follow-up: RT 8.7 ± 7.3 CON 8.9 ± 4.5	NR	MDI ↑ in RT compared with CON	Depression ↑ HRQoL ↑ Fatigue ↑ Strength (PO) ↑ (data could not be reproduced in CON during follow-up)	5/10
Sabapathy *et al.* (2010) [39]	Secondary PO mobility, fatigue, HRQoL	BDI Cut-off 10	RT 9.8 ± 9.0 ET 9.7 ± 11.6	RT 8.7 ± 7.7 ET 10.3 ± 11.6	BDI: RT → ET →	BDI →	Depression → Fatigue (PO) → HRQoL (PO) →	5/10
Briken *et al.* (2013) [47]	Secondary PO VO_2-peak	IDS-SR30 Cut-off 18	ET1 18.4 ± 12.3 ET2 21.1 ± 10.2 ET3 13.9 ± 7.8 CON 14.1 ± 7.9	ET1 14.7 ± 9.5 ET2 12.3 ± 6.6 ET3 14.0 ± 9.6 CON 18.4 ± 10.4	NR	ET1 and ET2 ↑ compared with CON	Depression ↑ Fatigue ↑ VO_2-peak (PO) ET1 ↑	5/10
Skjerbæk *et al.* (2013) [49]	Secondary PO feasibility	MDI Cut-off 20	ET 10.6 ± 1.7 CON 14.6 ± 7.3	ET 4.4 ± 4.0 CON 11.8 ± 9.6	NR	MDI →	Depression → Fatigue → PO N/A	7/10
Hebert *et al.* (2011) [36]	Secondary PO fatigue and balance	BDI-II Cut-off 10	ET 17.3 ± 8.6 Balance 16.5 ± 9.1 CON 18.5 ± 6.4	ET 12.2 ± 6.5 Balance 7.0 ± 7.3 CON 14.0 ± 9.0	BDI: ET ↑ Balance ↑ CON →	BDI →	Depression NS Fatigue (PO) NS Balance (PO) NS	8/10
Cakit *et al.* (2010) [40]	Secondary PO gait speed	BDI Cut-off 10	ET 22.8 ± 12.7 A-CON 40.2 ± 15.8 CON 27.0 ± 17.6	ET 17.2 ± 12.3 A-CON 41.8 ± 18.3 CON 25.4 ± 22.8	ET: BDI ↑ A-CON → CON →	BDI: ET ↑ compared with A-CON and CON A-CON vs. CON →	Depression ↑ Fatigue ↑ HRQoL ↑ Gait speed (PO) ↑	5/10
Dettmers *et al.* (2009) [42]	Secondary PO walking distance	BDI Cut-off 10	ET 9.9 ± 6.8 A-CON 9.9 ± 5.5	NR	NR	NR	Depression NR due to incomplete data set (more subjects in A-CON ↑ on BDI than in ET) HRQoL: → Fatigue → Walking distance (PO) ↑	6/10
Oken *et al.* (2004) [43]	Secondary PO alertness and attention	CES-D Cut-off 16 POMS-SF	CES-D: ET 6.8 ± 5.0 YT 9.1 ± 4.3 CON 11.3 ± 5.5 POMS: ET 8.6 ± 8.3	CES-D: ET 6.4 ± 5.8 YT 7.5 ± 4.7 CON 11.2 ± 5.8 POMS: ET 4.6 ± 6.2	CES-D: ET → YT → CON → POMS: ET →	CES-D → POMS-SF →	Depression → HRQoL ↑ Fatigue ↑ Alertness (PO)→ Attention (PO)→	5/10

(continued)

Table 4 *(Continued)*

Study	Outcome level and primary outcome	Depression instrument and cut-off	Baseline score depression	Post value depression score	Time effects on depression score	Time × group interaction on depression score	Effects of training	PEDro score (0–10)
			YT 10.6 ± 10.0 CON 11.4 ± 10.7	YT 8.6 ± 6.4 CON 9.7 ± 10.6	YT → CON →			
Schulz *et al.* (2004) [45]	Secondary PO NR	HADS[a] Cut-off 8 POMS	HADS: ET 9.5 ± 1.4 CON 9.1 ± 2.2 POMS: ET 7.2 ± 8.2 CON 10.7 ± 7.4	HADS: ET 9.2 ± 1.4 CON 9.7 ± 1.9 POMS: ET 6.7 ± 8.0 CON 16.5 ± 16.1	NR	HADS → POMS →	Depression → HRQoL (mood) ↑ Fatigue ↑	4/10
Petajan *et al.* (1996) [46]	Secondary PO NR	POMS	ET 39.3 ± 1.4 CON 38.6 ± 1.1	ET 36.7 ± 1.6 CON 38.7 ± 1.2	POMS: ET ↑ at weeks 5 and 10, but → at week 15 CON →	NR	Depression → (↑ temporarily) Fatigue →	5/10
Learmonth *et al.* (2012) [37]	Secondary PO gait speed	HADS Cut-off 8	CT 15.9 ± 6.5 CON 15.8 ± 9.3	CT 11.7 ± 5.9 CON 13.8 ± 6.6	HADS →	HADS →	Depression → HRQoL → Fatigue → Gait speed (PO) →	7/10
Romberg *et al.* (2005) [44]	Secondary PO gait speed	CES-D[a] Cut-off 16	CT 14.7 ± 10.5 CON 15.6 ± 9.5	CT 14.3 ± 11.0 CON 14.5 ± 9.0	NR	CES-D →	Depression → HRQoL → Fatigue → Gait speed (PO) ↑	6/10
Castro-Sanchez *et al.* (2012) [35]	Secondary PO pain and disability	BDI Cut-off 10	HT 14 ± 7.7 CON 15 ± 8.7	HT 5 ± 3.2 CON 13 ± 5.9	BDI: HT ↑ MFISphys: HT ↑ MFIScog: HT ↑ MFISpsyc: HT ↑ FSS: HT ↑	NR	Depression ↑ Fatigue ↑ Pain (PO) ↑ Disability ↑	7/10
Velikonja *et al.* (2010) [38]	Not stated PO not stated	CES-D[b] Cut-off 16	SC 10.0 (6.5–19) YT 9.5 (3.8–20.3)	SC 5.0 (3.0–22.5) YT 3.0 (1.8–13.0)	CES-D: SC/YT → MFIStotal: SC ↑ MFISphys: SC ↑ MFIScog: SC ↑	NR	Depression → Fatigue ↑	3/10
Sutherland *et al.* (2001) [48]	Primary	POMS-SF	ET 7.8 ± 6.5 CON 6.6 ± 7.2	WA 4.5 ± 3.9 CON 6.8 ± 7.1	NR	POMS →	Depression → HRQoL ↑	6/10

A-CON, active control; BDI, Beck Depression Inventory; CES-D, Center for Epidemiologic Studies – Depression Scale; CON, control; DSM, Diagnostic and Statistical Manual of Mental Disorders; ET, endurance training; HADS-D/A, Hospital Anxiety and Depression Scale – Depression/Anxiety; HRQoL, health related quality of life; HT, hydrotherapy; IDS-SR, Inventory of Depressive Symptomatology – Self Report; MDI, Major Depression Inventory; MFIS, Modified Fatigue Impact Scale; N/A, not applicable; NS, non significant; NR, not reported; PO, primary outcome; POMS, Profile of Mood States; RT, resistance training; SC, sports climbing; SF, Short Form; WA, water aerobics; YT, yoga training.
Values are mean ± SD.
[a]Data obtained from personal communication.
[b]Data are median and range.

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Influence of exercise modality, volume, duration and intensity

The physiological and mental effects of exercise generally depend on exercise modality, volume, frequency and intensity [59]. The studies included in the present review covered a broad range of exercise modalities and protocols, but it could not be concluded whether certain exercise modalities, frequencies or volumes were superior to others in the prevention and treatment of depressive symptoms in MS. A preliminary moderator analysis, performed as an addendum to a meta-analysis evaluating the effects of physical activity interventions on depressive symptoms in people without a clinically confirmed MDD, showed that supervised physical activity interventions were more effective when they included flexibility and resistance training and when exercise was performed at low intensity [21]. In contrast a meta-analysis based on studies in cancer survivors showed that increases in the weekly volume of aerobic exercise reduced depressive symptoms in a dose–response fashion, a pattern evident only in higher quality trials. It was further reported that exercise reduced depressive symptoms most when exercise sessions were supervised [60]. Our systematic review suggested that exercise intensity may be an important factor in determining the effects of exercise on depressive symptoms. This is in line with Eng and Reime [33] who reported a significant effect of exercise on depressive symptoms in stroke patients when higher intensity studies were pooled, but not for lower intensity exercise protocols. Consequently, exercise intensity should be considered carefully in future studies.

Influence of depression instrument

Our analysis suggested that some of the applied depression instruments may be more responsive to changes induced by exercise than others, but the limited and heterogeneous results prohibit solid conclusions. To our knowledge no studies have provided recommendations regarding preferred depression instruments for screening of MDD or for measuring changes in the level of depressive symptoms in people with MS. In rheumatology a comprehensive literature review of the psychometric properties of different depression instruments exists [61]. Based on that work the Center for Epidemiologic Studies Depression Scale seems less appropriate since validity studies show that the scale does not provide a specific measure of depression but rather measures 'general distress'. More recommendable is the BDI-II which is a valid screening tool for MDD and for assessment of changes in depressive symptoms in a number of clinical populations, but the results need to be interpreted cautiously due to overlap between somatic and mental symptoms. The Patient Health Questionnaire is also being recommended as a diagnostic instrument for physicians in general medical settings, aiming to identify persons with mental disorders. The Patient Health Questionnaire has high clinical and research usability and efficiently identifies depressive disorders and quantifies depressive symptoms in medical populations. However, the most appropriate depression instrument for future exercise studies in MS might be the HADS, even though none of the identified studies that applied this scale showed any effects [37,45]. The advantage of the HADS is that symptoms such as insomnia and weight loss are not measured by the scale. As such the HADS seems a proper scale for a disease with a complex symptomatology like MS [62]. Despite its brevity, results from HADS screens for possible anxiety and depressive symptoms are similar to more comprehensive clinical measures [61]. Also, HADS was found to perform well in assessing symptom severity and caseness of anxiety disorders and depression in somatic, psychiatric and primary care patients and in the general population [62].

Influence of primary outcome and fatigue

Our analysis showed that reduced depressive symptoms after exercise were accompanied by improvements in the primary outcome of the study and in fatigue score, contrasting with most studies that show no effects of exercise on depressive symptoms. This finding suggests that exercise interventions that effectively induce improvements in other (targeted) areas seem more likely to also influence depressive symptoms positively. Furthermore, it may suggest that the positive effects on typical MS symptoms such as fatigue may explain at least some of the effects seen on depressive symptoms. It also suggests that improvements of depressive symptoms are particularly related to fatigue in MS. One study on resistance training showed a weak but significant correlation between the changes of fatigue and depressive symptoms after the intervention, and this persisted when questions regarding fatigue were removed from the depression instrument. The direction of this relationship, however, was not examined in this study [41]. Other intervention studies [63,64] examining fatigue and depressive symptoms have also found a relationship between depressive symptoms and fatigue. Moreover, Bakshi [65] has suggested that fatigue and depressive symptoms share common underlying mechanisms such as psychological factors or brain lesions in specific

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neural pathways. The association between fatigue and depressive symptoms needs to be carefully addressed in future studies.

Mechanisms

The identified studies do not identify the mechanisms underlying the possible link between exercise and depressive symptoms, and an in-depth discussion of this is beyond the scope of this study. Nevertheless, several physiological and psychological mechanisms have been described [33]. However, there is little research evidence to either support or refute most of these theories. Furthermore, it cannot be excluded that interactions with peers during some of the group exercise interventions may be a key element, since this has not been controlled for in most MS studies.

Limitations

Limitations of the present systematic review include that (i) only few and heterogeneous studies were identified on the effects of exercise on depressive symptoms, (ii) no studies evaluated the treatment effects of exercise on MDD, (iii) depressive symptoms were most often a secondary outcome which probably limits the power of many identified studies, (iv) participants were primarily mild to moderately impaired MS patients without any serious comorbidities, and (v) studies did not control or report on depressive medication. Finally, the results of the meta-analysis should be interpreted cautiously, given the heterogeneous exercise interventions and the use of different depression instruments which may measure different constructs.

Conclusion

Exercise may be a potential treatment to prevent or reduce depressive symptoms in individuals with MS, but the existing studies do not allow solid conclusions. Future well-designed studies evaluating the effects of exercise on depressive symptoms and MDD in MS are highly warranted.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Included papers rated according to the PEDro scale.
Table S2. Depression scales applied in exercise studies involving people with multiple sclerosis.

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