Ver documento original

Exercise therapy for multiple sclerosis

Rietberg MB, Brooks D, Uitdehaag BMJ, Kwakkel G

This review should be cited as: Rietberg MB, Brooks D, Uitdehaag BMJ, Kwakkel G. Exercise therapy for multiple sclerosis (Cochrane Review). In: *The Cochrane Library,* Issue 1, 2006. Oxford: Update Software.

A substantive amendment to this systematic review was last made on 28 February 2004. Cochrane reviews are regularly checked and updated if necessary.

Abstract

Background: No intervention has proven effective in modifying long-term disease prognosis in Multiple Sclerosis (MS) but exercise therapy is considered to be an important part of symptomatic and supportive treatment for these patients.

Objective: To assess the effectiveness of exercise therapy for patients with MS in terms of activities of daily living and health-related quality of life.

Search strategy: We searched the Cochrane MS Group Specialised Register (searched: March 2004), Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 2, 2004), MEDLINE (from 1966 to March 2004), EMBASE (from 1988 to March 2004), CINAHL (from 1982 to March 2004), PEDro (from 1999 to March 2004) . Manual search in the journal 'Multiple Sclerosis' and screening of the reference lists of identified studies and reviews. We also searched abstracts published in proceedings of conferences.

Selection criteria: Randomised Controlled Trials (RCTs) that reported on exercise therapy for adults with MS, not presently experiencing an exacerbation; outcomes that include measures of activity limitation or health-related quality of life or both.

Data collection and analysis: Two reviewers independently extracted data and methodological quality of the included trials. Disagreements were resolved by discussion. The results were analysed using a best-evidence synthesis based on methodological quality.

Main results: Nine high-methodological-quality RCTs(260 participants) met the inclusion criteria. Six trials focussed on comparison of exercise therapy versus no exercise therapy, whereas three trials compared two interventions that both met our definition of exercise therapy. Best evidence synthesis showed strong evidence in favour of exercise therapy compared to no exercise therapy in terms of muscle power function, exercise tolerance functions and mobility-related activities. Moderate evidence was found for improving mood. No evidence was observed for exercise therapy on fatigue and perception of handicap when compared to no exercise therapy. Finally, no evidence was found that specific exercise therapy programmes were more successful in improving activities and participation than other exercise treatments. No evidence of deleterious effects of exercise therapy was described in included studies.

Reviewers' conclusions: The results of the present review suggest that exercise therapy can be beneficial for patients with MS not experiencing an exacerbation. There is an urgent need for consensus on a core set of outcome measures to be used in exercise trials. In addition, these studies should experimentally control for 'dose' of treatment, type of MS and should include sufficient contrast between experimental and control groups.

Background

Multiple sclerosis (MS) is a chronic disease of the central nervous system. The variable distribution of demyelination and axonal loss throughout the central nervous system may lead to disorders of strength, sensation, co-ordination and balance, as well as visual, cognitive and affective deficits, that may lead to severe progressive limitations of functioning in daily life. Although the exact aetiology of the disease is unknown, it is generally accepted that MS

involves an abnormal immune response within the central nervous system. In Europe, at least 350,000 persons have the disease. Wide variations exist between and within European countries in the incidence of MS (3.4/100,00 between 1983 and 1987 in Western areas of Norway to 11.6/100,000 between 1979 and 1993 in western Seinäjoki, Finland) and its prevalence (38-58/100,000 in France to 144/100,000 in North-western Sardinia), as well as in the general standard of care for MS patients (Pozzilli 2002).

One of the primary aims of rehabilitation for patients with multiple sclerosis is to increase their levels of activity and participation and increase their independence (Langdon 1999). Recent advances in drug therapies, such as with ÃŸ-interferon that reduce relapse rate offer renewed hope (Anonymous 1995). However, a clinically meaningful effect of drug therapy on disability (activity) has not yet been demonstrated (Freeman 1997). Therefore, the symptomatic and supportive therapies that aim to achieve an optimisation of daily functioning of patients with MS remain important. The role of rehabilitation with physical training being a central component is perceived to be important in this process. In most cases the exercise therapy is part of a goal-orientated, multidisciplinary approach (for example Freeman 1997; Patti 2003); although, sometimes, exercise therapy is offered by one discipline only (for example Fuller 1996; Svensson 1994).

To our knowledge, the effectiveness of exercise-based rehabilitation programmes for multiple sclerosis has not been formally assessed in a systematic review. In 2001, a meta-analysis on the effectiveness of physical, psychological, and functional interventions in treating clients with multiple sclerosis was performed (Baker 2001), suggesting that occupational therapy (OT) was effective in treating the deficits in MS. However, this systematic review was not focussed on effects of exercise therapy alone, but also on the effects of other intervention regimes, such as psychotherapy and electrotherapy. In addition, pre-experimental designs without a control group were included in the analysis, which may have biased the found outcomes. Recently, a systematic review on the effectiveness of OT interventions on functional ability, social participation or health-related quality of life or both in patients with MS was performed (Steultjens 2003). No recommendations could be made on whether occupational therapy improves outcome in MS patients. The authors conclude that further research is needed, due to lack of (randomised controlled) efficacy studies. In addition, Steultjens review (Steultjens 2003) was not focused on effects of exercise therapy alone, but also examined the effects of education, advice and counselling. In addition, quasi-experimental trials (Cook 1980) were included in the analysis. This review focused only on the effects of exercise therapy for MS.

Objectives

- The primary aim of the present review was to determine whether exercise therapy is an effective treatment for patients with MS in terms of Activities of Daily Living (ADL).
- The secondary objective is to determine the effects of exercise therapy on health-related quality of life (HRQoL) in these patients.

Criteria for considering studies for this review

Types of studies

The review was restricted to randomised controlled clinical trials (RCT's). RCT's are defined as trials in which investigators allocate eligible people to treatment and control group on a random basis (Clarke 2000). Randomized Cross-over trials were considered as RCT's (Clarke 2000).

Types of participants

Studies with patients, of all ages and of either sex, who fulfilled a clinical diagnosis of Multiple Sclerosis (as described by McDonald 2001; Poser 1983; Schumacher 1965) were included. For inclusion in this review the patients under research have to be free of exacerbation.

Types of intervention

All trials that fitted the authors' definition of exercise therapy were considered for inclusion. Exercise therapy was defined as: "a series of movements with the aim of training or developing the body by a routine practise or as a physical training to promote good physical health" (Webster's New World Dictionary 1982)

The goal of the exercise therapy had to be associated to one or more of the following codes of the International Classification of Functioning (ICF) (Appendix I): code b455 (exercise tolerance functions), code d410 (changing basic body position), code d415 (maintaining a body position), code d430 (lifting and carrying objects), code d435 (moving objects with lower extremities), code d440 (fine hand use), code d445 (hand and arm use) code d450 (walking), code d455 (moving around), code d460 (moving around in different locations), code d510 (washing oneself), code d530 (toileting), code d540 (dressing), code d550 (eating), code d560 (drinking).

- Therefore, the included interventions concerned studies that applied:
- rehabilitation, physical therapy (with or without using training equipment), training, functional training, home physical training, and aquatic exercise. Studies were excluded if the goal of the therapy primaraly focussed on improving physical functions, but was associated with learning to handle products, technology and equipment in daily living. As a result, the following codes of the ICF-classifications were excluded: code e120 (products and technology for personal indoor and outdoor mobility and transportation), code e1151 (assistive products and technology for personal use in daily living).
- In line with the above codes for exclusion, the following interventions were not incorporated in the present analysis: baths, electrotherapy, electric stimulation (functional, neuromuscular), transcutaneous electrical nerve stimulation (See Appendix I).

Types of outcome measures

Studies that used types of outcome that measured aspects of activities limitation or HRQoL were included

Search strategy for identification of studies

See: Cochrane Multiple Sclerosis Group search strategy

- We searched the following databases:
- (1) The Cochrane MS Group Specialised Register (March 2004)
- (2) the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, Issue 2, 2004)
- (3) MEDLINE (January 1966 to March 2004)
- (4) EMBASE (January 1988 to March 2004)
- (5) CINAHL (from 1982 to March 2004)
- (6) PEDro (from 1999 to March 2004)
- (7) Dutch electronic databases PICarta and DOC-online (1999 to March 2004)
- In addition, a manual search in the journal 'Multiple Sclerosis' was performed. References presented in relevant publications were examined and abstracts published in proceedings of conferences were searched. The principal author of the study was contacted whenever more information about the trial was needed.

The following procedures were used to identify trials in the database of Pubmed (MEDLINE) and was adapted to make it applicable to the other databases:

- Indication:
- #1 Search Multiple Sclerosis
- #2 Search MS
- #3 Search Demyelinating Autoimmune Diseases, CNS
- #4 Search #1 OR #2 OR #3

- Intervention:
- #5 Search effectiveness

- #6 Search cohort effect
- #7 Search effect$
- #8 Search #5 OR #6 OR #7
- #9 Search exercise therapy
- #10 Search physiotherapy
- #11 Search occupational therapy
- #12 Search functional therapy
- #13 Search physical therapy
- #14 Search #9 OR #10 OR #11 OR #12 OR #13
- #15 Search $therapy
- #16 Search physical$
- #17 Search physio$
- #18 Search training$
- #19 Search function$
- #20 Search #15 OR #16 OR #17 OR # 18 OR #19
- #21 Search activities of daily living
- #22 Search ADL
- #23 Search #21 OR #22
- #24 Search recovery of function
- #25 Search disability of function
- #26 Search disability
- #27 Search #24 OR #25 OR #26
- #28 Search rehabilitation
- #29 Search #8 OR #14 OR #20 OR #23 OR #27 OR #28

- Publication Type:
- #30 Search randomised controlled trial
- #31 Search randomised controlled trials
- #32 Search randomised clinical trial
- #33 Search randomised clinical trials
- #34 Search random$
- #35 Search random allocation
- #36 Search RCT
- #37 Search controlled clinical trial
- #38 Search clinical trial
- #39 Search experimental clinical trial
- #40 Search true experimental clinical trial
- #41 Search research design
- #42 Search human
- #43 Search#32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 AND #44

- Indication, Intervention and Publication Type:
- #44 Search #4 AND #29 AND #43

Methods of the review

- Study selection
- Two reviewers (MJCP & MBR) independently screened titles and abstracts of all studies identified by the search strategy and discarded irrelevant publications in order to create a list of eligible studies. After the potential trials had been retrieved, each reviewer independently applied the inclusion/exclusion criteria to unblinded full reports. Additional information was sought, where necessary, for all trials that appeared to meet the inclusion criteria. Consensus was used to resolve disagreements concerning the final inclusion of studies, and a third reviewer was consulted if disagreements persisted.

- Methodological quality assessment
- Two reviewers (DB, MBR) independently assessed the methodological quality of included trials, using an 11-items scoring list (see Appendix 2). This list contains seven criteria for internal validity and four descriptive criteria. All items were scored as clearly yes (2 points), clearly no (0 points) or not sure (1 point). Equal weight was applied to all items. Scores of individual items were summed to obtain overall score. Inter-rater agreement on methodological quality scale scores was assessed by means of the kappa statistic (Cohen 1960). The kappa coefficient ranges between zero (completely chance-explained agreement) and one (perfect agreement). A third reviewer resolved disagreements.

- Data extraction
- The following information was systematically extracted by the reviewers: study design, description of randomisation, characteristics of the participants (number, type of MS, disease duration, age, gender and Expanded Disability Status Scale [EDSS]-score), inclusion/exclusion criteria, description of the study and control treatment, outcome measures, length of follow up, and number of patients withdrawn or dropping out of the trial. For studies where the required data were missing, further details were requested from the main author of the manuscript.

- Analysis
- In order to allow for differences in applied treatment contrast, the analysis focused on comparisons of an exercise therapy intervention with a non-exercise intervention. Studies that applied exercise training for the control group as well were separated from those studies in which the control group received no exercise training. In case of comparability between two or more independent studies we pooled reported results into summary effect sizes. If a quantitative analysis was not applicable due to diversity of outcome measures, then a qualitative best-evidence synthesis was performed on the basis of the Cochrane list (see "Methodological quality of included studies"). Included studies that obtained at least 50% (or 11 out of 22 points) of the maximum feasible methodological quality score were considered to be of 'high quality', whereas studies that achieve 10 points or less on the Cochrane list were judged as 'low quality' RCTs (van Tulder 2003).

Evidence was graded into 'Strong evidence' (evidence from studies providing consistent, statistically significant findings in outcome measures in multiple high-quality RCTs), 'Moderate evidence' (evidence from studies providing at least consistent findings among multiple low-quality RCTs, or CCTs, or one high-quality RCT, or a combination of these), or 'Limited evidence' (one low-quality RCT, or CCT, or both). 'Conflicting evidence' was classified as conflicting statistically significant positive and statistically significant negative results among RCTs, or CCTs, or both. 'No evidence' was classified as no RCTs or CCTs if the number of studies showing evidence is less than 50% of the total number of retrieved studies within the same category of methodological quality (van Tulder 2003).

Description of studies

Electronic and manual searches identified 2593 titles and abstracts. Of these, 2570 were excluded. Reasons for exclusion were: reference to diseases or disorders of the central nervous system other than MS, reference to MS but not in combination with exercise therapy, and duplicate publications. Theses were excluded unless an article was published from it in a journal. Of the remaining 24 articles, seven met all the inclusion criteria as stated above

(DeBolt 2004; Jones 1999; Lord 1998; Mostert 2002; Petajan 1996; Solari 1999; Wiles 2001). The 17 excluded trials (Craig 2003; DeSouza 1984; Di Fabio 1997; Di Fabio 1998; Freeman 1997; Freeman 1999; Fuller 1996; Gehlsen 1984; Gehlsen 1986; Ketelaer 1978; Langdon 1999; Lanzetta 2004; Patti 2003; Peterson 2001; Rodgers 1999; Svensson 1994; Wiles 2003) and details of why they failed to meet the inclusion criteria for this review are outlined in the Table of Characteristics of Excluded Studies. Freeman 1999 was discussed, but finally rejected because the objective of the trial was multi disciplinary treatment and not exercise therapy. In addition, examination of conference proceedings for unpublished and ongoing trials of exercise therapy in MS resulted in two additional RCTs (Carter 2003; O'Connell 2003). The first authors of these two RCTs then provided us with information.

The search strategy revealed nine RCTs (Carter 2003; DeBolt 2004; Jones 1999; Lord 1998; Mostert 2002; O'Connell 2003; Petajan 1996; Solari 1999; Wiles 2001) which were included in the present review. Details of the nine trials included in the present review are presented in the Table of Characteristics of Included Studies and in the Additional Table 1. The included nine trials were conducted in five different countries (seven trials in Europe and two in the United States). All trials were published after 1995 and written in English. The included nine trials involved a total of 260 participants. Six trials contained between 20 and 50 participants (DeBolt 2004;Lord 1998; Mostert 2002; Petajan 1996; Solari 1999; Wiles 2001), whereas in three trials fewer than 20 participants were involved (Carter 2003; Jones 1999; O'Connell 2003).

Six trials (Carter 2003; DeBolt 2004; Jones 1999; O'Connell 2003; Petajan 1996; Wiles 2001), involving 164 participants, compared one or two exercise therapy interventions with a no treatment condition and three trials (Lord 1998; Mostert 2002; Solari 1999), involving 96 participants, compared two interventions that both met our criteria of exercise therapy. The study characteristics are provided in detail in the Table of Characteristics of Included Studies and in Additional Table 2.

Methodological quality

- Initially methodological quality scores could not be obtained for the studies of Carter 2003 and O'Connell 2003, since only the abstracts as published in proceedings of conferences were available. The methodological quality scores of the above studies were based on additional information as provided by the first authors. Two reviewers (DB, MBR) independently assessed the methodological quality of the remaining trials. These results are presented in Additional Table 2. There was disagreement between two independent reviewers on six of the 77 criteria scored (7.8%). Cohen's kappa was 0.88. The methodological quality scores of the six included studies that investigated exercise therapy versus no exercise therapy ranged from 50% to 73% of the maximum feasible score, whereas the three studies focused on exercise therapy versus a control exercise intervention ranged from 64% to 82%. All studies were classified as high-methodological-quality RCTs. For all nine studies a summary of key indicators of internal validity is listed below.
- Concealed allocation: Six studies (DeBolt 2004; Jones 1999; Lord 1998; O'Connell 2003; Solari 1999; Wiles 2001) provided some information about the method of randomisation that was used, which suggested that randomisation was probably concealed or randomisation lists were appropriately generated, or both.
- Intention-to-treat analysis: Three studies (Carter 2003; O'Connell 2003; Solari 1999) stated that they had used intention-to-treat analysis.
- Blinded outcome assessment: Two studies (Solari 1999; Wiles 2001) stated that they had used a blinded assessor for all outcome measures.
- All studies provided information on ethical issues. All participants gave written consent and trial protocols were approved by research ethics committees.

Results

- Participant characteristics
- Details are presented in the Table of Characteristics of Included Studies and in Additional Table 2. The participants of the studies considered in the present review all fulfilled a clinical diagnosis of Multiple Sclerosis. Most included studies describe that a neurologist assessed patients' eligibility for inclusion. Criteria for exacerbation or relapse were not defined. For trials comparing exercise therapy with no exercise therapy, the severity of the disease, as expressed by the EDSS-score, ranged from 1 to 6.5. In addition, different types of MS (benign, relapsing-remitting, secondary-progressive, progressive and chronic MS) were considered. Mean disease duration of the subjects ranged from 4.3 to 15.1 years. The

mean percentage of women ranged from 30% to 83% and the mean age of the participants ranged from 34.8 to 51.6 years. For the trials comparing exercise therapy with a control exercise intervention, EDSS-scores ranged from 1 to 6.5, relapsing-remitting-, primary-progressive-, secondary-progressive- and chronic progressive MS were considered. The mean disease duration of the participants ranged from 11.2 to 18.3 years. The mean percentage of woman ranged from 48 to 85 and the mean age of the participants ranged from 44 to 54 years.

Study characteristics

- Exercise therapy versus no exercise therapy
- In the study of Petajan 1996, ambulatory patients with MS participated in a 15-week outpatient exercise training programme to improve measures of physical fitness and to determine its effects on ADL, mood and levels of fatigue. Patients with MS were randomly assigned to an exercise or non-exercise group. Exercise therapy consisted of 3 x 40 minute sessions per week of combined arm and leg ergometry. Of the 54 patients originally selected for the study, six were excluded for reasons unrelated to the research project and to MS. Two additional subjects were excluded secondary to an MS exacerbation. Thus, data from 46 participants were used for statistical analysis. Compared with the control group, the exercise therapy group showed statistically significant increases in maximal aerobic capacity (VO2 max.) and Physical Work Capacity (PWC) after the treatment period. For maximum isometric strength, significant differences between groups after 15 weeks of intervention were found for summed upper extremity strength (i.e., shoulder flexion, shoulder extension, elbow flexion, and elbow extension) and for summed lower extremity strength (i.e., hip extension, hip flexion, knee flexion, and knee extension). For the upper extremity three (i.e., shoulder flexion, shoulder extension, and elbow flexion) out of the four measured muscle groups reached statistically significant changes. Whereas for the lower extremity one (knee extension) out of the four measured muscle groups reached statistically significant change. Compared with the non-exercise group, the exercise therapy group improved significantly on all aspects of the physical subscale (i.e., ambulation, mobility, body care and movement) of the Sickness Impact Profile (SIP) after 10 weeks of training. After 15 weeks of training there was still a significant effect for the total score on the physical subscale (but only the mobility aspect reached significance).

Jones 1999 compared a mobility exercise programme with a weighted leg exercise training programme and with a control group receiving no exercise. Both exercise programmes were performed at home. Nineteen patients with MS were randomly allocated to the three arms of the trial. One patient of the weighted leg exercise group left the study after four weeks, due to back pain, which was believed not to be the result of the intervention. One patient of the mobility exercise group had a relapse shortly after the beginning of the study. These dropouts left 17 patients for statistical analyses. Muscle strength (MVC) of quadriceps and the functional activities walking and transferring (Timed Walk and Timed Transfer) were measured, respectively. Although the weighted leg group improved significantly on time needed for chair transfers, no significant differences were found between the three groups for gait speed, ability to transfer and muscle strength.

Wiles 2001 performed a randomised cross-over trial to determine whether physiotherapy can improve mobility in patients with chronic MS and whether there is a difference between treatments at home and in the outpatient clinic. Forty-two patients with chronic MS were randomly allocated to one of the six permutations of three-week intervals: treatments consisted of physiotherapy at home, in the outpatient clinic and no therapy. Forty patients formed the basis of the analysis, because two patients declined further assessments. No statistically significant differences were found between both exercise groups on the Rivermead Mobility Index (RMI) or any of the secondary mobility measures (i.e. balance time, timed walk, nine hole peg test, assessor global mobility change scale, VAS-patient mobility, VAS-carer mobility, and VAS-falls). Wiles 2001 reported a significant treatment effect on the primary outcome RMI when hospital or home-based physiotherapy were compared with no physiotherapy. This was corroborated by significant effects on all above-mentioned secondary measures in favour of exercise therapy compared to no exercise. In addition, statistically significant effects were found in favour of exercise therapy for mood and reduction in anxiety and depression measured with the Hospital Anxiety and Depression Scale (HADS).

In Carter 2003, 11 participants with mild to moderate MS, who were able to walk for at least four minutes, were randomly assigned to an exercise group or to a non-exercise group. The 12-week outpatient exercise-training programme consisted of twice-weekly supervised general aerobic, strengthening and flexibility exercise sessions. Of the 13 participants originally selected for the study, two were excluded before the start of the intervention, one having severe hypertension and one having developed abdominal cancer. There was a significant reduction in the normalised physiological cost index (PCI, represented by the formula: Working heart rate - Resting heart rate (beats per minute) divided by speed of walking (metres per minute) scores after 12 weeks in the exercising group, but not in the non-exercising control group. In addition, there was a significant difference between the groups in the percentage change in PCI. When comparing the exercise with the non-exercise group, significant effects were observed for isometric strength in the hip flexors and knee flexors of both limbs, the knee extensors and the ankle dorsal flexors of the right limb, but not in the ankle dorsal flexors or the knee extensors of the left limb.

O'Connell 2003 conducted a randomised controlled trial to assess the effects of an outpatient exercise therapy programme on MS patients with mild disability. Eleven participants, in the relapse-remitting stage of the disease, were randomly allocated to an exercise or non-exercise group. Exercise training consisted of twice-weekly, one hour supervised aerobic training in circuit style and once-weekly individual exercise. Two participants from the experimental group were excluded due to relapse. Following the three-month exercise training programme, the exercise group had improved significantly regarding fitness as measured with a Modified Graded Exercise Test (MGET) and quality of life as measured with the Functional Assessment of Multiple Sclerosis (FAMS) compared to baseline. The mean change in heart rate, cadence and Borg's Perception of Exertion were statistically significantly larger in favour of the exercise group when compared to the non-exercise group. No significant differences were found on the Multiple Sclerosis Impact Scale (MSIS) and gait speed.

In the study of DeBolt 2004, MS patients participated in an eight-week home-based resistance exercise programme to examine the effects on balance, leg extension power, and mobility. After stratification by disability level and age, participants were randomly assigned to an exercise or a non-exercise group. Exercise therapy consisted of resistance training (i.e., chair raises, forward lunges, step-ups, heel-toe raises, and leg curls) three times a week. The control group maintained their current level of activity. Of the 37 patients originally selected for the study, 1 was excluded secondary to an MS exacerbation. Thus, data from 36 (exercise group n = 19, and controls n = 17) participants remained for statistical analysis. After the intervention a significant difference between groups was found for leg extensor power. No between-group effects were found for exercise therapy on mobility and balance.

- Exercise therapy versus a control exercise intervention
- Lord 1998 used a pilot study to compare two exercise therapy approaches to improve walking in outpatients with gait disturbances due to MS. Comparison was made between a facilitation and a task-oriented approach. In total twenty-three patients with clinically stable MS were randomised; however, three participants (two from the facilitation group and one from the task group) were excluded due to a relapse or further medical intervention. Ten in each group completed the study, and were treated for a minimum of 15 treatments over a five to seven week period. Participants in both groups showed a significant overall improvement in mobility, as measured with the 10-metre timed walk, stride length, RMI and the Rivermead Visual Gait Assessment and in balance using the Berg Balance Test. No significant differences between the two exercise groups were found.

Solari 1999 assessed the efficacy of an inpatient physical rehabilitation programme on impairment (body functions and structures), disability (activities) and quality of life (QoL) of patients with MS in a randomised, single-blind controlled study. Fifty ambulatory patients with MS were assigned to three weeks of physical rehabilitation (study group) or to exercises performed at home (controls). The inpatient rehabilitation programme consisted of twice-daily exercise periods, each 45 minutes long, and included passive (stretching, mobilisation) and active interventions (for example facilitation of a normal gait pattern). Patients were evaluated at baseline, 3, 9, and 15 weeks. Five patients withdrew from the study before the end of the study period (three in the rehabilitation group: one had an exacerbation, two deteriorated clinically; two controls: one failed to present for the last examination, one deteriorated), but all were included in the analyses. No significant differences were found for impairment (body functions and structures), as measured by the Expanded Disability Status Scale (EDSS). At the end of the intervention significant differences were observed between the study group and the control group in disability (activities), as assessed by the Functional Independence Measure (FIM) motor domain and overall health-related QoL as measured with the mental composite score (emotional role-limitation, mental health, vitality and social functioning) of the SF-36. These differences remained at nine weeks.

In Mostert 2002 37 MS patients taking part in an inpatient rehabilitation programme were randomly assigned to an aerobic exercise training group or to a non-training group. The four weeks aerobic training intervention consisted of five 30 minute sessions per week of bicycle exercise with individualised intensity. The non-exercise group took part in the normal physical therapy of the rehabilitation programme but agreed not to increase their physical activity level. Of the 37 patients originally included, 26 remained for statistical analyses. Two were excluded because of significant change in the exercise electrocardiogram . Three patients quit the study directly after random assignment to the exercise group. Two suffered from elevated spasticity of the lower extremities after testing. Of the non-exercise group, three patients had motivational problems to sustain the intervention program; two others had symptom exacerbations. Compared with baseline, the exercise group demonstrated a significant improvement of the aerobic threshold, an improvement in HRQoL (as measured with the SF-36), and an increase in activity level. However, in the present study statistical analyses were restricted to within-group comparison. Therefore, the differential effects between the groups remain inconclusive.

- Best evidence syntheses
- All details of outcome measures based on between-group assessments are presented in Additional Table 3.

- Exercise therapy versus no exercise therapy
- The best evidence synthesis of studies comparing exercise therapy versus no exercise therapy for MS patients was based on six RCTs (164 participants). All studies were of high methodological quality.

Strong evidence was found in favour of exercise therapy on outcome of muscle power functions (ICF code b730, see Appendix 1), as measured with maximum voluntary contraction (Jones 1999; Jones 1999), Quantitative Myometry Assessment (Carter 2003) and leg extensor power (DeBolt 2004) and exercise tolerance functions (ICF code b455), as measured by the Modified Graded Exercise Test (O'Connell 2003), Physical Work Capacity (Petajan 1996), VO2-max. (Petajan 1996), the Physiological Cost Index (Carter 2003) and the Borg's Perception of Exertion Scale (O'Connell 2003O). In addition, strong evidence was found for exercise therapy on mobility related activities (ICF codes d410 changing basic body position, d415 maintaining a body position, d450 walking, d455 moving around and d460 moving around in different locations) as measured with the Rivermead Mobility Index (Wiles 2001), timed transfer (Jones 1999), balance time (Wiles 2001) and walking cadence (O'Connell 2003).

Moderate evidence was found that exercise therapy improved hand and arm use (ICF code d445) as measured with the Nine-Hole Peg Test (Wiles 2001), and that it improved mood, as assessed with the Hospital Anxiety and Depression Scale (Wiles 2001) and the Profile of Mood States (Petajan 1996).

No evidence was found that exercise therapy has a significant effect on outcome of blood lipids, body composition and EDSS (Petajan 1996), fatigue, as measured with the Fatigue Severity Scale (Petajan 1996) and cognitive impairment, as measured with the Short Orientation-Memory-Concentration Test (Wiles 2001). In addition, no evidence was found for outcome on ADL and instrumental ADL in general. Finally, no evidence was found for exercise therapy on outcome of HRQoL, as measured with the Multiple Sclerosis Impact Scale and the Functional Assessment of Multiple Sclerosis (O'Connell 2003) and the Sickness Impact Profile (Petajan 1996).

- Exercise therapy versus a control exercise intervention
- Three high-methodological-quality RCTs (96 participants) compared exercise therapy with a control intervention. In all three studies the control intervention met our criteria of exercise therapy as well. Best evidence synthesis shows that there is no evidence (Lord 1998;Mostert 2002; Solari 1999) that exercise therapy is more effective than a control exercise intervention for MS patients on factors related to physical fitness (VO2-max.), mobility (gait speed, stride length, Rivermead Mobility Index, Rivermead Visual Gait Assessment, Berg Balance Test, Functional Independence Measure motor domain and Baecke Activity Questionnaire), fatigue (Fatigue severity Scale) and health related quality of life (SF-36).

Discussion

This systematic review investigated the effectiveness of exercise therapy for MS patients in terms of activities of daily living and health-related quality of life. Unfortunately, statistical pooling of data was not possible mainly due to differences in measurements of outcome. Instead, a qualitative analysis using levels of evidence was performed showing strong evidence in favour of exercise therapy compared to no exercise therapy in terms of muscle power functions, exercise tolerance functions and mobility-related activities. Moderate evidence was found for improving mood. However, no evidence was observed for exercise therapy on fatigue and perception of handicap when compared to no exercise therapy. Finally, no evidence was found that specific exercise therapy programmes, including type of exercise therapy and type of setting, were superior in improving activities and participation than other exercise treatments. This latter finding suggests that the contrast of treatment between experimental and control treatment is an important element in determining the effectiveness of treatment in MS. Although the above conclusions are based on high-quality RCTs, it should be noted that most studies included a small number of patients. This lack of statistical power could have introduced type-II-error. In addition, it seems that included studies emphasised when presenting the results on the within group differences. Moreover, one study restricted the statistical analysis to within-group changes and not between-group differences (Mostert 2002).

Interestingly, only the study of Mostert 2002Mdescribes evidence of deleterious effects after testing, by means of elevated spasticity of the lower extremity in two subjects. However, no evidence of deleterious effects of exercise therapy was described by any of the nine included studies. Although in seven trials, dropouts due to an MS exacerbation were reported in groups receiving exercise training (two in Petajan 1996; one in Jones 1999; three in Lord 1998; one in Solari 1999; two in Mostert 2002; two in O'Connell 2003; one in DeBolt 2004), none of the authors of the concerned trials related these dropouts to the applied intervention. This latter finding seems to be important, because people with MS have traditionally been advised by doctors to avoid exercise therapy due to the potential effect on triggering an exacerbation or worsening disease activity. Increases in core temperature can lead to a transient increase in the frequency of clinical signs and symptoms of MS (White 2000). Acknowledging that fatigue affects the vast majority of patients, it was believed that exercise could not be tolerated and that it was

preferable to focus on conserving energy. On the other hand, avoiding exercise also has its disadvantages. Sedentary people have an increased risk of developing a large number of other health problems, like obesity and cardiovascular disease. In addition, the very low activity levels observed in people with MS (Ng 1997; Stuifbergen 1997) often coincide with a loss in leisure activities, social contacts, or normal activities of daily life, which are important for self-esteem and psychological well-being.

- Participants
- All participants considered in the present review fulfilled a clinical diagnosis of Multiple Sclerosis, as described by Poser 1983 or McDonald 2001. However, there was much diversity among studies with regard to patient characteristics. The large range of 1 to 6.5 in the EDSS-scores, best illustrates the diversity in severity of the disease among participants. In the studies considered different types of MS were included. However, none of the trials stratified patients on the basis of type of MS. Therefore, the effectiveness of exercise therapy for different types of MS remains indistinct in the present review. Finally, patients of all ages and of either sex were included. The percentage of female participants (64%) seems to reflect the epidemiological findings about the between-gender distribution of MS (Pozzilli 2002). The mean age of the participants ranged from 34 to 54 years. Most studies had an upper limit of 65 years of age for participants, restricting the generalisation of the present findings.

- Exercise programmes
- The present review did not control for 'dose' (intensity, duration and frequency) of exercise therapy. However, intensity, duration and frequency seem to be important factors in modifying treatment effects. In the present review, there was diversity among the included trials with regard to duration and frequency of training sessions, while intensity was often poorly described. Thus, it is impossible to state the best 'dose' of treatment to achieve optimal beneficial effects of exercise therapy in terms of activities and participation for patients suffering from MS. Optimum number, duration and intensity of treatment sessions all need further study.

- Methodological quality of the RCTs
- RCTs are generally considered to be the best paradigm of intervention research providing the strongest scientific proof of the effectiveness of an intervention (van Tulder 2003v). Most systematic reviews evaluating the effectiveness of therapeutic interventions are confined to evaluating RCTs. The methodological quality score of the RCTs included in the present review ranged from 55% to 82% of the maximum feasible score of 22 points. Even though adequate methodological approaches such as concealment of allocation, blinding of the outcome assessor, and inclusion in the analysis of all randomised participants are recognised as the most important factors in reducing bias (Schulz 1995), only one trial (Solari 1999) included in this review met all three of the above methodological criteria. In addition, reviewers were unable to obtain a methodological quality score for the studies of Carter 2003 and O'Connell 2003, since only the abstracts as published in proceedings of conferences were available. Instead, the methodological quality scores of these studies were based on information as provided by the first authors, which may have biased the results.

- Outcome measures
- Although some studies measured the same domains, different test protocols were used for strength, physical fitness, balance, gait speed and HRQoL, which impeded pooling of data. The large variety in outcome measures used underscores the need for a general agreement about most important measures to assess effects of exercise intervention. International consensus about a core set of outcome measures to determine the effect of exercise therapy would enable comparison of the magnitude of effect of different exercise regimens.

- Potential biases of systematic reviews
- Selection of all relevant studies is crucial to the validity of a systematic review. However, several biases can be introduced by the literature search and selection procedure (van Tulder 2003v). We might have missed relevant unpublished trials, which are more likely to be small studies with non-significant or negative results due to publication bias (Egger 1998). Screening references of identified trials and systematic reviews may result in an overrepresentation of positive studies in the review, because trials with a positive result are more likely to be referred to in other publications, leading to reference bias (Goetzsche 1987). The literature search was restricted to English, German, French and Dutch

publications. Although reviewers acknowledge that systematic reviews should aim at inclusion of all relevant trials, independent of language, identifying trials published in any language is difficult, time consuming and costly. It is possible to include trials, of other languages, in a future update of this review.

- Summary and future research
- In summary, the present research synthesis suggests that exercise therapy can be beneficial for patients with MS on isometric strength, physical fitness and mobility-related ADLs such as time needed for transfer, walking cadence and balance time. In addition, positive findings were found for outcomes related to mood, such as anxiety and depression. Finally, no evidence was found that specific exercise therapy programmes were more successful in improving activities and participation than other exercise treatments. These conclusions were based on a best research evidence synthesis due to lack of comparability between measurements of outcome, acknowledging that defining the levels of evidence is essentially an arbitrary and subjective way of summarising evidence (De Vet 2003). No evidence of deleterious effects of exercise therapy were described in the identified studies.

This review provides a template for the inclusion of future trials and could be used to guide further research. It shows the need for research in older individuals, those more disabled (EDSS-score over 6.5) and those diagnosed for over 18 years. To overcome the problem of heterogeneity between subjects, future studies should stratify patients on the basis of type of MS. There is an urgent need for a general agreement about core set of measurements to be applied in MS trials investigating effectiveness of exercise therapy. Outcome measures in the activities of daily living and HRQoL domains should be included. In addition, these studies should experimentally control for 'dose' of treatment and sufficient contrast in type of intervention and adhere to the methodological principles, especially concealment of allocation, blind recording and an adequate description of the number of dropouts.

Reviewers' conclusions

Implications for practice

The results of this review suggest that exercise therapy, whether similar to that recommended for the healthy population or modified to simply maintain function, does have efficacy in MS. There was no evidence described of deleterious effects of exercise therapy for patients with MS and the effect of type of MS remains unclear. Based on these results, it seems reasonable to promote exercise therapy to patients with MS not experiencing an exacerbation.

Implications for research

There is an urgent need for a consensus on a core set of measurements of outcome to be used in exercise trials. These outcome measures should be reliable and valid and reflect activities of daily living and quality of life domains. In addition, these studies should experimentally control for 'dose' of treatment and sufficient contrast in type of intervention between experimental and control groups and adhere to the methodological principles, especially concealment of allocation, blind recording and description of dropouts.

Acknowledgements

The authors would like to thank Mrs. I Wijbrands and Mr. PCW van Wieringen (PhD) for their valuable contribution to this manuscript. A special thanks to Mrs. M.J.C. Pieper and Mrs. L.M. Selhorst for their assistance on the protocol.

Potential conflict of interest

None known.

Appendix I. International Classification of Functions coding

- b455 Exercise tolerance functions
- Functions related to respiratory and cardiovascular capacity as required for enduring physical exertion.

- Inclusions: functions of physical endurance, aerobic capacity, stamina and fatigability
- Exclusions: functions of the cardiovascular system; haematological system functions; respiration functions; respiratory muscle functions; additional respiratory functions
- b455 Exercise tolerance functions
- >b455 Exercise tolerance functions
- >b4550 General physical endurance
- >b4551 Aerobic capacity
- >b4552 Fatigability
- >b4558 Exercise tolerance functions, other specified
- >b4559 Exercise tolerance functions, unspecified

- Neuromusculoskeletal and movement-related functions
- + Functions of the joints and bones (b710-b729)
- + b710 Mobility of joint functions
- + b715 Stability of joint functions
- + b720 Mobility of bone functions

- > b729 Functions of the joints and bones, other specified and unspecified
- + Muscle functions (b730-b749)
- + b730 Muscle power functions
- + b735 Muscle tone functions
- + b740 Muscle endurance functions
- > b749 Muscle functions, other specified and unspecified

- + Movement functions (b750-b789)
- + b750 Motor reflex functions
- > b755 Involuntary movement reaction functions
- + b760 Control of voluntary movement functions
- + b765 Involuntary movement functions
- > b770 Gait pattern functions
- + b780 Sensations related to muscles and movement functions
- > b789 Movement functions, other specified and unspecified functions (b750-b789)
- > b798 Neuromusculoskeletal and movement-related functions, other specified
- > b799 Neuromusculoskeletal and movement-related functions, unspecified

- d410 Changing basic body position
- Getting into and out of a body position and moving from one location to another, such as getting up out of a chair to lie down on a bed, and getting into and out of positions of kneeling or squatting.
- Inclusion: changing body position from lying down, from squatting or kneeling, from sitting or standing, bending and shifting the body's centre of gravity
- Exclusion: transferring oneself
- +d410 Changing basic body position
- >d410 Changing basic body position

- >d4100 Lying down
- >d4101 Squatting
- >d4102 Kneeling
- >d4103 Sitting
- >d4104 Standing
- >d4105 Bending
- >d4106 Shifting the body's centre of gravity
- >d4108 Changing basic body position, other specified
- >d4109 Changing basic body position, unspecified

- d415 Maintaining a body position
- Staying in the same body position as required, such as remaining seated or remaining standing for work or school.
- Inclusions: maintaining a lying, squatting, kneeling, sitting and standing position
- +d415 Maintaining a body position
- >d415 Maintaining a body position
- >d4150 Maintaining a lying position
- >d4151 Maintaining a squatting position
- >d4152 Maintaining a kneeling position
- >d4153 Maintaining a sitting position
- >d4154 Maintaining a standing position
- >d4158 Maintaining a body position, other specified
- >d4159 Maintaining a body position, unspecified

- d430 Lifting and carrying objects
- Raising up an object or taking something from one place to another, such as when lifting a cup or carrying a child from one room to another.
- Inclusions: lifting, carrying in the hands or arms, or on shoulders, hip, back or head; putting down
- +d430 Lifting and carrying objects
- >d430 Lifting and carrying objects
- >d4300 Lifting
- >d4301 Carrying in the hands
- >d4302 Carrying in the arms
- >d4303 Carrying on shoulders, hip and back
- >d4304 Carrying on the head
- >d4305 Putting down objects
- >d4308 Lifting and carrying, other specified
- >d4309 Lifting and carrying, unspecified

- d435 Moving objects with lower extremities
- Performing co-ordinated actions aimed at moving an object by using the legs and feet, such as kicking a ball or pushing pedals on a bicycle.
- Inclusions: pushing with lower extremities; kicking

- d435 Moving objects with lower extremities
- +d435 Moving objects with lower extremities
- >d4350 Pushing with lower extremities
- >d4351 Kicking
- >d4358 Moving objects with lower extremities, other specified
- >d4359 Moving objects with lower extremities, unspecified

- d440 Fine hand use
- Performing the co-ordinated actions of handling objects, picking up, manipulating and releasing them using one's hand, fingers and thumb, such as required to lift coins off a table or turn a dial or knob.
- Inclusions: picking up, grasping, manipulating and releasing
- Exclusion: lifting and carrying objects
- >d440 Fine hand use
- >d4400 Picking up
- >d4401 Grasping
- >d4402 Manipulating
- >d4403 Releasing
- >d4408 Fine hand use, other specified
- >d4409 Fine hand use, unspecified

- d445 Hand and arm use
- Performing the co-ordinated actions required to move objects or to manipulate them by using hands and arms, such as when turning door handles or throwing or catching an object Inclusions: pulling or pushing objects; reaching; turning or twisting the hands or arms; throwing; catching
- Exclusion: fine hand use
- >d445 Hand and arm use
- >d445 Hand and arm use
- >d4450 Pulling
- >d4451 Pushing
- >d4452 Reaching
- >d4453 Turning or twisting the hands or arms
- >d4454 Throwing
- >d4455 Catching
- >d4458 Hand and arm use, other specified
- >d4459 Hand and arm use, unspecified

- d450 Walking
- Moving along a surface on foot, step by step, so that one foot is always on the ground, such as when strolling, sauntering, walking forwards, backwards, or sideways.
- Inclusions: walking short or long distances; walking on different surfaces; walking around obstacles
- Exclusions: transferring oneself; moving around
- >d450 Walking
- >d4500 Walking short distances
- >d4501 Walking long distances

- >d4502 Walking on different surfaces
- >d4503 Walking around obstacles
- >d4508 Walking, other specified
- >d4509 Walking, unspecified

- d455 Moving around
- Moving the whole body from one place to another by means other than walking, such as climbing over a rock or running down a street, skipping, scampering, jumping, somersaulting or running around obstacles.
- Inclusions: crawling, climbing, running, jogging, jumping, and swimming
- Exclusions: transferring oneself; walking
- +d455 Moving around
- >d455 Moving around
- >d4550 Crawling
- >d4551 Climbing
- >d4552 Running
- >d4553 Jumping
- >d4554 Swimming
- >d4558 Moving around, other specified
- >d4559 Moving around, unspecified

- d460 Moving around in different locations
- Walking and moving around in various places and situations, such as walking between rooms in a house, within a building, or down the street of a town.
- Inclusions: moving around within the home, crawling or climbing within the home; walking or moving within buildings other than the home, and outside the home and other buildings
- +d460 Moving around in different locations
- >d460 Moving around in different locations
- >d4600 Moving around within the home
- >d4601 Moving around within buildings other than home
- >d4602 Moving around outside the home and other buildings
- >d4608 Moving around in different locations, other specified
- >d4609 Moving around in different locations, unspecified

- d510 Washing oneself
- Washing and drying one's whole body, or body parts, using water and appropriate cleaning and drying materials or methods, such as bathing, showering, washing hands and feet, face and hair, and drying with a towel.
- Inclusions: washing body parts, the whole body; and drying oneself
- Exclusions: caring for body parts; toileting
- +d510 Washing oneself
- >d510 Washing oneself
- >d5100 Washing body parts
- >d5101 Washing whole body

- >d5102 Drying oneself
- >d5108 Washing oneself, other specified
- >d5109 Washing oneself, unspecified

- d530 Toileting
- Planning and carrying out the elimination of human waste (menstruation, urination and defecation), and cleaning oneself afterwards.
- Inclusions: regulating urination, defecation and menstrual care
- Exclusions: washing oneself; caring for body parts
- +d530 Toileting
- >d530 Toileting
- >d5300 Regulating urination
- >d5301 Regulating defecation
- >d5302 Menstrual care
- >d5308 Toileting, other specified
- >d5309 Toileting, unspecified

- d540 Dressing
- Carrying out the co-ordinated actions and tasks of putting on and taking off clothes and footwear in sequence and in keeping with climatic and social conditions, such as by putting on, adjusting and removing shirts, skirts, blouses, pants, undergarments, saris, kimono, tights, hats, gloves, coats, shoes, boots, sandals and slippers.
- Inclusions: putting on or taking off clothes and footwear and choosing appropriate clothing.
- +d540 Dressing
- >d5400 putting on clothes
- >d5401 Taking off clothes
- >d5402 Putting on footwear
- >d5403 Taking off footwear
- >d5404 Choosing appropriate clothing
- >d5408 Dressing, other specified
- >d5409 Dressing, unspecified

- d550 Eating
- Carrying out the co-ordinated tasks and actions of eating food that has been served, bringing it to the mouth and consuming it in culturally acceptable ways, cutting or breaking food into pieces, opening, bottles and cans, using eating implements, having meals, feasting or dining.
- Exclusion: drinking

Appendix 2. Assessment of methodological quality of included trials

- A: Was the assigned treatment adequately concealed prior to allocation?
- 2 = method did not allow disclosure of assignment
- 1 = small but moderate change of disclosure of assignment or unclear
- 0 = quasi-randomised or open list/tables
- B: Were the outcomes of participants who withdrew or were excluded after allocation described and

included in an 'intention to treat' analysis?

- 2 = withdrawals well described and accounted for in analysis
- 1 = withdrawals described and analysis is not possible
- 0 = no mention, inadequate mention, or obvious differences and no adjustment
- C: Were the outcome assessors blind to assignment status?
- 2 = effective action taken to blind the assessors
- 1 = small or moderate chance of unblinding of assessors
- 0 = not mentioned or not possible
- D: Were the treatment and control group, or in case of more treatment groups the treatment groups, comparable at entry?
- 2 = good comparability of groups
- 1 = confounding is small, but mentioned
- 0 = large potential for confounding, or not mentioned
- E: Were the participants blind to assignment status following allocation?
- 2 = effective action taken to blind the participants
- 1 = small or moderate chance of unblinding of participants
- 0 = not mentioned or not possible
- F: Were the treatment providers blind to assignment status?
- 2 = effective action taken to blind the treatment providers
- 1 = small or moderate chance of unblinding of treatment providers
- 0 = not mentioned or not possible
- G: Were care programmes, other than the trial options, identical?
- 2 = care programmes clearly identical
- 1 = clear but trivial differences
- 0 = not mentioned or clear and important differences in care programmes
- H: Were the inclusion and exclusion criteria for entry clearly defined?
- 2 = clearly defined
- 1 = inadequately defined
- 0 = not defined
- I: Were the interventions clearly defined?
- 2 = clearly defined interventions are applied with a standardised protocol
- 1 = clearly defined interventions are applied but the applied protocol is not standardised
- 0 = intervention and/or application protocol are poorly or not defined
- J: Were the outcome measures used clearly defined?
- 2 = clearly defined
- 1 = inadequately defined
- 0 = not defined
- K: Were diagnostic tests used in outcome assessment clinically useful?
- 2 = optimal
- 1 = adequate
- 0 = not defined, not adequate

Tables

Characteristics of included studies

Study	Carter 2003
Methods	RCT. Random assignment to exercise (EX) or non-exercise (NEX) groups
Participants	N = 11EX: N = 6, NEX: N = 5Inclusion criteria: EDDS score of 6.0 or less, stable disease process within the last 6 weeks, able to walk for 4 minutes, full understanding of written and spoken EnglishExclusion criteria: acute exacerbation of MS, ongoing corticosteroid therapy, other significant medical conditionsType MS: Relapsing-remitting or secondary-progressive MSDisease duration (yr) ± SD (range): EX: 4.6 ± 1.4 (1-14), NEX: 13.8 ± 1.0 (12-18)Mean age (yr) ± SD (range): EX: 41 ± 3.2 (23-55), NEX: 44 ± 2.8 (37-53)% female: EX: 50%, NEX: 67% Mean EDSS-score ± SD: EX: 3.7 (2.0-5.5), NEX: 3.4 (2.5-5.0)
Interventions	Outpatient supervised general aerobic, strengthening and flexibility exercise sessions. Twice a week for a period of 12 weeks. In addition, subjects were encouraged to undertake one further unsupervised session per weekSubjects in the non-exercise group were asked to maintain their normal activity level.
Outcomes	PCI and QMA of muscle force in lower limbs. Assessments at baseline and after 12 weeks.
Notes	Drop outs: Not when the study started , however 2 subjects were not entered due to 1 having severe hypertension and 1 developing abdominal cancerTrial presented at the World Confederation for Physical Therapy 2003 in Barcelona. Article will be submitted for publication
Allocation concealment	D
Study	**DeBolt 2004**
Methods	RCT. Random assignment to exercise (EX) or non-exercise (NEX) groups
Participants	N = 37: EX = 19, NEX= 17Inclusion criteria: Healthy adults with MS, ability to walk (with or without assistive devices) at least 20 m without restExclusion criteria: -Type MS: B,P, CP, RRDisease duration (yr) ± SD (range): EX: 15.1 ± 12.2 , NEX:13.1 ± 11.2Mean age (yr) ± SD (range): EX: 51.6 ± 7.3, NEX: 47.8 ± 10.5 % female: EX: 79, NEX: 78Mean EDSS-score ± SD: EX: 4.0 ± 1.8 (1-6.5), NEX: 3.5 ± 1.5 (1.5-6
Interventions	Home-based, lower-extremity resistance training Individualised 3 times a week for 8 weeks. Mean adherence 95%. Controls Maintained current level of activity
Outcomes	Balance measured with force platform resulting in measurement of postural sway (anterior-posterior, mediolateral) and sway velocity. Leg extensor power, Up and Go testAssessments before and after the 8weeks of training
Notes	Drop outs: 1 subjects was excluded secondary to an MS exacerbation
Allocation concealment	D
Study	**Jones 1999**
Methods	RCT. Random assignment to the no activity (NEX), general physiotherapy exercises (EX) or the weighted leg raises (WLR) groups, using sealed envelopes
Participants	N = 17: NEX= 5, EX= 6, WLR = 6Inclusion criteria: Clinically confirmed relapsing/ remitting MS, ambulant with or without the use of walking aidsExclusion criteria: Relapse of MS in the preceding 6 monthsType MS: Relapsing-remitting MS Dis. dur. (yr)±SD (range): NEX: 10(2.5-20), EX: 5(1-15), WLR: 5(1.5-8)Mean age (yr) ± SD (range): NEX: 43 (36-54), EX: 49 (41-59), WLR: 38 (40-48) % female: NEX: 80, EX: 83.3, WLR: 83.3Mean EDSS-score ± SD: ?
Interventions	EX: general mobility exercises, performed at home, with the aim of improving the patient's physical function (exercise duration and frequency similar for each person)WLR: weighted leg raises specifically to strengthen the quadriceps (5 sets of 10 leg extensions on both legs, twice a day), performed at homeEX & WLR: Mean adherence % (range)69% (45-100%) controls: Programme of supportive phone calls, but no physical intervention
Outcomes	10 and 50m Timed Walk Test (time and pulse rate), quadriceps MVC (KgF), EMG turns (turns/sec) and Timed transferAssessments: Baseline and after 8 weeks

Notes	Drop outs: 2: 1 subject was excluded due to back pain and 1 subject was excluded due to a relapse of MS Definition MS not specified
Allocation concealment	D
Study	**Lord 1998**
Methods	RCT. Random assignment to one of two treatment groups (facilitation approach (F) and a task-oriented approach (T)), by using sealed envelopes and block randomisation.
Participants	N = 20: F=10, T=10Inclusion criteria: Able to walk 10m inside with or without supervision, clinically apparent relapse within 3 months before entry, clinically stable chronic progressive or relapsing-remitting MSType MS: Chronic progressive or relapsing-remittingDis.dur.(yr)±SD(range): F:18.3±7.0(9-28), T: 14±8.1(4-26)Mean age (yr)±SD (range): F:52.1±11(35-69),T: 54.1±8.1(43-65)% female: F: 80, T: 70Mean EDSS-score ± SD: ?
Interventions	facilitation(F) versus functional(T) out patient trainingF: reducing impairments in terms of postural control, balance responses, ability to recruit motor activity in different parts of the range, muscle length, tonus change and bony malignment by using both passive and active techniquesT: disability focused programme of functional exercises based on necessary components required for walking and functional mobilityF&T: 15-19 (one hour) treatment sessions over a period of 5-7 weeks
Outcomes	10m Timed Walk Test, RMI, RVGA, BBT and AS.Assessment at baseline and after 5-7 weeks
Notes	Drop outs: 3 drop-outs ; 2 from the facilitation group and 1 from the task group were excluded due to a relapse or further medical intervention Definition MS not specified
Allocation concealment	D
Study	**Mostert 2002**
Methods	RCT. Random assignment to the exercise training (EX) or the non exercise (NEX) group
Participants	N= 26: EX=13, NEX =13Inclusion criteria: Diagnosis of clinically definite MS (Poser 1983), able to pedal on a free standing bicycle ergometerExclusion criteria: History of cardiovascular, respiratory, orthopaedic or metabolic diseases or other medical conditions, acute exacerbations of MS during at least two previous monthsType MS: Relapsing-remitting, chronic-progressive or relapsing-progressive MS Disease duration (yr) ± SD (range): EX: 11.2 ± 8.5 (2-27), NEX: 12.6 ± 8.1 (2-25) Mean age (yr) ± SD (range): EX: 45.23 ± 8.66, NEX: 43.92 ± 13.90 % female: EX: 76.9, NEX: 84.6 Mean EDSS-score ± SD: EX: 4.6 ± 1.2 (2.5 - 6.5), NEX: 4.5 ± 1.9 (1 - 6.5)
Interventions	Inpatient bicycle exercise training with individualised intensity For a period of 4 weeks, 5x30-min training sessions a weekControls: Normal inpatient physiotherapy of the rehabilitation programme.
Outcomes	Kurtzke's FS, Kurtzke's EDSS, BAECKE -Activity Questionnaire, SF-36, FSS and maximal aerobic capacity Assessment at baseline and after 4 weeks
Notes	Drop outs: 12: 2 subjects quit due to motivational problems, 2 subjects were excluded due to elevated spasticity, 2 subjects were excluded because of significant ST segment change in the exercise ECG, 3 subjects decided to quit directly after random assignment to the exercise group and 3 subjects were excluded due to symptom exacerbationsThe study mentioned 11 dropouts instead of 12. Number of subjects in each group is 13, while in table 2 the number of subjects in the exercise groups is 12
Allocation concealment	D
Study	**O'Connell 2003**
Methods	RCT. Random assignment to exercise (EX) or non-exercise (NEX) group
Participants	N = 11: EX = 5, NEX = 6Inclusion criteria: Kurtzke's EDDS-score between 0 and 3, Relapse-remission stage of MS, independently mobile and static in physical abilityExclusion criteria: changes in medication and physical status over last 3 months, need for aid/appliance for mobility Type MS: Relapsing-remitting MSDisease duration (yr) ± SD (range): EX: 4.4 ± 4.5 , NEX: 4.3 ± 3.2Mean age (yr) ± SD (range): EX: 39.4 ± 6.5 , NEX :34.8 ± 12.8 % female: EX: 40, NEX: 30Mean EDSS-score ± SD: EX: (1 - 2), NEX: (1- 2.5)

Interventions	Outpatient aerobic training sessions in circuit style performed in classes.2x1h sessions in class and one session alone per week for a period of 3 months.controls: No exercise training
Outcomes	MGET, Borg's Perception of Exertion, Timed Walk (50m.), Cadence, MSIS and FAMS. Assessments at baseline and after 3 months
Notes	Drop outs: 2: 2 subjects (EX) were excluded due to a new relapse.Trial presented at the World Confederation for Physical Therapy 2003 in Barcelona. Part of a continuing trial
Allocation concealment	D
Study	**Petajan 1996**
Methods	RCT. Random assignment to exercise (EX) or non-exercise (NEX) group.
Participants	N = 46: EX = 21, NEX = 25.Inclusion criteria: Diagnosis of clinically definite MS (Poser 1983) and Kurtzke's EDSS-score of 6.0 or less.Exclusion criteria: History of cardiovascular, respiratory, orthopaedic, metabolic or other medical conditions involvement in any form of regular physical activity for 6 months prior to the studyType MS: ?Disease duration (yr) ± SD: EX: 9.3 ± 1.6 , NEX: 6.2 ± 1.1Mean age (yr) ± SD: EX: 41.1 ± 2.0, NEX: 39.0 ± 1.7 % female: EX: 71.4, NEX: 64.0Mean EDSS-score ± SD: EX: 3.8 ± 0.3, NEX: 2.9 ± 0.3
Interventions	EX: Outpatient training sessions of combined arm & leg ergometry 3x40-min training sessions a week for a period of 15 weeksMean adherence 97% (91-100)NEX: No exercise training15 weeks
Outcomes	Kurtzke's FS, Kurtzke's EDSS, ISS, POMS, SIP, FSS, maximal aerobic capacity, isometric strength, blood lipids and body composition Assessments at baseline and after 5, 10 and 15 weeks
Notes	Drop outs: 8: 6 subjects were excluded for reasons unrelated to the project and MS, 2 subjects were excluded secondary to an MS exacerbation
Allocation concealment	D
Study	**Solari 1999**
Methods	RCT. Random assignment to exercise (EX) or non-exercise (NEX) group. A stratification procedure, in relation to disease severity (EDSS-score: 3.0-4.5 and 5.0- 6.5), was undertaken before randomisation
Participants	N = 50: EX = 27, NEX = 23Inclusion criteria: Clinically definite or laboratory supported MS (Poser ,1983), Kurtzke's EDDS-score between 3.0 and 6.5, age between 18-65 yearsExclusion criteria: one or more exacerbations in the preceding 3 months, cognitive impairment (MMSE < 23.8), history of cardiovascular, respiratory, orthopaedic, psychiatric or other medical conditions, pregnancy, Treatment with immunosuppressants, interferons, 4-aminopyridine or experimental drugs in the 6 months before enrolment, rehabilitation therapy in the 3 months before admissionType MS: Relapsing-remitting, primary-progressive or secondary- progressive MSDisease duration (yr) ± SD (range): EX: 44.6 ± 10.2, NEX: 44.9 ± 10.6Mean age (yr) ± SD (range): EX: 44.6 ± 10.2, NEX: 44.9 ± 10.6% female: EX: 63, NEX: 48Mean EDSS-score ± SD: 5.5 (3.0-6.5), NEX: 5.5 (3.5-7.0)
Interventions	Inpatient physical rehabilitation programme with passive and active interventions.15 weeks; 2x45-min exercise sessions a day for a period of 3 weeks, versus 12 weeks of a self-executed exercise programme at home
Outcomes	Kurtzke's EDSS, FIM, SF-36, HAI and HRSDAssessment at baseline and after 3, 9 and 15 weeks
Notes	Drop outs: 5- patients withdrew from the study before the end of the study period (3 rehabilitation: 1 had a exacerbation, 2 deteriorated clinically; 2 controls: 1 failed to present for the last examination, 1deteriorated), but all were included in the analysesDetails of physical rehabilitation program have been described elsewhere (in Italian). The study is ongoing. The range of EDDS-scores of the control group exceeds the 6.5 of the inclusion criteria
Allocation concealment	D
Study	**Wiles 2001**

Methods	RCT. Random assignment to one of the 6 permutations of 3 (EX/EXH/NEX) eight week treatment periods separated by 8 week intervals, using sealed envelopes
Participants	N = 42: PT/PTH/NT: N = 42Inclusion criteria: Diagnosis of definite or probable MS, complaining of difficulties with walking, age 18 years or older, able to walk 5m with or without a mechanical aidExclusion criteria: Current relapse of MS, major general medical or surgical disorders, pregnancy Type MS: Chronic MSDis. duration (yr) ± SD (range): EX/ EXH/NEX: 12.3 ± 8.4Mean age (yr) ± SD (range): EX/EXH/NEX: 47.2 (28.2-68.8) % female: EX/EXH/NEX: 64.3 Mean EDSS-score ± SD: 6.0 (4.0-6.5)
Interventions	EX: outpatient physiotherapy, with an individualised problem solving approach, focusing on specific facilitation techniques EXH: physiotherapy at home with a individualised problem solving approach, focusing on specific functional activities at home EX & EXH: twice a week (45-min) for a period of 8 weekscontrols: no therapy
Outcomes	Timed Walk (6m. with one turn), NHP-test, RMI, BI, FAI, NE-ADL-I, HADS, SOMCT, VAS. Assessments 1 week before and the week after each treatment period and 8 weeks after the final treatment period
Notes	Drop outs: 2: 1 subject declined further assessment after a single treatment period and 1 subject withdrew after recruitment but before treatment
Allocation concealment	D

E/C, experimental vs. control group
N indicates number of patients in each group
OT: occupational therapy
PT: physiotherapy
Type MS: B = benign, C = chronic, CP = chronic progressive, RR = relapsing-remitting, SP = secundair progressive

*Only median figures given
** Only range figures given
$ Randomised crossover design,
# Only findings of the MS-groups are considered

Outcomes:
AS: Ashworth Scale
BAQ: Baecke Activity Questionnaire
BBT: Berg Balance Test
BI: Barthel Index
BPE: Borg's Perception of Exertion
EDSS: Expanded Disability Status Scale
EMG: Electromyography
FAI: Frenchay Activities Index
FAMS: Functional Assessment of Multiple Sclerosis
FIM: Functional Independence Measure
FS: Functional System scale
FSS: Fatigue Severity Scale
HADS: Hospital Anxiety and Depression Scale
HAI: Hauser's Ambulation Index
Hr-max: maximal hart rate
HRSD: Hamilton Rating Scale for Depression
ISS: Incapacity Status Scale
LHS: London Handicap Scale
MGET: Modified Graded Exercise Test
MSIS: Multiple Sclerosis Impact Scale
MSWS-12: 12 item Multiple Sclerosis Walking Scale
MVC: Maximum Voluntary Contraction
NEADL-I: Nottingham Extended Activities of Daily Living Index
NHP: Nine Hole Peg-test
PCI: Physiological Cost Index
PWC: physical Work Capacity
QMA: Quantitative Myometry assessment
POMS: Profile of Mood States
RMI: Rivermead Mobility Index
RVGA: Rivermead Visual Gait Assessment
SF-36: 36-item Short Form Health Survey Questionnaire
SIP: Sickness Impact Profile
SOMCT: Short Orientation-Memory-Concentration Test
VAS: Visual Analogue Scales

VO2-max: maximal aerobic capacity.

Characteristics of excluded studies

Study	Reason for exclusion
Craig 2003	Intervention is not restricted to exercise therapy
DeSouza 1984	Not a RCT
Di Fabio 1997	Not a RCT
Di Fabio 1998	Not a RCT
Freeman 1997	Not a RCT
Freeman 1999	Intervention not restricted to exercise therapy
Fuller 1996	Not a RCT
Gehlsen 1984	Not a RCT
Gehlsen 1986	Not a RCT
Ketelaer 1978	Not a RCT
Langdon 1999	Not a RCT
Lanzetta 2004	Type of subjects not restricted to MS patients
Patti 2003	Intervention not restricted to exercise therapy
Peterson 2001	Not a RCT
Rodgers 1999	Not a RCT
Svensson 1994	Not a RCT
Wiles 2003	Partecipants in this study are already included in the RCT of Wiles published in 2001

Additional tables

Table 01 Methodological Quality Score

Trial	ABCDEFGHIJK	Sum score	% of maximum score	High Quality
Exercise therapy versus no exercise therapy				
Petajan 1996	11120022222	15	68	Yes
Jones 1999	21010022121	12	55	Yes
Wiles	21220012222	16	73	Yes
Carter	02020012222	13	59	Yes
O'Connell	22020002222	14	64	Yes
deBolt	10020002222	11	50	Yes
Exercise therapy versus control exercise therapy				
Lord 1998	21020022222	15	68	Yes
Solari 1999	22220022222	18	82	Yes
Mostert 2002	11020022222	17	64	Yes

Table 02 Characteristics of included studies

Reference Year	N (E/ C)	Type MS	Disease duration Y	EDSS score Y	Age Y	% female	Intervention	Dose of intervention	Outcome

Petajan 1996	46 (21/25)	?	9.3/6.2	3.8/2.9	41/39	71/64	Outpatient combined arm and leg ergometry vs. No treatment	3x40 min. weekly for 15 wk	EDSS, ISS, FS, POMS, SIP, FSS, VO2-max, PWC, isometric strength, HRmax, body composition, blood lipids
Jones1999	17 (5/6/6)	RR	10/5/5	?	43/49/38	80/83/83	Home mobility exercises & home weighted leg exercise vs. No treatment	? / 5 sets of 10 leg extensions, twice a day for 8 wk.	Timed Walk, MVC, Timed Transfer, EMG
Wiles2001	42	C	12.3	6.0	47	64	PT at home vs. PT outpatient vs. No PT	2x45 min. weekly for 8 wk.	Timed Walk, Balance time, RMI, NHP, HADS, BI, FAI, SOMCT, VAS, NEADLI
Carter 2003	11(6/5)	RR, SP	4.6/13.8	3.7/3.4	41/44	50/67	Outpatient general exercise programme vs. no exercise	Twice a week for 12 weeks	PCI, QMA
O'Connel2003	11(5/6)	RR	4.4/4.3	1.5/1.5	39.4/34.8	40/30	Outpatient aerobic training vs. n o exercise	2 x 1h in class, 1 h alone per week for 3 months	MGET, BPE, Timed Walk (50m.), Cadence, MSIS and FAMS
DeBolt2004	37 (19/17)	B, RR, P, CP	15.1/13.1	4.0/3.5	51.6/47.8	79/78	Home-based resistance exercise vs. No treatment	3 times a week for 8 weeks	Balance met postural sway & sway velocity, Leg extensor power, up and Go test
Exercise therapy versus control exercise therapy									
Lord 1998	20 (10/10)	CP, RR	14.0/18.3	?	54/52	70/80	Outpatient task-oriented training vs. facilitation training	15-19 / 16-19 (1h) sessions in 5-7 wk.	Timed Walk, RMI, RVGA, BBT, Stride length
Solari 1999	50 (27/23)	RR, PP, SP	16.6/13.3	5.5/5.5	45/45	63/48	Inpatient physical rehabilitation vs. Home performed exercises	2x45 min¤ daily vs. self-executed exerc. for 3 wk	SF-36, FIM, EDSS, HAI, HRSD

Mostert 2002	26 (13/13)	CP, RR, RP	11.2/12.6	4.6/4.5	45/44	77/85	Inpatient bicycle training vs. inpatient PT	5x30 min. weekly for 3-4 wk.	FS, EDSS, BAQ, SF-36, FSS, VO2-max,

Table 03 Between group effects of included trials (BGE)

Study	Impairment	BGE	Activities	BGE	Participation	BGE
Exercise therapy versus no exercise therapy						
Petajan1996 Combined arm & leg ergometry vs. no exercise	Physical Work capacity VO2-max S MVC UE & LE Blood Lipids Body composition EDSS & FS FS Bowel/Bladder score	+ + + - - - +	ISS	-	POMS FSS SIP Physical sub scale SIP Psychosocial sub scale	- - + -
Jones 1999 Weighted leg exercise vs.Mobility exercise vs. No exercise	EMG MVC Quadriceps	- -	Timed walk 10&50 m. Timed transfer	- + (1)		
Wiles 2001 Exercise therapy at home vs.Exercise therapy in hospital vs. None treatment group	SOMCT	-	Balance time Timed Walk RMI VAS mobility NHP mob. UE NHP mob. UE BI FAI NE-ADL-I	+ (2) + (2) + (2) + (2) - (3) + (4) ? nrr nrr	HADS anxiety HADS depression	+ (2) + (2)
Carter 2003 General exercise vs. non-exercise	PCI QMA	+ +				
O'Connell, 2003 Aerobic training exercise vs. non-exercise	HR BPE MGET	+ + -	Timed Walk 50 m. Cadence	- +	MSIS FAMS	- -
DeBolt 2004 Resistance training vs. no treatment	Leg extensor power	+	Up and Go test Postural sway Sway velocity	- - -		
Exercise therapy versus a control exercise intervention						
Lord 1998 Facilitation exercise vs. task orientated exercise			Timed walk 10 m. Stride length RMI RVGA Berg Balance test	- - - - -		
Solari 1999 Physical rehab.vs. exercise performed at home	EDSS	-	FIM motor domain at 3 & 9 weeks	+ (5)	SF-36 MCS at 3 & 9 wk SF-36 PCS at 3 & 9 wk SF-36 MCS at 15 wk SF-36 PCS at 15 wk	+ (5) - - -
Mostert 2002 Bicycle exercise vs. normal physical therapy	VO2-max	nrr	BAQ	nrr	FSS SF-36	nrr nrr

Table 04 Footnotes table 3

BGE indicates between groups effect in each group
+ = significant between groups effect in favour of exercise therapy intervention
- = non -significant between groups effect
nrr = no results reported
vs. = versus
UE: upper extremity
LE: lower extremity
(1)for weighted leg exercise group as compared to mobility exercise and no exercise
(2)comparing hospital or home-based physiotherapy with no physiotherapy
(3)comparing home-based physiotherapy with no physiotherapy
(4)comparing hospital-based physiotherapy with no physiotherapy
(5)for physical rehabilitation group as compared to exercise performed at home.

Outcomes:
BAQ: Baecke Activity Questionnaire
BBT: Berg Balance Test
BI: Barthel Index
BPE: Borg's Perception of Exertion
EDSS: Expanded Disability Status Scale
EMG: Electromyography
FAI: Frenchay Activities Index
FAMS: Functional Assessment of Multiple Sclerosis
FIM: Functional Independence Measure
FS: Functional System Scale
FSS: Fatigue Severity Scale
HADS: Hospital Anxiety and Depression Scale
ISS: Incapacity Status Scale
LHS: London Handicap Scale
MGET: Modified Graded Exercise Test
MSIS: Multiple Sclerosis Impact Scale
MVC: Maximum Voluntary Contraction
NEADL-I: Nottingham Extended Activities of Daily Living Index
NHP: Nine Hole Peg-test
PCI: Physiological Cost Index
POMS: Profile of Mood States; PhCS.: Physical Composite Score & MCS: Mental Composite Score
QMA: Quantitative Myometry Assessment
RMI: Rivermead Mobility Index
RVGA: Rivermead Visual Gait Assessment
SF-36: 36 item Short Form Health Survey Questionnaire
SIP: Sickness Impact Profile
SOMCT: Short Orientation-Memory-Concentration Test
VAS: Visual Analogue Scales
VO2-max: maximal aerobic capacity.

References

References to studies included in this review

Carter 2003 *{published and unpublished data}*

Carter P, White CM. The effect of a general exercise training on effort of walking in patients with multiple sclerosis. In: 14th International World Confederation for Physical Therapy. Barcelona: 2003.

DeBolt 2004 *{published data only}*

DeBolt LS, McCubbin JA. The effects of home-based resistance exercise on balance, power, and mobility in adults with multiple sclerosis. Archives of Physical and Medical Rehabilitation 2004;85 (2):290-7.

Jones 1999 *{published data only}*

Jones R, Davies-Smith A, Harvey L. The effect of weighted leg raises and quadriceps strength, EMG

and functional activities in people with multiple sclerosis. Physiotherapy 1999;85(3):154-61.

Lord 1998 *{published data only}*

Lord SE, Wade DT, Halligan PW. A comparison of two physiotherapy treatment approaches to improve walking in multiple sclerosis: a pilot randomized controlled study. Clinical rehabilitation 1998;2(6):477-86.

Mostert 2002 *{published data only}*

Mostert S, Kesselring J. Effects of a short-term exercise training program on aerobic fitness, fatigue, health perception and activity level of subjects with multiple sclerosis. Multiple sclerosis 2002;8 (2):161-8.

O'Connell 2003 *{published and unpublished data}*

O'Connell R, Murphy RM, Hutchinson M, Cooke G, Coote S. A controlled study to assess the effects of aerobic training on patients with multiple sclerosis. In: 14th International World Confederation for Physical Therapy. Barcelona: 2003.

Petajan 1996 *{published data only}*

Petajan JH, Gappmaier E, White AT, Spencer MK, Mino L, Hicks RW. Impact of aerobic training on fitness and quality of life in multiple sclerosis. Annals of Neurology 1996;39(4):432-41.

Solari 1999 *{published data only}*

Solari A, Filippini G, Gasco P, Colla L, Salmaggi A, La Mantia L. Physical rehabilitation has a positive effect on disability in multiple sclerosis patients. Neurology 1999;52(1):57-62.

Wiles 2001 *{published data only}*

Wiles CM, Newcombe RG, Fuller KJ, Shaw S, Furnival-Doran J, Pickersgill TP. Controlled randomised crossover trial of the effects of physiotherapy on mobility in chronic multiple sclerosis. Journal of Neurology, Neurosurgery & Psychiatry 2001;70(2):174-9.

** indicates the major publication for the study*

References to studies excluded from this review

Craig 2003

Craig J, Young CA, Ennis M, Baker G, Boggild M. A randomised controlled trial comparing rehabilitation against standard therapy in multiple sclerosis patients receiving intravenous steroid treatment. Journal of Neurology, Neurosurgery & Psychiatry 2003;74:1225-30.

DeSouza 1984

DeSouza LH. A different approach to physiotherapy for multiple sclerosis patients. Physiotherapy 1984;70(11):26-9.

Di Fabio 1997

Di Fabio RP, Choi T, Soderberg J, Hansen CR. Health-related quality of life for patients with progressive multiple sclerosis: influence of rehabilitation. Physical Therapy 1997;77(12):1704-16.

Di Fabio 1998

Di Fabio RP, Soderberg J, Choi T, Hansen CR, Schapiro RT. Extended outpatient rehabilitation: its influence on symptom frequency, fatigue, and functional status for persons with progressive multiple sclerosis. Archives of Physical Medicine & Rehabilitation 1998;79(2):141-6.

Freeman 1997

Freeman JA, Langdon DW, Hobart JC, Thompson AJ. The impact of inpatient rehabilitation on progressive multiple sclerosis. Annals of Neurology 1997;42(2):236-44.

Freeman 1999

Freeman JA, Langdon DW, Hobart JC, Thompson AJ. Inpatient rehabilitation in multiple sclerosis: do the benefits carry over into the community?. Neurology 1999;52(1):50- 6.

Fuller 1996

Fuller KJ, Dawson K, Wiles CM. Physiotherapy and mobility in multiple sclerosis: a controlled study. Clinical rehabilitation 1996;10:195-204.

Gehlsen 1984

Gehlsen GM, Grigsby SA, Winant DM. Effects of an aquatic fitness program on the muscular strength and endurance of patients with multiple sclerosis. Physical Therapy 1984;64(5):653-7.

Gehlsen 1986

Gehlsen G, Beekman K, Assmann N, Winant D, Seidle M, Carter A. Gait characteristics in multiple sclerosis: progressive changes and effects of exercise on parameters. Archives of Physical Medicine & rehabilitation 1986;67(8):536-9.

Ketelaer 1978

Ketelaer P, Van Diest R, Van Muysewinkel A, Van Geyseghem L, Keersmaekers A, Delaite D, et al. Evaluation and results of the rehabilitation in multiple sclerosis (author's transl). Journal Belge de medicine Physique Rehabilitation 1978;1(3):227- 45.

Langdon 1999

* Langdon DW, Thompson AJ. Multiple sclerosis: a preliminary study of selected variables affecting rehabilitation outcome. Multiple Sclerosis 1999;5(2):94-100.

Lanzetta 2004

Lanzetta D, Cattaneo D, Pellegatta D, Cardini R. Trunk control in unstable sitting posture during functional activities in healthy subjects and patients with multiple sclerosis. Archives of Physical and Medical Rehabilitation 2004;85(2):279- 83.

Patti 2003

Patti F, Ciancio MR, Cacopardo M, Reggio E, Fiorilla T, Palermo F et al. Effects of a short outpatient rehabilitation treatment on disability of multiple sclerosis patients: a randomised controlled trial. Journal of Neurology 2003;250(7):861- 6.

Peterson 2001

Peterson C. Exercise in 94 degrees F water for a patient with multiple sclerosis. Physical Therapy 2001;81(4):1049-58.

Rodgers 1999

Rodgers MM, Mulcare JA, King DL, Mathews T, Gupta SC, Glaser RM. Gait characteristics of individuals with multiple sclerosis before and after a 6-month aerobic training program. Journal of Rehabilitation and Research 1999;36(3):183-88.

Svensson 1994

Svensson, B, Gerdle B, Elert J. Endurance training in patients with Multiple Sclerosis: Five case studies. Physical Therapy 1994;74(11):1017-24.

Wiles 2003

Wiles CM, Newcombe RG, Fuller KJ, Jones A, Proce M. Use of videotape to assess mobility in a controlled randomized crossover trial of physiotherapy in chronic multiple sclerosis. Clinical Rehabilitation 2003;17(3):256-63.

Additional references

Anonymous 1995

IFN-ÃŸ Multiple Sclerosis Study Group and the University of British Colombia MS/ MRI Analysis Group. Interferon beta-1b in the treatment of multiple sclerosis: final outcome of the randomised controlled trial. Neurology 1995;45(7):1277-85.

Baker 2001

Baker NA, Tickle-Degnen L. The effectiveness of physical, psychological and functional interventions in treating clients with Multiple Sclerosis: A meta-analysis. The American Journal of Occupational Therapy 2001;55(3):324-31.

Clarke 2000

Clarke M, Oxman AD editors. Analysing and presenting results. Cochrane Reviewers Handbook 4.1 [update June 2000]. In: Review Manager (RevMan) [Computer programme]. Version 4.1 Oxford, England: The Cochrane Collaboration, 2000.

Cohen 1960

Cohen, J. A coefficient of agreement for nominal scales. Educational and Psychological measurements 1960;20:37-46.

Cook 1980

Cook & Campbell. Quasi-Experimentation: Design & Analysis Issues for Field Settings. Rand McNally, 1980.

De Vet 2003

De Vet HC, van Tulder MW , Bouter LM. Levels of evidence: intellectual aid or absolute judgement?. Journal of Clinical Epidemiology 2003;56(9):917-8; author reply 919.

Egger 1998

Egger M, Smith GD. Bias in location and selection of studies. British Medical Journal 1998;316 (7124):61-6.

Goetzsche 1987

Goetzsche PC. Reference bias in reports of drug trials. British Medical Journal 1987;295:654-6.

Langdon 1999

Langdon DW, Thompson AJ. Multiple Sclerosis: a preliminary study of selected variables affecting rehabilitation outcome. Multiple Sclerosis 1999;5(2):94-100.

McDonald 2001

McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Annals of Neurology 2001;50(1):121-7.

Ng 1997

Ng AV, Kent-Braun JA. Quantitation of lower physical activity in persons with multiple sclerosis. Medicine and Science in Sports and Exercise 1997;29(4):517-23.

Poser 1983

Poser CM, Paty DW, Scheinberg L, McDonald, Davis FA, Ebers GC, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Annals of Neurology 1983;13(3):227-31.

Pozzilli 2002

Pozzilli C, Romano S, Cannoni S. Epidemiology and current treatment of multiple sclerosis in Europe today. Journal of Rehabilitation Research and Development 2002;39(2):175-85.

Schulz 1995

Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. Journal of American Medical Association 1995;273(5):408-12.

Schumacher 1965

Schumacher GA, Beebe GW, Kibler RF, Kurland LT, Kurtzke JF, McDowell F, et al. Problems of experimental trials of therapy in multiple sclerosis. Annals of the New York Academy of Sciences 1965;122:552-68.

Steultjens 2003

Steultjens EMJ, Dekker LJ, Bouter LM, Cardol M, Van de Nes JCM, Van den Ende CHM. Occupational Therapy for multiple sclerosis. In: The Cochrane Library, Issue 3, 2003. Oxford: Update Software.

Stuifbergen 1997

Stuifbergen AK. Physical activity and perceived health status in persons with multiple sclerosis. Journal of Neuroscience Nursing 1997;29(4):238-43.

van Tulder 2003

van Tulder M, Furlan A, Bombardier C, Bouter L. Updated method guidelines for systematic reviews in the cochrane collaboration back review group. Spine 2003;28(12):1290-9.

White 2000

White AT, Wilson TE, Davis SL, Petajan JH. Effect of precooling on physical performance in multiple sclerosis. Multiple Sclerosis 2000;6(3):176-80.

Cover sheet

Exercise therapy for multiple sclerosis

Reviewer(s)	Rietberg MB, Brooks D, Uitdehaag BMJ, Kwakkel G
Contribution of Reviewer(s)	M. Rietberg is author of the review, G. Kwakkel the supervisor. D.Brooks took part in rating the methodological quality. D. Brooks and B.Uitdehaag critically reviewed the manuscript. All reviewers discussed, the protocol, data collection, results and conclusions.
Issue protocol first published	2002 issue 4
Issue review first published	2005 issue 1
Date of last minor amendment	23 June 2004
Date of last substantive amendment	28 February 2004
Most recent changes	Information not supplied by reviewer
Date new studies sought but none found	Information not supplied by reviewer
Date new studies found but not yet included / excluded	Information not supplied by reviewer
Date new studies found and included / excluded	28 February 2004
Date reviewers' conclusions section amended	Information not supplied by reviewer
Contact address	Dr Gert Kwakkel De Boelelaan 1117 HV 1081 Amsterdam NETHERLANDS Telephone: +31-20-4440460 Facsimile: E-mail: g.kwakkel@vumc.nl
Cochrane Library number	CD003980
Editorial group	Cochrane Multiple Sclerosis Group
Editorial group code	MS

Sources of support

External sources of support

- No sources of support supplied

Internal sources of support

- The VU University Medical Centre covered expenses and provided access to electronic databases and internet for identification of studies NETHERLANDS

Synopsis

Exercise therapy is considered an important part of symptomatic and supportive treatment for multiple sclerosis (MS) patients

MS is a chronic disease of the central nervous system. The variable distribution of the damage in the myelin sheath of nerves may lead to loss of strength, sensation, co-ordination and balance causing severe and progressive limitations of function in daily life. To date, there is no effective treatment for MS, however, a number of studies suggest that exercise interventions aimed to improve daily functioning of patients with MS are effective. Nine randomized controlled trials of exercise therapy for MS patients were included in this review six of which used no therapy as the comparator. There was strong evidence in favor of exercise therapy, compared to no therapy, regarding muscle function and mobility while no evidence was found of improved fatigue, in one study only. No one specifically targeted exercise program was more successful than others. No eleterious effects were described in the included studies.

Keywords

Humans; *Exercise Therapy; Multiple Sclerosis[*rehabilitation]; *Quality of Life; Randomized Controlled Trials