Evidence Portfolio – Chronic Conditions Subcommittee, Question 5

In individuals with multiple sclerosis, what is the relationship between physical activity and (1) risk of co-morbid conditions, (2) physical function, and (3) health-related quality of life?

Sources of Evidence: Existing Systematic Reviews and Meta-Analyses

Conclusion Statements and Grades

RISK OF CO-MORBID CONDITIONS
Insufficient evidence is available to determine the relationship between physical activity and risk of co-morbid conditions in adults with multiple sclerosis. **PAGAC Grade: Not Assignable.**

PHYSICAL FUNCTION
Strong evidence demonstrates that physical activity—particularly aerobic and muscle-strengthening activities—improves physical function, including walking speed and endurance, in adults with multiple sclerosis. **PAGAC Grade: Strong.**

HEALTH-RELATED QUALITY OF LIFE
Limited evidence suggests that physical activity improves quality of life, including symptoms of fatigue and depressive symptoms, in adults with multiple sclerosis. **PAGAC grade: Limited.**

Description of the Evidence

The Chronic Conditions Subcommittee chose to rely exclusively on existing reviews including systematic reviews, meta-analyses, pooled analyses, and reports for this question. As determined by the Subcommittee, the search for existing reviews identified sufficient literature to answer the research question. Additional searches for original research were not conducted based on the a priori decision to focus on existing reviews.

PHYSICAL FUNCTION

Existing Systematic Reviews and Meta-Analyses

Overview

Twelve existing reviews assessing the relationship between physical activity and physical function in individuals with multiple sclerosis were included. Of these, 4 were meta-analyses[1-4] and 8 were systematic reviews.[5-12] The reviews were published between 2013 and 2017.

The meta-analyses included a range of 9 to 21 studies and all covered a timeframe from inception to 2014.[1-4]

The systematic reviews included a range of 3 to 54 studies and covered the following timeframes: 2011 to 2016[5]; inception to 2016[6, 11]; inception to 2011[7]; inception to 2014 and 2015[8, 10]; 2004 to 2012[9]; and 1985 to 2016.[12]

Exposures

The included reviews examined different types of physical activity, including aerobic and resistance training,[3, 4, 6, 7, 9] strength training only,[2] aquatic-based exercise interventions,[5, 8] and yoga and/or tai chi.[1, 11, 12]

Outcomes

The included reviews examined various physical function outcomes, including gait, mobility, balance, muscular strength, flexibility, and fatigue.

HEALTH-RELATED QUALITY OF LIFE

Existing Systematic Reviews and Meta-Analyses

Overview

Eleven existing reviews assessing the relationship between physical activity and health-related quality of life in individuals with multiple sclerosis were included. Of these, 6 were meta-analyses[1, 2, 13-16] and 5 were systematic reviews.[6, 7, 9, 11, 12] The reviews were published between 2012 and 2017.

The meta-analyses included a range of 9 to 21 studies and covered the following timeframes: 2008 to 2015,[13] inception to 2014,[1, 2] inception to 2011 and 2013,[14, 16] and 1960 to 2013.[15]

The systematic reviews included a range of 8 to 54 studies and covered the following timeframes: inception to 2016,[6, 11] inception to 2011,[7] 2004 to 2012,[9] and 1985 to 2016.[12]

Exposures

The majority of included reviews examined various exercise modalities, including aerobic training, resistance training, and/or yoga.[1, 6, 7, 9, 11-16] Three reviews focused on yoga and/or tai chi[1, 11, 12] and 1[2] focused on strength training only.

Outcomes

All the included reviews examined health-related quality of life.

Populations Analyzed

The table below lists the populations analyzed in each article.

Table 1. Populations Analyzed by All Sources of Evidence

	Age	Chronic Conditions
Afkar, 2017	Adults, mean age 33.75	Multiple sclerosis
Corvillo, 2017	Adults 19–69	Multiple sclerosis
Cramer, 2014	Adults, mean age 31.6–54.4	Multiple sclerosis
Cruickshank, 2015		Parkinson's disease, multiple sclerosis
Dalgas, 2015		Multiple sclerosis
Edwards, 2017	Adults	Multiple sclerosis
Ensari, 2014		Multiple sclerosis
Kuspinar, 2012	Adults ≥18	Multiple sclerosis
Latimer-Cheung, 2013	Adults	Multiple sclerosis
Methajarunon, 2016	Adults ≥18	Stroke, multiple sclerosis, Parkinson's disease, hemiplegia
Pearson, 2015	Adults ≥18	Multiple sclerosis
Platta, 2016		Multiple sclerosis
Sa, 2014	Adults, mean age 37.1–54.6	Multiple sclerosis
Sosnoff, 2015		Multiple sclerosis
Taylor, 2017	Average age 46	Multiple sclerosis
Zou, 2017	Adults 20–60	Multiple sclerosis

Supporting Evidence

Existing Systematic Reviews and Meta-Analyses

Table 2. Existing Systematic Reviews and Meta-Analyses Individual Evidence Summary Tables

<table>
<tr><th colspan="2">Health-Related Quality of Life</th></tr>
<tr><td colspan="2">Meta-Analysis
Citation: Afkar A, Ashouri A, Rahmani M, Emami Sigaroudi A. Effect of exercise therapy on quality of life of patients with multiple sclerosis in Iran: a systematic review and meta-analysis. Neurol Sci. July 2017. doi:10.1007/s10072-017-3047-x.</td></tr>
<tr><td>Purpose: To estimate the effect size of exercise therapy on each of the mental and physical dimensions of the quality of life among multiple sclerosis patients in Iran, only by using the results of randomized controlled trials as the best evidence.</td><td rowspan="5">Abstract: Multiple sclerosis (MS) is a chronic and progressive disease charachterized by disabilities which adversely affect individuals' quality of life (QOL). In the present study, the effect size of exercise therapy on patients' QOL in both physical and mental dimensions were investigated and the moderator effect of a number of selected theoretical and significant practical variables were assessed. Relevant studies, published before July 2015, were identified by searching PubMed, Scopus, Google scholar, and Persian medical databases including IranMedex, Irandoc, Magiran, Scientific Information Database (SID), and Medlib. Supplementary searches were also performed manually by reviewing the reference lists of the relevant articles. Next, using a randomized controlled trial (RCT) design, English and/or Persian-language articles conducted in Iran and evaluating the effect of exercise therapy on physical and/or mental aspects of QOL of MS patients were pooled. Afterwards, two competent reviewers in the field extracted the required data and rated the quality of the studies. Twenty-one journal articles were identified and reviewed, but only 13 of them contained the as much data as required to serve the purpose of the study. The mean effect size of exercise therapy on mental, physical, and overall QOL of the patients were 1.021 (95%CI 0.712-1.331, P < .001), 1.040 (95%CI 0.730-1.349, P < .001), and 0.846 (95%CI 0.508-1.184, P < .001), respectively. Based on the investigated Iranian studies, there is strong evidence confirming the effect of exercise therapy on QOL of patients with MS; there, however, exists a need for more studies to identify and establish effective exercise programs due to the heterogeneity of the studies conducted in this area.</td></tr>
<tr><td>Timeframe: 2008–July 2015</td></tr>
<tr><td>Total # of Studies: 21</td></tr>
<tr><td>Exposure Definition: Exercise interventions varied in modality and included aerobic, endurance training, resistance training, aquatics, and yoga, or a combination of these exercises, with aquatic exercise as the most common. The mean intervention length was 9.57 weeks, with sessions held 2–3 times per week. The duration of an exercise bout ranged from 20 to 75 minutes per session.
Measures Steps: No
Measures Bouts: No
Examines HIIT: No</td></tr>
<tr><td>Outcomes Addressed: Mental, physical, and overall quality of life: Multiple Sclerosis Quality of Life-54 Questionnaire, Short-Form Health Survey-36, Short-form 8, World Health Organization Quality of Life-short version, Functional Assessment of Multiple Sclerosis (FAMS).
Examine Cardiorespiratory Fitness as Outcome: No</td></tr>
<tr><td>Populations Analyzed: Asian, Mean age 33.75 years, Multiple sclerosis</td><td>Author-Stated Funding Source: Not reported.</td></tr>
</table>

<table>
<tr><th colspan="2">Physical Function</th></tr>
<tr><td colspan="2">Systematic Review
Citation: Corvillo I, Varela E, Armijo F, Alvarez-Badillo A, Armijo O, Maraver F. Efficacy of aquatic therapy for multiple sclerosis: a systematic review. Eur J Phys Rehabil Med. Feb 2017:17. doi:10.23736/S1973-9087.</td></tr>
<tr><td>Purpose: To systematically review the current state of aquatic treatment (hydrotherapy, aquatic therapy, aquatic exercises, spa therapy) for persons with multiple sclerosis and to evaluate the scientific evidence supporting the benefits of this therapeutic option.</td><td rowspan="5">Abstract: BACKGROUND: Multiple sclerosis (MS) is a chronic, inflammatory, progressive, disabling autoimmune disease affecting the central nervous system. Symptoms and signs of MS vary widely and patients may lose their ability to walk. To date the benefits of aquatic therapy often used for rehabilitation in MS patients have not been reviewed. OBJECTIVE: To systematically review the current state of aquatic treatment for persons with MS (hydrotherapy, aquatic therapy, aquatic exercises, spa therapy) and to evaluate the scientific evidence supporting the benefits of this therapeutic option. METHODS: The databases PubMed, Scopus, WoS and PEDro were searched to identify relevant reports published from January 1, 2011 to April 30, 2016. RESULTS: Of 306 articles identified, only 10 fulfilled the inclusion criteria: 5 randomized controlled, 2 simple randomized quasi-experimental, 1 semi-experimental, 1 blind controlled pilot and 1 pilot. CONCLUSIONS: Evidence that aquatic treatment improves quality of life in affected patients was very good in two studies, good in four, fair in two and weak in two.</td></tr>
<tr><td>Timeframe: 2011–April 2016</td></tr>
<tr><td>Total # of Studies: 10</td></tr>
<tr><td>Exposure Definition: Aquatic-based interventions, including aquatic exercise programs (warm-up, stretches, resistance, coordination, strengthening, and relaxation), aquatic cycling, aquatic training with pilates (ambulation, stretches, strength, relaxation, balance, and pilates), aquatic aerobic exercise in the form of water walking, and tai chi (continuous, wide movements combined with deep breathing). Interventions ranged from 3 to 20 weeks in length and were conducted approximately
2–3 days a week.
Measures Steps: No
Measures Bouts: No
Examines HIIT: No</td></tr>
<tr><td>Outcomes Addressed: Fatigue. Balance impairment. Functional mobility alteration. Muscle weakness. Walking disorder. Physical deconditioning. Quality of life.
Examine Cardiorespiratory Fitness as Outcome: No</td></tr>
<tr><td>Populations Analyzed: Age 19–69, Multiple sclerosis</td><td>Author-Stated Funding Source: No funding source used.</td></tr>
</table>

<table>
<tr><th colspan="2">Health-Related Quality of Life, Physical Function</th></tr>
<tr><td colspan="2">Meta-Analysis
Citation: Cramer H, Lauche R, Azizi H, Dobos G, Langhorst J. Yoga for multiple sclerosis: a systematic review and meta-analysis. PLoS One. 2014;9(11):e112414. doi:10.1371/journal.pone.0112414.</td></tr>
<tr><td>Purpose: To systematically evaluate and meta-analyze the available data on efficacy and safety of yoga in improving health-related quality of life, fatigue, and mobility in patients with multiple sclerosis.</td><td rowspan="4">Abstract: While yoga seems to be effective in a number of neuropsychiatric disorders, the evidence of efficacy in multiple sclerosis remains unclear. The aim of this review was to systematically assess and meta-analyze the available data on efficacy and safety of yoga in patients with multiple sclerosis. Medline/PubMed, Scopus, the Cochrane Central Register of Controlled Trials, PsycINFO, CAM-Quest, CAMbase, and IndMED were searched through March 2014. Randomized controlled trials (RCTs) of yoga for patients with multiple sclerosis were included if they assessed health-related quality of life, fatigue, and/or mobility. Mood, cognitive function, and safety were defined as secondary outcome measures. Risk of bias was assessed using the Cochrane tool. Seven RCTs with a total of 670 patients were included. Evidence for short-term effects of yoga compared to usual care were found for fatigue (standardized mean difference [SMD] = -0.52; 95% confidence intervals (CI) = -1.02 to -0.02; p = 0.04; heterogeneity: I2 = 60%; Chi2 = 7.43; p = 0.06) and mood (SMD = -0.55; 95%CI = -0.96 to -0.13; p = 0.01; heterogeneity: I2 = 0%; Chi2 = 1.25; p = 0.53), but not for health-related quality of life, muscle function, or cognitive function. The effects on fatigue and mood were not robust against bias. No short-term or longer term effects of yoga compared to exercise were found. Yoga was not associated with serious adverse events. In conclusion, since no methodological sound evidence was found, no recommendation can be made regarding yoga as a routine intervention for patients with multiple sclerosis. Yoga might be considered a treatment option for patients who are not adherent to recommended exercise regimens.</td></tr>
<tr><td>Timeframe: Inception–March 2014</td></tr>
<tr><td>Total # of Studies: 9</td></tr>
<tr><td>Exposure Definition: Yoga (Hatha, Iyengar), with yoga postures and meditation or relaxation. Eight weeks to 6 months in length, with 1–3 weekly sessions of 60–90 minutes in duration. Separate meta-analyses conducted to compare yoga with usual care and yoga with exercise.
Measures Steps: No
Measures Bouts: No
Examines HIIT: No</td></tr>
<tr><td>Outcomes Addressed: Health-related quality of life: Multiple Sclerosis Quality of Life Scale-29 or the Short Form-36 Health Survey. Fatigue: Fatigue Severity Scale, Modified Fatigue Impact Scale, or Multidimensional Fatigue Inventory.
Examine Cardiorespiratory Fitness as Outcome: No</td></tr>
<tr><td>Populations Analyzed: Mean age 31.6–54.4, Multiple sclerosis</td><td>Author-Stated Funding Source: Rut- and Klaus-Bahlsen-Foundation.</td></tr>
</table>

Health-Related Quality of Life, Physical Function	
Meta-Analysis **Citation:** Cruickshank TM, Reyes AR, Ziman MR. A systematic review and meta-analysis of strength training in individuals with multiple sclerosis or Parkinson disease. *Medicine (Baltimore).* 2015;94(4):e411. doi:10.1097/MD.0000000000000411.	
Purpose: To explore whether differences in response to strength training exist between individuals with multiple sclerosis or Parkinson's disease.	**Abstract:** Strength training has, in recent years, been shown to be beneficial for people with Parkinson disease and multiple sclerosis. Consensus regarding its utility for these disorders nevertheless remains contentious among healthcare professionals. Greater clarity is required, especially in regards to the type and magnitude of effects as well as the response differences to strength training between individuals with Parkinson disease or multiple sclerosis. This study examines the effects, magnitude of those effects, and response differences to strength training between patients with Parkinson disease or multiple sclerosis. A comprehensive search of electronic databases including Physiotherapy Evidence Database scale, PubMed, EMBASE, Cochrane Central Register of Controlled Trials, and CINAHL was conducted from inception to July 2014. English articles investigating the effect of strength training for individuals with neurodegenerative disorders were selected. Strength training trials that met the inclusion criteria were found for individuals with Parkinson disease or multiple sclerosis. Individuals with Parkinson disease or multiple sclerosis were included in the study. Strength training interventions included traditional (free weights/machine exercises) and nontraditional programs (eccentric cycling). Included articles were critically appraised using the Physiotherapy Evidence Database scale. Of the 507 articles retrieved, only 20 articles met the inclusion criteria. Of these, 14 were randomized and 6 were nonrandomized controlled articles in Parkinson disease or multiple sclerosis. Six randomized and 2 nonrandomized controlled articles originated from 3 trials and were subsequently pooled for systematic analysis. Strength training was found to significantly improve muscle strength in people with Parkinson disease (15%-83.2%) and multiple sclerosis (4.5%-36%). Significant improvements in mobility (11.4%) and disease progression were also reported in people with Parkinson disease after strength training. Furthermore, significant improvements in fatigue (8.2%), functional capacity (21.5%), quality of life (8.3%), power (17.6%), and electromyography activity (24.4%) were found in individuals with multiple sclerosis after strength training. The limitations of the study were the heterogeneity of interventions and study outcomes in Parkinson disease and multiple sclerosis trials. Strength training is useful for increasing muscle strength in Parkinson disease and to a lesser extent multiple sclerosis.
Timeframe: Inception–July 2014	
Total # of Studies: 20 (12 in meta-analysis)	
Exposure Definition: Strength training, with training protocols ranging from 2 to 24 months with sessions conducted 2–5 times per week. **Measures Steps:** No **Measures Bouts:** No **Examines HIIT:** No	
Outcomes Addressed: Muscle strength: 1 repetition maximum, maximum voluntary isometric contraction protocols. Functional mobility: 10-meter timed walk test, 2 minute walk test, and timed up and go. Balance: functional reach test, Four Square Step Test, Accusway force platform. Functional capacity. Quality of life: Short Form-36, World Health Organisation Quality of Life-BREF. Skeletal muscle volume and architecture. Fatigue: Modified Fatigue Scale, Fatigue Severity Scale, Multidimensional Fatigue Inventory. Mood: Major Depression Inventory, Beck Depression Inventory. **Examine Cardiorespiratory Fitness as Outcome:** No	

Populations Analyzed: Parkinson's disease, Multiple sclerosis	**Author-Stated Funding Source:** Not reported.

<table>
<tr><th colspan="2">Health-Related Quality of Life</th></tr>
<tr><td colspan="2">Meta-Analysis
Citation: Dalgas U, Stenager E, Sloth M, Stenager E. The effect of exercise on depressive symptoms in multiple sclerosis based on a meta-analysis and critical review of the literature. Eur J Neurol. 2015;22(3):443-e34. doi:10.1111/ene.12576.</td></tr>
<tr><td>Purpose: To conduct a systematic review and meta-analysis of the existing literature on the effects of exercise therapy on depressive symptoms in people with multiple sclerosis.</td><td rowspan="5">Abstract: 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.</td></tr>
<tr><td>Timeframe: Inception–October 2013</td></tr>
<tr><td>Total # of Studies: 15 (12 for meta-analysis)</td></tr>
<tr><td>Exposure Definition: Exercise intervention defined as "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." Classified as resistance training, endurance training, combined (resistance and endurance training), or as other exercise modalities such as sports climbing, yoga, and water activities. Interventions lasted from 3 to 26 weeks.
Measures Steps: No
Measures Bouts: No
Examines HIIT: No</td></tr>
<tr><td>Outcomes Addressed: Measure of depressive symptoms or depression or an instrument with a depression subscale (e.g., Beck Depression Inventory, the Major Depression Inventory, the Inventory of Depressive Symptomatology, Hospital Anxiety and Depression Scale, Profile of Mood States, and Center for Epidemiologic Studies Depression Scale).
Examine Cardiorespiratory Fitness as Outcome: No</td></tr>
<tr><td>Populations Analyzed: Multiple sclerosis</td><td>Author-Stated Funding Source: No funding source used.</td></tr>
</table>

Health-Related Quality of Life, Physical Function	
Systematic Review **Citation:** Edwards T, Pilutti LA. The effect of exercise training in adults with multiple sclerosis with severe mobility disability: a systematic review and future research directions. *Mult Scler Relat Disord*. 2017;16:31–39. doi:10.1016/j.msard.2017.06.003.	
Purpose: To conduct a systematic review of the current literature pertaining to exercise training in individuals with multiple sclerosis with severe mobility disability.	**Abstract:** INTRODUCTION: There is evidence for the benefits of exercise training in persons with multiple sclerosis (MS). However, these benefits have primarily been established in individuals with mild-to-moderate disability (i.e., Expanded Disability Status Scale [EDSS] scores 1.0-5.5), rather than among those with significant mobility impairment. Further, the approaches to exercise training that have been effective in persons with mild-to-moderate MS disability may not be physically accessible for individuals with mobility limitations. Therefore, there is a demand for an evidence-base on the benefits of physically accessible exercise training approaches for managing disability in people with MS with mobility impairment. OBJECTIVE: To conduct a systematic review of the current literature pertaining to exercise training in individuals with multiple sclerosis (MS) with severe mobility disability. METHODS: Four electronic databases (PubMed, EMBASE, OvidMEDLINE, and PsychINFO) were searched for relevant articles published up until October 2016. The review focused on English-language studies that examined the effect of exercise training in people with MS with severe mobility disability, characterized as the need for assistance in ambulation or EDSS score >/= 6.0. The inclusion criteria involved full-text articles that: (i) included participants with a diagnosis of MS; (ii) included primarily participants with a reported EDSS score >/= 6.0 and/or definitively described disability consistent with this level of neurological impairment; and (iii) implemented a prospective, structured exercise intervention. Data were analyzed using a descriptive approach and summarized by exercise training modality (conventional or adapted exercise training), and by outcome (disability, physical fitness, physical function, and symptoms and participation). RESULTS: Initially, 1164 articles were identified and after removal of duplicates, 530 articles remained. In total, 512 articles did not meet the inclusion criteria. 19 articles were included in the final review. Five studies examined conventional exercise training (aerobic and resistance training), and thirteen studies examined adapted exercise modalities including body-weight support treadmill training (BWSTT), total-body recumbent stepper training (TBRST), and electrical stimulation cycling (ESAC). Outcomes related to mobility, fatigue, and quality of life (QOL) were most frequently reported. Two of five studies examining conventional resistance exercise training reported significant improvements in physical fitness, physical function, and/or symptomatic and participatory outcomes. Nine of 13 studies examining adapted exercise training reported significant improvements in disability, physical fitness, physical function, and/or symptomatic and participatory outcomes. CONCLUSIONS: There is limited, but promising
Timeframe: Inception–October 2016	
Total # of Studies: 19	
Exposure Definition: Interventions consisted of conventional exercise training (aerobic and resistance exercise) or adaptive exercise training that consisted of body weight supported treadmill training, total-body recumbent stepper training, and electrical stimulated assisted cycling. Intervention length ranged from 2 to 24 weeks. Sessions were conducted 2–3 times per week for 20–60 minutes at varied intensities. **Measures Steps:** No **Measures Bouts:** No **Examines HIIT:** No	
Outcomes Addressed: Disability: Expanded Disability Status Scale (EDSS) or Multiple Sclerosis Functional Composite. Cardiorespiratory fitness: VO2 peak. Physical function: tests of walking, gait, agility, balance, spasticity, and upper	

extremity function. Fatigue. Quality of Life. **Examine Cardiorespiratory Fitness as Outcome:** Yes	evidence for the benefits of exercise training in persons with MS with severe mobility disability. Considering the lack of effective therapeutic strategies for managing long-term disability accumulation, exercise training could be considered as an alternative approach. Further research is necessary to optimize the prescription and efficacy of exercise training for adults with MS with severe mobility disability.
Populations Analyzed: Adults; Multiple sclerosis	**Author-Stated Funding Source:** No funding source used.

Health-Related Quality of Life	
Meta-Analysis **Citation:** Ensari I, Motl RW, Pilutti LA. Exercise training improves depressive symptoms in people with multiple sclerosis: results of a meta-analysis. *J Psychosom Res*. 2014;76(6):465–471. doi:10.1016/j.jpsychores.2014.03.014.	
Purpose: To examine the overall magnitude of effect for exercise training for improving depressive symptoms in people with multiple sclerosis.	**Abstract:** OBJECTIVE: There is a high prevalence, yet under-treatment of depressive disorder and symptoms by conventional therapy in people with multiple sclerosis (MS). We conducted a meta-analysis examining the overall effect of exercise training on depressive symptoms in MS. METHODS: We searched PubMed for randomized controlled trials (RCT) of exercise training and depression as an outcome in samples with MS. There were 13 RCTs that met inclusion criteria and yielded data for effect size (ES) generation (Cohen's d). An overall ES was calculated using a random effects model and expressed as Hedge's g. RESULTS: The weighted mean ES was small, but statistically significant (Hedge's g=0.36, SE=0.09, 95% CI=0.18-0.54, z=3.92, p<.001) indicating the exercise training resulted in an improvement in depressive symptoms compared to control. The overall effect was not heterogeneous (Q=16.46, df=12, p=0.17, I2=27.08); and post-hoc, exploratory analyses only identified depression symptom scale as a potential moderator variable (p=0.04). CONCLUSION: The cumulative evidence indicates that exercise training can yield a small, yet statistically significant and reliable reduction in depressive symptoms for people with MS.
Timeframe: 1960–November 2013	
Total # of Studies: 13	
Exposure Definition: Exercise training. Moderator analyses by exercise mode (aerobic, nonaerobic), number of exercise conditions (combined, single), exercise frequency (≤12, >12, <3, and ≥3 times per week). **Measures Steps:** No **Measures Bouts:** No **Examines HIIT:** No	
Outcomes Addressed: Depressive symptoms: e.g., Hospital Anxiety and Depression Scale, Center for Epidemiologic Studies Depression Scale. Moderator analyses included depressive symptom category (none/mild or moderate) and specific depressive symptoms scale used. **Examine Cardiorespiratory Fitness as Outcome:** No	
Populations Analyzed: Multiple sclerosis	**Author-Stated Funding Source:** Not reported.

Health-Related Quality of Life	
Meta-Analysis **Citation:** Kuspinar A, Rodriguez AM, Mayo NE. The effects of clinical interventions on health-related quality of life in multiple sclerosis: a meta-analysis. *Mult Scler*. 2012;18(12):1686–1704. doi:10.1177/1352458512445201.	
Purpose: To estimate the extent to which existing health care interventions designed specifically to target health-related quality of life in persons with multiple sclerosis achieve this aim.	**Abstract:** The objective is to estimate the extent to which existing health care interventions designed specifically to target health-related quality of life (HRQL) in persons with multiple sclerosis (MS) achieve this aim. The structured literature search was conducted using multiple electronic databases including Ovid MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature and the Cochrane Central Register of Controlled Trial, for the years 1960 to 2011. The methodological quality of selected randomized controlled trials (RCTs) was assessed using the Cochrane Collaboration's recommended domain-based method. Effect size (ES) was used to measure the effect of each intervention on HRQL. The studies were combined using a random-effects model to account for inter-study variation. Heterogeneity was tested for using the I-test and publication bias was assessed using funnel plots and the Egger weighted regression statistic. Thirty-nine RCTs met the criteria, all with acceptable methodological quality. Six major types of interventions were identified through the search. The smallest effect was observed for self-management and complementary and alternative medicine (ES=0.2), followed by medication (ES=0.3) then cognitive training and exercise (ES=0.4), and psychological interventions to improve mood (ES=0.7). The magnitude of positive effect on HRQL varied between the different types of interventions. The extent to which interventions are able to improve HRQL depends on delivering a potent intervention to those persons who have the potential to benefit.
Timeframe: Inception–September 2011	
Total # of Studies: 39 (13 focused on exercise or rehabilitation)	
Exposure Definition: Exercise programs included aerobic, resistance, and combined (aerobic and resistance) training, and yoga. Programs varied in length, duration, and frequency. **Measures Steps:** No **Measures Bouts:** No **Examines HIIT:** No	
Outcomes Addressed: Health-related quality of life: questionnaires such as Short Form 36 and Multiple Sclerosis Impact - 29. **Examine Cardiorespiratory Fitness as Outcome:** No	
Populations Analyzed: Age ≥18, Multiple sclerosis	**Author-Stated Funding Source:** Fonds de la Recherche en Sanue du Quebec, Multiple Sclerosis Society of Canada, and the Physiotherapy Foundation of Canada.

<table>
<tr><th colspan="2">Health-Related Quality of Life, Physical Function</th></tr>
<tr><td colspan="2">Systematic Review
Citation: Latimer-Cheung AE, Pilutti AE, Hicks AL, et al. Effects of exercise training on fitness, mobility, fatigue, and health-related quality of life among adults with multiple sclerosis: a systematic review to inform guideline development. Arch Phys Med Rehabil. 2013;94(9):1800–1828.e3. doi:10.1016/j.apmr.2013.04.020.</td></tr>
<tr><td>Purpose: To examine the minimum dose of exercise needed to elicit benefits in physical fitness, mobility, fatigue, and health-related quality of life in persons with multiple sclerosis.</td><td rowspan="5">Abstract: OBJECTIVE: To conduct a systematic review of evidence surrounding the effects of exercise training on physical fitness, mobility, fatigue, and health-related quality of life in adults with multiple sclerosis (MS). DATA SOURCES: The databases included EMBASE, 1980 to 2011 (wk 12); Ovid MEDLINE and Ovid OLDMEDLINE, 1947 to March (wk 3) 2011; PsycINFO, 1967 to March (wk 4) 2011; CINAHL all-inclusive; SPORTDiscus all-inclusive; Cochrane Library all-inclusive; and Physiotherapy Evidence Database all-inclusive. STUDY SELECTION: The review was limited to English-language studies (published before December 2011) of people with MS that evaluated the effects of exercise training on outcomes of physical fitness, mobility, fatigue, and/or health-related quality of life. DATA EXTRACTION: One research assistant extracted data and rated study quality. A second research assistant verified the extraction and quality assessment. DATA SYNTHESIS: From the 4362 studies identified, 54 studies were included in the review. The extracted data were analyzed using a descriptive approach. There was strong evidence that exercise performed 2 times per week at a moderate intensity increases aerobic capacity and muscular strength. The evidence was not consistent regarding the effects of exercise training on other outcomes. CONCLUSIONS: Among those with mild to moderate disability from MS, there is sufficient evidence that exercise training is effective for improving both aerobic capacity and muscular strength. Exercise may improve mobility, fatigue, and health-related quality of life.</td></tr>
<tr><td>Timeframe: Inception–April 2011</td></tr>
<tr><td>Total # of Studies: 54</td></tr>
<tr><td>Exposure Definition: Exercise programs included aerobic, resistance, and combined (aerobic and resistance) training, and alternative forms of exercise (such as yoga and aquatic exercises). Programs varied in duration, frequency, and length.
Measures Steps: No
Measures Bouts: No
Examines HIIT: No</td></tr>
<tr><td>Outcomes Addressed: Mobility, fatigue, and health-related quality of life.
Examine Cardiorespiratory Fitness as Outcome: Yes</td></tr>
<tr><td>Populations Analyzed: Adults, Multiple sclerosis</td><td>Author-Stated Funding Source: Canadian Institutes of Health Research (CIHR), an Ontario Neurotrauma Foundation, and CIHR Canada Research.</td></tr>
</table>

<table>
<tr><th colspan="2">Physical Function</th></tr>
<tr><td colspan="2">Systematic Review
Citation: Methajarunon P, Eitivipart C, Diver C, Foongchomcheay A. Systematic review of published studies on aquatic exercise for balance in patients with multiple sclerosis, Parkinson's disease, and hemiplegia. HKPJ. 2016;35:12–20. doi:10.1016/j.hkpj.2016.03.002.</td></tr>
<tr><td>Purpose: To assess the effectiveness of aquatic exercises for balance improvement in patients with multiple sclerosis, Parkinson's disease, and stroke.</td><td rowspan="5">Abstract: Background Multiple sclerosis, Parkinson's disease, and hemiplegia are common disorders that directly cause impairment of balance and gait. Aquatic exercises are used for neurological rehabilitation. It is suggested that the contributing factors of the water setting such as buoyancy, viscosity, and hydrostatic pressure offer an ideal environment for rehabilitative programmes. Objective To conduct a systematic review of studies that assess the effect of aquatic exercises on balance in neurological patients (i.e., patients with multiple sclerosis, Parkinson's disease, and hemiplegia). Methods A systematic literature search of six databases (MEDLINE, PEDro, AMED, CINAHL, Embase, SPORTDiscus) for randomized controlled trials and quasi-experimental trials on aquatic exercises in three different neurological disorders, namely, multiple sclerosis, Parkinson's disease, and hemiplegia, was performed. Reference lists from identified studies were manually searched for additional studies. Methodological quality was assessed using the Downs and Black checklist. The data were analyzed and synthesized by two independent reviewers. Disagreements in extracted data were resolved by discussion among the reviewers. Results The methodological quality of eight studies included in this review ranged from fair to good. The findings illustrated that there were statistically significant improvements in static and dynamic balance in patients with multiple sclerosis and hemiplegia. The statistically significant improvements in gait ability were only found in the studies conducted on multiple sclerosis. No conclusions can be drawn in Parkinson's populations as only two trials conducted with a small sample size were available. Conclusion Aquatic exercises may be effective at improving balance impairment in patients with hemiplegia and multiple sclerosis. There is a need for further research investigating its effect on Parkinson's disease before encouraging the use of aquatic exercises.</td></tr>
<tr><td>Timeframe: Inception–December 2014</td></tr>
<tr><td>Total # of Studies: 8 (3 on multiple sclerosis patients)</td></tr>
<tr><td>Exposure Definition: Aquatic exercise-based programs, including those with Ai-Chi, obstacle training, and task-oriented training. Swimming was not considered an aquatic exercise and not included. The duration of the program varied between 35 to 60 minutes and frequency between 2–3 times per week. The length of program ranged from 4 weeks to 12 weeks.
Measures Steps: No
Measures Bouts: No
Examines HIIT: No</td></tr>
<tr><td>Outcomes Addressed: Physical function: measured through various tests including Timed Up and Go Test, 6-minute walk test, Berg Balance scale, 6 minute walk test, and gait speed.
Examine Cardiorespiratory Fitness as Outcome: No</td></tr>
<tr><td>Populations Analyzed: Age ≥ 18, Stroke, Multiple sclerosis, Parkinson's disease, Hemiplegia</td><td>Author-Stated Funding Source: No funding source used.</td></tr>
</table>

<table>
<tr><th colspan="2">Physical Function</th></tr>
<tr><td colspan="2">Meta-Analysis
Citation: Pearson M, Dieberg G, Smart N. Exercise as a therapy for improvement of walking ability in adults with multiple sclerosis: a meta-analysis. Arch Phys Med Rehabil. 2015;96(7):1339–1348.e7. doi:10.1016/j.apmr.2015.02.011.</td></tr>
<tr><td>Purpose: To provide an updated meta-analysis and quantify the benefits of exercise for improving walking ability in patients with multiple sclerosis .</td><td rowspan="4">Abstract: OBJECTIVE: To quantify improvements in walking performance commonly observed in patients with multiple sclerosis (pwMS), a systematic literature search and meta-analysis were conducted quantifying the expected benefits of exercise on walking ability in pwMS. DATA SOURCES: Potential studies were identified by systematic search using PubMed (1966 to March 31, 2014), EMBASE (1974 to March 31, 2014), CINAHL (1998 to March 31, 2014), SPORTDiscus (1991 to March 31, 2014), and the Cochrane Central Register of Controlled Trials (1966 to March 31, 2014). The search used key concepts of "multiple sclerosis" AND "exercise." STUDY SELECTION: Randomized controlled trials of exercise training in adult pwMS. DATA EXTRACTION: Data on patient and study characteristics, walking ability, 10-m walk test (10mWT), timed 25-foot walk test (T25FW), 2-minute walk test (2MWT), 6-minute walk test (6MWT), and timed Up and Go (TUG) were extracted and archived. DATA SYNTHESIS: Data from 13 studies were included. In pwMS who exercised, significant improvements were found in walking speed, measured by the 10mWT (mean difference [MD] reduction in walking time of -1.76s; 95% confidence interval [CI], -2.47 to -1.06; P<.001), but no change in the T25FW (MD=-.59s; 95% CI, -2.55 to 1.36; P=.55). In pwMS who exercised, significant improvements were found in walking endurance as measured by the 6MWT and 2MWT, with an increased walking distance of MD=36.46m (95% CI, 15.14-57.79; P<.001) and MD=12.51m (95% CI, 4.79-20.23; P=.001), respectively. No improvement was found for TUG (MD=-1.05s; 95% CI, -2.19 to .09; P=.07). CONCLUSIONS: Our meta-analysis suggests that exercise improves walking speed and endurance in pwMS.</td></tr>
<tr><td>Timeframe: Inception–March 2014</td></tr>
<tr><td>Total # of Studies: 13</td></tr>
<tr><td>Exposure Definition: Exercise interventions compared in analyses included aerobic, resistance, and combined (aerobic and resistance) training, and yoga training. Interventions implemented for at least 2 weeks.
Measures Steps: No
Measures Bouts: No
Examines HIIT: No</td></tr>
<tr><td>Outcomes Addressed: Physical function: walking speed (10-m walk test, timed 25-ft walk test, and 500-m walk test); walking endurance (2-minute walk test and 6-minute walk test); mobility and balance (Timed Up and Go).
Examine Cardiorespiratory Fitness as Outcome: No</td></tr>
<tr><td>Populations Analyzed: Age ≥18; Multiple sclerosis</td><td>Author-Stated Funding Source: Not reported.</td></tr>
</table>

<table>
<tr><th colspan="2">Physical Function</th></tr>
<tr><td colspan="2">Meta-Analysis
Citation: Platta ME, Ensari I, Motl RW, Pilutti LA. Effect of exercise training on fitness in multiple sclerosis: a meta-analysis. Arch Phys Med Rehabil. 2016;97(9):1564–1572. doi:10.1016/j.apmr.2016.01.023.</td></tr>
<tr><td>Purpose: To provide a quantitative synthesis of randomized controlled trials examining the effect of exercise training on muscular and cardiorespiratory fitness in persons with multiple sclerosis.</td><td rowspan="5">Abstract: OBJECTIVE: To provide a quantitative synthesis of randomized controlled trials (RCTs) examining the effect of exercise training on muscular and cardiorespiratory fitness in persons with multiple sclerosis (MS). DATA SOURCES: Three electronic databases, PubMed, Google Scholar, and Web of Science, were searched for all relevant articles published up until October 2014. STUDY SELECTION: Keywords included exercise or aerobic or strength or resistance training or cardiorespiratory and multiple sclerosis. Trials examining the effect of exercise training on muscular and/or cardiorespiratory fitness parameters were included. DATA EXTRACTION: The initial search yielded 1501 articles; of these, 62 were reviewed in detail, and 20 RCTs met the inclusion criteria and provided enough data to compute effect sizes (ESs) (Cohen d). The meta-analyses was conducted using a random effects model to compute the overall or mean ES per fitness parameter. DATA SYNTHESIS: The mean ES was .27 (SE=.05; 95% confidence interval [CI], .17-.38; z=5.05; P<.001) for muscular fitness outcomes and .47 (SE=.09; 95% CI, .30-.65; z=5.4; P<.001) for cardiorespiratory fitness outcomes. The weighted mean ES was not heterogeneous for muscular (Q13=11.09, P=.60, I(2)=.00) or cardiorespiratory (Q9=7.83, P=.55, I(2)=.00) fitness outcomes. CONCLUSIONS: The cumulative evidence supports that exercise training is associated with changes in muscular (small in magnitude) and cardiorespiratory (moderate in magnitude) fitness outcomes in persons with MS. Such an indication of magnitude is important for clinical research and practice by providing an evidence-based estimate of the actual benefit that exercise training confers on physiological fitness.</td></tr>
<tr><td>Timeframe: Inception–October 2014</td></tr>
<tr><td>Total # of Studies: 21</td></tr>
<tr><td>Exposure Definition: Exercise training intervention defined as a planned, structured, and repetitive form of physical activity conducted over an extended period of time, with the goal of improving health-related fitness (i.e., cardiorespiratory, muscular, motor, metabolic, morphologic components). Interventions consisted of aerobic, resistance, or combination training for 14–60 minutes, 2–5 times per week, for 3–26 weeks.
Measures Steps: No
Measures Bouts: No
Examines HIIT: No</td></tr>
<tr><td>Outcomes Addressed:
Cardiorespiratory fitness: VO2 peak.
Muscular fitness: isokinetic strength.
Examine Cardiorespiratory Fitness as Outcome: Yes</td></tr>
<tr><td>Populations Analyzed: Multiple sclerosis</td><td>Author-Stated Funding Source: Not reported.</td></tr>
</table>

<table>
<tr><th colspan="2">Health-Related Quality of Life, Physical Function</th></tr>
<tr><td colspan="2">Systematic Review
Citation: Sa MJ. Exercise therapy and multiple sclerosis: a systematic review. J Neurol. 2014;261(9):1651–1661. doi:10.1007/s00415-013-7183-9.</td></tr>
<tr><td>Purpose: To investigate the effects of exercise therapy in multiple sclerosis patients.</td><td rowspan="4">Abstract: Multiple sclerosis (MS) is an incurable disease, and despite current pharmacologic treatment being effective in reducing relapse rates and lesion burden, there is little evidence that these treatments work as effectively in preventing disability progression. In such cases, non-pharmacologic techniques such as exercise therapy with rehabilitation purposes may play an important role. This systematic review of randomised controlled trials (RCTs) aims at investigating the effects of exercise therapy in MS patients. The electronic database PubMed was searched for studies indexed between February 2004 and June 2012. Studies eligibility criteria included: clinical diagnosis of MS free of exacerbation; and intervention with exercise therapy, measured as activities of daily living (ADL). Two reviewers independently screened the titles and abstracts of the references retrieved. The methodological quality of the RCTs was assessed using the Physiotherapy Evidence Database scale (PEDro scale). The PubMed search resulted in a total of 72 articles, 11 of which were included in this review. The analysis included 591 participants, of which 358 (60.6 %) were women. Patients had a mean age between 37.1 and 54.6 years. Duration of MS since diagnosis was reported in nine of the 11 studies and varied between 5.2 and 15.9 years. According to PEDro scale, nine of the 11 included studies were considered to be of high methodological quality, with scores ranging from 7 to 10. In eight of the 11 included studies, the effectiveness of exercise therapy was compared to standard care, in two it was compared to those on a waiting list, and in one, to control treatment. The results of this review suggest that exercise therapy may have a beneficial effect in patients with MS, and therefore may be recommended for the rehabilitation of these patients.</td></tr>
<tr><td>Timeframe: February 2004–June 2012</td></tr>
<tr><td>Total # of Studies: 11</td></tr>
<tr><td>Exposure Definition: Exercise therapy: regimen or plan of physical activity designed and prescribed for the therapeutic goal of restoring normal musculoskeletal function of multiple sclerosis patients. Interventions included aerobic training, breathing exercises, endurance exercises, progressive resistance training, strengthening, and yoga.
Measures Steps: No
Measures Bouts: No
Examines HIIT: No</td></tr>
<tr><td>Outcomes Addressed: Activities of daily living: fatigue, exercise tolerance, walking, gait, and maintaining body position. Various instruments used.
Examine Cardiorespiratory Fitness as Outcome: No</td></tr>
<tr><td>Populations Analyzed: Mean age 37.1–54.6, Multiple sclerosis</td><td>Author-Stated Funding Source: Not reported.</td></tr>
</table>

<table>
<tr><th colspan="2">Physical Function</th></tr>
<tr><td colspan="2">Systematic Review
Citation: Sosnoff JJ, Sung J. Reducing falls and improving mobility in multiple sclerosis. Expert Rev Neurother. 2015;15(6):655–666. doi:10.1586/14737175.2015.1046377.</td></tr>
<tr><td>Purpose: To discuss the effects of interventions on fall incidence in persons with multiple sclerosis and determine characteristics of these programs that might optimize the reductions of falls.</td><td rowspan="4">Abstract: Falls are common in persons with multiple sclerosis (MS), and are related to physical injury and reduce the quality of life. Mobility impairments are a significant risk factor for falls in persons with MS. Although there is evidence that mobility in persons with MS can be improved with rehabilitation, much less is known about fall prevention. This review focuses on fall prevention in persons with MS. Ten fall prevention interventions consisting of 524 participants with a wide range of disability were systematically identified. Nine of the 10 investigations report a reduction in falls and/or proportion of fallers following treatment. The vast majority observed an improvement in balance that co-occurred with the reduction in falls. Methodological limitations preclude any firm conclusions. Numerous gaps in the understanding of fall prevention in persons with MS are discussed. Well-designed randomized control trials targeting mobility and falls are warranted.</td></tr>
<tr><td>Timeframe: Inception–February 2015</td></tr>
<tr><td>Total # of Studies: 10 (7 with exercise interventions)</td></tr>
<tr><td>Exposure Definition: Primarily exercise-based fall prevention interventions that targeted aspects of mobility but varied in setting (hospital, community vs. home based), length (3–12 weeks), and mode of exercise. Balance training was a common training intervention among the included studies.
Measures Steps: No
Measures Bouts: No
Examines HIIT: No</td></tr>
<tr><td>Outcomes Addressed: Fall incidence and risk. Physical function: mobility, balance (Berg balance scale), walking speed.
Examine Cardiorespiratory Fitness as Outcome: No</td><td></td></tr>
<tr><td>Populations Analyzed: Multiple sclerosis</td><td>Author-Stated Funding Source: National Multiple Sclerosis Society and Consortium of MS Centers.</td></tr>
</table>

<table>
<tr><th colspan="2">Health-Related Quality of Life, Physical Function</th></tr>
<tr><td colspan="2">Systematic Review
Citation: Taylor E, Taylor-Piliae RE. The effects of tai chi on physical and psychosocial function among persons with multiple sclerosis: a systematic review. Complement Ther Med. 2017;31:100–108. doi:10.1016/j.ctim.2017.03.001.</td></tr>
<tr><td>Purpose: To evaluate the effects of tai chi on physical and psychosocial function among individuals with multiple sclerosis.</td><td rowspan="4">Abstract: OBJECTIVES: Conduct a systematic review to evaluate the effects of Tai Chi on physical and psychosocial function among individuals with Multiple Sclerosis. METHODS: An electronic literature search of 12 databases using controlled vocabulary function and keywords from inception through August 2016. All Tai Chi intervention studies assessing physical and psychosocial function among persons with Multiple Sclerosis were included. Study quality was scored using an established tool examining 16 study elements (range=0-32). RESULTS: A total of 91 articles were retrieved, with 3 additional articles identified through reviewing bibliographies of relevant articles. A total of 8 studies (randomized controlled trials, n=3; quasi-experimental, n=5) enrolled 193 participants with Multiple Sclerosis. Studies were conducted in the USA (n=3), Europe (n=3), Iran, (n=1), and India (n=1). A total of 3 studies reported using the Yang style of Tai Chi (not specified, n=5 studies). The Tai Chi intervention averaged 27 sessions over 11 weeks. Study quality scores for the randomized controlled trials had a mean score of 23 (range 19-26), while quality scores for quasi-experimental studies had a mean score of 20 (range 13-26). Overall, participants enrolled in Tai Chi had better balance, gait and flexibility, less fatigue and depression, and better quality of life after the intervention; though mixed results were reported. CONCLUSION: The results indicate that Tai Chi is likely safe and may provide physical and psychosocial benefits in individuals with Multiple Sclerosis. Further research is needed using more rigorous study designs to assess the benefits of Tai Chi for individuals with Multiple Sclerosis.</td></tr>
<tr><td>Timeframe: Inception–August 2016</td></tr>
<tr><td>Total # of Studies: 8</td></tr>
<tr><td>Exposure Definition: Interventions involved Yang style or non-specified style tai chi for an average of 27 sessions (range 6–50) over 11 weeks (range 3–25 weeks).
Measures Steps: No
Measures Bouts: No
Examines HIIT: No</td></tr>
<tr><td>Outcomes Addressed: Physical function: balance (Berg Balance Scale, Modified Clinical Test of Sensory Organization and Balance, single leg standing test, other varied tests), gait (dynamic gait index, timed up and go, 25-foot walking speed test), flexibility (foot tapping test, hamstring flexibility), strength (time to complete five chair raises). Psychosocial: fatigue (Fatigue Severity Scale, Fatigue Scale of Motor and Cognitive Functions, Modified Fatigue Impact Scale). Quality of life (Short-Form 36, Questionnaire of Life Satisfaction). Disease symptoms.
Examine Cardiorespiratory Fitness as Outcome: No</td></tr>
<tr><td>Populations Analyzed: Average age 46, Multiple sclerosis</td><td>Author-Stated Funding Source: No funding source used.</td></tr>
</table>

<table>
<tr><th colspan="2">Health-Related Quality of Life, Physical Function</th></tr>
<tr><td colspan="2">Systematic Review
Citation: Zou L, Wang H, Xiao Z, et al. Tai chi for health benefits in patients with multiple sclerosis: a systematic review. PLoS One. 2017;12(2):e0170212. doi:10.1371/journal.pone.0170212.</td></tr>
<tr><td>Purpose: To evaluate the existing evidence on the effectiveness and safety of tai chi, which is critical in providing guidelines for clinicians to improve symptomatic management in multiple sclerosis patients.</td><td rowspan="5">Abstract: The aim of this systematic review was to evaluate the existing evidence on the effectiveness and safety of Tai chi, which is critical to provide guidelines for clinicians to improve symptomatic management in patients with multiple sclerosis (MS). After performing electronic and manual searches of many sources, ten relevant peer-reviewed studies that met the inclusion criteria were retrieved. The existing evidence supports the effectiveness of Tai chi on improving quality of life (QOL) and functional balance in MS patients. A small number of these studies also reported the positive effect of Tai chi on flexibility, leg strength, gait, and pain. The effect of Tai chi on fatigue is inconsistent across studies. Although the findings demonstrate beneficial effects on improving outcome measures, especially for functional balance and QOL improvements, a conclusive claim should be made carefully for reasons such as methodological flaws, small sample size, lack of specific-disease instruments, unclear description of Tai chi protocol, unreported safety of Tai chi, and insufficient follow-up as documented by the existing literature. Future research should recruit a larger number of participants and utilize the experimental design with a long-term follow-up to ascertain the benefits of Tai chi for MS patients.</td></tr>
<tr><td>Timeframe: 1985–April 2016</td></tr>
<tr><td>Total # of Studies: 10</td></tr>
<tr><td>Exposure Definition: Tai chi interventions, ranging from 30 to 90 minutes for 2 or 3 sessions weekly, for 2 to 6 months.
Measures Steps: No
Measures Bouts: No
Examines HIIT: No</td></tr>
<tr><td>Outcomes Addressed: Multiple Sclerosis Quality of Life Questionnaire, 36-item Short Form Health Status Survey, visual analogue scale for pain, Patient-determined Disease Steps Questionnaire, 5-item Modified Fatigue Impact Scale, Center for Epidemiological Studies Depression Scale, Fatigue Scale of Motor and Cognitive Function, Questionnaire of Life Satisfaction, Dynamic Gait Index, Functional Lateral-Forward Reach test, Timed Up and Go, Activities-specific Balance Confidence, Berg Balance Scale, and Profile of Mood States.
Examine Cardiorespiratory Fitness as Outcome: No</td></tr>
<tr><td>Populations Analyzed: Age 20–60, Multiple sclerosis</td><td>Author-Stated Funding Source: No funding source used.</td></tr>
</table>

Table 3. Existing Systematic Reviews and Meta-Analyses Quality Assessment Chart

AMSTARExBP: SR/MA	Afkar, 2017	Corvillo, 2017	Cramer, 2014	Cruicksha nk, 2015	Dalgas, 2015	Edwards, 2017
Review questions and inclusion/exclusion criteria delineated prior to executing search strategy.	Yes	Yes	Yes	Yes	Yes	Yes
Population variables defined and considered in methods.	Yes	No	No	No	No	No
Comprehensive literature search performed.	Yes	Partially Yes	Yes	Yes	Yes	Yes
Duplicate study selection and data extraction performed.	Yes	No	Yes	No	No	Yes
Search strategy clearly described.	Yes	Yes	Yes	Yes	Yes	Yes
Relevant grey literature included in review.	No	No	Yes	Yes	No	No
List of studies (included and excluded) provided.	No	No	Yes	No	No	No
Characteristics of included studies provided.	Yes	Yes	Yes	Yes	Yes	Yes
FITT defined and examined in relation to outcome effect sizes.	No	N/A	No	No	Yes	N/A
Scientific quality (risk of bias) of included studies assessed and documented.	Yes	Yes	Yes	Yes	Yes	Yes
Results depended on study quality, either overall, or in interaction with moderators.	Yes	No	Yes	No	No	No
Scientific quality used appropriately in formulating conclusions.	Yes	Yes	Yes	Yes	Yes	Yes
Data appropriately synthesized and if applicable, heterogeneity assessed.	Yes	N/A	Yes	Yes	Yes	N/A
Effect size index chosen justified, statistically.	Yes	N/A	Yes	Yes	Yes	N/A
Individual-level meta-analysis used.	No	N/A	No	No	No	N/A
Practical recommendations clearly addressed.	Yes	Yes	Yes	Yes	Yes	Yes
Likelihood of publication bias assessed.	Yes	No	No	Yes	No	No
Conflict of interest disclosed.	No	Yes	Yes	No	Yes	Yes

AMSTARExBP: SR/MA	Ensari, 2014	Kuspinar, 2012	Latimer-Cheung, 2013	Methajarunon, 2016	Pearson, 2015	Platta, 2016
Review questions and inclusion/exclusion criteria delineated prior to executing search strategy.	Yes	Yes	Yes	Yes	Yes	Yes
Population variables defined and considered in methods.	Yes	No	No	No	Yes	No
Comprehensive literature search performed.	Yes	Partially Yes	Yes	Yes	Yes	Yes
Duplicate study selection and data extraction performed.	No	Yes	Yes	Yes	No	No
Search strategy clearly described.	Yes	Yes	Yes	Yes	Yes	Yes
Relevant grey literature included in review.	No	No	No	No	Yes	No
List of studies (included and excluded) provided.	Yes	No	No	No	Yes	No
Characteristics of included studies provided.	Yes	Yes	Yes	Yes	Yes	No
FITT defined and examined in relation to outcome effect sizes.	Yes	No	N/A	N/A	No	Yes
Scientific quality (risk of bias) of included studies assessed and documented.	Yes	Yes	Yes	Yes	Yes	Yes
Results depended on study quality, either overall, or in interaction with moderators.	No	Yes	Yes	Yes	No	No
Scientific quality used appropriately in formulating conclusions.	Yes	Yes	Yes	Yes	Yes	Yes
Data appropriately synthesized and if applicable, heterogeneity assessed.	Yes	Yes	N/A	N/A	Yes	Yes
Effect size index chosen justified, statistically.	Yes	Yes	N/A	N/A	Yes	Yes
Individual-level meta-analysis used.	No	No	N/A	N/A	No	No
Practical recommendations clearly addressed.	Yes	Yes	Yes	Yes	Yes	Yes
Likelihood of publication bias assessed.	Yes	Yes	No	No	Yes	Yes
Conflict of interest disclosed.	No	Yes	Yes	Yes	No	No

AMSTARExBP: SR/MA	Sa, 2014	Sosnoff, 2015	Taylor, 2017	Zou, 2017
Review questions and inclusion/exclusion criteria delineated prior to executing search strategy.	Yes	Yes	No	Yes
Population variables defined and considered in methods.	Yes	No	Yes	Yes
Comprehensive literature search performed.	No	Yes	Yes	Yes
Duplicate study selection and data extraction performed.	Yes	No	No	Yes
Search strategy clearly described.	Yes	Yes	Yes	Yes
Relevant grey literature included in review.	No	No	Yes	No
List of studies (included and excluded) provided.	No	No	No	No
Characteristics of included studies provided.	Yes	Yes	Yes	Yes
FITT defined and examined in relation to outcome effect sizes.	N/A	N/A	N/A	N/A
Scientific quality (risk of bias) of included studies assessed and documented.	Yes	Yes	Yes	Yes
Results depended on study quality, either overall, or in interaction with moderators.	Yes	No	No	No
Scientific quality used appropriately in formulating conclusions.	Yes	Yes	Yes	Yes
Data appropriately synthesized and if applicable, heterogeneity assessed.	N/A	N/A	N/A	N/A
Effect size index chosen justified, statistically.	N/A	N/A	N/A	N/A
Individual-level meta-analysis used.	N/A	N/A	N/A	N/A
Practical recommendations clearly addressed.	Yes	Yes	Yes	Yes
Likelihood of publication bias assessed.	No	No	No	No
Conflict of interest disclosed.	No	Yes	Yes	Yes

Appendices

Appendix A: Analytical Framework

Topic Area
Chronic Conditions

Systematic Review Question
In individuals with multiple sclerosis, what is the relationship between physical activity and (1) risk of co-morbid conditions, (2) physical function, and (3) health-related quality of life?

Population
Individuals of all ages with multiple sclerosis

Exposure
All types and intensities of physical activity, including sedentary behavior

Comparison
Individuals with multiple sclerosis who participate in varying levels of physical activity

Endpoint Health Outcomes
- Risk of co-morbid conditions
- Physical function
- Health-related quality of life

Key Definitions

- Multiple sclerosis refers to an immune-mediated process in which an abnormal response of the body's immune system is directed against the central nervous system (CNS), which consists of the brain, spinal cord, and optic nerves. It is marked by symptoms such as fatigue, gait disturbances, and spasticity and is typically characterized by evidence of damage in at least two separate areas of the CNS that occurred at least one month apart. Source: National Multiple Sclerosis Society. What is MS? National Multiple Sclerosis Society website. http://www.nationalmssociety.org/What-is-MS. Accessed December 21, 2017.
- Risk of co-morbid conditions: The chance of having one or more additional conditions.
- Physical function: "Physical function" and "physical functioning" are regarded as synonyms that refer to: "the ability of a person to move around and to perform types of physical activity."
    - For example, measures of physical function include measures of ability to walk (e.g., usually gait speed), run, climb stairs, carry groceries, sweep the floor, stand up, and bathe oneself.
    - As measures of behavioral abilities, physical function measures do not include:
        - Physiologic measures, including measures of physiologic capacity (e.g., maximal lung capacities, maximal aerobic capacity, maximal muscle strength, bone density).
        - Measures of the environment or of the host-environmental interaction (e.g., disability accommodation).
        - Measures of what a person usually does (e.g., physical activity level), as opposed to what a person is capable of doing.
- Health-related quality of life: "Health-related quality of life (HRQOL) is a multi-dimensional concept that includes domains related to physical, mental, emotional, and social functioning." Source: Healthy People 2020. Health-related quality of life & well-being. HealthyPeople.gov website. https://www.healthypeople.gov/2020/topics-objectives/topic/health-related-quality-of-life-well-being. Accessed December 21, 2017.

Appendix B: Final Search Strategy

Search Strategy: PubMed (Systematic Reviews, Meta-Analyses, Pooled Analyses, and High-Quality Reports

Database: PubMed; Date of Search: 8/9/17; 138 results

Set	Search Strategy
Limit: Language	(English[lang])
Limit: Exclude animal only	NOT ("Animals"[mh] NOT ("Animals"[mh] AND "Humans"[mh]))
Limit: Publication Date (Systematic Reviews/Meta-Analyses)	AND ("2011/01/01"[PDAT] : "3000/12/31"[PDAT])
Limit: Publication Type Include (Systematic Reviews/Meta-Analyses)	AND (systematic[sb] OR meta-analysis[pt] OR “systematic review”[tiab] OR “systematic literature review”[tiab] OR metaanalysis[tiab] OR "meta analysis"[tiab] OR metanalyses[tiab] OR "meta analyses"[tiab] OR "pooled analysis"[tiab] OR “pooled analyses”[tiab] OR "pooled data"[tiab])
Limit: Publication Type Exclude (Systematic Reviews/Meta-Analyses)	NOT (“comment”[Publication Type] OR “editorial”[Publication Type])
Physical activity	AND (("Aerobic endurance"[tiab] OR "Bicycl*"[tiab] OR "Endurance training"[tiab] OR "Exercise"[mh] OR "Exercise"[tiab] OR "Exercises"[tiab] OR "Free living activities"[tiab] OR "Free living activity"[tiab] OR "Functional training"[tiab] OR "Leisure-time physical activity"[tiab] OR "Lifestyle activities"[tiab] OR "Lifestyle activity"[tiab] OR "Muscle stretching exercises"[mh] OR "Physical activity"[tiab] OR "Qi gong"[tiab] OR "Recreational activities"[tiab] OR "Recreational activity"[tiab] OR "Resistance training"[tiab] OR "Running"[tiab] OR "Sedentary lifestyle"[mh] OR "Speed training"[tiab] OR "Strength training"[tiab] OR "Tai chi"[tiab] OR "Tai ji"[mh] OR "Tai ji"[tiab] OR "Training duration"[tiab] OR "Training frequency"[tiab] OR "Training intensity"[tiab] OR "Treadmill"[tiab] OR "Walking"[tiab] OR "Weight lifting"[tiab] OR "Weight training"[tiab] OR "Yoga"[mh] OR "Yoga"[tiab]) OR (("Aerobic activities"[tiab] OR "Aerobic activity"[tiab] OR "Cardiovascular activities"[tiab] OR "Cardiovascular activity"[tiab] OR "Endurance activities"[tiab] OR "Endurance activity"[tiab] OR "Physical activities"[tiab] OR "Physical conditioning"[tiab] OR "Sedentary"[tiab]) NOT medline[sb]))
Population	AND ("Multiple Sclerosis"[tiab] OR "Multiple Sclerosis"[mh])

Search Strategy: CINAHL (Systematic Reviews, Meta-Analyses, Pooled Analyses, and High-Quality Reports

Database: CINAHL; Date of Search: 8/9/17; 18 results
Terms searched in title or abstract

Set	Search Terms
Physical activity	("Aerobic endurance" OR "Bicycl*" OR "Endurance training" OR "Exercise" OR "Exercises" OR "Free living activities" OR "Free living activity" OR "Functional training" OR "Leisure-time physical activity" OR "Lifestyle activities" OR "Lifestyle activity" OR "Muscle stretching exercises" OR "Physical activity" OR "Qi gong" OR "Recreational activities" OR "Recreational activity" OR "Resistance training" OR "Running" OR "Sedentary lifestyle" OR "Speed training" OR "Strength training" OR "Tai chi" OR "Tai ji" OR "Tai ji" OR "Training duration" OR "Training frequency" OR "Training intensity" OR "Treadmill" OR "Walking" OR "Weight lifting" OR "Weight training" OR "Yoga" OR "Aerobic activities" OR "Aerobic activity" OR "Cardiovascular activities" OR "Cardiovascular activity" OR "Endurance activities" OR "Endurance activity" OR "Physical activities" OR "Physical conditioning" OR "Sedentary")
Outcomes	("Multiple Sclerosis")
Systematic Reviews and Meta-Analyses	("systematic review" OR "systematic literature review" OR metaanalysis OR "meta analysis" OR metanalyses OR "meta analyses" OR "pooled analysis" OR "pooled analyses" OR "pooled data")
Limits	2011–present English language Peer reviewed Exclude Medline records Human

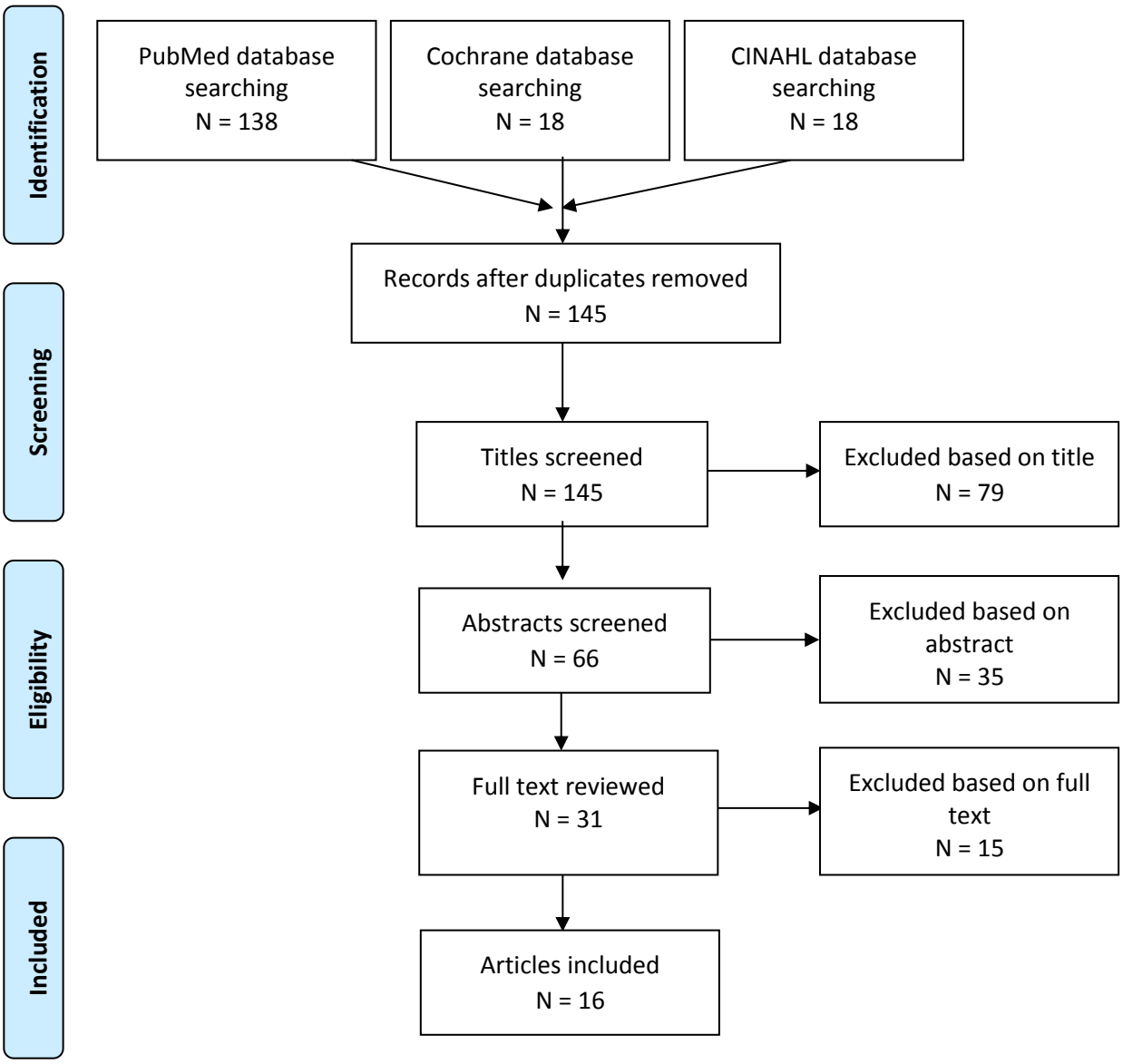
Search Strategy: Cochrane (Systematic Reviews, Meta-Analyses, Pooled Analyses, and High-Quality Reports

Database: Cochrane; Date of Search: 8/9/17; 18 results
Terms searched in title, abstract, or keywords

Set	Search Terms
Physical activity	("Aerobic endurance" OR "Bicycl*" OR "Endurance training" OR "Exercise" OR "Exercises" OR "Free living activities" OR "Free living activity" OR "Functional training" OR "Leisure-time physical activity" OR "Lifestyle activities" OR "Lifestyle activity" OR "Muscle stretching exercises" OR "Physical activity" OR "Qi gong" OR "Recreational activities" OR "Recreational activity" OR "Resistance training" OR "Running" OR "Sedentary lifestyle" OR "Speed training" OR "Strength training" OR "Tai chi" OR "Tai ji" OR "Tai ji" OR "Training duration" OR "Training frequency" OR "Training intensity" OR "Treadmill" OR "Walking" OR "Weight lifting" OR "Weight training" OR "Yoga" OR "Aerobic activities" OR "Aerobic activity" OR "Cardiovascular activities" OR "Cardiovascular activity" OR "Endurance activities" OR "Endurance activity" OR "Physical activities" OR "Physical conditioning" OR "Sedentary")
Population	("Multiple Sclerosis")
Limits	2011–present Word variations not searched Cochrane Reviews and Other Reviews

Appendix C: Literature Tree

Existing Systematic Reviews, Meta-Analyses, Pooled Analyses, and Reports Literature Tree



Appendix D: Inclusion/Exclusion Criteria

Chronic Conditions Subcommittee
Q5: In individuals with multiple sclerosis, what is the relationship between physical activity and (1) risk of co-morbid conditions, (2) physical function, and (3) health-related quality of life?

Category	Inclusion/Exclusion Criteria	Notes/Rationale
Publication Language	**Include:** • Studies published with full text in English	
Publication Status	**Include:** • Studies published in peer-reviewed journals • Reports determined to have appropriate suitability and quality by PAGAC **Exclude:** • Grey literature, including unpublished data, manuscripts, abstracts, conference proceedings	
Research Type	**Include:** • Original research • Meta-analyses • Systematic reviews • Reports determined to have appropriate suitability and quality by PAGAC	
Study Subjects	**Include:** • Human subjects	
Age of Study Subjects	**Include:** • People of all ages	
Health Status of Study Subjects	**Include:** • Studies of people with multiple sclerosis • Studies of people with multiple sclerosis in combination with other chronic conditions will be reviewed on a case by case basis **Exclude:** • Studies that include people with multiple sclerosis as part of the study sample, but do not analyze results separately for people with multiple sclerosis	
Comparison	**Include:** • Adults who participate in varying levels of physical activity, including acute or chronic exercise or no reported physical activity • Recreational athletes (marathons ok as long as the study looks at a diverse group of runners—not just the elites) **Exclude:** • High performance athletes	

	• Studies comparing athletes to non-athletes • Studies comparing athlete types (e.g., comparing runners to soccer players)	
Date of Publication	**Include:** • Systematic reviews, meta-analyses, pooled analyses, and reports published from 2011–2016	
Study Design	**Include:** • Systematic reviews • Meta-analyses • Pooled analyses • PAGAC-approved reports **Exclude:** • Randomized controlled trials • Prospective cohort studies • Narrative reviews • Commentaries • Editorials • Non-randomized controlled trials • Retrospective cohort studies • Case-control studies • Cross-sectional studies • Before-and-after studies	
Intervention/ Exposure	**Include studies in which the exposure or intervention is:** • All types and intensities of physical activity, including sedentary behavior • Studies with single, acute bouts of exercise as the exposure **Exclude:** • Studies that do not include physical activity • Studies where physical activity is used solely as a confounding variable • Studies of a single, acute session of exercise • Studies of multimodal interventions that do not present data on physical activity alone • Studies of a disease-specific therapeutic exercise (e.g., rehabilitation) delivered by a medical professional (e.g., physical therapist) • Studies with measures of physical fitness as the exposure	
Outcome	**Include studies in which the outcome is:** • Risk of co-morbid conditions • Physical function • Health-related quality of life	

Appendix E: Rationale for Exclusion at Abstract or Full-Text Triage for Existing Systematic Reviews, Meta-Analyses, Pooled Analyses, and Reports

The table below lists the excluded articles with at least one reason for exclusion, but may not reflect all possible reasons.

Citation	Outcome	Population	Study Design	Exposure	Not ideal fit for replacement of de novo search	Other
Adamson BC, Ensari I, Motl RW. Effect of exercise on depressive symptoms in adults with neurologic disorders: a systematic review and meta-analysis. *Arch Phys Med Rehabil*. 2015;96(7):1329-1338. doi:10.1016/j.apmr.2015.01.005.		X				
Amatya B, Khan F, La Mantia L, Demetrios M, Wade DT. Non pharmacological interventions for spasticity in multiple sclerosis. *Cochrane Database Syst Rev*. 2013;(2):Cd009974. doi:10.1002/14651858.CD009974.pub2.	X					
Asano M, Finlayson ML. Meta-analysis of three different types of fatigue management interventions for people with multiple sclerosis: exercise, education, and medication. *Mult Scler Int*. 2014:798285. doi:10.1155/2014/798285.				X		
Buechter RB, Fechtelpeter D. Climbing for preventing and treating health problems: a systematic review of randomized controlled trials. *Ger Med Sci*. 2011;9:Doc19. doi:10.3205/000142.						X
Campbell E, Coulter E, Mattison P, McFadyen A, Miller L, Paul L. Access, delivery and perceived efficacy of physiotherapy and use of complementary and alternative therapies by people with progressive multiple sclerosis in the United Kingdom: an online survey. *Mult Scler Relat Disord*. 2017;12:64-69. doi:10.1016/j.msard.2017.01.002.			X			
Casey B, Coote S, Donnelly A. Objective physical activity measurement in people with multiple sclerosis: a review of the literature. *Disabil Rehabil Assist Technol*. March 2017:1-8. doi:10.1080/17483107.2017.1297859.	X			X		
Casey B, Coote S, Shirazipour S, et al. Modifiable psychosocial constructs associated with physical activity participation in people with multiple sclerosis: a systematic review and meta-analysis. *Arch Phys Med Rehabil*. 2017;98(7):1453-1475. doi:10.1016/j.apmr.2017.01.027.	X					
Dalgas U, Stenager E. Exercise and disease progression in multiple sclerosis: can exercise slow down the progression of multiple sclerosis? *Ther Adv Neurol Disord*. 2012;5(2):81–95. doi:10.1177/1756285611430719.	X					

Citation	Outcome	Population	Study Design	Exposure	Not ideal fit for replacement of de novo search	Other
Field T. Yoga research review. *Complement Ther Clin Pract*. 2016;24:145-161. doi:10.1016/j.ctcp.2016.06.005.			X			
Florindo M. Inflammatory cytokines and physical activity in multiple sclerosis. *ISRN Neurol*. Jan 2014:151572. doi:10.1155/2014/151572.	X					
Gross T, Wells C, Vincent M. Does pilates exercise improve balance and walking in people with multiple sclerosis? A systematic review. *Arch Phys Med Rehabil*. 2016;97(12):e39-e39.			X			
Haselkorn JK, Hughes C, Rae-Grant A, et al. Summary of comprehensive systematic review: rehabilitation in multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology*. 2015;85(21):1896–1903. doi:10.1212/WNL.0000000000002146.				X		
Heesen C, Kopke S, Kasper J, et al. Behavioral interventions in multiple sclerosis: a biopsychosocial perspective. *Expert Rev Neurother*. 2012;12(9):1089-1100. doi:10.1586/ern.12.103.			X			
Heine M, van de Port I, Rietberg MB, van Wegen EE, Kwakkel G. Exercise therapy for fatigue in multiple sclerosis. *Cochrane Database Syst Rev*. 2015;(9):Cd009956. doi:10.1002/14651858.CD009956.pub2.			X			
Hempel S, Graham GD, Fu N, et al. A systematic review of the effects of modifiable risk factor interventions on the progression of multiple sclerosis. *Mult Scler*. 2017;23(4):513-524. doi:10.1177/1352458517690271.	X					
Herring MP, Fleming KM, Hayes SP, Motl RW, Coote SB. Moderators of exercise effects on depressive symptoms in multiple sclerosis: a meta-regression. *Am J Prev Med*. 2017;53(4):508-518. doi:10.1016/j.amepre.2017.04.011.	X					
Hobart J, Blight AR, Goodman A, Lynn F, Putzki N. Timed 25-foot walk: direct evidence that improving 20% or greater is clinically meaningful in MS. *Neurology*. 2013;80(16):1509-1517. doi:10.1212/WNL.0b013e31828cf7f3.				X		
Jorgensen M, Dalgas U, Wens I, Hvid LG. Muscle strength and power in persons with multiple sclerosis—a systematic review and meta-analysis. *J Neurol Sci*. 2017;376:225-241. doi:10.1016/j.jns.2017.03.022.	X					
Khan F, Amatya B. Rehabilitation in multiple sclerosis: a systematic review of systematic				X		

Citation	Outcome	Population	Study Design	Exposure	Not ideal fit for replacement of de novo search	Other
reviews. *Arch Phys Med Rehabil*. 2017;98(2):353–367. doi:10.1016/j.apmr.2016.04.016.						
Kinnett-Hopkins D, Adamson B, Rougeau K, Motl RW. People with MS are less physically active than healthy controls but as active as those with other chronic diseases: an updated meta-analysis. *Mult Scler Relat Disord*. 2017;13:38-43. doi:10.1016/j.msard.2017.01.016.	X					
Kjolhede T, Vissing K, Dalgas U. Multiple sclerosis and progressive resistance training: a systematic review. *Mult Scler*. 2012;18(9):1215–1228. doi:10.1177/1352458512437418.						X
Latimer-Cheung AE, Martin Ginis KA, Hicks AL, et al. Development of evidence-informed physical activity guidelines for adults with multiple sclerosis. *Arch Phys Med Rehabil*. 2013;94(9):1829-1836.e7. doi:10.1016/j.apmr.2013.05.015.			X			
Learmonth YC, Ensari I, Motl RW. Cognitive motor interference in multiple sclerosis: insights from a systematic quantitative review. *Arch Phys Med Rehabil*. 2017;98(6):1229-1240. doi:10.1016/j.apmr.2016.07.018.				X		
Learmonth YC, Ensari I, Motl, RW. Physiotherapy and walking outcomes in adults with multiple sclerosis: systematic review and meta-analysis. *Physical Therapy Reviews*. 2016;21(3-6):160-172. doi:10.1080/10833196.2016.1263415.				X		
Learmonth YC, Motl RW. Physical activity and exercise training in multiple sclerosis: a review and content analysis of qualitative research identifying perceived determinants and consequences. *Disabil Rehabil*. 2016;38(13):1227-1242. doi:10.3109/09638288.2015.1077397.	X					X
Luu K, Hall PA. Hatha yoga and executive function: a systematic review. *J Altern Complement Med*. 2016;22(2):125-133. doi:10.1089/acm.2014.0091.	X					
Mooventhan A, Nivethitha L. Evidence based effects of yoga in neurological disorders. *J Clin Neurosci*. 2017;43:61-67. doi:10.1016/j.jocn.2017.05.012.			X			
Morrison JD, Mayer L. Physical activity and cognitive function in adults with multiple sclerosis: an integrative review. *Disabil Rehabil*. 2017;39(19):1909-1920. doi:10.1080/09638288.2016.1213900.	X					
Motl RW, Pilutti LA. Is physical exercise a multiple sclerosis disease modifying			X			

Citation	Outcome	Population	Study Design	Exposure	Not ideal fit for replacement of de novo search	Other
treatment? *Expert Rev Neurother*. 2016;16(8):951-960. doi:10.1080/14737175.2016.1193008.						
Motl RW. Benefits, safety, and prescription of exercise in persons with multiple sclerosis. *Expert Rev Neurother*. 2014;14(12):1429-1436. doi:10.1586/14737175.2014.983904.			X			
Motl RW, Sandroff BM. Benefits of exercise training in multiple sclerosis. *Curr Neurol Neurosci Rep.* 2015;15(9):62. doi:10.1007/s11910-015-0585-6.			X			
Nicholas R, Rashid W. Multiple sclerosis. *BMJ Clin Evid*. Feb 2012:pii:1202.	X					
Paul L, Coote S, Crosbie J, et al. Core outcome measures for exercise studies in people with multiple sclerosis: recommendations from a multidisciplinary consensus meeting. *Mult Scler*. 2014;20(12):1641-1650. doi:10.1177/1352458514526944.	X					
Pedersen BK, Saltin B. Exercise as medicine—evidence for prescribing exercise as therapy in 26 different chronic diseases. *Scand J Med Sci Sports*. 2015;25(suppl 3):1-72. doi:10.1111/sms.12581.	X					
Rae-Grant AD, Turner AP, Sloan A, Miller D, Hunziker J, Haselkorn JK. Self-management in neurological disorders: systematic review of the literature and potential interventions in multiple sclerosis care. *J Rehabil Res Dev*. 2011;48(9):1087-1100.				X		
Rintala A, Hakala S, Paltamaa J, Heinonen A, Karvanen J, Sjögren T. Effectiveness of technology-based distance physical rehabilitation interventions on physical activity and walking in multiple sclerosis: a systematic review and meta-analysis of randomized controlled trials. *Disabil Rehabil*. Dec 2016:1-15. doi:10.1080/09638288.2016.1260649.	X					
Sandroff BM, Motl RW, Scudder MR. Systematic review of exercise, physical activity, and physical fitness effects on cognition in persons with multiple sclerosis. *Arch Phys Med Rehabil.* 2016;97(10):e143. doi:10.1016/j.apmr.2016.08.445.	X					
Sandroff BM, Dlugonski D, Weikert M, Suh Y, Balantrapu S, Motl RW. Physical activity and multiple sclerosis: new insights regarding inactivity. *Acta Neurol Scand*. 2012;126(4):256-262. doi:10.1111/j.1600-0404.2011.01634.x.			X			
Sandroff BM, Motl RW, Scudder MR, DeLuca J. Systematic, evidence-based review of exercise, physical activity, and physical fitness effects on cognition in persons with multiple sclerosis.	X					

Citation	Outcome	Population	Study Design	Exposure	Not ideal fit for replacement of de novo search	Other
Neuropsychol Rev. 2016;26(3):271-294. doi:10.1007/s11065-016-9324-2.						
Sangelaji B, Smith CM, Paul L, Sampath KK, Treharne GJ, Hale LA. The effectiveness of behaviour change interventions to increase physical activity participation in people with multiple sclerosis: a systematic review and meta-analysis. *Clin Rehabil*. 2016;30(6):559-576. doi:10.1177/0269215515595274.				X		
Senders A, Wahbeh H, Spain R, Shinto L. Mind-body medicine for multiple sclerosis: a systematic review. *Autoimmune Dis*. Nov 2012:567324. doi:10.1155/2012/567324.						X
Simpson R, Booth J, Lawrence M, Byrne S, Mair F, Mercer S. Mindfulness based interventions in multiple sclerosis—a systematic review. *BMC Neurology*. 2014;14(1):15. doi:10.1186/1471-2377-14-15.				X		
Spooren AI, Timmermans AA, Seelen HA. Motor training programs of arm and hand in patients with MS according to different levels of the ICF: a systematic review. *BMC Neurol*. 2012;12:49. doi:10.1186/1471-2377-12-49.	X			X		
Streber R, Peters S, Pfeifer K. Systematic review of correlates and determinants of physical activity in persons with multiple sclerosis. *Arch Phys Med Rehabil*. 2016;97(4):633-645.e29. doi:10.1016/j.apmr.2015.11.020.	X					
Swinnen E, Beckwee D, Pinte D, Meeusen R, Baeyens JP, Kerckhofs E. Treadmill training in multiple sclerosis: can body weight support or robot assistance provide added value? A systematic review. *Mult Scler Int*. May 2012:240274. doi:10.1155/2012/240274.			X			
Toomey E, Coote SB. Physical rehabilitation interventions in nonambulatory people with multiple sclerosis: a systematic review. *Int J Rehabil Res*. 2012;35(4):281-291. doi:10.1097/MRR.0b013e32835a241a.				X		
Wajda DA, Mirelman A, Hausdorff JM, Sosnoff JJ. Intervention modalities for targeting cognitive-motor interference in individuals with neurodegenerative disease: a systematic review. *Expert Rev Neurother*. 2017;17(3):251-261. doi:10.1080/14737175.2016.1227704.	X					
Xie X, Sun H, Zeng Q, et al. Do patients with multiple sclerosis derive more benefit from robot-assisted gait training compared with conventional walking therapy on motor function? A meta-analysis. *Front Neurol*. 2017;8:260. doi:10.3389/fneur.2017.00260.				X		
Yadav V, Bever C Jr, Bowen J, et al. Summary of evidence-based guideline: complementary and				X		

Citation	Outcome	Population	Study Design	Exposure	Not ideal fit for replacement of de novo search	Other
alternative medicine in multiple sclerosis: report of the guideline development subcommittee of the American Academy of Neurology. *Neurology*. 2014;82(12):1083-1092. doi:10.1212/WNL.0000000000000250.						
Yu CH, Mathiowetz V. Systematic review of occupational therapy-related interventions for people with multiple sclerosis: part 1. Activity and participation. *Am J Occup Ther*. 2014;68(1):27-32. doi:10.5014/ajot.2014.008672.	X					

References

1. Cramer H, Lauche R, Azizi H, Dobos G, Langhorst J. Yoga for multiple sclerosis: a systematic review and meta-analysis. *PLoS One*. 2014;9(11):e112414. doi:10.1371/journal.pone.0112414.

2. Cruickshank TM, Reyes AR, Ziman MR. A systematic review and meta-analysis of strength training in individuals with multiple sclerosis or Parkinson disease. *Medicine (Baltimore)*. 2015;94(4):e411. doi:10.1097/MD.0000000000000411.

3. Pearson M, Dieberg G, Smart N. Exercise as a therapy for improvement of walking ability in adults with multiple sclerosis: a meta-analysis. *Arch Phys Med Rehabil*. 2015;96(7):1339–1348.e7. doi:10.1016/j.apmr.2015.02.011.

4. Platta ME, Ensari I, Motl RW, Pilutti LA. Effect of exercise training on fitness in multiple sclerosis: a meta-analysis. *Arch Phys Med Rehabil*. 2016;97(9):1564–1572. doi:10.1016/j.apmr.2016.01.023.

5. Corvillo I, Varela E, Armijo F, Alvarez-Badillo A, Armijo O, Maraver F. Efficacy of aquatic therapy for multiple sclerosis: a systematic review. *Eur J Phys Rehabil Med*. 2017;17. doi:10.23736/S1973-9087.

6. Edwards T, Pilutti LA. The effect of exercise training in adults with multiple sclerosis with severe mobility disability: a systematic review and future research directions. *Mult Scler Relat Disord*. 2017;16:31–39. doi:10.1016/j.msard.2017.06.003.

7. Latimer-Cheung AE, Pilutti AE, Hicks AL, et al. Effects of exercise training on fitness, mobility, fatigue, and health-related quality of life among adults with multiple sclerosis: a systematic review to inform guideline development. *Arch Phys Med Rehabil*. 2013;94(9):1800–1828.e3. doi:10.1016/j.apmr.2013.04.020.

8. Methajarunon P, Eitivipart C, Diver C, Foongchomcheay A. Systematic review of published studies on aquatic exercise for balance in patients with multiple sclerosis, Parkinson's disease, and hemiplegia. *HKPJ*. 2016;35:12–20. doi:10.1016/j.hkpj.2016.03.002.

9. Sa MJ. Exercise therapy and multiple sclerosis: a systematic review. *J Neurol*. 2014;261(9):1651–1661. doi:10.1007/s00415-013-7183-9.

10. Sosnoff JJ, Sung J. Reducing falls and improving mobility in multiple sclerosis. *Expert Rev Neurother*. 2015;15(6):655–666. doi:10.1586/14737175.2015.1046377.

11. Taylor E, Taylor-Piliae RE. The effects of tai chi on physical and psychosocial function among persons with multiple sclerosis: a systematic review. *Complement Ther Med*. 2017;31:100–108. doi:10.1016/j.ctim.2017.03.001.

12. Zou L, Wang H, Xiao Z, et al. Tai chi for health benefits in patients with multiple sclerosis: a systematic review. *PLoS One*. 2017;12(2):e0170212. doi:10.1371/journal.pone.0170212.

13. Afkar A, Ashouri A, Rahmani M, Emami Sigaroudi A. Effect of exercise therapy on quality of life of patients with multiple sclerosis in Iran: a systematic review and meta-analysis. *Neurol Sci*. 2017;doi:10.1007/s10072-017-3047-x.

14. Dalgas U, Stenager E, Sloth M, Stenager E. The effect of exercise on depressive symptoms in multiple sclerosis based on a meta-analysis and critical review of the literature. *Eur J Neurol*. 2015;22(3):443-e34. doi:10.1111/ene.12576.

15. Ensari I, Motl RW, Pilutti LA. Exercise training improves depressive symptoms in people with multiple sclerosis: results of a meta-analysis. *J Psychosom Res*. 2014;76(6):465–471. doi:10.1016/j.jpsychores.2014.03.014.

16. Kuspinar A, Rodriguez AM, Mayo NE. The effects of clinical interventions on health-related quality of life in multiple sclerosis: a meta-analysis. *Mult Scler*. 2012;18(12):1686–1704. doi:10.1177/1352458512445201.