Comparative Effectiveness Review
Number 241

Physical Activity and the Health of Wheelchair Users: A Systematic Review in Multiple Sclerosis, Cerebral Palsy, and Spinal Cord Injury

Agency for Healthcare Research and Quality

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Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
5600 Fishers Lane
Rockville, MD 20857
www.ahrq.gov

Contract No. 290-2015-00009-I

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AHRQ Publication No. 21(22)-EHC017
October 2021

This report is based on research conducted by the Pacific Northwest Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2015-00009-I). The report was commissioned and funded by the National Institutes of Health (NIH) Office of Disease Prevention to inform a Pathways to Prevention Workshop. The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ or NIH. Therefore, no statement in this report should be construed as an official position of NIH, AHRQ, or the U.S. Department of Health and Human Services.

None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help healthcare decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of healthcare services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

AHRQ appreciates appropriate acknowledgment and citation of its work. Suggested language for acknowledgment: This work was based on an evidence report, Physical Activity and the Health of Wheelchair Users: A Systematic Review in Multiple Sclerosis, Cerebral Palsy, and Spinal Cord Injury, by the Evidence-based Practice Center Program at the Agency for Healthcare Research and Quality (AHRQ).

Suggested citation: Selph SS, Skelly AC, Wasson N, Dettori JR, Brodt ED, Ensrud E, Elliot D, Dissinger KM, Hart E, Kantner S, Graham E, Junge M, Dana T, McDonagh M. Comparative Effectiveness Review No. 241. Physical Activity and the Health of Wheelchair Users: A Systematic Review of Evidence in Multiple Sclerosis, Cerebral Palsy, and Spinal Cord Injury. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2015-00009-I.) AHRQ Publication No. 21(22)-EHC017. Rockville, MD: Agency for Healthcare Research and Quality; October 2021.
DOI: https://doi.org/10.23970/AHRQEPCCER241. Posted final reports are located on the Effective Health Care Program search page.

Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of healthcare in the United States.

The National Institutes of Health (NIH) Office of Disease Prevention requested this report from the EPC Program at AHRQ to inform a Pathways to Prevention Workshop. The NIH Office of Disease Prevention provided the funding for this report through an Interagency Agreement with AHRQ. AHRQ assigned this report to the following EPC: Pacific Northwest Evidence-based Practice Center (Contract Number 290-2015-00009-I).

The report was presented at the NIH Office of Disease Prevention's Pathways to Prevention Workshop public meeting—"Can Physical Activity Improve the Health of Wheelchair Users?"—December 1, 2020, to December 3, 2020.

The reports and assessments provide organizations with comprehensive, evidence-based information on common medical conditions and new healthcare technologies and strategies. For the NIH Pathways to Prevention program, the EPC reports identify research gaps in the selected scientific area, identify methodological and scientific weaknesses, suggest research needs, and move the field forward through an unbiased, evidence-based assessment of the available literature. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for healthcare quality improvement projects throughout the Nation. The reports undergo peer review and public comment prior to their release as a final report.

AHRQ expects that the EPC evidence reports and technology assessments, when appropriate, will inform individual health plans, providers, and purchasers as well as the healthcare system as a whole by providing important information to help improve healthcare quality.

If you have comments on this evidence report, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Acknowledgments

The authors gratefully acknowledge the following individuals for their contributions to this project: David Niebuhr, M.D., M.P.H., M.Sc., AHRQ Task Order Officer; Keisha Shropshire, M.P.H., Public Health Analyst, P2P Coordinator, NIH Office of Disease Prevention (ODP) Working Group and NIH partners; Meera Viswanathan (Associate Editor); Christine Chang, M.D., M.P.H., Acting Director, Evidence-based Practice Center Program, Center for Evidence and Practice Improvement, AHRQ; Technical Expert Panel members; Peer Reviewers; Leah Williams, B.S., publications editor; Roger Chou, M.D., FACP, Pacific Northwest EPC Director.

Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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Physical Activity and the Health of Wheelchair Users: A Systematic Review in Multiple Sclerosis, Cerebral Palsy, and Spinal Cord Injury

Structured Abstract

Objectives. Although the health benefits of physical activity are well described for the general population, less is known about the benefits and harms of physical activity in people dependent upon, partially dependent upon, or at risk for needing a wheelchair. This systematic review summarizes the evidence for physical activity in people with multiple sclerosis, cerebral palsy, and spinal cord injury regardless of current use or nonuse of a wheelchair.

Data sources. We searched MEDLINE®, CINAHL®, PsycINFO®, Cochrane CENTRAL, Embase®, and Rehabilitation and Sports Medicine Source from 2008 through November 2020, reference lists, and clinical trial registries.

Review methods. Predefined criteria were used to select randomized controlled trials, quasiexperimental nonrandomized trials, and cohort studies that addressed the benefits and harms of observed physical activity (at least 10 sessions on 10 different days of movement using more energy than rest) in participants with multiple sclerosis, cerebral palsy, and spinal cord injury. Individual study quality (risk of bias) and the strength of bodies of evidence for key outcomes were assessed using prespecified methods. Dual review procedures were used. Effects were analyzed by etiology of impairment and physical activity modality, such as treadmill, aquatic exercises, and yoga, using qualitative, and when appropriate, quantitative synthesis using random effects meta-analyses.

Results. We included 146 randomized controlled trials, 15 quasiexperimental nonrandomized trials, and 7 cohort studies (168 studies in 197 publications). More studies enrolled participants with multiple sclerosis (44%) than other conditions, followed by cerebral palsy (38%) and spinal cord injury (18%). Most studies were rated fair quality (moderate risk of bias). The majority of the evidence was rated low strength.

- In participants with multiple sclerosis, walking ability may be improved with treadmill training and multimodal exercise regimens that include strength training; function may be improved with treadmill training, balance exercises, and motion gaming; balance is likely improved with postural control exercises (which may also reduce risk of falls) and may be improved with aquatic exercises, robot-assisted gait training, treadmill training, motion gaming, and multimodal exercises; activities of daily living may be improved with aquatic therapy; sleep may be improved with aerobic exercises; aerobic fitness may be improved with multimodal exercises; and female sexual function may be improved with aquatic exercise.
- In participants with cerebral palsy, balance may be improved with hippotherapy and motion gaming, and function may be improved with cycling, treadmill training, and hippotherapy.

- In participants with spinal cord injury, evidence suggested that activities of daily living may be improved with robot-assisted gait training.
- When randomized controlled trials were pooled across types of exercise, physical activity interventions were found to improve walking in multiple sclerosis and likely improve balance and depression in multiple sclerosis. Physical activity may improve function and aerobic fitness in people with cerebral palsy or spinal cord injury. When studies of populations with multiple sclerosis and cerebral palsy were combined, evidence indicated dance may improve function.
- Evidence on long-term health outcomes was not found for any analysis groups. For intermediate outcomes such as blood pressure, lipid profile, and blood glucose, there was insufficient evidence from which to draw conclusions. There was inadequate reporting of adverse events in many trials.

Conclusions. Physical activity was associated with improvements in walking ability, general function, balance (including fall risk), depression, sleep, activities of daily living, female sexual function, and aerobic capacity, depending on population enrolled and type of exercise utilized. No studies reported long-term cardiovascular or metabolic disease health outcomes. Future trials could alter these findings; further research is needed to examine health outcomes, and to understand the magnitude and clinical importance of benefits seen in intermediate outcomes.

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Evidence Summary

Main Points

- We found physical activity to be associated with improvements in walking ability, general function, balance (including fall risk), depression, sleep, activities of daily living, aerobic capacity, and female sexual function, depending on population and type of activity.
- No studies reported long-term cardiovascular or metabolic disease health outcomes.
- Evidence was also limited by heterogeneity in interventions and control groups and by small sample sizes; evidence in spinal cord injury was limited by the small number of trials.
- Evidence was lacking for many prioritized outcomes.
- Adverse effects of the interventions were inadequately reported in many studies.

Background and Purpose

The benefits of regular physical activity (movement using more energy than rest) for the general population include reduced risk of heart disease, stroke, type 2 diabetes, dementia, depression, falls with injuries among the elderly, and breast, colon, endometrial, esophageal, kidney, stomach, and lung cancer.[1] Although routine physical activity combining aerobic exercise with strength and balance training is recommended for people with physical disabilities,[2] less is known about the specific benefits and potential harms for this diverse population. In particular, the various populations using wheelchairs as a result of their physical disabilities is broad and poorly captured in the literature on physical activity. This review includes three diverse conditions commonly associated with wheelchair use: multiple sclerosis, cerebral palsy, and spinal cord injury. The three populations were chosen as representative of those using a wheelchair or those who might benefit from using a wheelchair in the future. While there are differences in etiology and pathophysiology, a common denominator is the involvement of the corticospinal tracts of the central nervous system, which results in impaired central control and/or coordination of the peripheral muscles. This may lead to paralysis or reduced extremity muscle force and increased spasticity, which can greatly affect general mobility or coordinated movement such as posture and gait.

Methods

We employed methods consistent with those outlined in the Agency for Healthcare Research and Quality Evidence-based Practice Center Program Methods Guidance (https://effectivehealthcare.ahrq.gov/topics/cer-methods-guide/overview), and these are described in the full report. Our searches covered publication dates from 2008 to November 2020. (See Appendix A of the full report for search strategies.)

Results

We included 168 studies in 197 publications (n=7,511), comprising of 146 randomized controlled trials, 15 quasiexperimental nonrandomized trials, and 7 cohort studies. More studies enrolled participants with multiple sclerosis (44%) than other conditions, followed by cerebral palsy (38%) and spinal cord injury (18%).

Key Question 1: Prevention of Cardiovascular Conditions, Diabetes, and Obesity

No included study (n=168) or study excluded at the full-text level provided evidence on the prevention of cardiovascular conditions (e.g., myocardial infarction, stroke, development of hypertension) or the development of diabetes or obesity.

Key Question 2: Benefits and Harms

Compared with no physical activity or usual care, physical activity improved walking ability, function, balance, sleep, activities of daily living, cardiovascular fitness as measure with VO_2 peak, female sexual function (e.g., desire, lubrication, pain), and depression in participants with multiple sclerosis. Physical activity improved balance, function, and VO_2 peak in trials that enrolled participants with cerebral palsy. The evidence in spinal cord injury was sparse. Physical activity improved activities of daily living, function, and VO_2 peak in participants with spinal cord injury. All studies focused on benefits of physical activity, with inadequate reporting of adverse events in many studies. However, physical activity was associated with increased episodes of autonomic dysreflexia in spinal cord injury. Table A summarizes the strength of evidence on effects of physical activity interventions compared with usual care and general exercise effect across interventions compared with usual care.

Key Question 3: Patient Factors Affecting Benefits and Harms

In patients with incomplete spinal cord injury, having better function and more recent injury at baseline was associated with better response to aerobic interventions (2 randomized controlled trials). Other subgroup analyses (3 randomized controlled trials) did not find evidence of variation in effects based on baseline function or spasticity in children with cerebral palsy (total body vibration), or based on weight category in multiple sclerosis patients (cycling). There were no differences across cerebral palsy trials in walking outcomes when stratified by age group (children, adolescents, and adults).

Table A. Effects of physical activity interventions compared with usual care[a]

Intervention Category Intervention	Multiple Sclerosis Studies Strength of Evidence[b] (Direction of Finding)	Cerebral Palsy Studies Strength of Evidence[b] (Direction of Finding)	Spinal Cord Injury Studies Strength of Evidence[b] (Direction of Finding)
Aerobic Exercise Dance (1 RCT in MS and 1 RCT in CP)[a]	Low (function improvement)	Low (function improvement)	Insufficient
Aerobic Exercise Aerobics	Low (sleep improvement)	Insufficient	Insufficient
Aerobic Exercise Aquatics	Low (balance, ADL improvement, female sexual function)	Insufficient	Insufficient
Aerobic Exercise Cycling	Low (no clear benefit on walking)	Low (function improvement)	Insufficient
Aerobic Exercise	Low	Insufficient	Low

Intervention Category Intervention	Multiple Sclerosis Studies Strength of Evidence[b] (Direction of Finding)	Cerebral Palsy Studies Strength of Evidence[b] (Direction of Finding)	Spinal Cord Injury Studies Strength of Evidence[b] (Direction of Finding)
Robot-Assisted Gait Training	(balance improvement) Low (no clear benefit in function)		(ADL improvement) Low (no clear benefit on function)
Aerobic Exercise **Treadmill**	Low (walking, function, and balance improvement)	Low (function improvement)	Insufficient
Postural Control **Balance Exercises**	Moderate (balance improvement)	Insufficient	Insufficient
Postural Control **Balance Exercises**	Low (fall risk improvement)	Insufficient	Insufficient
Postural Control **Balance Exercises**	Low (function improvement)	Insufficient	Insufficient
Postural Control **Hippotherapy**	Insufficient	Low (balance and function improvement)	Insufficient
Postural Control **Tai Chi**	Insufficient	Insufficient	Insufficient
Postural Control **Motion Gaming**	Low (function, balance improvement)	Low (balance improvement)	Insufficient
Postural Control **Whole Body Vibration**	Insufficient	Insufficient	Insufficient
Postural Control **Yoga**	Low (no clear benefit on function)	Insufficient	Insufficient
Strength Interventions **Muscle Strength Exercise**	Low (no clear benefit on walking, function, balance, quality of life, spasticity)	Low (no clear benefit on walking and function)	Insufficient
Multimodal Exercise **Progressive Resistance or Strength Exercise Plus Aerobic and/or Balance Exercise**	Low (walking, balance, VO_2 improvement)	Low (no clear benefit on function, quality of life)	Insufficient
All Types of Exercise	High (walking improvement)	Low (function)	Low (function)

Intervention Category Intervention	Multiple Sclerosis Studies Strength of Evidence[b] (Direction of Finding)	Cerebral Palsy Studies Strength of Evidence[b] (Direction of Finding)	Spinal Cord Injury Studies Strength of Evidence[b] (Direction of Finding)
	Moderate (balance, depression improvement, no clear benefit on function)	Low (VO_2 improvement)	Low (VO_2 improvement, increased episodes of autonomic dysreflexia[c], no clear benefit on depression)

Abbreviations: ADL = activities of daily living; CP = cerebral palsy; MS = multiple sclerosis; RCT = randomized controlled trial
[a] Strength of evidence color shading: blue=high strength of evidence, green=moderate, yellow=low, white=insufficient

[b] Strength of evidence based on combining the two populations, multiple sclerosis and cerebral palsy.
[c] Whole-body exercise versus exercise limited to upper body

Limitations

Key Question 4: Methodological Weaknesses or Gaps

Conclusions that can be drawn from the evidence on physical activity in patients with multiple sclerosis, cerebral palsy, and spinal cord injury are limited by small sample sizes; few trials (in spinal cord injury); inadequate descriptions of population characteristics, control group activities, and intensity of physical activity; incomplete data analysis; inadequate reporting of adverse events; and relatively few trials considered to be high quality (low risk of bias). The addition of larger, well-conducted randomized controlled trials of longer duration and including all disability levels would greatly strengthen the evidence base and may alter the current conclusions.

Implications and Conclusions

Physical activity was associated with improvements in walking ability, general function, balance (including fall risk), depression, aerobic capacity, activities of daily living, female sexual function, and sleep, depending on population and type of physical activity. No studies reported long-term cardiovascular or metabolic disease health outcomes. Future trials could alter these findings, and further research is needed to examine health outcomes to understand the magnitude and clinical importance of benefits seen in intermediate outcomes.

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2. UK Chief Medical Officers' Physical Activity Guidelines Care UKDoHS; Sept. 7, 2019. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/829841/uk-chief-medical-officers-physical-activity-guidelines.pdf Accessed Sept. 15, 2019.

Introduction

Purpose

This systematic review summarizes the current evidence on the health effects of physical activity interventions in people with multiple sclerosis (MS), cerebral palsy (CP), and spinal cord injury (SCI). These three diverse conditions were chosen to represent individuals using a wheelchair or individuals who may benefit from using a wheelchair in the future. ("Wheeled mobility device" is sometimes used to encompass manual wheelchairs, motorized wheelchairs, and motorized scooters; this report uses the term wheelchair in this broad sense.) The review is focused on four Key Questions developed by the National Institutes of Health to inform a Pathways to Prevention Workshop. It is anticipated that the evidence synthesis on the health effects of physical activity intervention in people with multiple sclerosis, cerebral palsy, and spinal cord injury will be of ongoing interest to primary and specialty care providers, health researchers, policymakers, and other stakeholders.

Background

For the general population, the health benefits of regular physical activity are well-recognized, as highlighted in 2008 and 2018 reports to the Department of Health and Human Services from the Physical Activity Guidelines Advisory Committee.[1,2] In addition to a reduced risk of death, greater amounts of regular moderate-to-vigorous physical activity reduces the risk of many of the most common and expensive diseases or conditions in the United States. Heart disease, stroke, hypertension, type 2 diabetes, dementia, depression, postpartum depression, excessive weight gain, falls with injuries among the elderly, and breast, colon, endometrial, esophageal, kidney, stomach, and lung cancer are all less common among individuals who are or become more physically active.[2] Physical activity may also help reduce the natural progression of disability in certain populations.[3] In 2016 one in four noninstitutionalized U.S. adults (25.7%, representing an estimated 61.4 million people) reported having a physical and/or cognitive disability, and mobility was the most prevalent disability type (13.7% of the total).[4] Newly released physical activity guidelines suggest adults with disability benefit from similar amounts of physical activity and muscle strengthening as the general population, although there may be some risk of injury for populations who are not accustomed to exercise.[5] The U.S. Department of Health and Human Services indicates that routine physical activity programs combining aerobic exercise with muscle strength and balance training improve fitness, function, and quality of life for individuals with physical disabilities.[2] Less is known regarding specific health benefits of physical activity in people who use a wheelchair.

The various populations using wheelchairs are broad and poorly captured in the literature on physical activity, making a systematic review of all "wheelchair users" unfeasible. Additionally, some individuals may only need the use of a wheelchair some of the time—to cover longer distances or when experiencing a disease flare-up, for example. In order to generate a meaningful result from representative populations that reflect relatively consistent examples of why and how wheelchairs are being used, the analysis is focused on a broad but representative sample of potential wheelchair users—individuals with MS, CP, and SCI. Wheelchair users with these conditions have diverse underlying physiologic mechanisms, demographic profiles, respective physical limitations, and potential outcomes from regular physical activity. Understanding those

differences assists in interpreting the literature relating to exercise among these diverse groups (Table 1).

Table 1. Characteristics, causes, and prevalence of multiple sclerosis, cerebral palsy, and spinal cord injury

Causes, Prevalence, and Characteristics	Cerebral Palsy	Multiple Sclerosis	Spinal Cord Injury
Etiology	Traumatic injury to a developing brain before, during, or after birth	Progressive autoimmune disease of the central nervous system with variable disease patterns; 10% primary progressive and others progressive after initial relapse and remitting course	Usually traumatic cord injury (motor vehicle accidents, falls, violence, sports); nervous system above the lesion is intact
Prevalence	1.5 to more than 4 per 1,000 live births; males 30% greater than females; 764,000 children and adults living with CP in the United States[6]	Nearly 1 million people in the United States have MS; average age onset 30 years old and females 2 to 3 times males[7]	Estimated 282,000 in the United States with SCI; recent evidence puts the average age 43 years old; 78% male[8,9]
Mobility	40% limitations in walking and 30% use walkers or wheelchairs	Mobility limitations generally occur later in disease course; after 45 years of disease, on average 76% of individuals require ambulatory aid and 52% bilateral assistance[10]	Variable and depends on level and completeness of injury; generally stable after injury and initial rehabilitation
Associated morbidity	40% of children with CP have intellectual disability, 35% epilepsy, and more than 15% had vision impairment	Sequela of immune suppression including urinary and respiratory infections, seizures, other autoimmune diseases, visual abnormalities, ataxia[11]	Respiratory complications, thromboembolism, autonomic dysreflexia, orthostatic hypotension, bladder dysfunction, neurogenic bowel, spasticity, pain, pressure ulcers[12]
Usual intent of physical activity	Increase mobility and overall level of function as component multimodality efforts during childhood development	Maintain mobility and attenuate limitations of progressive disease; because those with MS often have normal life expectancies the benefits of exercise for the general population would also apply	Maximize functional abilities; recreation; because long-term sequela SCI better prevented/managed, longer term health benefits of regular exercise also are relevant

Abbreviations: CP = cerebral palsy; MS = multiple sclerosis; SCI = spinal cord injury

SCI, MS, and CP have very different physiologic mechanisms (brain vs. spinal cord, degenerative vs. not) and demographic profiles (male vs. female predominance, childhood vs. adult onset). CP is usually present at birth. While the brain injury involved in CP can in general be relatively static, its early onset has effects on musculoskeletal development with functional sequela. In contrast, MS and SCI most often have onset after skeletal maturation is complete. MS can affect any central nervous system function, including vision, and can be progressive for many years. SCI does not affect motor or sensory systems above the level of the spinal cord lesion, sparing cerebral function, and the nervous system injury is usually static after the acute period.

While they are distinctly different in general etiology and pathophysiology, a common denominator for all three conditions is the involvement of the corticospinal tracts of the central nervous system, which results in an impaired central control and/or coordination of the

peripheral muscles. This may lead to paralysis or reduced extremity muscle force and increased spasticity, which can greatly affect general mobility or coordinated movement such as posture and gait. The consequences on ambulation of this corticospinal tract injury exist along a functional spectrum, from fully ambulatory despite motor involvement, to a wide range of overlap of independent ambulation with intermittent wheelchair use, to full-time wheelchair use. Having MS, CP, or SCI is typically permanent and may result in decades of being sedentary if engaging in physical activity is not made a priority. The potential benefits in these populations may be even greater than in able-bodied people who are still mobile and who achieve some benefit of activity through performing ordinary activities in daily life such as pushing a grocery cart around a store, fixing dinner, or carrying a child up the stairs.

Many users of wheelchairs encounter psychological and physical barriers as well as limitations of access to preventive healthcare and appropriate physical activity programs intended to maintain healthy weight or body composition and physical fitness. The preventive benefits of regular exercise are particularly relevant for people with disabilities, who experience accelerated risk for the conditions known to be attenuated by regular exercise, such as obesity or increased body fat,[13-15] dyslipidemia,[16,17] and cardiovascular events such as myocardial infarction,[17,18] stroke,[18-20] and death.[8,18] Increased risk for morbidity and mortality may be due, in part, to the specific disease that limits mobility or leads to the use of a wheelchair, the treatment for the disease (e.g., steroids used to treat MS), and/or a sedentary lifestyle.

The National Academies of Sciences, Engineering, and Medicine's 2017 report on the use of assistive technologies to enhance activity recommends that individuals who require wheeled and seated mobility devices receive regular evaluations of their physical condition.[21] Evaluation should include at least annual assessments of the functioning and fitting of the devices, ergonomics and safety, ability to use the device, underlying disorder and secondary health conditions, functional needs, and the individual's satisfaction. Access to appropriate care can facilitate education, linkage to activity resources, and encouragement of physical activity to help mitigate these risks.

People with disabilities face a number of barriers to exercise. Skill at using a wheelchair, fatigue, fear of falling, pain, heat sensitivity, negative bias/stigma,[22] and conflicting information from providers have been listed as barriers to exercise among those with MS.[23-27] Those with CP cite the need for caregiver support, prohibitive cost, and their medical condition as barriers to regular physical activity.[28] Additionally, it can be challenging to find physical activities that a child with quadriplegic CP can do to improve strength or aerobic conditioning when motor control is insufficient. For individuals with SCI, concern about autonomic dysfunction, blood pressure and temperature regulation during exercise, may limit exercise participation,[29,30] contributing to decreasing fitness levels with increasing time since injury.[21] All wheelchair users are limited by lack of access to facilities, lack of transportation, and insufficient Americans with Disabilities Act compliance at community fitness centers.[31-33] Individuals who infrequently need a wheelchair may not be completely comfortable with their wheelchair skills and therefore may not be active enough in participating in wheelchair sports or physical activities.[34] Special equipment such as robot-assisted gait training (RAGT) or body weight support treadmill devices can be prohibitively difficult for people outside of major urban areas to access.

A review of Canadian community-based physical activity and wheelchair mobility programs points out a clear need for more programs, particularly those that assess long-term impact.[32] Longer time since injury is associated with lower fitness levels in SCI with paraplegia.[35]

Decreased strength and muscle mass associated with aging increases risk for shoulder injury, and elderly wheelchair users need specific interventions to preserve mobility.[36]

Physical activity has been shown to improve body composition,[37-39] cognition,[40] glucose metabolism,[39,41,42] and lipid profiles,[39,43] and to decrease risk of morbidity and mortality in nondisabled people.[38,44] Physical activity could similarly benefit those with disabilities. Recently published SCI guidelines recommend moderate to vigorous intensity aerobic exercise at least twice weekly and strength exercise for each major functioning muscle group twice weekly.[45] Verschuren et al. recommend aerobic sessions and strength training twice weekly for individuals with CP,[46] while Halabchi et al. recommend aerobic exercises, strength training, and daily flexibility and stretching exercises for individuals with MS.[47] In the past, exercise was not recommended for individuals with MS due to fear of worsening of symptoms.[48] However, more recent evidence suggests that physical activity improves health outcomes in people with disabilities (including people with MS), and the updated *2018 Physical Activity Guidelines for Americans* now recommend between 2.5 to 5 hours of moderate aerobic exercise weekly, or over 1 hour to 2.5 hours of vigorous aerobic exercise weekly, plus muscle strengthening activities, for people with physical disabilities.[2] These guidelines suggest that children ages 3 through 5 years engage in physical activity throughout the day for normal growth and development and that school-aged children and adolescents receive 60 minutes of moderate to vigorous-intensity aerobic activity, 60 minutes of muscle-strengthening activity, and 60 minutes of bone-strengthening activity at least 3 days a week. The guidelines do not offer recommendations regarding physical activity in children or adolescents with chronic disease or physical disability.

Scope and Key Questions

This systematic review summarizes and synthesizes current research on the specific benefits and potential harms of physical activity for people with MS, CP, and SCI, regardless of current use of a wheelchair. This topic was nominated by the Director of the National Center for Medical Rehabilitation Research, and supported by the National Institute of Child Health and Human Development, the National Institute of Neurological Disorders and Stroke, the National Institutes of Health Office of Disease Prevention, and the National Institutes of Health Medical Rehabilitation Coordinating Committee, which has representatives from 20 Institutes and Centers, along with other federal partners for a Pathways to Prevention (P2P) workshop to assess the benefits and harms of physical activity on the physical and mental health of adults, children, and adolescents using a wheelchair, or who may benefit from using a wheelchair in the future. In considering studies related to physical activity among three representative populations who consistently use, sometimes use, or who may, at some point in their lives, need to use a wheelchair as a result of neurological conditions of MS, CP, and SCI, we prioritized certain outcomes. These included long-term health outcomes of: cardiovascular mortality; myocardial infarction; stroke; development of diabetes; and new or increased need for a wheelchair. Other prioritized immediate health outcomes included: pulmonary function tests; VO_2 peak; hemoglobin A1c (HbA1c); bowel, bladder, and sexual function; decubitus ulcers; development of obesity; body mass index; weight; depression; quality of life; falls; function; autonomic dysreflexia; and spasticity. We evaluated outcomes of diverse physical activity interventions, inclusion/exclusion criteria, and research methodologies to identify future research needs. The outcomes of pain and cognition were not included because it is expected that the magnitude of the literature involved would indicate that these topics should be separate reviews. Our overarching objective was to understand the specific benefits and potential harms of physical

activity for those currently using or those who may benefit from using a wheelchair in the future and to identify domains for future research focus—ultimately improving health and quality of life.

Key Questions

Key Question 1: What is the evidence base on physical activity interventions to prevent obesity, diabetes, and cardiovascular conditions, including evidence on harms of the interventions in people with multiple sclerosis, cerebral palsy, or spinal cord injury who are at risk for or currently using a wheeled mobility device?

a. What interventions have been studied?
b. What outcomes have been studied?
c. What inclusion/exclusion criteria have been used in studies?
d. What other research methodologies (control/comparison group design, length of intervention, research setting) have been used?

Key Question 2: What are the benefits and harms of physical activity interventions for people with multiple sclerosis, cerebral palsy, or spinal cord injury who are at risk for or currently using a wheeled mobility device?

a. Does physical activity improve clinical outcomes such as cardiovascular disease, diabetes, overweight or obesity, mental health, or sexual function?
b. Does physical activity improve intermediate outcomes such as physical fitness, obesity, or bone density?
c. Does physical activity reduce the harms of immobility, such as incidence of decubitus ulcer, urinary tract infection, bowel dysfunction, or autonomic dysfunction?
d. Does physical activity decrease the risk for adverse outcomes of disorders associated with wheeled mobility device use, such as spasticity, autonomic dysreflexia, or muscle contractures?
e. What are the harms of physical activity, such as injuries that are associated with wheeled mobility device use (e.g., falls, tips, overuse injuries)?
f. Do the benefits or harms of physical activity vary by the location of the intervention (e.g., home, community, clinic), amount of training or instruction (e.g., no training, some training, all physical activity sessions with training), or level of supervision (e.g., inpatient, telehealth)?

Key Question 3: What are the patient factors that may affect the benefits and harms of physical activity in patients with multiple sclerosis, cerebral palsy, or spinal cord injury who are at risk for or currently using a wheeled mobility device?

a. Do the benefits and harms of physical activity vary by age, sex, or race/ethnicity?
b. Do the benefits and harms of physical activity vary by primary disease or injury that led to wheelchair use?

Key Question 4: What are methodological weaknesses or gaps that exist in the evidence to determine benefits and harms of physical activity in patients with multiple sclerosis, cerebral palsy, or spinal cord injury who are at risk for or currently using a wheeled mobility device?

a. What types of studies supported conclusions in Key Questions 2 and 3?
b. What are the major weaknesses in study designs?
c. What would improve ability of future research to address the Key Questions?

PICOTS

The Methods section provides details on the Populations, Interventions, Comparators, Outcomes, Timing, Settings, and Study Designs (PICOTS) inclusion and exclusion criteria. An overview of the PICOTS for this review follows.

Populations

- *Include for Key Question (KQ) 1, KQ2, and KQ3:* Patients with MS, CP, or SCI; in studies of mixed populations, at least 80 percent will be individuals with MS, CP, and/or SCI. All ages included.
- *Exclude:* Other populations.

Interventions

- *Include for all KQs:* Any gross motor intervention with a defined period of directed physical activity that is expected to increase energy expenditure. Intervention must have a minimum of 10 sessions on 10 different days of activity in a supervised individual or group setting. Include: aerobic exercise, strength training, standing, balance, flexibility, and combination interventions.
- *Exclude:* Unobserved physical activity; parent or caregiver observed interventions; interventions that do not target the whole body (e.g., interventions to improve reaching or to improve the function of one joint, partial body vibration); single studies of one intervention.

Comparators

- *Include for all KQs:* Between-group comparisons with no physical activity or other types of physical activity or a behavioral intervention with a physical activity outcome.
- *Exclude:* Comparisons to other active comparators such as drug therapy; pre-post studies with only one group of participants.

Outcomes

- For KQ1: Outcome measures, physical activity interventions, inclusion/exclusion criteria, and research methodologies related to prevention of obesity, diabetes, cardiovascular

conditions, or harms; types of studies or bodies of studies supporting conclusions for KQs 2 and 3.

- For KQ2 and KQ3: Benefits and harms of physical activity including: (a) clinical outcomes such as cardiovascular mortality, myocardial infarction, stroke, diabetes, mental health, obesity/overweight, and sexual function; (b) intermediate outcomes such as physical fitness, HbA1c, bone density, and resting heart rate; and (c) subgroup differences based on location of intervention (e.g., home, community, clinic), level of instruction or training (e.g., no training, some training, all physical activity sessions with training), and level of supervision (e.g., inpatient, telehealth).
- For KQ4: Major weakness in study design, items that improve the ability to address the KQs.
- *Exclude:* Outcomes not used to make clinical decisions (e.g., estradiol level, muscle thickness).

Timing

- *Include for all KQs:* At least 10 sessions of physical activity spread out over no fewer than 10 days.
- *Exclude:* Acute spinal cord trauma stabilization period, immediate postoperative period (e.g., after surgeries to improve musculoskeletal function in CP).

Setting

- *Include for all KQs:* Any U.S. or U.S.-applicable study, including clinic, home (provided physical activity is observed by healthcare or research staff), or community setting (e.g., gym or athletic class).
- *Exclude:* Non-U.S.-applicable setting.

Study Designs

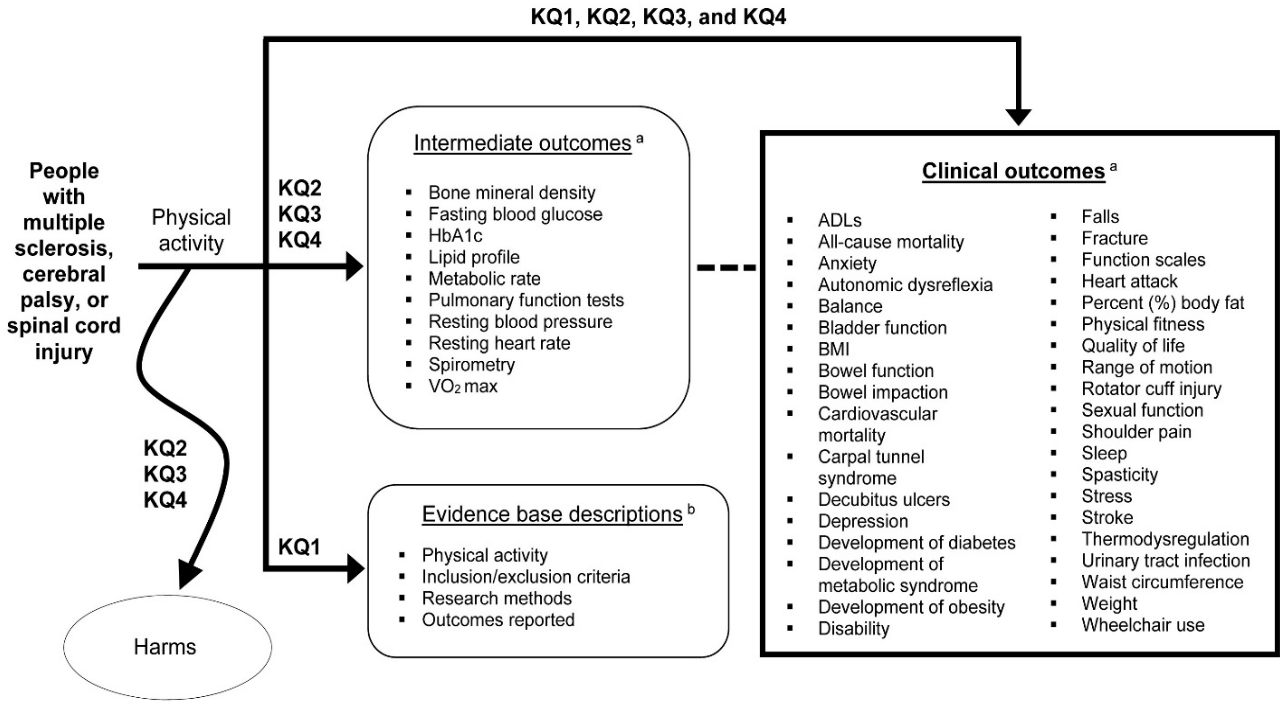
- *Include for all KQs:* Clinical trials and observational studies (cohort studies and case-control studies).
- *Include for all KQs:* Studies with the following minimum sample sizes analyzed: MS (n=30), CP (n=20), SCI (n=20).
- *Include for all KQs:* Studies published since 2008; systematic reviews published since 2014.
- *Include, if needed, due to lack of clinical trials or controlled observational studies:* Pre-post studies.
- *Exclude:* Case report, case series, and cross-sectional studies.

Analytic Framework

The analytic framework (Figure 1) illustrates the relationship between the KQs and the outcomes for this review. The figure indicates the questions associated with intermediate outcomes, descriptions of the evidence base, clinical outcomes, and harms. The complete

PICOTS criteria for inclusion and exclusion of studies in this review appear in the Methods section.

Figure 1. Analytic framework for physical activity and the health of wheelchair users with multiple sclerosis, cerebral palsy, and spinal cord injury



Abbreviations: ADL = activities of daily living; BMI = body mass index; HbA1c = hemoglobin A1c; KQ = Key Question; VO_2 max = maximal oxygen uptake

[a] Outcomes are specified in the Methods section

[b] Studies that evaluate prevention of obesity, diabetes, cardiovascular conditions, and harms

Organization of Report

This report is organized by sections. Each represents either a main section of the report (i.e., Introduction, Methods, Results, Discussion, and Conclusion) or a Key Question.

Key Question 1 provides an overview of the evidence base of included studies as well as identification of studies that did not meet the inclusion criteria of this report.

For Key Question 2 we present the results of the benefits and harms of physical activity interventions for clinical outcomes of interest (Figure 1), subdivided by intervention categories of aerobic exercise, postural control, strength interventions, and multimodal interventions. Interventions specific to each of these categories are indicated with a brief description of the subtype of exercise, key points specific to that intervention, and detailed results are organized by the specific population of MS, CP, and SCI. Studies that reported on only one or more intermediate outcomes (Figure 1) are reported separately.

The Key Question 2 intervention categories include:

Aerobic exercise interventions:
- Aerobics
- Aquatics
- Cycling
- Hand cycling
- RAGT
- Treadmill

Postural control interventions:
- Balance exercise
- Hippotherapy
- Tai Chi
- Motion gaming
- Whole body vibration
- Yoga

Strength interventions:
- Muscle strength exercise

Multimodal interventions:
- Progressive resistance or strengthening exercise plus aerobics and/or postural control interventions

For Key Question 2 the general effects of exercise were also assessed:

All exercise interventions:
- Interventions with sufficient outcomes data to be analyzed independent of population or intervention category

Key Question 3 evaluates patient factors that may affect the benefits and harms of physical activity, and Key Question 4 reports the methodological weaknesses or gaps in the evidence base.

Methods

This Comparative Effectiveness Review follows the methods suggested in the AHRQ *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (hereafter the "EPC Methods Guide").[49] All methods were determined *a priori* and the protocol was published on the Agency for Healthcare Research and Quality website (https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/wheelchair-users-amended-protocol.pdf). The protocol for this review was also submitted to the PROSPERO systematic review registry (CRD42019130060).

Topic Refinement

Prior to conducting this review, the Evidence-based Practice Center (EPC) refined the preliminary Key Questions and PICOTS (Populations, Interventions, Comparators, Outcomes, Timing, Studies, Settings) with the AHRQ Task Order Officer (TOO), representatives from National Institutes of Health (NIH), Key Informants and the Technical Expert Panel (TEP). NIH assisted in evaluating proposed changes based on the preliminary literature review and input from the stakeholders as well as prioritization of outcomes.

Literature Search Strategy

We searched MEDLINE®, CINAHL®, PsycINFO®, Cochrane CENTRAL, Embase®, and Rehabilitation and Sports Medicine Source. We also searched ClinicalTrials.gov to capture gray literature. These databases were broad enough to capture the study types, the populations (multiple sclerosis [MS], cerebral palsy [CP], and spinal cord injury [SCI]), and physical activities studied. The full search strategies are in Appendix A. We reviewed reference lists of systematic reviews for includable literature. In addition, TEP members were asked to provide suggestions about unpublished literature. We limited the search to studies published since 2008 and systematic reviews since 2014. An updated literature search was conducted in November 2020. Authors of three studies were contacted for information (no additional information was provided).[50-54]

The criteria for selection of studies to be included in the review were pre-established (Table 2) and used to determine eligibility for inclusion and exclusion of abstracts according to the EPC Methods Guide.[49] Two team members trained in systematic review methodology reviewed titles and abstracts for potential eligibility.[55] Excluded abstracts were dual reviewed. We retrieved the full text of articles for all abstracts selected by at least one reviewer as potentially eligible for inclusion in the review, and two team members independently reviewed the full-text articles. Disagreements on eligibility were resolved by consensus.

Inclusion and Exclusion Criteria and Study Selection

The criteria for inclusion and exclusion of studies were designed to identify outcomes that answer the Key Questions and are based on the PICOTS (Table 2).

The populations for this review are people who have MS, CP, or SCI. Limiting the population to these three groups was designed to capture a broad, diverse population of those who need or who may need the assistance of a wheelchair. Study designs indicated in Table 2 were included. We included studies from countries with a very high or high score on the Human Development Index because studies from these countries are more likely to generate results

similar to a study conducted in the United States. Pre-post studies that otherwise meet inclusion criteria were considered for inclusion in the absence of higher-quality evidence.

Interventions with a defined period of observed physical activity (movement using more energy than rest) with a minimum of 10 sessions of activity on 10 days or more in a supervised or group setting were included. Prioritized outcomes for which we assessed the strength of evidence include: cardiovascular mortality; myocardial infarction; stroke; pulmonary function tests; VO_2 max or peak; development of diabetes; hemoglobin A1c (HbA1c); bowel, bladder, and sexual function; decubitus ulcers; development of obesity; body mass index (BMI); weight; depression; quality of life; time to and amount of wheelchair use; falls; general function; autonomic dysreflexia; and spasticity (Table 3). The strength of evidence was as also assessed for balance. We did not include interventions that were reported in only one study.

Given the publication of the initial 2008 Physical Activity Guidelines[1] (updated with a second edition in 2018[5]) and the large number of potentially relevant publications for this review, we searched for studies published since 2008 and systematic reviews published since 2014. Systematic reviews were used only to identify additional studies because the populations, inclusion criteria, interventions, and timing of the studies in the systematic reviews differed in study eligibility from the inclusion criteria for this report. We examined reference lists from systematic reviews and if specific studies reported in the systematic reviews met our inclusion criteria based on the Key Questions and PICOTS (Table 2) those studies were dual reviewed and included in the report.

These decisions regarding study design, study size, publication date range, and prioritization of outcomes were developed in collaboration with the NIH Pathways 2 Prevention Working Group and reviewed with a panel of technical experts.

Table 2. PICOTS—inclusion and exclusion criteria

PICOTS	Inclusion	Exclusion
Populations	Patients using a wheelchair or those who may benefit from using a wheelchair in the future due to MS, CP, or SCI. All ages included.	• Other populations • Studies of mixed populations with <80% MS, CP, SCI
Interventions	Any gross motor intervention with a defined period of directed physical activity that is expected to increase energy expenditure. Intervention must have a minimum of 10 sessions of activity on 10 days or more in a supervised or group setting. Include aerobic exercise, strength training, standing, balance, flexibility, and combination interventions. *Included activities (not exhaustive, additional activities may qualify):* **Balance/flexibility** • Stretching/flexibility • Yoga or Pilates • Martial arts (e.g., Tai Chi) • Hippotherapy (equine-assisted therapy) **Physical/aerobic exercise** • Arm ergometry • Cycling (stationary, recumbent, or arm) • Weight lifting/strength training • Functional electronic stimulation • Robot-assisted gait training • Swimming • Aquatherapy • Group exercise • Team sports • Treadmill (including with body weight support) **Strength/resistance training** • Resistance bands • Weight lifting	• Interventions with <10 sessions • Interventions over a period lasting <10 days • Unobserved physical activity • Family- or caregiver-only observed physical activity • Patient-recalled physical activity • Postoperative physical activity • Intervention focused on improving reaching • Interventions without whole body effect (e.g., targeting one joint) • Intervention reported in only one study
Comparators	Comparisons to no physical activity or other types of physical activity or behavioral counseling.	• All other active controls
Outcomes	**Cardiovascular** • Cardiovascular mortality, myocardial infarction, stroke, all-cause mortality, resting heart rate, resting blood pressure, lipid profile **Respiratory** • Pulmonary function tests, VO_2 max/peak, spirometry **Endocrine** • Development of diabetes, HbA1c, fasting blood glucose, development of metabolic syndrome, metabolic rate **Gastrointestinal** • Bowel function, bowel impaction **Genitourinary** • Bladder function, urinary tract infection **Musculoskeletal** • Fracture, bone mineral density, muscle strength, rotator cuff injury, shoulder pain, range of motion **Reproductive** • Sexual function	• Outcomes not used to make clinical decisions (e.g., estradiol level) • Other outcomes (e.g., head pitch and roll, kinematic variables, stepping kinematics, reaching, muscle thickness, muscle quality, blood flow restriction, premotoneuronal control) • Hospitalization or length of stay • Cognition • Pain other than shoulder pain

PICOTS	Inclusion	Exclusion
Outcomes (continued)	**Integumentary** • Decubitus ulcers **Body composition** • Weight, BMI, development of obesity, waist circumference, % body fat **Mental health** • Depression, quality of life, anxiety, stress, sleep **General function** • Walking, falls, wheelchair use, function scales, disability, ADL, balance, physical fitness **Neurological** • Autonomic dysreflexia, spasticity, thermodysregulation, carpal tunnel syndrome	
Timing	At least 10 days with at least one session of physical activity per day.	• Acute SCI, undergoing stabilization • Immediate postoperative period
Setting	Any setting, including, clinic, home, or community setting (e.g., gym or athletic class). Physical activity occurring in the home must still be observed by medical, research, or athletic staff.	• Non-U.S. applicable studies
Study Designs	• Randomized controlled trials published since 2008 • Controlled observational studies published since 2008 • Systematic reviews published since 2014 to review for additional studies meeting inclusion criteria • Potentially include pre-post studies in the absence of clinical trials and controlled observational studies • Studies with the following sample sizes: MS (n≥30), CP (n≥20), SCI (n≥20).	• All other study designs (e.g., case series and case reports) • Studies published before 2008 • Systematic reviews published prior to 2015

Abbreviations: ADL = activities of daily living; BMI = body mass index; CP = cerebral palsy; HbA1c = hemoglobin A1c; MS = multiple sclerosis; SCI = spinal cord injury; VO_2 max = maximal oxygen uptake; VO_2 peak = highest value of VO_2 attained

Table 3. Outcomes

System	Prioritized Outcomes	Other Outcomes
Cardiovascular	• Cardiovascular mortality • Myocardial infarction • Stroke	• All-cause mortality • Lipid profile • Resting blood pressure • Resting heart rate
Respiratory	• Pulmonary function tests • VO_2 max/peak	• Spirometry
Endocrine	• Development of diabetes • HbA1c	• Development of metabolic syndrome • Fasting blood glucose • Metabolic rate
Gastrointestinal	• Bowel function	• Impaction
Genitourinary	• Bladder function	• Urinary tract infection
Musculoskeletal	None prioritized	• Bone mineral density • Fracture • Muscle strength • Range of motion • Rotator cuff injury • Shoulder pain
Reproductive	• Sexual function	None
Integumentary	• Decubitus ulcers	None
Body Composition	• Body mass index • Development of obesity • Weight	• Percent body fat • Waist circumference
Mental Health	• Depression • Quality of life	• Anxiety • Sleep • Stress
General Function	• Falls • Function scales • Wheelchair use	• Activities of daily living • Balance • Disability • Physical fitness
Neurological	• Autonomic dysreflexia • Spasticity	• Carpal tunnel syndrome • Thermodysregulation

Abbreviations: HbA1c = hemoglobin A1c; VO_2 max = maximal oxygen uptake; VO_2 peak = highest value of VO_2 attained

Data Abstraction and Data Management

Data was abstracted from studies meeting the inclusion criteria (Table 2, and Appendix B). We abstracted data on study design, year, setting, country, sample size, eligibility criteria, population, clinical characteristics, (e.g., age, sex, race, MS, CP, or SCI), current versus potential wheelchair users, interventions and comparators, characteristics of the intervention (e.g., number of sessions, level of training of session supervisor), and outcomes (e.g., body mass index, resting heart rate, 6-Minute Walk Test (6MWT), depression scale scores, balance scale scores), and funding. Abstracted study data was verified for accuracy and completeness by a second team member. A record of studies excluded at the full-text level with reasons for exclusion is included in Appendix C. Definitions and characteristics of the included and excluded studies and details of the systematic reviews evaluated for potential includable studies are in Appendix D.

Quality (Risk of Bias) Assessment of Individual Studies

We assessed the risk of bias of randomized controlled trials (RCTs), quasiexperimental studies (nonrandomized studies), and cohort studies following the EPC Methods Guide[56] using

study design-specific criteria adapted from the U.S. Preventive Services Task Force [57] and the Cochrane Collaboration.[58] For RCTs, we evaluated factors such as randomization and allocation concealment methods, attrition, use of intent-to-treat methods, and blinding. For nonrandomized studies, we assessed factors such as participant selection methods; attrition; accuracy of methods for measuring exposures, outcomes, and confounders; and appropriateness of methods to address potential confounding.

Studies rated "good" have the least risk of bias, and their results are considered valid. Good-quality studies include clear descriptions of the population, setting, interventions, and comparison groups; a valid method for allocation of participants to treatment; low dropout rates and clear reporting of dropouts; appropriate means for preventing bias; and appropriate measurement of outcomes.

Studies rated "fair" may be susceptible to some bias, though not enough to invalidate the results. These studies may not meet all the criteria for a rating of good quality, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems. The fair-quality category is broad, and studies with this rating will vary in their strengths and weaknesses. The results of some fair-quality studies are likely to be valid, while others may be only possibly valid.

Studies rated "poor" have significant flaws that imply biases of various types that may invalidate the results. They may have a serious or "fatal" flaw in design, analysis, or reporting; large amounts of missing information; discrepancies in reporting; or serious problems in the delivery of the intervention. The results of these studies will be at least as likely to reflect flaws in the study design as the true difference between the compared interventions.

Each included study was independently dual-reviewed for quality by two EPC team members and disagreements resolved by consensus. Criteria for assessing the quality and external validity of studies is provided in Appendix E.

Data Analysis and Synthesis

The findings are summarized in evidence tables indicating the study characteristics and outcome results and study quality ratings, and are included in summary tables of the key findings. Findings are organized by the intervention categories: aerobic exercise (including aquatics, cycling, dance, and robot-assisted gait training [RAGT]), postural control (including postural control exercises, hippotherapy, Tai Chi, motion games, whole body vibration [WBV], and yoga) as well as strength exercises (including; muscle strengthening exercise and multimodal exercise with strength as a major component). Results for each of these categories are reported by etiology of disability (i.e., MS, CP, SCI). Evidence from the included studies is in Appendix F, and Appendix G provides the quality ratings for individual studies.

Statistical Meta-Analysis

We conducted quantitative synthesis involving pooling of study findings in meta-analyses as appropriate (i.e., when studies are homogeneous enough to provide meaningful combined estimates) to summarize data from multiple studies and to obtain more precise and accurate estimates of effects. The difference between each intervention's mean change from baseline to followup, or the mean difference (MD), was the primary effect size. Standardized mean differences were calculated when the scale of units varied within an outcome. Methods for calculating the standard deviation of the change scores followed the recommendations given in The Cochrane Handbook 7.7.[58] Meta-analyses were conducted using STATA 14.0 and 14.2

(StataCorp, College Station Texas). In the case of nonconvergence with Profile Likelihood, or when there was no meaningful difference between analyses using Profile Likelihood and Dersimonian and Laird, the Dersimonian and Laird estimates were reported. The I-squared (I^2) statistic was used to assess statistical heterogeneity. When statistical heterogeneity is present (i.e., I^2 >30%), an attempt to understand the heterogeneity through stratification of data and/or sensitivity analysis was conducted.

When pooled studies varied in quality and included poor-quality RCTs, a sensitivity analysis was conducted by removing studies rated poor quality. Quasiexperimental and cohort studies were not included in meta-analyses involving RCTs due to the difference in study design and the relatively poor quality of these studies. Pooled analysis focused on prioritized outcomes for which there was sufficient data.

Due to the large number of potential outcomes, quantitative synthesis focused on those outcomes previously prioritized for strength of evidence rating (Table 3) with the addition of the Berg Balance Scale, which was not a prioritized outcome but was the outcome with the most evidence.

Grading the Strength of Evidence

The strength of evidence for each Key Question was initially assessed by one researcher and verified by a second reviewer for each outcome by using the approach described in the EPC Methods Guide.[56] To ensure consistency and validity of the evaluation, the grades reviewed for:

- Study limitations (low, medium, or high level of study limitations)
- Consistency (consistent, inconsistent, or unknown/not applicable)
- Directness (direct or indirect)
- Precision (precise or imprecise)
- Reporting bias (suspected or not detected)

The strength of evidence was assigned an overall grade of high, moderate, low, or insufficient according to a four-level scale by evaluating and weighing the combined results of the above domains:

- High: Very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. The findings are stable, meaning another study would not change the conclusions.
- Moderate: Moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. The findings are likely to be stable, but some doubt remains.
- Low: Limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). Additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
- Insufficient: No evidence, unable to estimate an effect, or have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

Individual strength of evidence domains are indicated in summary tables with ratings for the strength of evidence. Ratings for strength of evidence were assigned for prioritized outcomes only and focus on concepts when possible (e.g., an overall rating for depression rather than individual ratings for each depression scale). Strength of evidence ratings were assigned by study population (i.e., MS, CP, SCI). Appendix H describes the strength of evidence for each Key Question.

Assessing Applicability

Applicability was assessed in accordance with the *Methods Guide*,[56] which is based on the PICOTS framework. Applicability addresses the extent to which outcomes associated with an intervention are likely to be similar across different participants and settings in clinical practice based on the populations, interventions, comparisons, and outcomes evaluated in the studies. For example, exclusion of adults in CP trials may render findings that are not applicable to all CP patients seen in clinical practice. Results from trials of elite wheelchair athletes may not be applicable to the average wheelchair user. Factors that may affect applicability, which we have identified *a priori* include eligibility criteria and participant factors (e.g., age, gender, age at injury or diagnosis, duration of injury or diagnosis, baseline fitness level, degree of dependence on the use of a wheelchair, etiology of disability or potential disability), intervention factors (e.g., dose and duration of the intervention, degree of physical activity supervision), comparisons and rate in the comparison group (e.g., no physical activity, other physical activity), outcomes (e.g., clinical health outcomes, intermediate outcomes, validated or unvalidated outcomes), setting (e.g., home, community, research lab), and study design features (e.g., RCT vs. non-RCT, study location). We used this information to assess the situations in which the evidence is most relevant and to evaluate applicability to real-world clinical practice in typical U.S. settings, summarizing applicability assessments qualitatively.

Peer Review and Public Commentary

Clinical and methodological experts were invited to provide external peer review of this systematic review. Comments and editorial review were also be provided by the AHRQ TOO and an EPC Program Associate Editor. The peer-reviewed draft report was posted on the AHRQ website for 4 weeks to elicit public comment. We revised the text as needed and address all relevant reviewer comments in an associated disposition of comments report with the authors' individual responses. The final report of the review will be posted on AHRQ's website.

Results

Overview

Findings are presented in order of the Key Questions (KQ). For KQ1 we identified studies within the entire literature base (including studies that met inclusion criteria and those that did not) with results on prevention of obesity, diabetes, and cardiovascular conditions in participants with multiple sclerosis (MS), cerebral palsy (CP), or spinal cord injury (SCI). For KQ2 on the benefits and harms of physical activity interventions, we reported results by type of intervention: aerobics, postural control, strength, and multimodal exercise, and by population. We assessed the strength of evidence (SOE) for prioritized outcomes and described other outcomes. For KQ3 we examined patient factors that may affect the benefits and harms of physical activity, and for KQ4 we reported the methodological weaknesses or gaps in the evidence base.

We synthesized results qualitatively and quantitatively. We did meta-analysis for studies that had criteria similar enough to provide meaningful combined estimates. Meta-analyses included the 6-Minute Walk Test (6MWT), 10-Meter Walk Test (10MWT), Timed Up and Go Test (TUG), Gross Motor Function Measure (GMFM), MS Walking Scale, and Berg Balance Scale (BBS), among others.

Acronyms and abbreviations used are listed at the end of the report.

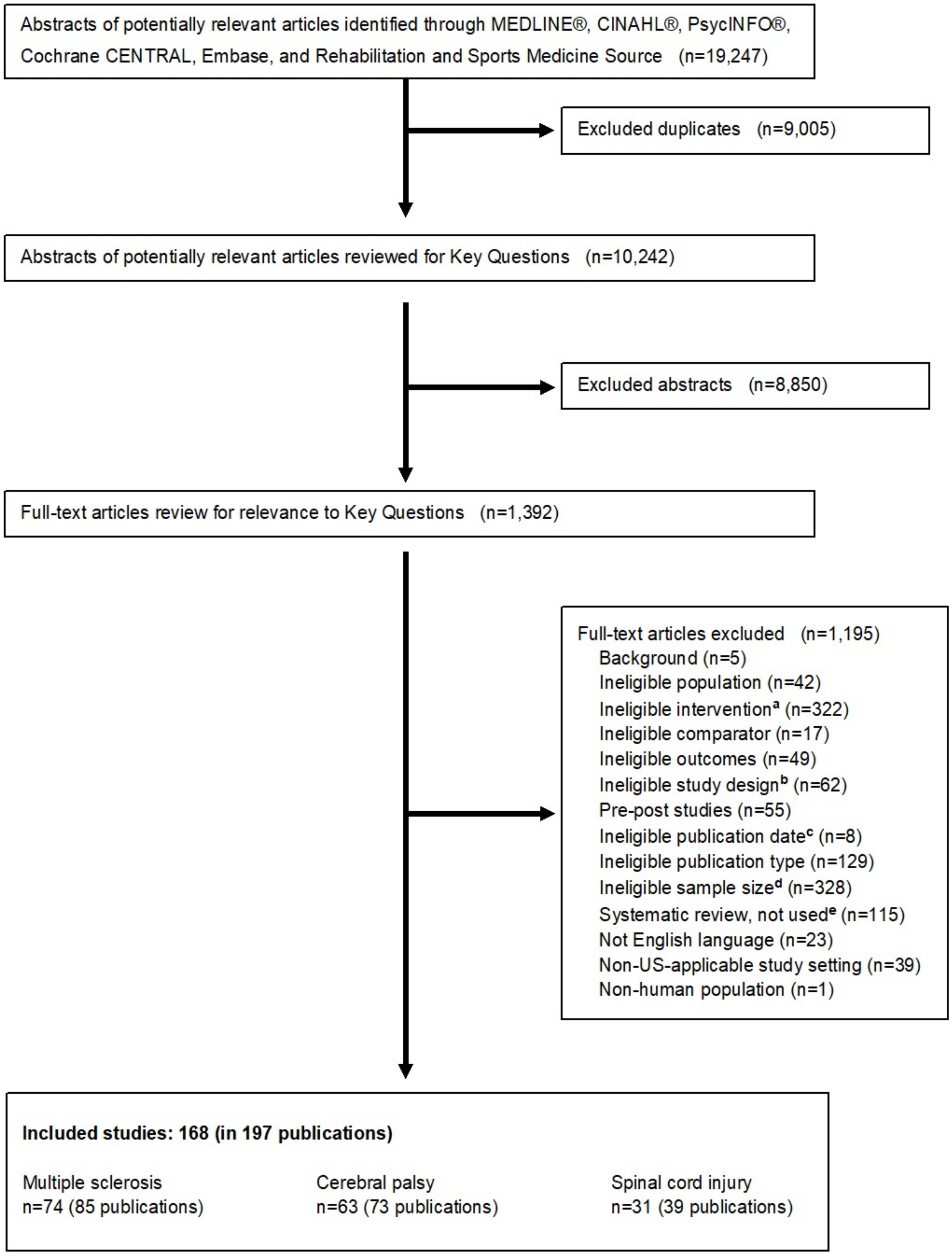
Results of Literature Searches

Searches identified 19,247 potentially relevant abstracts with 10, 242 nonduplicated abstracts. From the abstracts, 1,392 full-text articles were dual reviewed by two researchers, and 168 studies in 197 publications (n=7,511) met the inclusion criteria. We included 146 randomized controlled trials (RCTs), 15 quasiexperimental studies, and 7 cohort studies.

Results of the literature search are indicated in the literature flow diagram (Figure 2) which shows the number of excluded abstracts and the number of excluded articles, as well as exclusion reasons at the full-text level. The list of included studies is in Appendix B and excluded full-text studies list is in Appendix C. Full-text review resulted in inclusion of 74 studies (85 publications) for MS, 63 studies (73 publications) for CP, and 31 studies (39 publications) for SCI. We evaluated the lists of studies included in 116 different systematic reviews judged to be relevant to our review topic to identify additional publications of studies that might be eligible for inclusion in our review (Appendix D). We identified no studies of mixed populations that met inclusion criteria.

At the full-text review level there were 1,195 studies excluded. Primary reasons for exclusion included ineligible interventions and inadequate sample sizes. The majority of excluded studies did not meet our inclusion criteria due to sample size (328 studies with inadequate sample sizes) or intervention requirements (322 interventions did not have adequate duration or number of interventions, the exercise was unobserved, or otherwise did not meet criteria for inclusion). Evidence tables and quality assessment tables for all included studies are in Appendix F and Appendix G.

Figure 2. Literature flow diagram



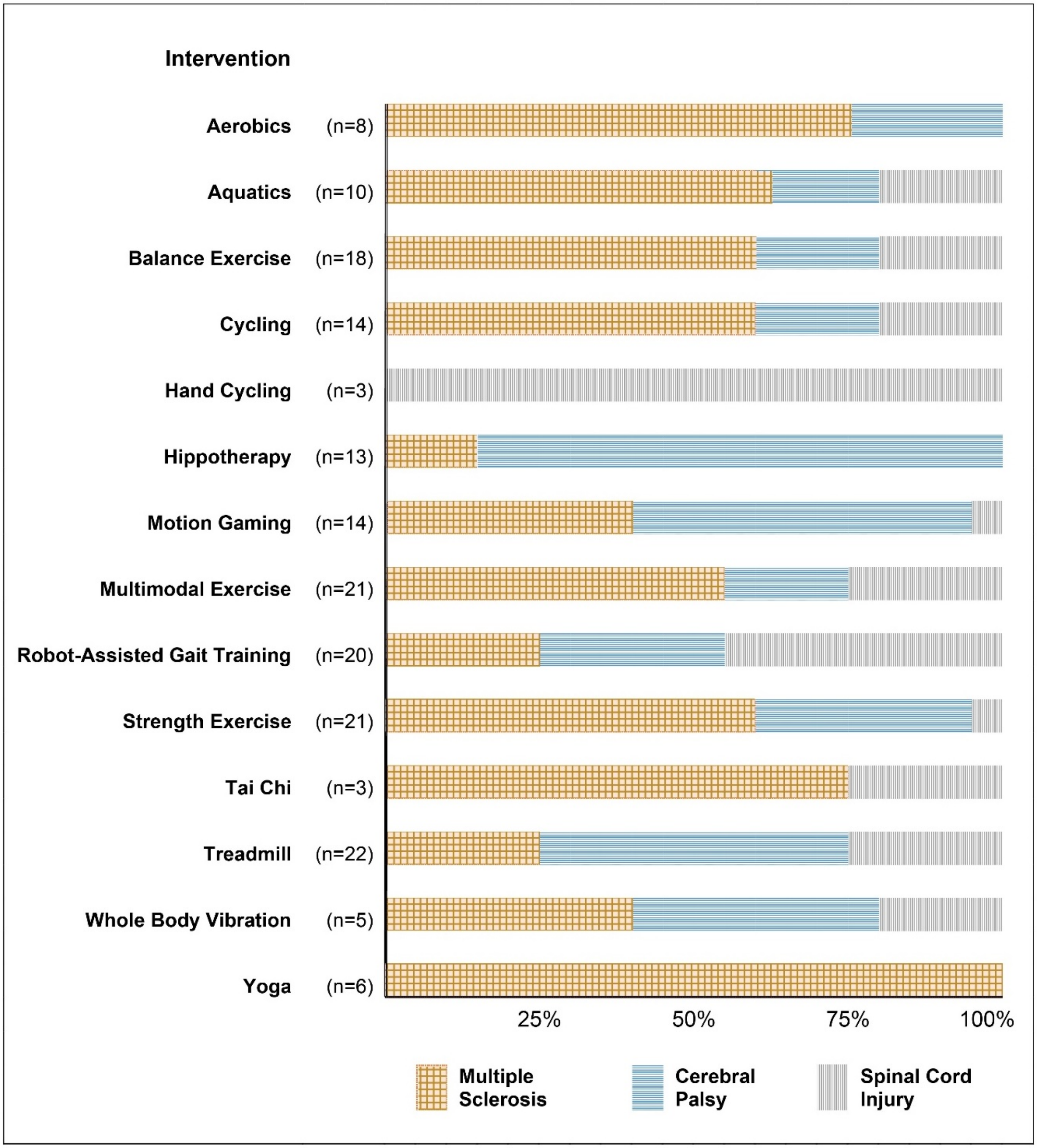
[a] Interventions with < than 10 sessions/< than 10 days, or only family/caregiver observed
[b] Case reports and case series are not included due to methodological limitations
[c] Studies before January 2008 and systematic reviews from 2014 or older are outside of the search dates
[d] Studies with sample sizes <30 for multiple sclerosis and cerebral palsy, and <20 for spinal cord injury
[e] Systematic reviews not used because they did not meet all inclusion criteria, but checked for includable studies

Description of Included Studies

A general overview of the included studies for each population by intervention categories of aerobics exercise, postural control, strength, and multimodal interventions is in Figure 3, which indicates the percentage of each type of exercise studied for people with MS, CP, and SCI. Table 4 shows the studies with primary outcomes from the 168 studies (in 197 publications) that met inclusion criteria and the details of the included studies. A visual summary of the interventions by each population (Figure 4) indicates that in patients with MS, the most frequent interventions were muscle strengthening, multimodal exercises, and cycling. For CP, treadmill and hippotherapy were frequent interventions, and for SCI, robot-assisted gait training (RAGT), treadmill training, hand cycling, and multimodal interventions were used most often. The mean number of participants per study was 45 (range 20 to 242) with only three studies having a sample size of 100 or more. Studies in MS and CP tended to enroll participants with less disability (average study mean Expanded Disability Status [EDSS] score in MS 3.6 standard deviation (SD) 1.77, with little evidence in participants with EDSS scores of 6.5 or higher; GMFCS in CP typically I to III (average study mean Gross Motor Function Classification System [GMFCS] I-IV) 2.40, SD 0.87). Studies in SCI enrolled a wider spectrum of disability. The mean number of exercise sessions and the mean duration of exercise in MS was 25 sessions over 9 weeks, in CP 28 sessions over 10 weeks, and in SCI 68 sessions over 17 weeks. Studies were conducted most often in Iran (26 studies), Turkey (19 studies), the United States (15 studies), Italy (12 studies), and South Korea (12 studies). The remaining studies were conducted in numerous countries with fewer studies per location. Most studies were conducted in an (usually unspecified) outpatient setting (51%) or in an inpatient hospital or rehabilitation center (14%). Some studies were conducted in more than one location; 18 percent did not report study setting. Most studies were funded by a government entity (25%) or by a nonprofit (13%). Twenty-nine percent of studies did not comment on funding and 15 percent reported that no funding was received. No study reported on the use of a wheeled scooter (as opposed to a wheelchair).

The distribution of quality ratings by intervention is shown in Figure 5**.** Two-thirds of the studies were fair quality (n=113), one-fourth were poor quality (n=42), and only 8 percent (n=13) were considered good quality.

Figure 3. Overview of included studies by population and intervention[a]



[a] Studies with multiple interventions appear more than once.

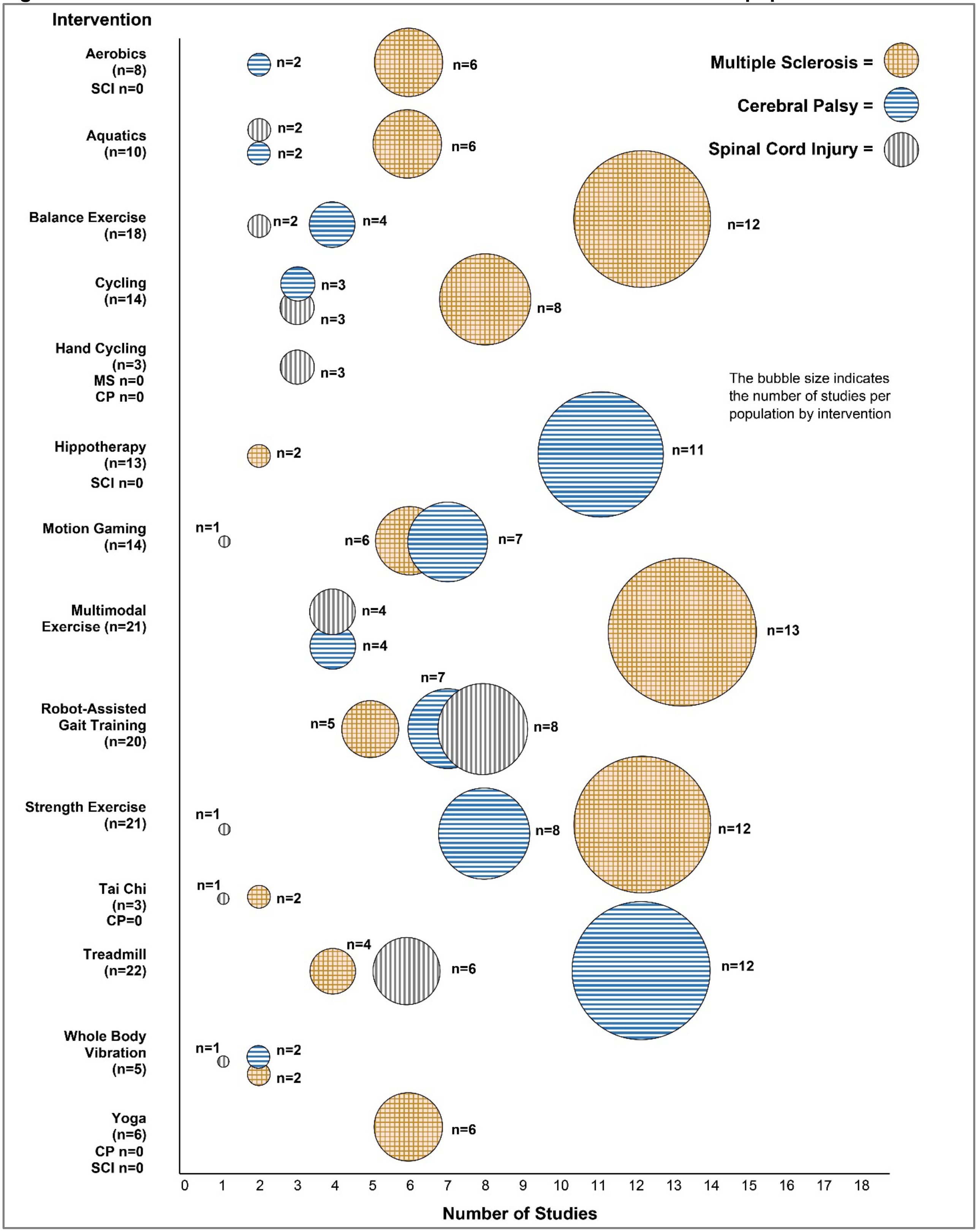
Table 4. Included studies by intervention category and population[a]

Category	Intervention	Multiple Sclerosis n=74 (85 Publications)	Cerebral Palsy n=63 (73 Publications)	Spinal Cord Injury n=31 (39 Publications)	Total Studies n=168 (197 Publications)
Aerobic Exercise	Aerobics	4 RCTs[54,59-61] 2 Quasiexperimental studies[62,63]	2 RCTs[64,65]	No studies	n=8 6 RCTs 2 Quasiexperimental studies
Aerobic Exercise	Aquatics	6 RCTs[66-72]	1 RCT[73] 1 Cohort[74]	2 RCTs[75,76]	n=10 9 RCTs 1 Cohort study
Aerobic Exercise	Cycling	7 RCTs[53,77-83] 1 Quasiexperimental study[84]	2 RCTs[85-87] 1 Quasiexperimental study[88]	1 RCT[89] 1 Cohort study[90] 1 Quasiexperimental study[91]	n=14 10 RCTs 3 Quasiexperimental studies 1 Cohort study
Aerobic Exercise	Hand Cycling	No studies	No studies	2 RCTs[89,92] 1 Cohort study[93]	n=3 studies 2 RCTs 1 Cohort study
Aerobic Exercise	Robot-Assisted Gait Training	5 RCTs[94-98]	5 RCTs[99-104] 1 Quasiexperimental study[105] 1 Cohort study[106]	8 RCTs[107-116]	n=20 studies 18 RCTs 1 Quasiexperimental study 1 Cohort study
Aerobic Exercise	Treadmill	4 RCTs[117-120]	10 RCTs[121-130] 2 Quasiexperimental studies[131,132]	6 RCTs[113,133-140]	n=22 20 RCTs 2 Quasiexperimental studies
Postural Control	Balance Exercises	12 RCTs[61,83,141-151]	1 RCT[152] 2 Quasiexperimental studies [153,154] 1 Cohort study[155]	2 RCT[156,157]	n=18 15 RCTs 2 Quasiexperimental studies 1 Cohort study
Postural Control	Hippotherapy	2 RCTs[158-160]	8 RCTs[161-168] 2 Quasiexperimental studies[169,170] 1 Cohort study[171]	No studies	n=13 studies 10 RCTs 2 Quasiexperimental studies 1 Cohort study
Postural Control	Tai Chi	1 RCT[172] 1 Quasiexperimental study[173]	No studies	1 RCT[174]	n=3 studies 2 RCTs 1 Quasiexperimental study
Postural Control	Motion Gaming	6 RCTs[51,83,151,175-177]	7 RCTs[50,178-183]	1 RCT[184]	n=14 studies 14 RCTs
Postural Control	Whole Body Vibration	2 RCTs[185,186]	2 RCTs[187,188]	1 RCT[189]	n=5 studies 5 RCTs
Postural Control	Yoga	6 RCTs[54,120,190-197]	No studies	No studies	n=6 studies 6 RCTs
Strength Exercise	Muscle Strength Exercises	11 RCTs[52,68,69,83,149,198-206] 1 Quasiexperimental study[62]	7 RCTs[207-216] 1 Quasiexperimental study[217]	1 RCT[218,219]	n=21 studies 19 RCTs 2 Quasiexperimental study
Multimodal Exercise	PRE or strength exercise plus aerobic or balance	12 RCTs[220-232] 1 Quasiexperimental study[233]	5 RCTs[234-243]	3 RCTs[244-249] 1 Cohort study[250]	n=21 studies 19 RCTs 1 Cohort study 1 Quasiexperimental study

Abbreviations: PRE = progressive resistance exercise; RCT = randomized controlled trial

[a] Studies with multiple interventions appear more than once on the table. Studies with only an intermediate outcome(s) appear in Tables 42, 43, 44, and 46.

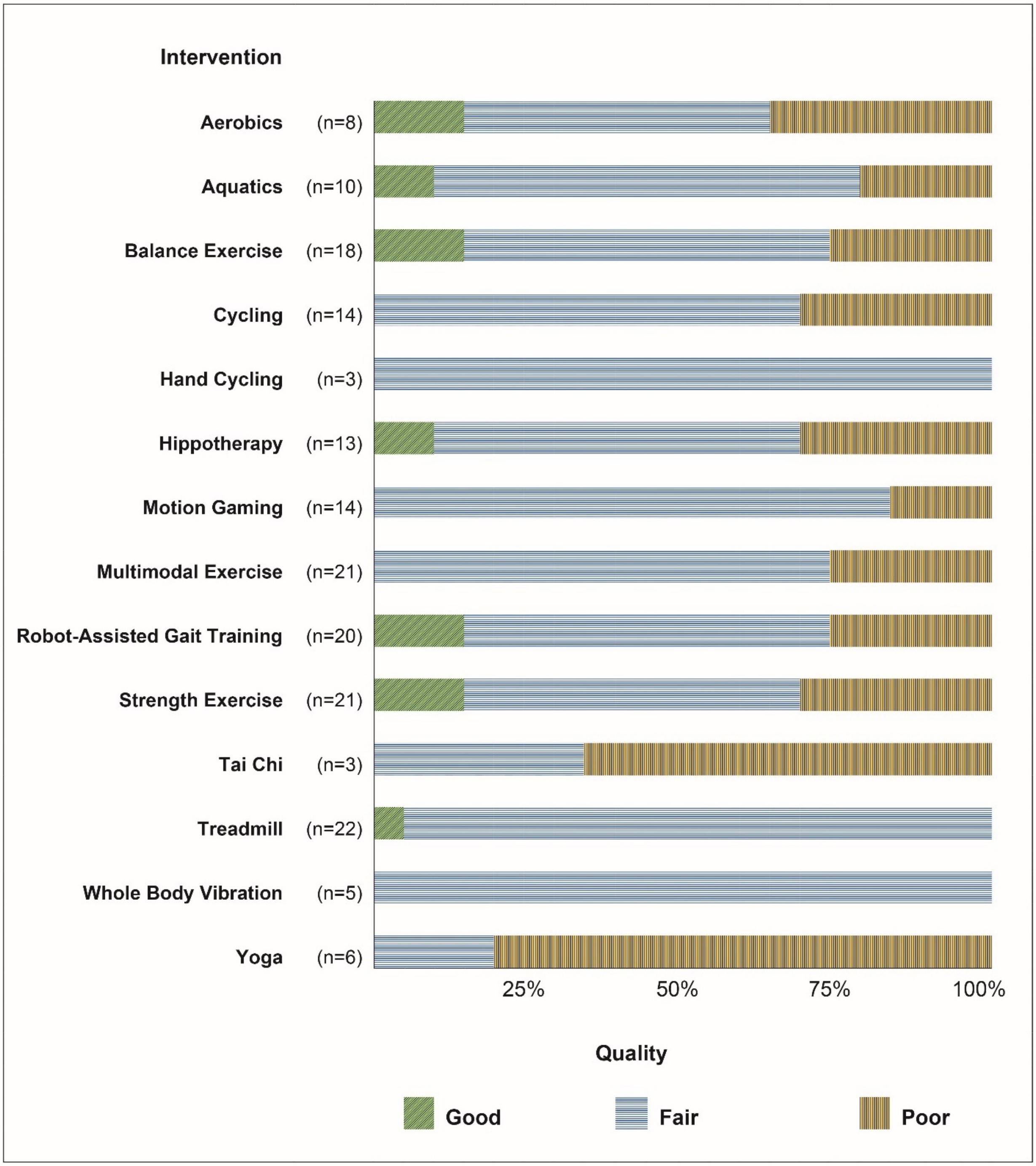
Figure 4. Wheelchair user and exercise number of studies: interventions and population[a]



Abbreviations: CP = Cerebral palsy; MS = Multiple Sclerosis; SCI = Spinal cord injury

[a] Studies with multiple interventions appear more than once.

Figure 5. Quality ratings by intervention[a]



[a] Studies with multiple interventions appear more than once.

KQ1: Prevention of Obesity, Diabetes, and Cardiovascular Conditions

This KQ identifies existing research that links physical activity to the prevention of long-term health outcomes such as myocardial infarction, stroke, and the development of diabetes or obesity, regardless of whether that study met inclusion criteria. No studies on the effects of physical activity in participants with MS, CP, or SCI reported long-term cardiovascular or long-term metabolic disease health outcomes, although some studies reported intermediate outcomes such as blood pressure, lipid profile, and blood glucose. Table 5 identifies the studies that met inclusion criteria for this review. Table 6 identifies the studies that did not meet inclusion criteria but nonetheless reported intermediate obesity, diabetes, and/or cardiovascular outcomes. The results of the included studies are discussed in KQ2. Studies not meeting inclusion criteria for this review may help identify gaps in the evidence and inform future research needs.

Table 5. Included trials with intermediate outcomes related to cardiovascular disease, diabetes, and obesity

Study (Author, Year)	Outcome Measure	Condition (MS, CP, SCI)	Intervention (Treatment Duration)	Study Inclusion/ Exclusion Criteria	Study Design
Akkurt, 2017[89]	BMI, weight, fat, lipids	SCI	Upper extremity cycling vs. general exercises (12 weeks)	Age 15-65, traumatic lesion, less than 2 hours per week of physical activity, CV disease	RCT
Faramarzi, 2020[230]	Lipids, fat	MS	Resistance exercises + endurance exercise + balance exercises + Pilates + Stretching (12 weeks)	Female, Age 18 to 50, less than 2 hours per week of physical activity, no history of cardiovascular, kidney or other chronic disease	RCT
Gervasoni, 2014[117]	Resting HR	MS	Treadmill + usual therapy vs. usual therapy (2 weeks)	Stand for 30 seconds, walk for 6 minutes/no cardiac, pulmonary, or metabolic disease	RCT
Giangregorio, 2012[134]	BMI, weight, fat	SCI	Treadmill walking with FES vs. aerobic and resistance training (16 weeks)	Traumatic incomplete SCI/no cardiac pacemaker, ulcer at harness site, orthostatic hypotension, unstable AD	RCT
Jones, 2014a/b[246,247]	BMI, weight, fat, glucose	SCI	Activity-based therapy vs. waitlist (24 weeks)	Age ≥ 18, motor incomplete SCI	RCT
Marandi, 2013[68,69]	BMI, weight, fat	MS	Aquatics vs. Pilates (12 weeks)	EDSS <4.5	RCT
Mogharnasi, 2019[219]	BMI, weight, fat, lipids	SCIk	Upper body resistance training vs. usual care (8 weeks)	Obese, paraplegic, male, traumatic lesions, could sit and maintain upper body balance/no braces, crutches or walkers	RCT
Sandroff, 2017[221]	BMI, weight, fat	MS	Resistance + aerobics + balance vs. toning and stretching (24 weeks)	Age 18-64, EDSS 4.0-6.0, engaging in low level of physical activity, low risk for exercise contraindication	RCT

Study (Author, Year)	Outcome Measure	Condition (MS, CP, SCI)	Intervention (Treatment Duration)	Study Inclusion/ Exclusion Criteria	Study Design
Slaman, 2014[235]	BMI, weight, fat, lipids	CP	Strength + aerobic training + counseling on physical activity and sports participation vs. usual care (12 weeks)	Age 16-24, GMFCS I-IV, spastic CP/no disabilities other than CP that affect physical activity, contraindications to maximal exercise, severe cognitive disorder	RCT
Totosy de Zepetnek, 2015[249]	Resting BP, HR, HbA1c, lipids, BMI	SCI	Progressive resistance + aerobic training (16 weeks)	Age 18-65, no progressive loss of neurologic function within past 6 months	RCT
Wens, 2015[224]	Resting HR, BMI, weight, fat, glucose	MS	Strength + high-intensity interval training vs. strength + high-intensity continuous aerobic training vs. sedentary control (12 weeks)	Age ≥18 years/no diabetes or other chronic disease (CV, pulmonary, and/or renal)	RCT

Abbreviations: AD = autonomic dysreflexia; BMI = body mass index; BP = blood pressure; CP = cerebral palsy; CV = cardiovascular; EDSS = Expanded Disability Status Scale; FES = functional electrical stimulation; GMFCS = Gross Motor Function Classification System; HbA1c = hemoglobin A1c; HR = heart rate; MS = multiple sclerosis; RCT = randomized controlled trial; SCI = spinal cord injury

Table 6. Studies with intermediate outcomes related to cardiovascular disease, diabetes, and obesity that did not meet inclusion criteria

Study (Author, Year)	Outcome Measure	Condition (MS, CP, SCI)	Intervention (Treatment Duration)	Study Inclusion/ Exclusion Criteria	Study Design
Brochetti, 2018[251]	Weight, waist circumference	SCI	Weight management program: working on healthy eating, exercise and lifestyle (12 weeks)	1 year post-SCI with chronic weight issue or obesity diagnosis	Pre-Post
de Groot, 2018[252]	Hip circumference, fat	SCI	Competitive self-guided training for Dutch cycling race HandbikeBattle (12 weeks)	Passed medical screening; no contraindications to exercise	Pre-Post
de Rossi, 2014[253]	LV function	SCI	None	Tetraplegic rugby players; paraplegic basketball players; sedentary SCI; no diabetes, smoking, CV or pulmonary disease, no cancer, no hypertension or hyperlipidemia	Cross-sectional
Gibbons, 2016[254,255] 2 studies	Cardiac structure and function	SCI	FES rowing: FES trained vs. untrained FES rowing: FES naïve (length varied based on progression)	Age 26-56, at least 12 months post-SCI between C4 and T10, ASIA A or B, otherwise healthy; FES trained and non-FES trained	Cross-sectional Pre-Post
Hubli, 2014[256]	Arterial stiffness, BP, HR	SCI	None	Elite hand cyclists; nonathletes	Cross-sectional

Study (Author, Year)	Outcome Measure	Condition (MS, CP, SCI)	Intervention (Treatment Duration)	Study Inclusion/ Exclusion Criteria	Study Design
Jorissen, 2018[257]	Lipids	MS	Medium vs. high-intensity CV training (12 weeks)	No hyperlipidemia, CV disease, diabetes, cholesterol modifying drugs	RCT
Keytsman, 2017[258]	Glucose, HOMA, fat, BP, lipids	MS	High-intensity interval and resistance training (12 weeks)	Age ≥ 18; No EDSS >6	Pre-Post
Lauglo, 2016[259]	Weight, BMI, fat	CP	High-intensity walking or running on treadmill (6 to 12 weeks)	Age 10-17, GMFCS I-IV	Pre-Post
Magnani, 2016[260]	Hemo-dynamic data	MS	Aerobic and strength training vs. no exercise control (6 months)	Age 18-65; no chronic cardio-pulmonary diseases	RCT
Myers, 2012[261]	Weight, HOMA	SCI	Visits by dietitian, physical therapist, exercise physiologist (2 years)	Male veteran at high risk for CVD, ≥ 20% 10 year risk of CVD; no CVD	Pre-Post
Zabay Neiro, 2018[262]	BMI, BP	MS	Walking with classes on healthy diet, rest, and physical activity vs. usual care (12 weeks)	EDSS score < 6.0	RCT
Orban, 2019[263]	Fat	MS	Aerobic exercise vs. guided stretching control (8 weeks)	Age 18-65, RRMS, fully ambulatory; no uncontrolled CV or pulmonary disease	Matched cohort

Abbreviations: ASIA = American Spinal Injury Association Impairment Scale; BMI = body mass index; BP = blood pressure; CV = cardiovascular; CVD = cardiovascular disease; EDSS = Expanded Disability Status Scale; FES = functional electrical stimulation; GMFCS = Gross Motor Function Classification System; HR = heart rate; HOMA = homeostatic model assessment; LV = left ventricular function; MS = multiple sclerosis; RCT = randomized controlled trial; RRMS = relapsing-remitting multiple sclerosis; SCI = spinal cord injury

KQ1a: Interventions

There is no evidence for any intervention studied on the prevention of cardiovascular conditions, diabetes, or obesity. Interventions paired with relevant intermediate outcomes of cardiac structure and function, heart rate, blood pressure, lipid profile, glucose levels or metabolism, body weight, body mass index (BMI), fat mass, or other measures of body composition are numerous. These interventions include aerobic exercise (e.g., aerobic exercises, treadmill walking or running, cycling, and aquatics), strength exercise (e.g., resistance training and Pilates), and postural control training. Physical activity interventions include multimodal therapies (e.g., strength plus aerobic training and/or balance exercises), training at different levels of effort (e.g., high-intensity interval and resistance training and medium-intensity aerobic training), and training with a guidance component (e.g., walking, with classes on healthy diet, rest, and physical activity). Interventions have also been self-guided, focused on weight management, or did not involve a specified physical activity (e.g., intervention focused on visits by exercise professionals plus a dietitian).

KQ1b: Outcomes

Only intermediate outcomes have been studied. Studies have evaluated blood pressure, heart rate, blood sugar, homeostatic model assessment (HOMA) (an estimate of insulin resistance), lipid profile, body weight, BMI, fat mass, percent body fat, waist and hip circumference, echocardiographic images of cardiac structure and function, measures of central arterial stiffness,

systemic vascular resistance, and other hemodynamic variables (e.g., stroke volume and ventricular filling rate).

KQ1c: Study Inclusion/Exclusion Criteria

Most studies in MS and SCI, when an age was specified, required participants to be 18 years or older (Tables 5 and 6). One study required veterans to be male[261] and another required participants to be female.[230] Two studies enrolled obese participants.[146,219] Several studies limited participants to those without known cardiometabolic disease. Sometimes study eligibility parameters were placed around degree of impairment (EDSS <6, wheelchair use only, GMFCS I-IV). Three studies enrolled elite athletes.[252,253,256] Several studies in SCI enrolled only participants with traumatic SCI (vs. atraumatic SCI)[89,134,219] or required American Spinal Injury Association Impairment Scale (ASIA) scores of A or B.[254,255]

KQ1d: Research Methodologies

Comparison and control groups of studies that assess intermediate outcomes for cardiovascular conditions, diabetes, and obesity have varied. The most frequent control group was usual care and no exercise/waitlist control. Other comparison groups included general exercise, aerobic plus resistance training, functional electrical stimulation (FES)-untrained and FES-naïve rowing. One study compared aquatics with Pilates;[68,69] another compared strength plus high-intensity interval training with strength plus high-intensity continuous aerobic training.[224] The duration of the intervention was most often 12 weeks (53%), which was also the median treatment duration (range 2 weeks to 2 years). The research setting was rarely specified in study publications.

KQ2: Physical Activity Interventions

This KQ presents the results of included studies subdivided by intervention categories. These include results for aerobic exercise (aerobics, aquatics, cycling, hand cycling, RAGT, and treadmill), postural control interventions (balance exercise, hippotherapy, Tai Chi, whole body vibration [WBV], and yoga), strength interventions (muscle strength exercises), and multimodal interventions (progressive resistance or strengthening exercise combined with aerobic or postural control interventions). Results for interventions with enough data to analyze outcomes independent of population or intervention category are also provided.

Aerobic Exercise Interventions

Aerobic exercise is exercise that raises heart rate and blood pressure through cardiovascular conditioning. Examples of aerobic exercise include running, fast walking, cycling, swimming laps, group exercise classes like Zumba®, fast sports like basketball, soccer, lacrosse, or football, and certain types of dance with a fast rhythm such a mambo, east-coast swing, or Viennese waltz.

Aerobics

Some aerobic programs incorporate music as a fitness motivator or use cadence to help participants keep in time or rhythm. Two dance programs met inclusion criteria and are

discussed below. This section also includes aerobic exercise studies that did not solely involve use of a treadmill, robot assistance, cycling, or a swimming pool, as studies employing these methods are presented in other sections under aerobic exercise. One study in this section that did not fit neatly into another section involved used of a treadmill, cycling, and/or walking/jogging as the aerobic activity of participant choice.[61]

Key Points

- Two fair-quality RCTs, one in participants with MS and one in participants with CP, provided evidence that function improved with dance compared with controls (SOE: low).
- One poor- and one fair-quality MS trial found aerobic exercise associated with improved sleep in pooled analysis (SOE: low).
- Evidence was insufficient for improvement in function with aerobic exercises not centered on music (SOE: insufficient).

Detailed Synthesis

One good-quality RCT (n=42),[65] four fair-quality RCTs (n=164),[54,59,61,64] one poor-quality RCT (n=30)[60] and two poor-quality, nonrandomized, quasiexperimental studies (n=67)[62,63] (total n=303) evaluated aerobic exercise versus no treatment,[54] usual care,[63,65] attention control,[61] traditional kinesiotherapy exercises,[64] home exercises,[59,60] and pilates.[62] Types of aerobic exercise included movement to music or dance,[54,64] and aerobic exercises, running,[65] stair stepping,[60] or calisthenics.[59,62,63] One RCT allowed participants to either walk or jog on or off a treadmill or to use an exercise bicycle for aerobic activity.[61] Study quality ratings were downgraded due to unclear methods of randomization and concealment of the allocation, differences between randomized groups based on prognostic characteristics, and high attrition.

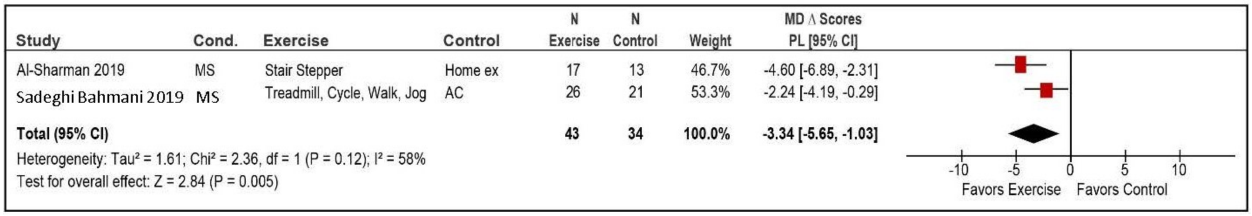
Aerobics—Multiple Sclerosis

Six studies with durations of 6,[60,63] 8,[59,61,62] and 12 weeks[54,59] enrolled 235 participants with MS (Table 7). The mean participant age across trials ranged from 35.5 to 48.5 years and the study proportion female ranged from 50 to 100 percent. Only one trial reported race and was 47.5 percent nonwhite.[54] No trial described the participant's degree of ambulation or need for wheelchair. Mean EDSS scores ranged from 2.0 to 3.1.

One fair-quality RCT (n=55) in MS patients found improved function with movement to music that involved three 60-minute sessions per week for 36 sessions and targeted strength, cardiorespiratory endurance, and balance.[54] Each session was choreographed and led by a dance instructor and accompanied by music. Outcomes that demonstrated improvement were TUG and 6MWT, although neither Movement to Music nor waitlist controls showed statistically significant improvement on 5 Times Sit-to-Stand. Average attendance was 53.7 percent with a mean of seven make-up classes offered.

Two RCTs (n=77) provided low-strength evidence of improved pooled sleep scores on the Insomnia Sleep Index (mean difference [MD] –3.34, 95% CI 5.65 to 1.03, I^2=58%) with aerobic exercise compared with home exercise or attention control[60,61] (Figure 6). One trial also reported improved sleep time.[60]

Figure 6. Insomnia Sleep Index in multiple sclerosis trials



Abbreviatons: Δ = change; AC = attention control; CI = confidence interval; MD = mean difference; MS = multiple sclerosis; PL = profile likelihood

One trial[61] and the two quasiexperimental studies found no clear evidence of differences between aerobic exercise and comparisons groups on function, balance, or quality of life.[61-63]

One study reported that adverse events in the Movement to Music group were one each muscle strain, stress fracture, and knee pain, compared with none reported in the control group.[54] The remaining studies did not address adverse events or harms.

Table 7. Aerobic exercise in multiple sclerosis

Author, Year Intervention Study Design Study Quality	**Intervention and Comparison**	**Population**	**Results**
Al-Sharman, 2019[60] Aerobics RCT Poor	A. Moderate-intensity exercise with stair stepper, 18 sessions over 6 weeks (n=17) B. Home exercises (n=13)	A vs. B Age: 39 vs. 32 Female: 76% vs. 77% EDSS: 2.1 vs. 1.9	A vs. B, mean (SD), p-value is between groups: PSQI: 8.0 (3.8) to 4.6 (2.3) vs. 8.9 (4.3) to 7.1 (3.2), p<0.001 ISI: 12.8 (5.3) to 6.6 (4.08) vs. 10.3 (3.3) to 8.7 (5.1), p=0.04 Total Sleep Time: 333.38 (84.6) to 372.4 (59.4) vs. 325.9 (84.5) to 320 (54), p=0.05
Aydin, 2014[59] Aerobics RCT Fair	A. Callisthenic exercises (in clinic): 60 sessions, over 12 weeks, (n=16) B. Callisthenic exercises (home-based): 60 sessions, over 12 weeks, (n=20)	A vs. B Age: 32.6 vs. 33 Female: 56% vs. 55% EDSS: 3.6 vs. 3.4	A vs. B, mean (SD) 10MWT: 10.81 (2.15) vs. 9.95 (1.92), p=0.211 (baseline) 9.47 (1.56) vs. 9.02 (1.78), p=0.386 (postintervention) Pre-post exercise intra-group comparison: Difference1.34 (1.26) vs. 0.93 (1.12), p=0.442 MusiQoL: 63.69 (17.00) vs. 59.75 (14.06), p=0.293 (baseline) 76.00 (18.81) vs. 69.00 (15.11), p= 0.119 (postintervention) Pre-post exercise intra-group comparison: Difference12.31 (7.45) vs. 9.25 (6.99), p=0.146 BBS: 47.56 (6.57) vs. 48.95 (5.38) (baseline) 50.94 (4.97) vs. 50.40 (5.27) (postintervention), p=0.031
Kara, 2017[62] Aerobics Quasiexperimental Poor	A. Aerobic exercise 16 sessions over 8 weeks (n=28) B. Pilates 16 sessions over 8 weeks (n=9)	A vs. B Age: 43 vs. 50 Female: 65% vs. 67% EDSS: 3.2 vs. 2.85	A vs. B mean difference between groups: TUG right: –0.47, 95% CI –2.98 to 2.04, p=0.71 TUG left: –3.07, 95% CI –6.34 to 0.20), p=0.07 BBS: –0.67, 95% CI –10.56 to 9.22, p=0.89

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Keser, 2011[63] Aerobic exercise Quasiexperimental Poor	A. Calisthenics, 18 sessions over 6 weeks (n=15) B. Neuro-rehabilitation 18 sessions over 6 weeks (n=15)	A vs. B Age: 36 vs. 35 Female: 53% vs. 47% EDSS: 2.9 vs. 2.8	A vs. B, mean change, p=between groups: MSFC: –0.002 (0.44) vs. 0.02 (0.23), p>0.05 SF-36: 0.20 (5.67) vs. 1.73 (7.75), p>0.05 BBS: –1.73 (3.03) vs. –1.80 (2.67), p>0.05
Sadeghi Bahmani, 2019[61] Aerobics RCT Fair	A. Endurance training (treadmill, cycling, walking, jogging), 24 sessions over 8 weeks (n=26) B. Attention control, 24 sessions over 8 weeks (n=21)	A vs. B Age: 38 vs. 38 Female: 100% EDSS: 2.46 vs. 2.02	A vs. B, mean (SD), p=between groups: EDSS: 2.46 (1.50) to 2.27 (1.64) vs. 2.02 (1.84) to 1.98 (1.70), p>0.05 ISI: 11.62 (5.23) to 8.81 (5.41) vs. 1.71 (5.43) to 11.14 (5.39), p>0.05
Young, 2019[54] Aerobic exercise RCT Fair	A. Movement to Music, 36 sessions over 12 weeks (n=27) B. Waitlist control (n=28)	A vs. B Age: 50 vs. 47 Female: 81% vs. 86% White: 44 vs. 61% PDDS: PDDS 0: 30% vs. 21% PDDS 3: 15% vs. 14% PDDS 6: 11% vs. 11%	A vs. B mean difference between groups: TUG: –1.89, 95% CI –3.30 to –0.48, p=0.01 6MWT: 40.98, 95% CI 2.21 to 79.75, p=0.04 5x Sit-to-Stand: –1.00, 95% CI –2.58 to 0.55, p=0.38

Abbreviations: 5x = five times; 6MWT = 6-Minute Walk Test; 10MWT = 10-Minute Walk Test; BMI = body mass index; BBS ISI = Insomnia Severity Index; MusiQoL = Multiple Sclerosis International Quality of Life Scale; PSQI = Pittsburgh Sleep Quality Index; SF-36; Short Form; MSFC = Multiple Sclerosis Functional Composite; n= number; PDDS = Patient Determined Disease Steps; RCT = randomized controlled trial; SD = standard deviation; TUG = Timed Up and Go Test

Aerobics—Cerebral Palsy

One good-quality trial found no improvement in running speed or mobility with a running program compared with usual care in adolescents (mean age 12 years, n=42) with CP.[65] All adolescents except one had scores on the Gross Motor Classification System of I or II. Changes in walking measures were not assessed (Table 8).

Another trial[64] enrolled young adult participants (mean age 17.5 years, n=26) with CP. Fifty-eight percent were female, and race was not reported. The proportions who could ambulate well or who used a wheelchair part time were also not reported. However, mean scores on the International Classification of Functioning, Disability and Health (ICF) indicated a severe to a complete problem walking a long distance such as a kilometer.

Dance, in this trial, involved 24 one-hour sessions that covered range of motion, motor coordination, space-time orientation, temporal coordination, proprioception, and skill and agility. Kinesiotherapy exercises consisted of range of motion, motor coordination, space-time orientation, proprioception, and skill and agility. Dance was conducted in a space with parallel bars, mirror, and sound equipment whereas the kinesiotherapy exercises were conducted as part of physical therapy (PT). Dance was associated with an improvement in function, disability, and health as measured by the Functional Independence Measure (FIM) and the ICF compared with traditional kinesiotherapy exercises. Harms and adverse events were not addressed.

Table 8. Aerobic exercise in cerebral palsy

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Gibson, 2018[65] Aerobics RCT Good	A. Running and running exercises, 48 sessions over 12 weeks (n=21) B. Usual care (n=21)	A vs. B Age: 12.4 vs. 12.5 Female: 33% vs. 38% GMFCS I: 57% vs. 60% GMFCS II: 38% vs. 40% GMFCS III: 5% vs. 0%	A vs. B, mean difference between groups: Shuttle Run Test (min): 0.9, 95% CI –0.3 to 2.2, p=0.142 HiMat: 0.8, 95% CI –2.7 to 4.3, p=0.651 10X5 sprint (sec): –1.3, 95% CI –5.4 to 2.8, p=0.535
Teixeira-Machado, 2018[64] Aerobic exercise RCT Fair	A. Dance exercise 24 sessions over 12 weeks (n=13) B. Kinesiotherapy exercises 24 sessions over 12 weeks (n=13)	A vs. B Age: 18 vs. 17.07 Female: 54% vs. 62% GMFCS II: 46% vs. 23% GMFCS III: 23% vs. 38% GMFCS IV: 23% vs. 31% GMFCS V: 8% vs. 8%	A vs. B mean change scores: FIM: 1.7 vs. 0.03, p<0.001 ICF: –44.56 vs. 14.90, p<0.001

Abbreviations: FIM = Functional Independence Measure; GMFCS = Gross Motor Function Classification System; HiMAT = High-level Mobility Assessment Tool; ICF = International Classification of Functioning; RCT= randomized controlled trial

Both trials that involved dancing or dance moves in participants with MS[54] or CP[64] found improvement in functioning with dancing (SOE: low), whereas the two poor-quality, nonrandomized studies[62,63] found no evidence of improvement in function with aerobic exercises.

Aerobics—Spinal Cord Injury

No studies were identified.

Aquatics

Aquatic exercise has advantages of providing body weight support for the exerciser while also increasing resistance against limb movement. Participants may be kept upright during aquatic exercise with the use of flotation devices.

Key Points

- Balance may be improved with aquatic exercises when compared with usual care in adults with MS (SOE: low).
- Evidence was too limited to draw conclusions about aquatic exercise for those with CP (SOE: insufficient).
- There were no studies of aquatics in SCI.

Detailed Synthesis

Five RCTs[66-69,71,73] and one cohort study[74] of aquatic exercise met inclusion criteria (n=231). These included three RCTs[66-69] and one cohort study[74] of aquatic exercise versus usual care and one RCT of aquatic exercise compared with cycling and strength exercises.[73] One trial met criteria for good quality,[71] one RCT was rated poor quality,[68,69] and the remainder were rated fair quality.[66,67,73,74] Trials were downgraded due to unclear randomization and concealment of the allocation, groups not similar at baseline on prognostic variables, unclear blinding of outcome

assessors, and lack of intent-to-treat analysis. The most frequently reported outcomes were related to function (e.g., GMFM, Wee-Functional Independence Measure for children [WeeFIM], 6MWT).

Aquatics—Multiple Sclerosis

Four trials (n=175)[66-69,71] enrolled participants with MS (Table 9). The mean age of participants ranged from 19 to 50 years; three trials enrolled only female participants and the fourth had predominately female enrollees.[71] Race was not reported in these trials, but three studies took place in Iran and one in Spain.[71] In three trials enrolled participants could ambulate at least 100 meters overground, but in one trial most participants needed consistent assistance to walk from 5 meters to 100 meters.[71]

Table 9. Aquatic exercise in multiple sclerosis

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Castro-Sanchez, 2012[71] Aerobic Exercise RCT Good	A. Ai-Chi aqua therapy with Tai-Chi music, 40 sessions over 20 weeks (n=36) B. Relaxation exercises on exercise mat without music, 40 sessions over 20 weeks (n=37)	A vs. B Age: 46 vs. 50 Female: 72% vs. 65% EDSS: 6.3 vs. 5.9 PPMS: 17% vs. 24% SPMS: 25% vs. 32%	A vs. B, median (SD), p-value=between groups: MSIS-29 Physical: 48 (15.91) to 41 (12.37) vs. 46 (18.34) to 45 (17.14), p=0.014 MSIS-29 Psychological: 34 (29.47) to 21 (15.73) vs. 30 (23.53) to 25 (19.36), p=0.023 Barthel Index: 91 (7.12) to 86 (9.23) vs. 87 (10.34) to 88 (8.92), p>0.05 Differences in MSIS-29 maintained at 30 weeks
Kargarfard, 2018[66] Aerobic Exercise RCT Fair	A. Aquatic exercise, 24 sessions over 8 weeks (n=17) B. Waitlist control group (n=15)	A vs. B Age: 36.5 vs. 36.2 Female: 100% EDSS 3.4 vs. 3.7	A vs. B, mean change scores: 6MWT: –52 vs. 29, p<0.001 Sit to Stand: 4.2 vs. –5.9, p<0.001 BBS: –1.6 vs. 2.1, p<0.001
Kooshiar, 2015[67] Aerobic Exercise RCT Fair	A. Aquatic exercise, 24 sessions over 8 weeks (n=20) B. Usual care (n=20)	A vs. B Age: 29.24 (<46 years) Female: 100% EDSS: 2.5 RRMS: 75.7% PPMS: 16.2% SPMS: 8.1%	A vs. B, mean change scores: MQLIM: –16.93 vs. –1.04, p<0.001
Marandi, 2013[68,69] Aerobic Exercise RCT Poor	A. Aquatics: 36 sessions over 12 weeks (n=15) B. Usual care (n=15)	A vs. B Age: Unclear Female: 100% Ambulatory: 100% EDSS: <4.5	A vs. B, Six Spot Step Test: Adjusted mean difference between groups: Right leg dynamic balance: –5.88 (SE 1.4), p<0.001 Left leg dynamic balance: –6.23 (SE 1.2), p<0.001

Abbreviations: 6MWT=6-Minute Walk Test; BBS=Berg Balance Scale; EDSS = Expanded Disability Status Scale; MQLIM=Multicultural Quality of Life Index; MSIS-29 = Multiple Sclerosis Impact Scale; PPMS = primary progressive multiple sclerosis; RCT = randomized controlled trial; RRMS = relapsing-remitting multiple sclerosis; SCI = spinal cord injury; SPMS = secondary progressive multiple sclerosis; SE = standard error

Two trials found low-strength evidence for improved balance with aquatic exercises compared with usual care or attention control,[66,68] as measured with the Berg Balance Scale, the Six Spot Step test, and dynamic balance.

The trial rated good quality found low-strength evidence for improvement in activities of daily living (ADL) with aquatic exercises compared with relaxation exercises out of water (on mat)[71] Scores on the Multiple Sclerosis Impact Scale-29 (MSIS-29) (physical and psychological) were better with Ai-Chi aqua therapy and the differences were maintained at 30 weeks (10 weeks postintervention), while scores on the Barthel Index favored aquatics, but the difference did not reach statistical significance.[71]

Of the Iranian trials, one found significant improvement with aquatic exercise in the 6MWT and Sit to Stand compared with usual care (p<0.001 for both outcomes)[66] and another trial found significant improvement in quality of life assessed with the Multicultural Quality of Life Index (MQLIM) compared with usual care (p<0.001).[67] No study addressed harms or adverse events.

Two additional trials of aquatics report depression outcomes and are found in table 40, KQ2a.[70,72]

Aquatics—Cerebral Palsy

One RCT (n=32)[73] and one cohort study (n=24)[74] enrolled children and adolescents with CP (Table 10). The mean age of participants ranged from 4 to 17 years with the proportion female 47 percent. Race was not reported in these trials. Baseline EDSS scores ranged from 1 to 4. All children were able to walk short distances either with or without assist devices.

Table 10. Aquatic exercise in cerebral palsy

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Outcomes
Adar, 2017[73] Aerobic exercise RCT Fair	A. Aquatic exercise, 30 sessions over 6 weeks (n=17) B. Land-based exercise, 30 sessions over 6 weeks (n=15)	A vs. B Age:10.1 vs. 9.3 Female: 53% vs. 40% Spastic diplegia: 65% vs. 67% Hemiplegia: 35% vs. 33% GMFCS: Median 2 vs. 2	A vs. B, mean change scores: TUG: –0.13 (0.14) vs. –0.16 (0.13), p=0.664 GMFM-88: 0.05 (0.05) vs. 0.05 (0.03), p=0.451 WeeFIM motor: 0.04 (0.04) vs. 0.06 (0.06),p=0.860 WeeFIM total: –0.13 (0.14) vs. –0.16 (0.13), p=0.287
Lai, 2015[74] Taiwan Aerobic exercise Cohort study Fair	A. Aquatic therapy, 24 sessions over 12 weeks, rehab exercises, 24-36 sessions over 12 weeks (n=11) B. Rehab exercises, 24-36 sessions over 12 weeks (n=13)	A vs. B Age: 7.6 vs. 6.6 Female: 64% vs.31% Diplegia: 27% vs. 46% Quadriplegia 45% vs. 31% Hemiplegia 27% vs. 23% GMFCS: 2.7 vs. 2.6	A vs. B, mean difference between groups: GMFM-66: 5.0 vs. 0.7, p=0.007 CPQoL scales for Social, Functioning, Participation, Emotional, Access, Pain and Disability, and Family Health: All NS

Abbreviations: CPQoL = Cerebral Palsy Quality of Life scale; FIM = Functional Independence Measure; GMFCS = Gross Motor Function Classification System; GMFM-66 = Gross Motor Function Measure 66; GMFM-88 = Gross Motor Function Measure 88; NS = not significant; RCT = randomized control trial; TUG = Timed Up and Go Test; WeeFIM = Wee-Functional Independence Measure for children

One trial in children with CP found no differences between 6 weeks of aquatic therapy and land-based exercises on the functional outcomes of TUG and GMFM-88 tests.[73] One cohort

study that enrolled children with CP compared aquatic therapy plus traditional rehabilitation over 12 weeks found a significant effect on GMFM-66 scores (p=0.007) compared with traditional rehabilitation, but did not show a significant effect on quality of life as measured with the Cerebral Palsy Quality of Life (CPQoL) scales.[74] Harms and adverse events were not addressed.

Aquatics—Spinal Cord Injury

No studies were identified.

Cycling

Stationary cycling has been studied as means for aerobic or endurance training. This exercise method has multiple attributes, including relatively easy access in a study setting, and the potential to be used as an exercise method at home. Another advantage of cycling is the possibility of exercising the lower and/or upper extremities. Two SCI trials[89,93] utilized upper extremity cycling, and one MS trial[53] used both upper and lower extremity cycling. All other trials utilized lower extremity cycling.

Key Points

- There was no clear benefit in function (primarily walking ability) versus control interventions with leg cycling in participants with MS (SOE: low); evidence on quality of life was too limited to draw conclusions (SOE: insufficient).
- Leg cycling interventions were associated with improvement in function in participants with CP over control interventions (SOE: low); evidence for quality of life was lacking (SOE: insufficient).
- Evidence for function and quality of life in participants with SCI was limited (SOE: insufficient).
- Evidence for hand cycling was insufficient.

Detailed Synthesis

Ten RCTs,[53,77-83,85-87,89] one quasiexperimental nonrandomized study,[84] and one cohort study[90] (n=596) involving cycling interventions met inclusion criteria. These included five RCTs[53,77,83,85-87] and one quasiexperimental study[84] of cycling versus usual care; one RCT,[89] one cohort study,[90] and one quasiexperimental study[84] of cycling versus active rehabilitation; one RCT of cycling using visual feedback compared with home exercise;[81] one RCT of cycling versus MS-nurse consultations;[78] one trial of cycling versus vestibular rehabilitation versus wait-list control;[79,80] and one trial of intermittent versus static cycling.[82]

Seven RCTs[53,77-82] and one quasiexperimental trial[84] enrolled participants with MS (Table 11), two RCTs[85-87] were conducted in participants with CP (Table 12), and one RCT[89] and one cohort study[90] were conducted in participants with SCI (Table 13). Two RCTs and one cohort study was rated poor quality and the remaining trials were rated fair quality. Methodological limitations for downgrading studies included unclear methods of the allocation, baseline differences in prognostic variables between randomized arms, and high attrition. The most frequently reported outcomes were related to function (e.g., GMFM, 6MWT) and quality of life (e.g., SF-36, World Health Organization Quality of Life scale [WHOQOL]).

Cycling—Multiple Sclerosis

Seven RCTs[53,77,78,80-83] and one quasiexperimental study[84] (n=459) enrolled participants with MS (Table 11). Mean ages of participants in the trials ranged from 32 to 52 years with a range of 58 to 93 percent female. Race was not reported in these trials. All studies enrolled participants who could ambulate with assistance or better.

Table 11. Cycling exercise in multiple sclerosis

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Baquet, 2018[77] Aerobic exercise RCT Fair	A. Bicycle ergometry, 24-36 sessions over 12 weeks (n=34) B. Waitlist control group (n=34)	A vs. B Age: 38.2 vs. 39.6 Female: 62% vs. 74% EDSS: 1.7 vs. 1.8 RRMS: 100%	A vs. B mean difference between groups: 6MWT: 4.0, 95% CI –36.5 to 44.5, p=0.85 25 foot walk: –0.1, 95% CI –0.4 to 0.2, p=0.49 MSWS-12: –0.3, 95% CI –2.1 to 1.6, p=0.78 HAQUAMS: –0.4, 95% CI –4.5 to 3.7, p=0.84
Collett, 2011[82] Aerobic exercise RCT Poor	A. Combined intermittent and continuous static cycling, 24 sessions over 12 weeks (n=20) B. Intermittent static cycling, 24 sessions over 12 weeks (n=21) C. Continuous static cycling, 24 sessions over 12 weeks (n=20)	A vs. B vs. C Age: 55 vs. 50 vs. 52 Female: 53% vs. 78% vs. 80% Ambulatory: 100%	Change postintervention: no data provided 2MWT, SF-36 total, TUG: All NS
Heine, 2017[78] Aerobic exercise RCT Fair	A. Leg cycling, 48 sessions over 16 weeks (n=43) B. MS nurse consultation, 3 consultations over 16 weeks (n=46)	A vs. B Age: 43.1 vs. 48.2 Female: 74% vs. 72% Ambulatory: 100% EDSS: 2.5 vs. 3.0 RRMS: 72% vs. 74% SPMS: 7% vs. 11% PPMS: 21% vs. 15%	A vs. B, mean difference (SE) between groups: IPA autonomy indoors: –0.11 (0.088), p=0.203 IPA family role: –0.082 (0.1222), p=0.502 IPA autonomy outdoors: –0.097 (0.125), p=0.438 IPA Social Relations: –0.138 (0.092), p=0.135 IPA Work/education: 0.225 (0.167), p=0.181
Hebert, 2011[80] Aerobic Exercise RCT Fair	A. Bicycle ergometry, 12 sessions for 6 weeks (n=12) B. Vestibular rehab (n=13) C. Waitlist control (n=13)	A vs. B vs. C Age: 46.8 vs. 42.6 vs. 50.2 Female: 75% vs. 85% vs. 85% Ambulatory: 100%	Mean difference between groups: 6MWT: A vs. B: 39.1, 95% CI –105 to 183, p=1.00 A vs. C: 62.7, 95% CI –81 to 2.7, p=1.00 B vs. C: 23.6, 95% CI –117 to 165, p=1.00
Hochsprung, 2017[81] Aerobic exercise RCT Poor	A. Visual biofeedback cycling training, 12 sessions over 12 weeks plus home exercise program (n=30) B. Home exercise program (n=31)	A vs. B Female: 66% vs. 50% Ambulatory: 100% RRMS: 37% vs. 52% PPMS: 20% vs. 26% SPMS: 43% vs. 23%	A vs. B mean change scores: FAP: 3.036 (p=0.002) vs. –1.06 (p=0.289) No comparison between groups provided

Author, Year Intervention Study Design Study Quality	**Intervention and Comparison**	**Population**	**Results**
Negaresh, 2019[53] Aerobic exercise RCT Fair	A. Normal BMI cycling UE/LE, 24 sessions over 8 weeks (n=18) B. Normal BMI control (n=15) C. Overweight cycling UE/LE, 24 sessions over 8 weeks (n=17) D. Overweight control (n=13)	A vs. B vs. C vs. D Age: 31.2 vs. 29.1 vs. 32.1 vs. 2.1 Female: 64% vs. 64% vs. 64% vs. 69% EDSS: <4 RRMS: 100%	A vs. B vs. C vs. D, mean difference between groups (scores are estimates from graph): TUG: –3.8 vs. –0.1 vs. –2.5 vs. 0, p=0.001 Interaction between weight and exercise p=0.52
Niwald, 2017[84] Aerobic exercise Quasiexperimental Fair	A. Cycle ergometry, 60 sessions over 4 weeks plus 480 minutes of rehab exercises over 4 weeks (n=21) B. 480 minutes of rehab exercises 480 over 4 weeks (n=32)	A vs. B Age: 57 vs. 60 Female: 62% vs. 65% Race: NR Ambulatory: 100% EDSS: 6.33 vs. 6.20	A vs. B, mean difference between groups: EDDS: 0.01, 95% CI –0.61 to 1.29, p=0.48 WHOQOL-Bref Physical: 1.45, 95% CI –0.72 to 3.62, p=0.19 WHOQOL-Bref Psychological: 3.05, 95%CI 1.30 to 4.80 to, p=0.001 WHOQOL-Bref Social: 0.60, 95% CI –0.64 to 1.84, p=0.34 WHOQOL-Bref Environmental: 2.56, 95% CI 0.20 to 4.92, p=0.03
Tollar, 2020[83] Aerobic exercise RCT Fair	A. Stationary cycling, 25 sessions over 5 weeks (n=14) B. Usual PT, 25 sessions over 5 weeks (n=12)	A vs. B Age: 48.1 vs. 44.4 Female: 93% vs. 92% EDSS median: 5.0 vs. 5.0 RRMS: 64% vs. 67%	A vs. B, mean difference between groups: MSIS-29: –6.3 (8.07) vs. 1.0 (3.46), p=0.008 6MWT: 32.1 (44.58) vs. 6.3 (49.27), p=0.174 BBS: 2.5 (2.62) vs. –0.2 (2.62), p=0.015 EQ-5 Sum score:–1.4 (1.7) vs. 0.0 (1.13), p=0.023

Abbreviations: 2MWT = 2-Minute Walk Test; 6MWT = 6-Minute Walk Test, BBB = Berg Balance Scale; BMI = body mass index; CI = confidence interval; EDSS = Expanded Disability Status Scale; FAP = Functional Ambulation Profile; IPA = Impact on Participation and Autonomy; LE = lower extremity; MS = multiple sclerosis; MSWS-12 = Multiple Sclerosis Walking Scale-12; MSIS-29 = Multiple Sclerosis Impact Scale; HAQUAMS = Hamburg Quality of Life Questionnaire in Multiple Sclerosis questionnaire; NR = not reported; NS = not significant; PPMS = primary progressive multiple sclerosis; PT = physical therapy; RCT = randomized controlled trial; RRMS = relapsing-remitting multiple sclerosis; SE = standard error; SF-36; Short Form-36; SPMS = secondary progressive multiple sclerosis; TUG = Timed Up and Go Test; UE = upper extremity; WHOQOL = World Health Organization Quality of Life scale

These studies provided low SOE of no clear difference in function (primarily walking outcomes) between cycling and usual rehabilitation/no intervention. One fair-quality RCT did find a difference in change from baseline BMI across four groups (two intervention arms and two control arms, p=0.001), but pairwise comparisons were not provided.[53] Change in ADLs as measured with the Impact of Participation and Autonomy questionaire[80] was insufficient from which to draw conclusions as was the evidence for quality of life on the Hamburg Quality of Life Questionnaire in Multiple Sclerosis.[77] A poor-quality RCT, without a usual care/no intervention arm, found no differences between three cycling intervention groups (combined intermittent continuous static cycling vs. intermittent static cycling vs. continuous static cycling) on the SF-36, a quality of life measure, or on function outcomes (i.e., 2-Minute Walk Test [2MWT], TUG).[82]

Of the seven studies, five did not address harms or adverse events. An RCT of only active groups reported that three participants in the combined exercise group experienced adverse events (tachycardia, leg pain, and exacerbation of knee injury), while four participants in the intermittent group left the study due to adverse events (pain with cycling, exacerbation of MS

symptoms, and loss of consciousness during cycling), and no adverse events were reported in the continuous exercise group.[82] Another RCT evaluated the risk of experiencing an MS relapse in patients with relapsing-remitting MS as a potential adverse event, but found lower risk in the aerobic training group (OR [odds ratio] 0.28, 95% CI 0.10 to 0.79, p=0.016) in favor of aerobic training.[78] The remaining study reported that no participant experienced any adverse event.[53]

Cycling—Cerebral Palsy

Two cycling RCTs[85-87] (n=85) enrolled participants with CP (Table 12). Mean ages of participants were 11 years and 13.9 years in the trial and mean proportion female was 53 and 60 percent. One RCT reported the proportion of nonwhite participants as 48 percent.[85,86] One trial enrolled participants who had markedly limited or no ambulation (GMFCS IV or V)[87] and one RCT enrolled only ambulatory participants (GMFCS I-III).[85,86]

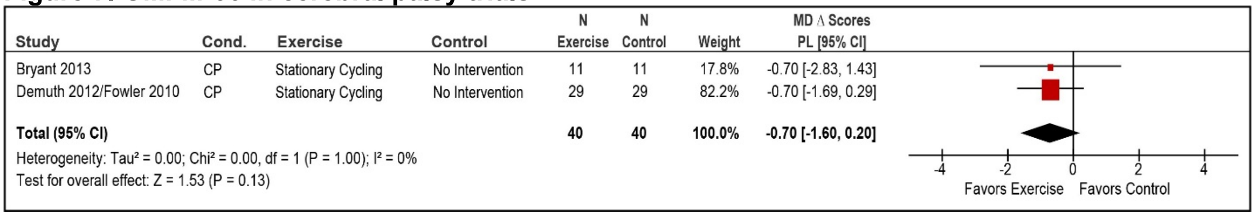
Table 12. Cycling exercise in cerebral palsy

Author, Year Intervention Study Design Study Quality	**Intervention and Comparison**	**Population**	**Results**
Bryant, 2013[87] Aerobic exercise RCT Fair	A. Static bike group, 18 sessions over 6 weeks (n=11) B: No intervention control (n=12)	A vs. B Age: 14.3 vs. 13.8 Female: 45% vs. 58% Race: NR Ambulatory: 0% Wheelchair user: 100% Bilateral CP: 100% GMFCS: 4.3 vs. 4.4	A vs. B mean difference between groups: GMFM-66: 0.70, 95% CI –1.43 to 2.83, p=0.52 GMFM-88-D: 5.4, 95% CI 1.23 to 9.57, p=0.01 GMFM-88-E: 2.3, 95% CI 0.20 to 4.40, p=0.03
Demuth, 2012[86] Fowler, 2010[85] Aerobic exercise RCT Fair	A. Stationary cycling, 30 sessions over 12 weeks (n=31) B. No intervention control (n=31)	A vs. B Age: 10.7 vs. 11.2 Female: 42% vs. 65% Race: African-American: 16% vs. 10% White: 58% vs. 48% Asian: 3% vs. 16 % Other: 23% vs. 26% Ambulatory: 100% GMFCS: 2.0 vs. 2.3	A vs. B GMFM-66: Change from baseline: 1.2, 95% CI 0.5 to 1.8 vs. 0.5, 95% CI –0.2 to 1.3, between groups p=0.23 600-Yard Walk-Run Test: Change from baseline: 5.6, 95% CI 1.6 to 9.5 vs. 2.5, 95% CI –1.1 to 6.0, p=0.24 Peds Quality of Life Total Score: Mean difference between groups: 3.5, 95% CI –2.0 to 8.8, p=0.21

Abbreviations: CI = confidence interval; CP = cerebral palsy; GMFCS = Gross Motor Function Classification System; GMFM-66 = Gross Motor Function Measure-66 items, GMFM-88 = Gross Motor Function Measure-88 items; GMFM-88-D = Gross Motor Function Measure 88 (standing); GMFM-88-E = Gross Motor Function Measure 88 (walking, running, jumping); NR = not reported; RCT = randomized controlled trial

One RCT found an improvement with cycling on the GMFM-88-D and GMFM-88-E subscales that focused on standing (D subscale) and walking, running, and jumping (E subscale).[87] Pooled analysis of GMFM-66 favored cycling over control condition, but did not reach statistical significance (MD –0.70, 95% confidence interval [CI] –1.60 to 0.20, I^2=0%)[85,87] (Figure 7). Similarly, performance on the 600-yard walk-run test favored cycling but was not significant.[85] These studies provided low-strength evidence that cycling may improve gross motor function when compared with no intervention[85] or usual care[87] in children with CP.

Figure 7. GMFM-66 in cerebral palsy trials



Abbreviations: Δ = change; CI = confidence interval; CP = cerebral palsy; GMFM-66 = Gross Motor Function Measure 66; MD = mean difference

One RCT found no statistically significant difference in quality of life between cycling and no intervention on the Pediatric Quality of Life Inventory total score (insufficient evidence).[86]

Although no overall harms or adverse events were reported by treatment group, one RCT reported that two participants withdrew from the treadmill group (one due to gastric problems and one to recurrence of hip pain).[87] The other RCT reported that there were mild adverse events (falls, soreness, muscle cramping, pain, fatigue, skin rash, colds, flu, tooth loss, headache, stomach ache, tonsillectomy) but did not specify the study group.[86]

Cycling—Spinal Cord Injury

One RCT[89] and one cohort study[90] enrolled participants (n=78) with SCI (Table 13). The mean age of participants was 35 and 36 years with 12 and 16 percent female. Racial background was not reported in these studies. Ambulatory status and wheelchair use were also not reported.

Table 13. Cycling exercise in spinal cord injury

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Akkurt, 2017[89] Aerobic exercise RCT Fair	A. Arm ergometer, 36 sessions over 12 weeks plus 120 sessions general exercises over 12 weeks (n=17) B. General exercises, 120 sessions over 12 weeks (n=16)	A vs. B Age: 33 vs. 37 Female: 5% vs. 19% Ambulatory: 41% vs. 50% Wheelchair user: 59% vs. 50% Paraplegia:100% vs. 94%	A vs. B, mean change scores: FIM: 0.5 vs. –0.5, p=1.00 CHART-sf, p>0.05 WHOQOL-Bref, p>0.05
Sadowsky, 2013[90] Aerobic exercise Cohort study Poor	A. FES cycle ergometry, 3 sessions per week over a mean of 120 weeks (n=25) B. Rehabilitation care, not specified (n=20)	A vs. B Age: 37.2 vs. 34.6 Female: 12% vs. 20% Quadriplegia: 52% vs. 75%	A vs. B, mean change scores: Total FIM: 80% vs. 60%, p<0.001 With significant improvement with FES in subscales: self-care, sphincter control, transfer, and locomotion SF-36: total and composite scores NR Significant improvement in physical function and role limit physical with FES, no difference in mental health subscales

Abbreviations: CHART = Craig Handicap and Assessment Reporting Technique; FES = functional electrical stimulation; FIM = Functional Independence Measure; NR = not reported; SF-36 = Short-Form 36; RCT = randomized controlled trial; WHOQOL = World Health Organization Quality of Life scale

One fair-quality RCT showed no significant improvement in function, quality of life, or ADL with upper extremity cycling versus general exercises in patients with SCI[89] (rated insufficient for all outcomes). One poor-quality cohort study reported that lower extremity cycling resulted in significant improvement in mean FIM total score compared with usual care, but this study has

substantial risk of bias based on study quality and nonrandomized design.[90] Harms and adverse events were not addressed in either study.

One additional trial of the reports the effects of hand cycling on asymptomatic bacteria is discussed in KQ2b.[92]

Robot-Assisted Gait Training

Robot-assisted gait training is a form of physical activity/gait training in which a motorized, computer-controlled orthotic device provides a guidance force to the lower extremities, usually coupled with body weight support, enabling a person with limited ambulation the ability to walk greater distances and with potentially increased speed and safety, without necessarily requiring physical assistance of a physical therapist or caregiver. The robotic device places the lower extremity in improved alignment and form throughout the gait cycle, which can improve gait mechanics overground after the training. RAGT's value as a form of aerobic exercise for patients with ambulation impairment may be limited by the cost and access of the device to most people with MS, CP, or SCI.

Key Points

- Evidence suggested that RAGT training may improve balance in patients with MS versus usual care (SOE: low); there was low-strength evidence of no clear benefit of RAGT on function (SOE: low).
- When compared with overground or treadmill walking, there was low-strength evidence of no clear benefit with RAGT on function, balance, or quality of life in MS (SOE: low).
- Evidence for the effectiveness of RAGT on function and balance in CP was insufficient due to the poor quality of the trials (SOE: insufficient).
- Evidence from RCTs suggested that RAGT may improve function in patients with SCI in head-to-head studies (SOE: low) but the evidence was less clear in three trials versus usual care (SOE: low); there was low-strength evidence that RAGT training may improve ADL in people with SCI (SOE: low).

Detailed Synthesis

Seventeen RCTs (n=810),[94-104,107,108,110-112,114-116] one quasiexperimental study (n=44),[105] and one cohort study[106] (n=24) evaluated RAGT interventions. These included eight RAGT studies versus usual care,[95,98,101,102,104,106,112,115,116] one versus no intervention,[114] two RCTs versus overground gait training,[107,108] and eight RCTs versus other interventions such as aquatics, task-oriented physical therapy (TOP), and nonrobotic treadmill training. Five RCTs enrolled participants with MS (Table 14), seven RCTs enrolled children and adolescents with CP (Table 15), one RCT enrolled adolescents and adults,[104] and the remaining RAGT studies were in adults, and ten RCTs were conducted in participants with SCI (Table 16).

Three studies[96-98] met criteria for good quality, eleven[94,95,99,100,103,107,108,110-112,115,116] for fair quality, and five[101,102,104-106,114] for poor quality. Studies were downgraded due to unclear methods of selection and concealment of the allocation, differences between groups in prognostic patient characteristics, and lack of intent-to-treat analysis. Almost all of the trials used the Lokomat® (manufactured by Hocoma)[264] as their RAGT device. The most frequently reported outcomes were gait parameters such as gait speed, walking endurance, and measures of overall physical function such as EDSS and GMFM.

Robot-Assisted Gait Training—Multiple Sclerosis

Five RAGT trials enrolled 252 participants with MS[94-98] (Table 13). Mean trial age of participants ranged from 42 to 56 years and the proportion female ranged from 52 to 68 percent. The length of the interventions ranged from 4 to 8 weeks, 3 to 5 sessions per week.

Participants' EDSS scores ranged from 4.0 to 7, encompassing a wide range of walking ability at baseline. One RCT[96] examined the effect of RAGT on less impaired participants with RRMS (relapsing-remitting multiple sclerosis) with EDSS of 4.0 to 5.5, indicating ability to ambulate 100 to 500 meters without aid, while the other three RCTs[94,95,97] enrolled only participants with EDSS scores between 6.0 and 7.5 (minimal ability to walk, from a few steps to 100 meters total with the use of an assistive device).

Table 14. Robot-assisted gait training in multiple sclerosis

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Calabro, 2017[96] Aerobic exercise RCT Good	A. Lokomat-Pros (RAGT + VR), 40 sessions over 8 weeks (n=20) B. Lokomat-Nanos (RAGT), 40 sessions over 8 weeks (n=20)	A vs. B Age: 44 vs. 41 Female: 65% vs. 60% EDSS: 4.40 vs. 4.75	A vs. B, mean difference between groups: TUG: –0.064, 95% CI –0.408 to 0.536, p=0.3 FIM: –0.054, 95% CI –1.73 to 2.839, p=0.5 BBS: –0.019, 95% CI –2.403 to 2.365, p=0.8
Pompa, 2017[94] Aerobic exercise RCT Fair	A. RAGT, 12 sessions over 4 weeks (n=21) B. Conventional Walking Training, 12 sessions over 4 weeks (n=22)	A vs. B Age: 47 vs. 50 Female: 48% vs. 55% PPMS: 0% vs. 13.6% EDSS: 6.62 vs. 6.50	A vs. B, mean difference between groups: 2MWT: 6.07, 95% CI –6.51 to 18.65, p=0.34 FAC: 0.66, 95% CI –0.07 to 1.39, p=0.08 Rivermead Mobility Index: 0.73, 95% CI –0.85 to 2.31, p=0.37 EDSS: 0.14, 95% CI –0.13 to 0.41, p=0.30 mBI: 3.99, 95% CI –6.69 to 14.67, p=0.46
Russo, 2018[95] Aerobic exercise RCT Fair	A. RAGT, 18 sessions over 6 weeks then 36 sessions of rehabilitation exercises over 12 weeks (n=30) B. Rehabilitation exercises, 54 sessions over 18 weeks (n=15)	A vs. B Age: 42 vs. 41 Female: 53% vs. 67%	A vs. B, mean difference between groups: TUG 6 weeks: 0.20, 95% CI –3.40 to 3.80, p=0.91 TUG 18 weeks: 0.20, 95% CI –2.90 to 3.30, p=0.90 FIM 6 weeks: –2.10, 95% CI –2.75 to –1.45, p<0.001 FIM 18 weeks: –2.20, 95% CI –2.85 to –1.55, p<0.001 TBS 6 weeks: –1.00, 95% CI –1.75 to –0.66, p<0.001 TBS 18 weeks: –0.50, 95% CI –1.10 to 0.10, p=0.10
Straudi, 2016[97] Aerobic exercise RCT Good	A. RAGT, 12 sessions over 6 weeks (n=27) B. Conventional physiotherapy, 12 sessions over 6 weeks (n=25)	A vs. B Age: 52 vs. 54 Female: 63% vs. 68% EDSS: 6.43 vs. 6.46 PPMS: 33% vs. 28% SPMS: 67% vs. 72%	A vs. B, mean change scores: TUG: 2.66 (13.79) vs. –3.96 (10.50), p=0.95 6MWT: 23.22 (32.23) vs. –0.75 (26.40), p=0.01 SF 36-PCS: 1.67 (7.74) vs. 1.84 (6.77), p=0.99 SF 36-MCS: 5.37 (9.58) vs. 1.60 (9.41), p=0.14 BBS: 3.24 (4.99) vs. 0.87 (6.45), p=0.19

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Straudi, 2019[98] Aerobic exercise RCT Good	A. RAGT, 12 sessions over 4 weeks (n=36) B. Overground walking, 12 sessions over 4 weeks (n=36)	A vs. B Age: 56 vs. 55 Female: 67% vs. 69% EDSS: 6.5 vs. 6.5 PPMS: 50% vs. 45% SPMS: 50% vs. 55%	A vs. B, mean difference between groups: 6MWT: 4, 95% CI –10 to 18, p=0.86 25FWT: 0, 95% CI –0.06 to 0.05, p=0.98 TUG: 7.8, –0.2 to 15.8, p=0.25 BBS: 0, 95% CI –2 to 2, p=0.91 MSIS-29 motor: –3, 95% CI –9 to 3, p=0.31 MSIS-29 psychological: –2, 95% CI –5 to 1, p=0.22 SF-36 PCS: –1, 95% CI –4 to 3, p=0.13 SF-36 MCS: 1, 95% CI –2 to 4, p=0.94

Abbreviations: 2MWT = 2-Minute Walk Test; 6MWT = 6-Minute Walk Test; 25FWT = 25-Foot Walk Test; BBS = Berg Balance Scale; CI = confidence interval; EDSS = Expanded Disability Status Scale; FAC = functional ambulation category; FIM = Functional Independence Measure; MSIS-29 = Multiple Sclerosis Impact Scale; PPMS = primary progressive multiple sclerosis; RAGT = robot-assisted gait training; RCT = randomized controlled trial; SF-36 = Short-Form 36; SF 36-MCS = Short-Form 36 Mental Component Summary; SF 36-PCS = Short-Form 36 Physical Component Summary; SPMS = secondary progressive multiple sclerosis; TBS = Tinetti Balance Scale; TUG = Timed Up and Go Test; VR = virtual reality

These studies indicated that use of RAGT can improve balance versus usual care without RAGT (SOE: low). There was low-strength evidence of no clear benefit of RAGT versus usual care on function as assessed with the TUG test,[95,97] while evidence for walking ability,[94,97] quality of life,[97] and ADL[94] was too limited to draw conclusions (SOE: insufficient).

One RCT enrolled participants with MS and compared RAGT with virtual reality versus RAGT alone.[96] In this RCT, there were no differences between groups on the TUG, FIM, and the BBS, indicating that virtual reality added to 40 sessions of RAGT did not improve balance, time up and go, or ADL compared with RAGT without virtual reality. However, this finding needs confirmation with other trials (SOE: insufficient).

Two head-to-head trials (n=95) compared RAGT with treadmill or overground walking[97,98] and found low-strength evidence of no clear difference between treatment groups on function, balance, or quality of life.

Four RCTs did not address harms or adverse events. One RCT reported that no participant withdrew from the study due to an adverse event.[96]

Robot-Assisted Gait Training—Cerebral Palsy

Five RAGT trials,[99-104] one quasiexperimental study,[105] and one cohort study[106] enrolled 220 participants with CP (Table 15). The trial mean age of participants ranged from 8 to 21 years (one trial did not report age but inclusion criteria were between 6 and 14 years[103]) with the mean proportion female ranging between 39 and 50 percent. GMFCS functional categories ranged from I-IV, with one study[101] enrolling only GMFCS level II participants.

Table 15. Robot-assisted gait training in cerebral palsy

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Outcomes
Aras, 2019[103] Aerobic exercise RCT Fair	A. RAGT, 20 sessions over 4 weeks (n=10) B. Partial body-weight supported treadmill training, 20 sessions over 4 weeks (n=10) C. Anti-gravity treadmill training, 20 sessions over 4 weeks (n=9)	A vs. B Age: NR Female: 40% vs. 40% vs. 33.3% GMFCS II: 90% vs. 70% vs. 88.9% Hemiplegic: 30% vs. 30% vs. 33.3%	A vs. B vs. C, mean change (SD): 6MWT: 39.6 (40.4) vs. 37.6 (20.2) vs. 48.3 (25.1), p>0.05 for all pairwise comparisons 6MWT (3-month followup): 45.2 (44.4) vs. 48.6 (37.8) vs. 58.2 (22.9), p>0.05 for all pairwise comparisons GMFM-D: 3.6 (2.5) vs. 4.6 (4.6) vs. 3.5 (2.5), p>0.05 for all pairwise comparisons GMFM-D (3-month followup): 3.6 (2.5) vs. 4.6 (4.6) vs. 3.5 (2.5), p>0.05 for all pairwise comparisons GMFM-E: 2.4 (2.0) vs. 2.6 (1.7) vs. 3.7 (1.9), p>0.05 for all pairwise comparisons GMFM-E (3-month followup): 2.6 (1.8) vs. 2.6 (1.7) vs. 3.7 (1.9), p>0.05 for all pairwise comparisons
Klobucka, 2020[104] Aerobic exercise RCT Poor	A. RAGT, 20 sessions over 4 to 6 weeks (n=21) B. Conventional therapy (n=26)	A vs. B Age: 18.3 vs. 23.4 Female: 48% vs. 39% GMFCS I: 4.8% vs. 0% GMFCS II: 14.3% vs. 15.4% GMFCS III: 42.9% vs. 46.2% GMFCS IV: 38.1% vs. 38.5% Mechanical wheelchair: 23.8% vs. 53.8% Electric wheelchair: 0% vs. 15.3%	A vs. B, mean change scores, p=between groups: Total GMFM: MD 9.43, 95% CI 6.989 to 11.891 vs. MD 0.80, 95% CI 0.154 to 1.446, p<0.001 GMFM D: MD 8.30, 95% CI 4.699 to 11.901 vs. MD 1.09, 95% CI -0.438 to 2.619, p<0.001 GMFM E: MD 9.32, 95% CI 5.329 to 13.310 vs. MD 0.53, 95% CI -0.208 to 1.268, p<0.001
Peri, 2017[105] Aerobic exercise Quasiexperimental Poor	A. RAGT plus TOP (20 sessions each over 10 weeks (n=10) B. Personalized RAGT plus TOP, 20 sessions each over 4 weeks (n=12) C. TOP 40 sessions over 10 weeks (n=10) D. RAGT 40 sessions over 10 weeks (n=12)	A vs. B vs. C vs. D Age: 6.8 vs. 10.8 vs. 9.3 vs. 8 Female: 60% vs. 42% vs. 50% vs. 50% Spastic bilateral CP: 100% Ambulatory: 100% with or without aid	A vs. B vs. C vs. D, mean (SD): 6MWT (meters, T0 to T1 to T2): 285.2 (219.2) to 300.9 (201.9) to 309.0 (214.9) vs. 222.1 (237.6) to 208.5 (252.7) to 225.0 (193.7) vs. 378.2 (182.6) to 381.7 (159.3) to 364.1 (179.8) vs. 324.4 (110.2) to 345.0 (92.4) to 346.5 (84.3) GMFM-66: 66.0 (12.1) to 67.0 (12.7) to 69.2 (10.4) vs. 66.2 (6.3) to 67.1 (6.2) to 68.1 (6.3) vs. 66.4 (13.4) to 68.2 (11.9) to 69.2 (9.7) vs. 68.5 (8.8) to 68.9 (8.6) to 69.2 (9.7) No differences between groups

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Outcomes
Yazici, 2019[106] Aerobic exercise Cohort Poor	A. RAGT, 36 sessions over 12 weeks (n=12) B. Physiotherapy assumed, 36 sessions over 12 weeks assumed (n=12)	A vs. B Age: 8.8 vs. 9.5 Female: 50% vs. 50% GMFCS I or II: 100%	A vs. B, mean or median (SD), MD calculated as if all are means, p=between groups 6MWT: 409.58 (49.1) to 475.17 (47.7) vs. 437.00 (55.0) to 459.17 (53.75); MD 43.42, 95% CI 19.64 to 67.21, p<0.001 GMFM-88: 253.00 (8.81) to 256.17 (8.23) vs. 253.67 (7.70) to 255.25 (7.94), MD 1.59, 95% CI –2.19 to 5.37, p=0.410 GMFM-88-D: 36.08 (2.27) to 36.92 (1.73) vs. 36.75 (2.22) to 37.42 (1.98), MD 0.17, 95% CI –0.79 to 1.13, p=0.729 GMFM-88-E: 64.00 (6.90) to 66.25 (6.78) vs. 64.08 (6.43) to 64.92 (6.72), MD 1.14, 95% CI –1.69 to 4.51, p=0.373 BBS: 50.08 (2.43) to 52.08 (2.68) vs. 50.25 (2.93) to 51.00 (3.30), MD 1.25, 95% CI –0.07 to 2.57, p=0.064
Wallard, 2017[101] Wallard, 2018[102] Aerobic exercise RCT Poor	A. RAGT, 20 sessions over 4 weeks (n=14) B. Usual care, 20 sessions over 4 weeks (n=16)	A vs. B Age: 8.3 vs. 9.6 Female: 43% vs. 56% Ambulatory: 100% Ambulatory without aids: 57% vs. 63% GMFCS II: 100%	A vs. B, mean difference between groups: GMFM-66-D: 4.73, 95% CI –6.14 to 15.60, p=0.39 GMFM-66-E: 7.54, 95% CI –2.64 to 17.42, p=0.15
Wu, 2017b[99] (effects of) Aerobic exercise RCT Fair	A. RAGT (resistive force), 18 sessions over 6 weeks (n=11) B. Treadmill training, 18 sessions over 6 weeks (n=12)	A vs. B Age: 11.3 vs. 10.5 Female: 45% vs. 33% Race: nonwhite: 54.5% vs. 58% GMFCS I: 9% vs. 17% GMFCS II: 55% vs. 25% GMFCS III: 27% vs. 42% GMFCS IV: 9% vs. 17%	A vs. B, mean difference between groups: GMFM-66 total: –5.1, 95% CI 13.62 to 3.42, p=0.24 GMFM-66-D: 3.6, 95% CI –5.40 to 12.60, p=0.43 GMFM-66-E: 0.2, 95% CI –17.79 to 19.19, p=0.98 PODCI self: 7.5, 95% CI –10.48 to 25.48, p=0.41 PODCI parent: 5.5, 95% CI –8.96 to 19.96, p=0.46
Wu, 2017a[100] Aerobic exercise RCT Fair	A. RAGT with resistance, 18 sessions over 6 weeks (n=12) B. RAGT with assistance,18 sessions over 6 weeks (n=11)	A vs. B Age: 10.6 vs. 10.8 Female: 50% vs. 45% GMFCS I: 8% vs. 0% GMFCS II: 42% vs. 45% GMFCS III: 42% vs. 36% GMFCS IV: 8% vs. 18%	A vs. B, mean difference between groups: 6MWT: 49.8, 95% CI –49.85 to 149.45, p=0.33 GMFM-66 total: 0.10, 95% CI –7.74 to 7.94, p=0.98 GMFM-66-D: 0.10, 95% CI –8.55 to 8.75, p=0.98 GMFM-66-E: 0.10, 95% CI –16.32 to 16.52, p=0.99 PODCI self: –3.5, 95% CI –20.80, 13.80, p=0.69 PODCI parent: 9.7, 95% CI –6.29 to 25.69, p=0.23

Abbreviations: 6MWT = 6-Minute Walk Test; CI = confidence interval; GMFCS = Gross Motor Function Classification System; GMFM-66 = Gross Motor Function Measure 66; GMFM-66-D = Gross Motor Function Measure 66 (standing); GMFM-66-E = Gross Motor Function Measure 66 (walking, running, jumping); GMFM-88 = Gross Motor Function Measure 88; GMFM-88-D = Gross Motor Function Measure 88 (standing); GMFM-88-E = Gross Motor Function Measure 88 (walking, running, jumping); MD = mean difference; PODCI = Pediatric Outcomes Data Collection Instrument; RAGT = robot-assisted gait training; RCT = randomized controlled trial; SD = standard deviation; TOP = task-oriented physical therapy

The RAGT studies in the CP population enrolled children who were generally limited community ambulators. The control groups received conventional PT, TOP, or treadmill training. There was little difference on function outcomes, regardless of comparator. One RCT[100] used a specific device that produced a resistive force during treadmill training (as opposed to the Lokomat®, which gives a guidance force to the patient). Between group differences were not significant, and the experimental group did not have statistically significant improvement in function from baseline, except for the 6MWT. One small RCT[104] that enrolled adolescents and adults found improved GMFM-88 scores with RAGT compared with usual care, but due to the poor-quality rating of this trial and two other studies that assessed GMFM and found no difference[101,102,106] this evidence was considered insufficient to draw conclusions regarding the benefit of RAGT on function in CP.

Another trial by the same author[99] assessed RAGT versus treadmill training on function as measured with the GMFM-66 and also did not find a difference between groups. A trial comparing RAGT with partial body-weight supported treadmill training and with anti-gravity treadmill training found no differences between groups on walking or function as assessed with the 6MWT, the GMFM-D and GMFM-E measures postintervention or at 3-month followup.[103]

A poor quality cohort study found improvement on the 6MWT with RAGT compared with physiotherapy, but no difference on the GMFM-88.[106] Finally, one quasiexperimental study[105] found no significant difference in function compared with TOP. However, due to the low quality of the included trials, along with small samples sizes, the evidence was considered insufficient to determine whether RAGT is beneficial in children with CP on function and balance.

None of the five studies included for primary outcomes addressed harms or adverse events.

Robot-Assisted Gait Training—Spinal Cord Injury

Seven RAGT RCTs enrolled 406 participants with SCI.[107,108,110-112,114-116] The study mean age of participants ranged from 35 to 50 years and the proportion female ranged from 0 to 38 percent. One study reported racial breakdown and was 47 percent White and 36 percent Hispanic. Number of training sessions ranged from 12 to 60 over the course of 4 to 12 weeks. Most of the study participants were limited ambulators.

Table 16. Robot-assisted gait training in spinal cord injury

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Outcomes
Duffell, 2014[114] Aerobic exercise RCT Poor	A. RAGT, 12 sessions over 4 weeks (n=23) B. No intervention (n=29)	A vs. B Age: NR Female: NR Incomplete: 100%	A vs. B, p=between groups 10MWT achieved minimal important difference (0.13m/s): 13% vs. 8%, p>0.05 6MWT and TUG: p>0.05
Esclarin-Ruz, 2014[107] Aerobic exercise RCT Fair	A. RAGT overground, 40 sessions over 8 weeks (n=44) B. Overground therapy without RAGT, 40 sessions over 8 weeks (n=44)	A vs. B Age UMN injury: 43.6 vs. 44.9 Age LMN injury: 36.4 vs. 42.7 Female UMN: 29% vs. 29% Female LMN: 30% vs. 29%	A vs. B, mean (SD): 10MWT: UMN: 0.48 (0.25) to 0.54 (0.31) vs. 0.36 (0.25) to 0.39 (0.31), LMN: 0.24 (0.11) to 0.46 (0.25), vs. 0.28 (0.27) to 0.45 (0.25), p=0.09 6MWT: UMN: 122.3 (49.2) to 187.48 (103.78) vs. 93.3 (53.1) to 119.41 (89.25), LMN: 82.7 (45.5) to 157.54 (89.51) vs. 94.3 (75.1) to 145.62 (125.15), p=0.047, favors RAGT FIM/Motor: UMN: 5 (2.7) to 8.95 (2.96) vs. 4.9 (4.1) to 7.05 (2.62), LMN: 6 (2.9) to 8.9 (2.61) vs. 5 (2.8) to 8.67 (2.65), p=0.09 WISCI-II: UMN: 5.9 (4.5) to 13.47 (5.65) vs. 4.9 (4.1) to 11.04 (5.09), LMN: 6 (3.2) to 12.45 (4.17) vs. 5 (3.7) to 10.8 (4.54), p=0.10 LEMS: UMN: 30 (10.4) to 38.33 (10.6) vs. 27 (10.9) to 32.28 (11.04) vs. LMN: 21 (10.3) to 27.15 (10.8) vs. 20 (9.9) to 22.57 (10.8), p<0.01 favors RAGT
Field-Fote, 2011[108] Kressler, 2013[110] Aerobic exercise RCT Fair	A. Treadmill BWS training with manual assistance, 60 sessions over 12 weeks (n=17) B. Treadmill BWS training with electrical stimulation, 60 sessions over 12 weeks (n=18) C. Overground BWS training with electrical stimulation, 60 sessions over 12 weeks (n=15) D. RAGT treadmill BWS training with robot assistance, 60 sessions over 12 weeks (n=14)	A vs. B Age: 39.3 vs. 38.5 vs. 42.2 vs. 45 Female: 17.7% vs. 22.2% vs. 13.9% vs. 18% White: 58.8% vs. 44.4% vs. 40.0% vs. 42.9% Hispanic: 29.4% vs. 38.9% vs. 40% vs. 35.7% African American: 11.8% vs. 16.7% vs. 20% vs. 21.4%	Mean difference between groups: 2MWT: A vs. B: –3.0, 95% CI –17.91 to 11.91, p=0.69 A vs. C: –13.4, 95% CI –36.82 to 10.02, p=0.26 A vs. D: –0.4, 95% CI –12.19 to 11.39, p=0.95 B vs. C: –10.4, 95% CI –34.21 to 13.41, p=0.39 B vs. D: 2.6, 95% CI –9.93 to 15.13, p=0.68 C vs. D: 13.0, 95% CI –8.99 to 34.99, p=0.25 Time X Group Interaction p<0.001 A vs. B vs. C vs. D, mean difference (SD): 2MWT: 0.8 (7.7) vs. 3.8 (6.3) vs. 14.2 (15.2) vs.1.2 (5.1), favors e-stim Velocity changed scores averaged across speeds: Group X Time Interaction p=0.004, favors e-stim A vs. B: NR, NS A vs. C: 3.66 (0.74) vs. 4.36 (0.74), p=0.15 A vs. D: NR, NS B vs. C: NR, NS B vs. D: 4.13 (0.74) vs. 3.33 (0.76), p=0.009 C vs. D: 4.36 (0.74) vs. 3.33 (0.76), p=0.001

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Outcomes
Kumru, 2016[111] Aerobic exercise RCT Fair	A. RAGT with rTMS, 20 sessions over 4 weeks, then RAGT (n=15) B. RAGT with sham rTMS, 20 sessions over 4 weeks (n=16)	A vs. B Age: 51 vs. 49 Female: 33% vs. 13% Cervical or thoracic: 100% Cervical: 53% vs. 38%	A vs. B, p=between groups: Change in number able to perform 10MWT between groups: 4 vs. 2, p=0.09 Change in WISCI-II between groups, p>0.05 Change in UEMS between groups, p=0.02 Change in LEMS between groups, p=0.001
Midik, 2020[116] Aerobic exercise RCT Fair	A. RAGT plus conventional rehab, 25 sessions over 5 weeks (n=15) B. Conventional rehab only, 25 sessions over 5 weeks (n=15)	A vs. B Age: 35.4 vs. 37.9 Female: 0% AIS C: 40% vs. 67% AIS D: 60% vs. 33%	A vs. B, mean change (SE), p=between groups: WISCI: 3.9 (0.8) vs. 2.5 (0.5), p=0.178 SCIM: 9.9 (2.5) vs. 7.0 (1.3), p=0.326 LEMS: 1.8 (0.4) vs. 0.6 (0.2), p=0.061 At 3 month followup, change from baseline: WISC: 4.3 (1.0) vs. 2.5 (0.5), p=0.139 SCIM: 16.5 (3.2) vs. 7.6 (1.5), p=0.127 LEMS: 2.1 (0.5) vs. 0.6 (0.2), p=0.049
Shin, 2014[112] Aerobic exercise RCT Fair	A. RAGT, 12 sessions over 4 weeks plus usual physiotherapy, 28 sessions over 4 weeks (n=27) B. Conventional overground training, 40 sessions over 4 weeks (n=26)	A vs. B Age: 43 vs. 48 Female: 26% vs. 46% Cervical: 52% vs. 62% Months since injury: 3.3 vs. 2.7	A vs. B, mean change, p=between groups: WISCI-II: 8 vs. 5, p=0.01 LEMS: 6 vs. 4, p=0.24 SCiM3-M: 6 vs. 3, p=0.13
Yildirim, 2019[115] Aerobic exercise RCT Fair	A. RAGT, 16 sessions over 8 weeks + conventional therapy (n=44) B. Conventional therapy (n=44)	A vs. B Age: 32 vs. 37 Female: 39% vs. 36% Tetraplegia: 20% vs. 16% ASIA Complete: 48% vs. 41%	A vs. B, median (IQR), p-value=between groups: FIM: 69 (31) to 85 (35) vs. 67 (36) to 77 (24), p=0.022 WISCI II: 5 (9) to 9 (7) vs. 5 (6.7) to 6.5 (5), p=0.011

Abbreviations: 2MWT = 2-Minute Walk Test; 6MWT = 6-Minute Walk Test; 10MWT = 10-Meter Walk Test; ASIA = American Spinal Injury Association Impairment Scale; BWS = body weight supported; CI = confidence interval; FIM = Functional Independence Measure; IQR = interquartile range; LEMS = Lower Extremity Motor Score; LMN = lower motor neuron; NR = not reported; NS = not significant; rTMS = transcranial magnetic stimulation; RAGT = robot-assisted gait training; RCT = randomized controlled trial; SD = standard deviation; TUG = Timed Up and Go Test; UEMS = Upper Extremity Motor Score; UMN = upper motor neuron; SCiM3-M = Spinal Cord Independence Measurement III mobility section; WISCI-II = Walking Index for Spinal Cord Injury

RAGT showed positive results in function for participants with SCI in head-to-head studies comparing RAGT with treadmill training or overground walking (SOE: low), but evidence was insufficient for comparisons with usual care due to inconsistent results.[107,108,110,112] There was also low-strength evidence that RAGT may improve ADL in SCI based on two RCTs.[107,115] There was insufficient evidence to determine the benefit of transcranial magnetic stimulation (rTMS) in conjunction with RAGT, but the trial was small.[111]

An RCT of overground therapy with and without RAGT stratified results according to upper motor neuron (UMN) versus lower motor neuron (LMN) SCI participants.[107] Both UMN and LMN injured individuals improved significantly more on the 6MWT and Lower Extremity

Motor Score (LEMS) with RAGT. A study that compared RAGT with treadmill training, overground training, and treadmill plus FES[108] did not find RAGT significantly different to the other groups in function outcomes.

Six studies did not address harms or adverse events. One RCT reported that three individuals left the study (2 in the RAGT plus rTMS group due to repeated urinary tract infection and severe spasticity; 1 in the sham rTMS group due to severe spasticity).[111] Other adverse events experienced in the rTMS group were twitching of facial muscles and headache.

One additional trial of reports the effects of RAGT on bowel dysfunction and is discussed in KQ2c.[113]

Treadmill

A motorized treadmill is a common means for aerobic or endurance training. Its speed and elevation can be manipulated to provide a wide range of training intensities. Handrails are used for support and stability, and for those unable to walk more than short distances, it can be modified to add a harness that provides partial body weight support. Specialized treadmills accommodate upper body training by self-propelling a wheelchair on a treadmill.

Key Points

- Among ambulatory individuals with MS, there was evidence that treadmill training may improve balance and function, including walking (SOE: low).
- When compared with usual care, there was low-strength evidence that treadmill training may improve function in CP (SOE: low).
- There was low-strength evidence of no clear benefit of treadmill training on walking in CP when compared with overground walking (SOE: low).
- Among study participants with SCI, there was low-strength evidence of no clear benefit of treadmill training compared with structured PT or aerobic plus strength training on function, including walking (SOE: low).

Detailed Synthesis

Seventeen RCTs,[117-130,133-138] and two quasiexperimental, nonrandomized studies[131,132] (n=583) using treadmill training met inclusion criteria.

These included six RCTs and one quasiexperimental trial of treadmill training versus usual care in CP,[121,126,129,132] MS,[117,120] and SCI;[133] three comparisons of treadmill versus overground walking in CP;[123,127,128] two RCTs where treadmill training was compared with strength training in CP[125] and MS;[118] and one treadmill training with direct-current stimulation of the motor cortex compared with treadmill training with sham stimulation study in participants with CP.[130]

An additional five RCTs and one quasiexperimental trial had unique comparisons, where treadmill training was compared with different alternative training methods or unique modifications of standard treadmill walking (SCI,[133,138] CP,[122,131,134-137] MS[119]). Thus, few studies used similar treadmill training and comparator/control training for the same condition. One trial[128] met criteria for good quality and the remainder were rated fair quality.

The most frequently reported outcomes were related to walking parameters (e.g., 6MWT, 10MWT), balance (e.g., BBS), combined gait and balance measures such as TUG, and standardized functional constructs combining several measures, such as the GMFM. The GMFM was used both to classify CP participants and as an outcome variable.

Treadmill—Multiple Sclerosis

Four trials[117-120] enrolled individuals (n=119) with MS (Table 17). The mean age of participants across trials ranged from 33 to 53 years with a range of 40 to 100 percent female. Each trial enrolled ambulatory individuals, and participants needed to be able to walk a minimum of 6 meters[117] or 10 meters,[118,119] with or without assistance.

Table 17. Treadmill exercise in multiple sclerosis

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Ahmadi, 2013[120] Aerobic exercise RCT Fair	A. Treadmill, 24 sessions over 8 weeks (n=10) B. Waitlist control (n=10)	A vs. B Age: 37 vs. 37 Female: 100% EDSS: 2.40 vs. 2.25	A vs. B, mean (SD), p-value between groups: 10MWT: 8.68 (1.93) to 7.07 (1.03) vs. 9.16 (1.88) to 9.47 (1.92), p=0.001 2MWT: 120.40 (20.29) to 139.90 (20.78) vs. 121.50 (27.73) to 119.05 (27.12), p=0.001 BBS: 46.20 (6.32) to 53.80 (2.34) vs. 44.50 (9.43) to 41.70 (8.48), p=0.001
Gervasoni, 2014[117] Aerobic exercise RCT Fair	A. 30 minutes conventional therapy + 15 minutes treadmill training, 12 sessions over 2 weeks (n=15) B. 45 minutes conventional therapy, 12 sessions over 2 weeks (n=15)	A vs. B Age: 49.6 vs. 45.7 Female: 40% Able to walk 6 meters with or without assist device RRMS: 47.6% PPMS: 19.0% SPMS: 33.3% EDSS (median): 5.5	A vs. B, mean change, p=between groups DGI: 2.16 vs. 2.07, p=0.51 BBS: 4.01 vs. 3.15, p=0.33
Jonsdottir, 2018[118] Aerobic exercise RCT Fair	A. Treadmill walking, 20 sessions over 4 weeks (n=26) B. Strength training, 16-20 sessions over 4 weeks (n=12)	A vs. B Age: 51.4 vs. 56.7 Female: 48% vs. 29% EDSS: 5.5 vs. 5.6 RRMS: 85% vs. 58% PPMS: 8% vs. 17% SPMS: 8% vs. 25%	A vs. B, mean difference between groups: TUG: –2.83, 95% CI –4.7 to –0.9, p=0.009 DGI: 0.2, 95% CI –1.95 to 2.27, p=0.87 2MWT: 28.3, 95% CI 13.04 to 43.60, p<0.001 SF-12 mental: –3.0, 95% CI –9.43 to 3.38, p=0.34 SF-12 physical: 1.8, 95% CI –2.08 to 5.59, p=0.36 BBS: 1.1, 95% CI –1.4 to 3.7, p=0.39
Samaei, 2016[119] Aerobic exercise RCT Fair	A. Downhill treadmill training, 12 sessions over 4 weeks (n=16) B. Uphill treadmill training, 12 sessions over 4 weeks (n=15)	A vs. B Age: 33.9 vs. 32.1 Female: 82% vs. 82% Ambulatory: 100%	A vs. B, mean change between groups: 25FWT: 8.7 (2.4) to 6.1 (1.8) vs. 7.9 (1.1) to 7.0 (1.6), p=0.001 2MWT: 120.01 (23.6) to 160.1 (35.7) vs. 132.6 (32.3) to 147.5 (29.8), p<0.001 TUG: 9.8 (1.7) to 7.5 (1.8) vs. 9.4 (2.3) to 8.9 (0.9), p=0.041 GNDS: 35.4 (9.1) to 21.8 (5.3) vs. 32.1 (8.6) to 27.5 (6.1), p=0.012 Modified Riverman Mobility Index: 10.6 (3.2) to 14.3 (2.7) vs.10.5 (2.3) to 11.9 (2.1), p=0.005

Abbreviations: 2MWT = 2-Minute Walk Test; 10MWT = 10-Meter Walk Test; 25FWT = 25-Foot Walk Test; BBS = Berg Balance Scale; CI = confidence interval; DGI = Dynamic Gait Index; EDSS = Expanded Disability Status Scale; GNDS = Guy's Neurological Disability Scale; PPMS = primary progressive multiple sclerosis; RCT = randomized controlled trial; RRMS = relapsing-remitting multiple sclerosis; SF-12 = Short Form (12) Health Survey; SPMS = secondary progressive multiple sclerosis; TUG = Timed Up and Go Test

The single trial using 2 weeks of training[117] did not find a benefit of treadmill walking. However, 2 weeks is less than the typical duration of exercise training studies. Combining with the longer duration study of 8 weeks[118,120] provided low-strength evidence for improved function, including walking with treadmill training. Two trials also provided low-strength evidence for improved balance versus usual care or waitlist control.[117l,120] There was insufficient evidence to determine whether downhill treadmill training is superior to uphill training,[119] or whether treadmill training is better than strength training, due to small sample sizes and only a single study evaluating each comparison.[118]

Each trial's treadmill sessions were closely supervised and the treadmill speeds adjusted to maintain appropriate intensities and safety while participants trained. Three RCTs did not address harms or adverse events; the fourth RCT reported that participants experienced only muscle and general fatigue that resolved in a few hours after exercising.[118]

Treadmill—Cerebral Palsy

The greatest number of treadmill trials were with children and adolescents with CP. Twelve trials[121-125,127,128,130-132] enrolled children (n=127) or adolescents (n=102) with CP (Table 18). Two RCTs[126,129] assessed 146 adults with CP (mean age 27 years and 52% to 56% male) (Table 18).

The trials with adults,[126,129] three of the four trials with adolescents,[121,131,132] and three of the six trials with children[123,124,130] enrolled ambulatory individuals and assessed treadmill walking without body weight support. Other trials[122,125,127,128] used partial body weight support as an intervention component.

Table 18. Treadmill exercise in cerebral palsy

Author, Year Intervention Study Design Study Quality	**Intervention and Comparison**	**Population**	**Results**
Aviram, 2017 [131] Aerobic exercise Quasiexperimental Fair	A. Treadmill walking, 30 sessions over 3 months (n=43) B. Group resistance training, 30 sessions over 3 months (n=52)	A vs. B Age: 43 vs. 52 Female: 21% vs. 48% GMFCS II: 72% vs. 75% GMFCS III: 28% vs. 25%	A vs. B, mean (SE) change from baseline and 6 months postintervention; p-values are between groups <u>6MWT:</u> 20.9 (4.0) vs. 27.9 (6.7), p=0.31 <u>TUG:</u> –2.82 (0.51) vs. 3.52 (0.60), p=0.014 <u>GMFM-66:</u> 1.98 (0.40) vs. 3.10 (0.44), p=0.001 <u>GMFM-66-D:</u> 5.53 (1.61) vs. 8.36 (1.24), p=0.013 <u>GMFM-66-E:</u> 4.80 (1.33) vs. 7.21 (0.96), p=0.81 <u>10MWT-self-paced:</u> 0.272 (0.045) vs. 0.276 (0.049), p=0.41 <u>10MWT-fast:</u> 0.387 (0.070) vs. 0.374 (0.069), p=0.30
Bahrami, 2019[129] Aerobic exercise RCT Fair	A. Treadmill, 16 sessions over 8 weeks (n=15) B. Physiotherapy, 16 sessions over 8 weeks (n=15)	A vs. B Age: 30 vs. 25 Female: 47% vs. 40% GMFCS I: 47% vs. 53% GMFCS II: 13% vs. 13% GMFCS III: 40% vs. 33%	A vs. B, mean (SD); percentage change score, p=between groups <u>10MWT</u>: 22.46% change vs. 1.28% change, $p<0.05$ <u>6MWT</u>: 23.68% change vs. 16.54% change, $p>0.05$ <u>WHOQOL-Brief</u>: % change 3.83% change vs. 8.94% change, $p>0.05$

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Chrysagis, 2012[121] Aerobic exercise RCT Fair	A. Treadmill training, 36 sessions over 12 weeks (n=11) B. Conventional PT, 36 sessions over 12 weeks (n=11)	A vs. B Age: 15.90 vs. 16.09 Female: 45% vs. 36% Ambulatory: 100% GMFM-D+E: 67.81 vs. 64.45	A vs. B, mean change, p=between groups: GMFM-D+E: 3.87 vs. 0.69, p=0.007 Self-selected walking speed: 8.06 vs. 0.48, p=0.009
Duarte Nde, 2014[130] Aerobic exercise RCT Fair May share participants with Grecco, 2014	A. Treadmill + tDCS, 10 sessions over 2 weeks (n=12) B. Treadmill + sham tDCS, 10 sessions over 2 weeks, (n=12)	A vs. B Age: 8 vs. 8 Female: NR GMFCS I: 25% vs. 17% GMFCS II: 50% vs. 57% GMFCS III: 25% vs. 25%	A vs. B, mean (SD), p-value=between groups: PBS: 40.5 (9.4) to 45.3 (7.9) vs.39.1 (9.8) to 39.7 (8.4); MD 4.2, 95% CI –2.88 to 11.28, p=0.245 PEDI self-care: 46.1 (10) to 48.0 (9.5) vs. 45.0 (9.2) to 45.5 (9.3); MD 1.4, 95% CI –6.21 to 9.01, p=0.718 PEDI mobility: 38.0 (8.5) to 41.7 (7.4) vs. 38.3 (7.4) to 39.5 (7.6); MD 2.5, 95% CI –3.71 to 8.71, p=0.430
Emara, 2016[122] Aerobic exercise RCT Fair	A. Treadmill walking, 36 sessions over 12 weeks (n=10) B. Overground walking with spider cage, 36 sessions over 12 weeks (n=10)	A vs. B Age: 6.6 vs. 6.9 Female: 70% vs. 60% Spastic diplegic CP: 100% GMFCS III: 100%	A vs. B, mean difference between groups: 10MWT: 0.4 (0.04) to 0.5 (0.04) vs. 0.4 (0.03) to 0.6 (0.04), p=0.12 5XSit-to-Stand: 21.5 (1.3) to 18.9 (1.0) vs. 21.7 (1.5) to 17.7 (0.8), p=0.26 GMFM-88-D: 12.5 (1.6) to 15.8 (1.5) vs.12.0 (0.7) to 19.2 (2.1), p=0.02 GMFM-88-E: 10.9 (1.3) to 14.8 (1.5) vs.10.4 (0.8) to 17.2 (2.1), p=0.05
Grecco, 2014[123] Aerobic exercise RCT Fair May share participants with Duarte Nde, 2014[130]	A. Treadmill training with transcranial direct current stimulation, 10 sessions over 2 weeks (n=12) B. Treadmill training with sham stimulation, 10 sessions over 2 weeks (n=12)	A vs. B Age: 7.8 vs. 8.0 Female: 75% vs. 67% GMFCS II: 67% vs. 67% GMFCS III: 33% vs. 33%	A vs. B, mean difference between groups: 6MWT: MD 1996.6 (133.1 to 266.0) vs. 111.8 (27.1 to 196.4), p<0.05 GMFM-88-D: MD 11.5 (-1.6 to 24.7) vs. MD 3.7 (-2.3 to 9.8), p>0.05 GMFM-88-E: MD 0.8 (-1.5 to 3.2) vs. MD 1.0 (-0.1 to 2.1), p>0.05
Grecco 2013[124] Aerobic exercise RCT Fair	A. Treadmill walking, 14 sessions over 7 weeks (n=16) B. Overground walking, 14 sessions over 7 weeks (n=17)	A vs. B Age: 6.8 vs. 6.0 Female: 63% vs. 47% GMFCS I: 31% vs. 47% GMFCS II: 50% vs. 41% GMFCS III: 19% vs. 12%	A vs. B, mean change, p=between groups: 6MWT: 149.7 vs. 44.8, p<0.001 TUG: –6.4 vs. –2.0, p=0.004 GMFM-88-D: 23.9 vs. 8.1, p<0.001 GMFM-88-E: 20.1 vs. 8.2, p<0.001 PEDI: 11.0 vs. 4.0, p=0.035 BBS: 11.8 vs. 3.3, p<0.001
Johnston, 2011[125] Aerobic exercise RCT Fair	A. Partial BWS treadmill training with 20 sessions over 2 weeks, then 50 sessions at home over 10 weeks (n=14) B. Individualized strength-based PT, 20 sessions over 2 weeks, then 50 session at home over 10 weeks (n=12)	A vs. B Age: 9.6 vs. 9.5 Female: 50% vs. 42% GMFCS II: 7% vs. 8% GMFCS III: 64% vs. 50% GMFCS IV: 29% vs. 42% Diplegic CP: 57% vs. 33% Triplegic CP: 0% vs. 17% Quadriplegic CP: 43% vs. 50%	A vs. B, mean scores (SD), p=between groups: GMFM: 62.7 (17.5) to 63.3 (16.2) vs. 58.4 (26.9) to 60.1 (25.1), p=0.66 PODCI (global): 50.4 (11.2) to 59.3 (11.4) to 60.0 (10.0) vs. 50.9 (14.9) to, 52.0 (22.6) to 55.4 (21.7), p=0.73

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Kim, 2015[126] Aerobic exercise RCT Fair	A. Treadmill walking, 20 sessions over 1-2 months plus PT (n=14) B. PT (n=7)	A vs. B Age: 28.6 vs. 24.4 Female: 50% vs. 43% Ambulatory without gait aid: 100%	A vs. B, mean difference between groups: <u>6MWT on treadmill</u>: 5.71, 95% CI –53.22 to 64.64, p=0.85 <u>6MWT on overground walking</u>: 24.07, 95% CI –46.80 to 94.94, p=0.51
Nsenga Leunkeu, 2012[132] Aerobic exercise Quasiexperimental Fair	A. Treadmill walking, 24 sessions over 8 weeks, (n=12) B. No training, (n=12)	A vs. B Age: 14.2 vs. 14.2 Female: 50% vs. 50% Hemiplegic CP: 83% vs. 83% GMFCS I: 67% vs. 67% GMFCS II: 33% vs. 33%	A vs. B, mean change: (estimates from bar graph) <u>6MWT</u>: 480 to 601 vs. 450 to 450, no difference in baseline values, significant difference in postintervention values favoring treatment
Swe, 2015[128] Aerobic exercise RCT Good	A. Partial BWS treadmill walking, 16 sessions over 8 weeks (n=15) B. Overground walking, 16 sessions over 8 weeks (n=15)	A vs. B Age: 13.03 vs. 13.37 Female: 33% vs. 33% GMFCS II: 67% vs. 53% GMFCS III: 33% vs. 47% 6MWT: 233.33 vs. 205.00	A vs. B, mean difference between groups: <u>6MWT</u>: –17.00, 95% CI –89.77 to 55.77, p=0.65 <u>10MWT</u>: –0.013, 95% CI –0.23, 0.21, p=0.91 <u>GMFM-88-D</u>: –2.94, 95% CI –16.42 to 10.64, p=0.67 <u>GMFM-88-E</u>: –2.8, 95% CI –20.02 to 14.42, p=0.75
Willoughby, 2010[127] Aerobic exercise RCT Fair	A. Partial BWS treadmill training, 18 sessions over 9 weeks (n=12) B. Overground walking, 18 sessions over 9 weeks (n=14)	A vs. B Age: 10.35 vs. 11.24 Female: 50% vs. 36% GMFCS III: 42% vs. 21% GMFCS IV: 58% vs. 79%	A vs. B, mean (SD), p=between groups: <u>10MWT</u>: 244.33 (115.41) to 219.38 (123.71) vs. 118.36 (89.89) to 135.82 (95.65), p=0.097

Abbreviations: 5x = five times; 6MWT = 6-Minute Walk Test; 10MWT = 10-Meter Walk Test; BBS = Berg Balance Scale ; BWS = body weight supported; CI = confidence interval; CP = cerebral palsy; GMFCS = Gross Motor Function Classification System; GMFM = Gross Motor Function Measure; GMFM-66-D = Gross Motor Function Measure 66 (standing); GMFM-66-E = Gross Motor Function Measure 66 (walking, running, jumping); GMFM-88-D = Gross Motor Function Measure 88 (standing); GMFM-88-E = Gross Motor Function Measure 88 (walking, running, jumping); MD = mean difference; NR = not reported; PBS = Pediatric Balance Scale; PEDI = Pediatric Evaluation Disability Inventory; PODCI = Pediatric Outcomes Data Collection Instrument; PT = physical therapy; RCT = randomized controlled trial; SD = standard deviation; SE = standard error; tDCS = transcranial direct current stimulation; TUG = Timed Up and Go Test; WHOQOL = World Health Organization Quality of Life scale

These trials provided low-strength evidence of benefit on function with treadmill training in CP compared with usual care, and low-strength evidence of no clear benefit of treadmill training when compared with overground walking. When trials enrolling participants of various ages are combined,[122,124,127,128] the evidence does not suggest a benefit of treadmill training when compared with various comparator interventions.

When treadmill training combined with transcranial direct current stimulation to the child's motor cortex was compared with treadmill training with sham stimulation, performance on the 6MWT was improved significantly, although GMFM-88-D and GMFM-88-E scores were not.[123] In another publication with the same trial registry number, there was no association between treadmill training with or without transcranial stimulation on balance or ADL.[130]

Two trials in children with CP evaluated ADL on the Pediatric Outcomes Data Collection Instrument[125] and the Pediatric Evaluation Disability Inventory[124] and found mixed results.

Activities of daily living were improved with treadmill training versus overground walking in younger children (mean age 6)[124] but not versus individualized strength-based PT in older children (mean age 9).[125] One trial reported balance as measured with the BBS and found BBS scores improved with treadmill training versus overground walking in younger children.[124] Trials in children were too varied and results were too inconsistent to draw conclusions regarding treadmill training versus other interventions in children with CP.

Six trials did not address harms or adverse events.[121,122,124,130-132] One RCT reported that there were no adverse events.[128] One RCT indicated that there were no reports of adverse events with transcranial stimulation during treadmill training but did not comment on other potential adverse events.[123] Another RCT reported that no injury occurred that was due to the intervention.[129] One trial reported that four children in the experimental group and one in the control group dropped out due to unexpected surgery or botulinum toxin administration and that one child dropped out due to back pain with walking.[127] Another trial reported that two children developed knee or leg pain and one child developed a blister underneath the ankle-foot arthrosis.[125]

Treadmill—Spinal Cord Injury

Three trials[133-139] enrolled individuals (n=89) with SCI (Table 19). Trial mean age of participants ranged from 37 to 55 years with an average mean proportion female between 14 and 30 percent. The disability of participants varied. One trial[138] enrolled individuals who could walk at least 5 meters with braces or walking aids, while another trial[133] only required that participants be able to independently advance one leg.

Table 19. Treadmill exercise in spinal cord injury

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Alexeeva, 2011[133] Aerobic exercise RCT Fair	A. BWS treadmill training, max 39 sessions over 13 weeks (n=9) B. BWS track training, max 39 sessions over 13 weeks (n=14) C. Structured PT, max 39 sessions over 13 weeks (n=12)	A vs. B vs. C Age: 43 vs. 36 vs. 35 Female: 11% vs. 14% vs. 17% Cervical: 89% vs. 57% vs. 58%	A vs. B vs. C: mean (SD), p=across all groups: 10MWT (m/s): 0.30 (0.26) to 0.46 (0.40) vs. 0.22 (0.20) to 0.44 (0.33) vs. 0.41 (0.34) to 0.51 (0.36), p>0.05 TBS: 9.8 (5.4) to 19.4 (5.0) vs. 10.5 (3.4) to 11.9 (2.5) vs. 10.1(3.6) to 12.9 (2.7), p<0.05, post-hoc group C improving (p<0.001) and B improving (p<0.01) but not A (p=0.23) SAWS: 39.3 ((8.3) to 35.2 (8.7) vs. 35.9 (6.9) to 32.4 (7.6) vs. 36.6 (9.9) to 29.0 (7.9), p>0.05

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Giangregorio, 2012[134] Hitzig, 2013[135] Kapadia, 2014[136] Craven, 2017[137] Aerobic exercise RCT Fair	A. BWS treadmill walking with FES, 48 sessions over 16 weeks (n=17) B. Aerobic and resistance training, 48 sessions over 16 weeks (n=17)	A vs. B Age: 56.6 vs. 54.1 Female: 18% vs. 29% Tetraplegia: 82% vs. 71% UEMS: 38.3 vs. 37.5 LEMS: 30.4 vs. 27.9 C2-T12: 100% AIS C or D: 100%	A vs. B, mean (SD), pre, post, and 8 months after intervention: 10MWT: 42.8 (46.2) to 35.2 (40.8) to 42.2 (67.7) vs. 49.1 (41.7) to 28.7 (8.3) to 35.1 (18.8), p=0.829 6MWT: 187.9 (123.4) to 217.1 (134.4) to 232.5 (138.9) vs. 79.4 (83.9) to 130 (46.0) to 126.4 (63.8), p=0.096 TUG: 43.6 (25.5) to 33.0 (15.7) to 32.2 (19.1) vs. 61.6 (36.2) to 49.5 (21.9) to 51.3 (19.6), p=0.138 FIM: 4.7 (1.82) to 5.19 (1.80) to 5.19 (1.83) vs. 4.18 (2.14) to 4.82 (1.66) to 5.09 (2.98), p=0.115 CHART Mobility subscale: 79.81 (21.00) to 85.28 (13.81) to 86.36 (14.44) vs. 82.09 (19.31) to 84.27 (11.89) to 88.45 (15.25), p=0.840 CHART Social subscale: 89.94 (13.12) to 90.31 (18.02) to 88.69 (17.10) vs. 72.73 (24.00) to 89.64 (12.63) to 73.73 (31.15), p=0.065 CHART Physical subscale: 92.35 (11.75) to 93.72 (8.02) to 93.81 (6.16) vs. 97.94 (2.49) to 94.99 (7.30) to 93.85 (5.01), p=0.214
Yang, 2014[138] Aerobic Exercise RCT (Crossover) Fair	A. BWS (if needed) treadmill walking, 40 sessions over 8 weeks (n=10) B. Precision track walking training, 40 sessions over 8 weeks (n=10)	A vs. B Age: 48 vs. 44 Female: 30% vs. 30% Able to walk ≥ 5 meters with walking aid or braces: 100% Cervical: 50%	A vs. B, mean change, p=between groups: 6MWT: 29 vs. 10, p=0.045 10MWT (self-selected): 0.070 vs. 0.025, p>0.05 10MWT (fast): 0.075 vs. 0.12, p>0.05 SCIFAP: –75 vs. –42, p>0.05 WISCI (self-selected): 0.08 vs. 0.85, p>0.05 WISCI (max): 0.04 vs. 0.08, p>0.05

Abbreviations: 6MWT = 6-Minute Walk Test; 10MWT = 10-Meter Walk Test; AIS = ASIA Impairment Scale; BWS = body weight supported; CHART = Craig Handicap and Assessment Reporting Technique; FES = functional electrical stimulation; FIM = Functional Independence Measure; LEMS = Lower Extremity Motor Score; PT = physical therapy; RCT = randomized controlled trial; SAWS = Satisfaction with Abilities and Well-Being Scale; SD = standard deviation; TBS = Tinetti Balance Scale; TUG = Timed Up and Go Test; UEMS = Upper Extremity Motor Score; WISCI = Walking Index for Spinal Cord Injury

All three trials provided low-strength evidence for no clear benefit of treadmill training versus all comparators on function, including walking (SOE: low). Evidence was insufficient to draw conclusions on the effects of treadmill training on quality of life or balance in study participants with SCI.

One RCT did not address harms or adverse events.[133] One RCT[138] reported a single participant withdrew due to wrist pain and that no other adverse events that were related to training occurred; one RCT reported adverse events that were considered a result of the intervention (bruising, blistering, fall on treadmill, and pain in heel/ankle and hip/groin) and loss of consciousness, muscle strain, swollen knees, elbow pain, and dizziness in the control group.[134]

One additional trial of reports the effects of RAGT on bowel dysfunction and is discussed in KQ2c.[113]

Postural Control Interventions

Balance Exercises

Balance training involves muscle-strengthening exercises to improve stability and coordination. Balance exercises may involve specific methods (e.g., Cawthorne-Cooksey exercises, Frenkel exercises, core stability, dual tasking, sensory strategies [CoDuSe] exercises) or individual or group standard balance exercises or traditional rehabilitation with a balance

focus. These exercises are designed to improve postural control and walking, or other functional outcomes, and/or to decrease falls and near falls.

Key Points

- Balance exercises were associated with improved balance in MS compared with usual care or waitlist controls (SOE: moderate), a lower risk of falls (SOE: low), and low-strength evidence of improved function (SOE: low).
- Due to poor-quality studies, evidence for the effects of balance exercises in CP was rated insufficient to draw conclusions (SOE: insufficient).
- There was also limited evidence for the effects of balance training in SCI (SOE: insufficient).

Detailed Synthesis

Fifteen RCTs,[61,83,141-149,151,152,156,157] two quasiexperimental nonrandomized studies,[153-155] and one cohort study[155] involving 751 participants evaluated balance training. Fifteen studies compared balance training interventions with usual care, waitlist, or attention control,[61,83,141,143,145-149,151-157] and one study[142] compared balance training alone and in combination with lumbar stabilization exercises or task-oriented training exercises. Twelve studies enrolled people with MS,[61,83,141-143,145-149,151] four studies enrolled people with CP,[152-155] and two studies were conducted in participants with SCI.[156,157] Among the trials, three met criteria for good quality,[145,146,148] and eleven were rated fair quality.[61,83,141-143,147,149,151,152,156,157] The three quasiexperimental nonrandomized studies were rated poor quality due to unclear enrollment methods, unbalanced study group allocation, and/or lack of clear adjustment for clinical or demographic confounders.[153-155] The most frequently reported outcomes were related to balance and function.

Balance Exercise—Multiple Sclerosis

Twelve trials enrolled people (n=640) with MS (Table 20).[61,83,141-143,145-149,151] The trial mean age of participants ranged from 32 to 59 years with a mean proportion female from 59 to 100 percent. Race/ethnicity was not reported in any of the trials. Mean baseline EDSS score ranged from 2.4 to 6.1.

BBS scores were evaluated in eight trials (Table 20).[83,141-146,151] Seven trials (n=332) comparing balance training with usual care found balance training consistently associated with significant improvements in BBS scores relative to usual care (MD –4.14, 95% CI –5.57 to –2.70, I^2=79%).[83,141,143-146,151] Two other RCTs measured balance with the Mini Balance Evaluation System Test (MiniBEST) and found similar results (MD 2.40, 95% CI 1.10 to 3.70, I^2=51%).[148,149] One study reported improvements in static and dynamic balance with balance exercises.[147] These studies provide moderate-strength evidence of improved balance with balance exercises in MS compared with usual care or waitlist controls.

Two RCTs reported falls or near falls as an outcome, with both reporting significantly fewer falls in the intervention groups than the control groups, based on patient diaries.[141,143] Comparing the average number of falls and near falls before, during, and after the intervention in one study showed they significantly decreased over time (falls: 4.18, 2.17, 1.68, before-after p=0.0011; near falls: 23.2, 18.0, 8.64, before-after p=0.0038). The other RCT found that the likelihood of having an unexpected fall was lower with balance training than with usual care (p=0.005).[141] These studies provide low-strength evidence of improvement in fall risk with balance training.

A trial (n=42) comparing balance training alone with balance training combined with lumbar stabilization or task-oriented training found the combination therapies improved balance more than balance training alone (mean change from baseline 3.57 [balance training alone] versus 5.78 [balance training with lumbar stabilization] versus 5.57 [balance training with task-oriented training]), but the difference between groups was not statistically significant (SOE: insufficient).[142]

Seven studies provided low-strength evidence of benefit of balance exercises on function. Subjective assessment of walking was improved with balance training in four studies (n=248, MD –4.66, 95% CI –6.65 to –2.67, I^2=0%).[143,144,149,150] Objective measures of walking (e.g., 6MWT, Functional Gait Assessment) largely favored balance exercises compared with usual care, although individual results were not always statistically significant.[83,143,144,147,149-151] One trial reported improved scores on the MSIS-29 with balance exercises versus usual PT.[83] However, there was no improvement in TUG with balance exercises in pooled analysis of three trials (n=127, MD 0.45, 95% CI –1.92 to 2.82, I^2=54%).[143,144,151]

One fair-quality RCT (n=45) found no difference between balance exercises and attention control on sleep as measured by the Insomnia Sleep Index but future trials are needed to confirm these findings.[61] (SOE: insufficient). Quality of life, based on Multiple Sclerosis Quality of Life (MSQOL)-54 score, was not significantly different between balance training with conventional rehabilitation one trial (n=80).[141] (SOE: insufficient).

Six RCTs did not address harms or adverse events.[61,83,146-148,151] Of the studies that did report on adverse events, one reported no falls or adverse events during the study, and another reported two falls during CoDuSe training.[143,145,149] Two other studies reported that there were no adverse events related to training.[141,142]

Table 20. Balance training in multiple sclerosis

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Afrasiabifar, 2018[145] Postural control RCT Good	A. Cawthorne-Cooksey exercise: 36 sessions over 12 weeks (n=24) B. Frenkel exercises, number of sessions NR, over 12 weeks (n=23) C. Usual care (n=25)	A vs. B vs. C Age: 32.4 vs. 32 vs. 33.6 Female: 83% vs. 74% vs. 76% RRMS: 96% vs. 96% vs. 92% PPMS+SPMS: 4% vs. 4% vs. 8%	A vs. B vs. C, mean change from baseline (SD): <u>BBS</u>: 8.9 (SD 1.8) vs. 2.3 (SD 0.9) vs. –1.2 (SD 1.05) <u>BBS</u>: mean difference between-groups: A vs. B: 5.9, 95% CI 1.9 to 9.9, p=0.001 A vs. C: 10.7, 95% CI 6.8 to 14.6, p=0.001 B vs. C: 4.8, 95% CI 0.9 to 8.8, p=0.01
Amiri, 2019[147] Postural control RCT Fair	A. Core stability training, 30 sessions over 10 weeks (n=35) B. Conventional treatment (n=34)	A vs. B Age: 32 vs. 31 Female: 100% EDSS: 3.58 vs. 3.74 RRMS: 100%	Significant interaction between time and group according to baseline EDSS score for core muscle function (i.e., core endurance and core strength tests) and static and dynamic stability (p<0.05)

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Arntzen, 2019[148] Arntzen, 2020[150] Postural control RCT Good	A. GroupCoreDIST, 18 sessions over 6 weeks + home exercises (n=39) B. Usual care (n=40)	A vs. B Age: 52 vs. 48 Female: 69% vs. 73% EDSS: 2.45 vs. 2.28 RRMS: 82% vs. 90% PPMS: 13% vs. 5% SPMS: 5% vs. 5%	A vs. B, mean difference between groups: MiniBEST: MD 1.91, 95% CI 1.07 to 2.76, p<0.001 2MWT at 7 weeks: MD 16.7, 95% CI 8.15 to 25.25 2MWT at 30 weeks: MD 16.38, 95% CI 7.65 to 25.12 10MWT at 7 weeks: MD 0.48, 95% CI 0.11 to 0.85 10MWT at 30 weeks: MD 0.33, 95% CI –0.04 to 0.71 MSWS-12 at 7 weeks: MD 9.77, 95% CI 3.19 to 16.35 MSWS-12 at 30 weeks: MD 3.87, 95% CI –2.80 to 10.54
Brichetto, 2015[146] Postural control RCT Good	A. Personalized rehab (tailored to sensory impairment), 12 sessions over 4 weeks (n=16) B. Traditional rehab (visual rehab for balance disorders), 12 sessions over 4 weeks (n=16)	A vs. B Age: 50.1 vs. 51.0 Female: 69% vs. 75% RRMS: 56% vs. 63% SPMS: 31% vs. 25% PPMS: 13% vs. 13% EDSS: 3.7 vs. 3.7	A vs. B, mean (SD), p=between groups: BBS: 46.5 (3.6) to 52.8 (2.8) vs. 45.8 (6.6) to 47.8 (6.1), p<0.001
Callesen, 2019[149] Postural control RCT Fair	A. Balance and motor control training, 20 sessions over 10 weeks (n=28) B. Waitlist control (n=18)	A vs. B Age: 51 vs. 56 Female: 82% vs. 80% EDSS: 4 vs. 3.5 RRMS: 75% vs. 65% SPMS: 14% vs. 15% PPMS: 11% vs. 20%	A vs. B, mean difference, p=between groups 6MWT: MD 17.5, 95% CI –4.1 to 39.2, p=0.11 25FWT (m/s): MD 0.10, 95% CI 0.00 to 0.20, p=0.04 MSWS-12: MD –7.3, 95% CI –12.7 to –2.0, p=0.01 MiniBEST: MD 3.3, 95% CI 1.6 to 5.0, p<0.01
Carling, 2017[143] Postural control RCT Fair	A. Group CoDuSe, 14 sessions over 7 weeks (n=23) B. Waitlist (Late start) controls (n=25)	A vs. B Age: 62 vs. 55 Female: 76% vs. 62% EDSS: 6.16 vs. 6.06 RRMS: 0% vs. 23% SPMS: 68% vs. 58% PPMS: 32% vs. 19%	A vs. B, mean change (SE): BBS: 3.65 (1.44), p=0.015 TUG: 4.41 (3.17), p=0.17 2MWT: –3.24 (3.37), p=0.34 Sit-to-Stand: 0.24 92.12), p=0.17 10MWT: 1.49 (3.84), p=0.70 Falls Efficiency Scale: –1.66 (2.39), p=0.49 MSWS-12: –7.21 (3.60), p=0.051 Falls: –1.24 (1.66), p<0.001 Near Falls: –8.24 (14.78), p=0.002
Forsberg, 2016[144] Postural control RCT Fair	A. Group CoDuSe, 14 sessions over 7 weeks (n=35) B. No intervention (n=38)	A vs. B Age: 52 vs. 56 Female: 80% vs. 82% EDSS 6.0 or less: 100% RRMS: 57% vs. 34% PPMS: 11% vs. 13% SPMS: 31% vs. 53%	A vs. B, least squares mean, 95% CI p=between groups TUG: 1.4, 95% CI –1.7 to 4.5, p=0.37 MSWS-12: –3.7, 95% CI –6.0 to –1.3, p=0.0026 FGA: 2.1, 95% CI 0.6 to 3.6, p=0.0079 BBS: –2.1, 95% CI –3.8 to –0.5, p=0.011

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Gandolfi, 2015[141] Postural control RCT Fair	A. Balance training (sensory integration), 15 sessions over 5 weeks (n=39) B. Conventional rehabilitation, 15 sessions over 5 weeks (n=41)	A vs. B Age: 47.21 vs. 49.56 Female: 72% vs. 76% EDSS (median): 3.00 vs. 3.66 RRMS: 100%	A vs. B, mean (SD), p=between groups: <u>MSQOL-54 PHC</u>: 63.09 (11.09) to 65.56 (10.31) vs. 58.77 (11.05) to 59.64 (9.80), p>0.05 (postintervention); 63.09 (11.09) to 63.56 (10.27) vs. 58.77 (11.05) to 58.54 (11.64), p>0.05 (1 month posttreatment) <u>MSQOL-54 MHC</u>: 61.05 (20.15) to 65.32 (18.29) vs. 60.50 (16.6) to 63.09 (12.19), p>0.05 (postintervention); 61.05 (20.15) to 63.19 (17.94) vs. 60.50 (16.6) to 63.25 (13.18), p>0.05 (1 month posttreatment) <u>BBS:</u> 47.97 (4.89) to 52.77 (3.15) vs. 46.49 (5.21) to 47.79 (6.05), p<0.001 (postintervention); 47.97 (4.89) to 52.92 (2.97) vs. 46.49 (5.21) to 48.33 (5.88), p<0.001 (1 month posttreatment) <u>Number of Falls</u>: 0.59 (0.99) to 0.03 (0.16) vs. 0.37 (0.54) to 0.29 (0.34), p=0.005 (postintervention); 0.59 (0.99) to 0.08 (0.27) vs. 0.37 (0.54) to 0.27 (0.55), p=0.053 (1 month posttreatment)
Ozkul, 2020[151] Postural control RCT Fair	A. Balance training, 16 sessions over 8 weeks (n=13) B. Relaxation exercises at home, 16 sessions over 8 weeks (n=13)	A vs. B Age: 34 vs. 34 Female: 85% vs. 77% EDSS median: 1 vs. 2 Number of relapses: 2 vs. 2	Pre-post median (IQR): <u>BBS:</u> 47 (44, 56) to 52 (46, 56) vs. 55 (53, 56) to 56 (53.5, 56), p>0.05 TUG: 7.3 (6.7, 8.5) to 7.3 (6, 7.9) vs. 6.9 (6.5, 7.5) to 7.4 (6.4, 7.7), p<0.017
Sadeghi Bahmani, 2019[61] Postural control RCT Fair	A. Balance and coordination exercises, 24 sessions over 8 weeks (n=24) B. Attention control, 24 sessions over 8 weeks (n=21)	A vs. B Age: 39 vs. 38 Female: 100% EDSS: 3.38 vs. 2.02	A vs. B, mean (SD), p=between groups: <u>EDSS:</u> 3.38 (1.87) to 3.10 (1.86) vs. 2.02 (1.84) to 1.98 (1.70), p>0.05 <u>ISI:</u> 13.46 (5.81) to 10.13 (4.92) vs. 1.71 (5.43) to 11.14 (5.39), p>0.05
Salci, 2017[142] Postural control RCT Fair	A. Balance training, 18 sessions over 6 weeks (n=14) B. Lumbar stabilization plus balance training, 18 sessions over 6 weeks (n=14) C. Task-oriented training (individualized exercises) plus balance training, 18 sessions over 6 weeks (n=14)	A vs. B vs. C Age: 35.36 vs. 37.29 vs. 34.36 Female: 43% vs. 62% vs. 71% Ambulatory: 100% EDSS (median): 3.5 vs. 3.5 vs. 3.5 RRMS: 79% vs. 79% vs. 86% PPMS: 7% vs. 7% vs. 0% SPMS: 14% vs. 14% vs. 14%	A vs. B vs. C, mean change (SD), p=between groups: <u>2MWT:</u> 10.75 (SD 9.97) vs. 25.55 (SD 16.90) vs. 18.69 (SD 14.24) A vs. B: p=0.08; A vs. C: p=0.085; B vs. C: p=0.265 <u>BBS:</u> 3.57 (SD 2.20) vs. 5.78 (SD 3.40) vs. 5.57 (SD 3.73); p=>0.05 for all comparisons

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Tollar, 2020[83] Postural control RCT Fair	A. Balance training, 25 sessions over 5 weeks (n=14) B. Usual PT, 25 sessions over 5 weeks (n=12)	A vs. B Age: 46.9 vs. 44.4 Female: 86% vs. 92% EDSS median: 5.0 vs. 5.0 RRMS: 64% vs. 67%	A vs. B, mean difference between groups: MSIS-29: –6.3 (4.36) vs. 1.0 (3.46), p=0.008 6MWT: 19.2 (35.40) vs. 6.3 (49.27), p=0.174 BBS: 3.9 (2.25) vs. –0.2 (2.62), p=0.015 EQ-5 Sum score:–0.6 (1.15) vs. 0.0 (1.13), p=0.023

Abbreviations: 2MWT = 2-Minute Walk Test; 6MWT = 6-Minute Walk Test; 10MWT = 10-Meter Walk Test; 25FWT = 25-Foot Walk Test; BBS = Berg Balance Scale; CoDuSe = core stability, dual tasking, sensory strategies; EDSS=Expanded Disability Status Scale; EQ-5 = Euro Quality of Life; FGA = Functional Gait Assessment; ISI = Insomnia Severity Index; IQR = interquartile range; MiniBEST = Mini Balance Evaluation Systems Test; MSIS-29 = Multiple Sclerosis Impact Scale; MSQOL=Multiple Sclerosis Quality of Life; MSWS-12 = Multiple Sclerosis Walking Scale-12; NR = not reported; PPMS = primary progressive multiple sclerosis; PT = physical therapy; RRMS = relapsing-remitting multiple sclerosis; RCT = randomized controlled trial; SD = standard deviation; SE = standard error; SPMS = secondary progressive multiple sclerosis; TUG = Timed Up and Go Test

Balance Exercise—Cerebral Palsy

One RCT,[152] two quasiexperimental studies,[153,154] and one cohort study[155] enrolled people (n=117) with CP (Table 21). Three studies[152-154] enrolled children and one[155] enrolled young adults. In the studies conducted in children, mean age was 10 years (range 8 to 11 years) and 40 percent were female (range 32% to 50%). In the study conducted in adults, the mean age was 22 years and 46 percent were female. None of the studies reported race/ethnicity. Ambulatory status was not reported in any of the studies. Three studies reported baseline function using the GMFCS.[152-154] One study primarily enrolled people with Level I GMFCS classification[154] and the other two studies enrolled people classified Level III or higher.[152,153] One fair-quality trial[152] (n=28) and 2 poor-quality quasiexperimental studies (n=66)[153,154] provided evidence on the effects of balance exercises versus usual care on function in CP. Due to the high risk of bias in this body of evidence, evidence was considered insufficient to draw conclusions (SOE: insufficient). Similarly, evidence was insufficient to draw conclusions on the effects of balance training exercises on balance[152,154] and ADL.[152,153,155]

Harms and adverse events were not addressed in any of the studies of balance training in people with CP.[152-155]

Table 21. Balance training in cerebral palsy

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Bleyenheuft, 2017[153] Postural control Quasiexperimental Poor	A. Hand-arm bimanual intensive therapy including lower extremity, thirteen 6.5 hours per day over 13 days (n=10) B. Usual PT, 2 weeks (n=10)	A vs. B Age: 10.5 vs. 11.4 Female: 40% vs. 50% GMFCS II: 20% vs. 20% GMFCS III: 70% vs. 70% GMFCS IV: 10% vs. 10%	A vs. B, mean (SD); p=interaction of 2 interventions X 3 time points (baseline, postintervention and 3 months postintervention): GMFM-66: 55 (5.9) to 58 (6.2) to 62 (6.4) vs. 55 (8.7) to 56 (7.6) to 57 (6.6), p<0.001 6MWT: 190 (108.5) to 226 (100.8) to 236 (105.1) vs. 194 (101.1) to 180 (111.1) to 182 (101.1), p=0.026 PEDI: 52 (12.4) to 57 (11.5) to 60 (10.7) vs. 51 (14.6) to 51 (15.3) to 51 (15.8), p=0.001 PBS: 33 (17.5) to 43 (20.1) to 42 (21.3) vs. 30 (23.9) to 27 (22.2) to 26 (23.2), p=0.002

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Curtis, 2018[152] Postural control RCT Fair	A. Trunk control training: 120 sessions over 24 weeks (n=14) B. Usual care (n=14)	A vs. B Age: 8 vs. 8 Female: 21% vs. 50% Spastic: 50% vs. 64% Dyskinetic: 50% vs. 36% GMFCS III: 14% vs. 21% GMFCS IV: 29% vs. 14% GMFCS V: 57% vs. 64%	A vs. B, mean difference, p=between groups: GMFM–66: 1.1, 95% CI –2.2 to 4.4, p>0.05 (postintervention); 0.1, 95% CI –3.6 to 3.3, p>0.05 (12-month followup) SATCo: mean between group difference at end of treatment and at posttreatment followup: p>0.05 PEDI Self Care, PEDI Mobility, PEDI Mobility Caregiver Assistance: mean between group difference at end of treatment and at posttreatment followup: p>0.05
Kim, 2017[155] Postural control Social activity/exercise (Boccia) Cohort study Poor	A. Group boccia, 12 sessions over 6 weeks (n=11) B. Usual care (n=12)	A vs. B Age: 22.36 vs. 21.83 Female: 45% vs. 42%	A vs. B, mean (SD), p=between groups: Modified Barthel Index, mean change from baseline: 2.82 (SD 1.25) vs. 1.58 (SD 1.38), p<0.05; MD 1.24, 95% CI 0.09 to 2.34, p=0.04
Lorentzen, 2015[154] Postural control Quasiexperimental Poor	A. Interactive, home-based computer training, 140 sessions over 20 weeks (n=34) B. Usual care (n=12)	A vs. B Age: 10.9 vs. 11.3 Female: 32% vs. 42% GMFCS I: 97% vs. 92% GMFCS II: 3% vs. 8%	A. vs. B, mean (SD), p=between groups: Sit-to-stand, number of cycles performed: 20.0 (0.9) vs, 15.1 (0.9), p=0.04 Left leg lateral step up, number of steps: 23.5 (1.4) vs. 17.8 (2.2), p=0.004 Right leg lateral step up, number of steps: 22.1 (1.4) vs. 18.0 (2.0), p<0.001 Romberg Balance Test center of gravity maintenance area (mm2): 462.2 (62.5) vs. 314.6 (104.9), p=0.18

Abbreviations: 6MWT = 6-Minute Walk Test; CI = confidence interval; GMFCS = Gross Motor Function Classification System; GMFM = Gross Motor Function Measure; GMFM-66 = Gross Motor Function Measure 66; MD = mean difference; PBS = Pediatric Balance Scale; PEDI = Pediatric Evaluation of Disability Inventory; PT = physical therapy; RCT = randomized controlled trial; SATCo=Segmental Assessment of Trunk Control; SD = standard deviation

Balance Exercise—Spinal Cord Injury

There was insufficient evidence on the benefits and harms of balance training in SCI. One RCT compared the effects of Cawthorne/Cooksey exercises versus conventional therapy on balance in Iranian male veterans with SCI (n=20) (Table 22).[156] All participants had L3 to L4 injury. A second trial in SCI patients of various ages with CSI compared dual task exercises to a control group.[157] Both trials reported improved balance as assessed with the BBS with balance exercises (n=60, MD 4.53, 95% CI 2.61 to 6.46, I^2=0%). The second trial also reported improved coordination and walking speed in the intervention group compared with the control group.[157]

Table 22. Balance training in spinal cord injury

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Hota, 2020[157] Postural control RCT Fair	A. Dual task exercises for upper and lower limbs, 24 sessions over 4 weeks (n=20) B. Control group – details NR, (n=20)	A vs. B Age 11-25: 40% vs. 30% Age 26-40: 25% vs. 45% Age 41-55: 25% vs. 25% Age 56-70: 10% vs. 0% Female: 10% vs. 10%	A vs. B, mean (SD): BBS: MD 4.55, 95% CI 2.16 to 6.94 Motor Assessment Scale: MD 3.82, 95% CI 1.09 to 6.55, p=0.006
Norouzi, 2019[156] Postural control RCT Fair	A. Cawthorne/ Cooksey exercises, 12 sessions over 4 weeks (n=10) B. Usual care, 4 sessions over 4 weeks (n=10)	A vs. B Age: NR Female: 0% L3-L4: 100%	A vs. B, mean (SD), p-value=between groups BBS: 38.36 (6.01) to 48.39 (4.01) vs. 37.67 (6.07) to 43.20 (4.05), MD 4.5, 95% CI –0.17 to 9.17, p=0.059

Abbreviations: BBS = Berg Balance Scale; CI = confidence interval; MD = mean difference; NR = not reported; RCT = randomized controlled trial; SD = standard deviation

Hippotherapy

Hippotherapy is a type of therapeutic horseback riding that uses the movement of a horse (or a simulated horse) in conjunction with a physical and/or occupational therapist to improve function and stability and other outcomes in people with neuromuscular disease or disability.[265]

Key Points

- Although data from two fair-quality trials favored hippotherapy over usual care on walking, short-term quality of life, and balance in adults with MS, no firm conclusions can be drawn (SOE: insufficient).
- Low-strength evidence found hippotherapy associated with improved function and balance in CP (SOE: low).
- There were no studies of hippotherapy in SCI.

Detailed Synthesis

Nine RCTs,[158,160-162,164-168] two quasiexperimental nonrandomized studies,[169,170] and one cohort study[171] involving 567 participants evaluated hippotherapy. Five studies compared hippotherapy versus usual care,[158,162,165,169,170] four studies compared hippotherapy versus no hippotherapy (either waitlist or inactive hippotherapy simulator),[160,161,168,171] one trial compared hippotherapy versus home aerobic exercise,[164] one RCT compared hippotherapy versus outdoor recreation,[167] and one RCT examined the effects of hippotherapy versus a hippotherapy simulator.[166] Two RCTs enrolled participants with MS (Table 23),[158,160] and the remaining 11 studies were in participants with CP (Table 24).

Among the trials, one met criteria for good quality,[164] six for fair quality,[158,160-162,167,168] and one was rated poor quality and deemed to have high risk of bias due to unclear reporting of randomization method, allocation concealment, blinding of outcome assessors, and high loss to followup.[166] One quasiexperimental study was rated fair quality[169] and one quasiexperimental

study[170] and one cohort study[171] were rated poor quality due to unclear enrollment methods and lack of clear adjustment for prognostic clinical or demographic confounders. The most frequently reported outcomes were related to function (e.g., GMFM)[160-162,164,165,167,169,171] and balance (e.g. BBS, Pediatric Balance Scale [PBS]).[158,164,166,169-171]

Hippotherapy—Multiple Sclerosis

Two trials of hippotherapy enrolled patients with MS, one (MS-HIPPO) with a usual care control group, and the other with a waitlist control group (Table 23). Both trials enrolled more females with similar ages but EDSS scores were higher in one trial, indicating greater disability.[158]

The MS-HIPPO trial found that weekly hippotherapy was associated with significantly greater improvement in quality of life based on MSQoL-54 mental and physical health scores compared with usual care (mean difference 12.0, 95% CI 6.2 to 17.7 and 14.4, 95% CI 7.5 to 21.3).[158] Balance, measured by BBS score, was also significantly better with hippotherapy versus usual care after 12 weeks (mean difference 2.33, 95% CI 0.03 to 4.63) using imputed (last observation carried forward) data.[158] Subgroup analysis found hippotherapy associated with greater improvement in BBS score in participants with EDSS 5 or greater (vs. usual care, MD 5.1, 95% CI 2.3 to 7.9) and in participants age 50 years or older (MD 4.8, 95% CI 1.8 to 7.8) than in those with EDSS less than 5 at baseline (MD –0.8, 95% CI –4.2 to 2.5) or less than age 50 years (MD 1.8, 95% CI –1.3 to 4.9). The other hippotherapy study in patients with MS (n=33) found improved walking distance on the 6MWT and walking speed on the 25FWT.[160] Data from these trials provides insufficient evidence from which to draw firm conclusions.

One trial did not address adverse events,[160] while the other trial reported similar numbers of participants with any adverse event (43% vs. 41%; p=0.82) and serious adverse events (3% vs. 5%; p=0.69) in hippotherapy and control groups. Participants in the hippotherapy group were more likely to experience unspecified accidents versus control (13% vs. 3%; p=0.14).[158]

Table 23. Hippotherapy in multiple sclerosis

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Moraes, 2020[160] Postural control RCT Fair	A. Hippotherapy, 16 sessions over 8 weeks (n=17) B. Waitlist control (n=16)	A vs. B Age: 45.5 vs. 48.4 Female: 94% vs. 94% EDSS, median: 2.0 vs. 1.75 RRMS: 100%	A vs. B, mean (SD): 6MWT: 459.06 (118.34) to 503.59 (126.38) vs. 513.00 (101.97) to 497.13 (88.88), p<0.001 25FWT: 6.37 (1.70) to 5.36 (1.43) vs. 5.82 (1.29) to 5.84 (1.08), p<0.001
Vermohlen, 2018[158] Postural control RCT Fair	A. Hippotherapy plus standard care, 12 sessions over 12 weeks (n=32) B. Control group (standard care), 12 weeks (n=38)	A vs. B Age (median): 50 vs. 51 Female: 90% vs. 73% EDSS: 5.4 vs. 5.3	A vs. B, mean difference, p=between groups: MSQoL-54 mental health subscale score: 14.4, 95% CI 7.5 to 21.3, p<0.001 MSQoL-54 physical health subscale score: 12.0, 95% CI: 6.2 to 17.7, p<0.001 BBS: 2.33, 95% CI: 0.03 to 4.63, p=0.047

Abbreviations: 6MWT = 6-Minute Walk Test; 25FWT = 25-Foot Walk Test; BBS = Berg Balance Scale; CI = confidence interval; EDSS = Expanded Disability Status Scale; MSQoL = Multiple Sclerosis Quality of Life; RCT = randomized controlled trial; SD = standard deviation

Hippotherapy—Cerebral Palsy

Seven RCTs,[161,162,164-168] two quasiexperimental nonrandomized studies,[169,170] and one cohort study[171] enrolled children (n=464) with CP (Table 24). The trial mean age ranged from 6 to 11 years with a trial mean of 29 to 58 percent female. None of the studies reported race/ethnicity. Two trials[169,170] specified that they enrolled ambulatory participants but participants' ambulatory status was not reported in the remaining seven studies. Ten studies reported baseline function using the GMFCS.[161-165,167-171] GMFCS classification at baseline varied widely among the studies (Table 24). Three studies enrolled only participants classified GMFCS Level I or II.[168-170]

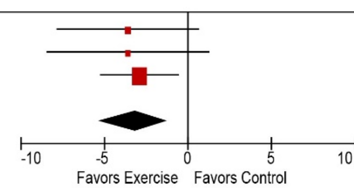
Evidence on functional outcomes with hippotherapy in children with CP was based on seven studies (Table 24) and provided low-strength evidence of a benefit of hippotherapy on function versus control groups.[161,162,164,165,167,169,171] The largest (n=92) and only good-quality trial found significantly higher GMFM-66 scores after 8 weeks (16 sessions) of hippotherapy compared with at-home exercise; GMFM-88 and subscale scores D and E (standing and walking, running, jumping) were also improved with hippotherapy.[164]

The effect of hippotherapy on balance/sitting ability was assessed in four fair- and two poor-quality studies, using the PBS[164,166,169] or Sitting Assessment Scale.[161,168,170] Most trials compared hippotherapy with usual care or, in one case, a hippotherapy simulator.[161] These trials provided low-strength evidence for improved balance scores on the PBS in pooled analysis (MD –3.14, 95% CI –5.28 to –1.18, I^2=0%) (Figure 8). Sitting ability was assessed in three studies and showed a benefit in two,[168,170] but one of the two studies was rated poor quality and in the other study the control group had worse baseline disability (SOE: insufficient).

Figure 8. Pediatric Balance Scale in cerebral palsy trials

Study	Cond.	Exercise	Control	N Exercise	N Control	Weight	MD Δ Scores PL [95% CI]
Kwon 2011	CP	Hippotherapy+PT	PT	16	16	19.7%	-3.60 [-7.83, 0.63]
Kwon 2015	CP	Hippotherapy+PT	Home-based ex. + PT	45	46	15.1%	-3.60 [-8.43, 1.23]
Lee 2014	CP	Hippotherapy	Horse-back simulator	13	13	65.2%	-2.90 [-5.22, -0.58]
Total (95% CI)				**74**	**75**	**100.0%**	**-3.14 [-5.28, -1.18]**

Heterogeneity: Tau² = 0.00; Chi² = 0.12, df = 2 (P = 0.94); I² = 0%
Test for overall effect: Z = 3.28 (P = 0.001)



Abbreviations: Δ = change; CI = confidence interval; CP = cerebral palsy; MD = mean difference; PL = profile likelihood; PT = physical therapy

One fair-quality RCT (n=24) reported improvement in positive feeling and self-esteem scores on the WHOQOL instrument with hippotherapy compared with outdoor recreation, whereas negative feeling scores were similar between groups (Table 24).[167] The only other evidence on the effect of hippotherapy on quality of life was from a poor-quality, crossover trial of 73 children with CP.[165] The trial found no difference between hippotherapy and conventional physiotherapy on the Child Health Questionnaire-28 psychosocial or physical subscale scores or on KIDSCREEN-27 parental scale scores. These studies provided insufficient evidence to draw a conclusion on the effects of hippotherapy on quality of life in children with CP.

One cohort study[171] (n=55) found ADL as assessed with the Pediatric Evaluation Disability Inventory (PEDI) to favor hippotherapy over waitlist control, but the study had high risk of bias and the data were too limited to draw conclusions.

Six studies did not address harms or adverse events. The good-quality trial reported one fall in the hippotherapy group versus no falls in the control group (2% [1/46] vs. 0% [0/46]; OR 3.01, 95% CI 0.12 to 77). A poor-quality crossover study also reported one fracture as a result of a fall from a horse during hippotherapy.[165]

One additional trial that reports the effects of hippotherapy on spasticity is found in Table 46, KQ2d.[163]

Table 24. Hippotherapy in cerebral palsy

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Deutz, 2018[165] Postural control RCT Poor	A. Hippotherapy, 16 to 32 sessions over 16 to 20 weeks plus usual physiotherapy (n=35) B. Usual physiotherapy over 16 to 20 weeks (n=38) Crossover study	A vs. B Age: 9.29 vs. 8.87 Female: 34% vs. 45% GMFCS II: 29% vs. 45% GMFCS III: 20% vs. 26% GMFCS IV: 51% vs. 29%	A vs. B, mean difference, p=between groups: GMFM-66 total: 0.52, 95% CI –0.52 to 1.55, p>0.05 GMFM-66-D: 0.016, 95% CI –1.09 to 1.12, p>0.05 GMFM-66-E: 2.30, 95% CI 0.28 to 4.33, p<0.05 CHQ-28 social: 0.21, 95% CI –3.89 to 3.47, p>0.05 CHQ-28 physical: 4.77, 95% CI –1.12 to 10.66, p>0.05 KIDSCREEN-27: mean difference 1.07, 95% CI –2.53 to 4.68, p>0.05
Herrero, 2012[161] Postural control RCT Fair	A. Hippotherapy simulator ON, 10 sessions over 10 weeks (n=19) B. Hippotherapy simulator OFF, 10 sessions over 10 week (n=19)	A vs. B Age: 9.95 vs. 9.05 Female: 26% vs. 32% GMFCS I: 11% vs. 11% GMFCS II: 11% vs. 5% GMFCS III: 16% vs. 11% GMFCS IV: 16% vs. 21% GMFCS V: 47% vs. 53%	A vs. B, mean difference, p=between groups GMFM total: 0.27, 95% CI –0.07 to 0.62, p>0.05 GMFM total, 22 weeks: 0.25, 95% CI –0.10 to 0.60, p>0.05 GMFM total: Proportion with improvement from baseline, 10 weeks: (11/19) vs. (8/19); OR 1.89 (95% CI 0.5 to 6.9), p>0.05 GMFM total: Proportion with improvement from baseline, 22 weeks: (10/19) vs. (12/19); OR 0.65 (95% CI 0.18 to 2.37), p>0.05 Sitting Assessment Scale: 0.26 (0.65) vs. –0.21 (0.92), p>0.05
Kwon, 2011[169] Postural control Quasiexperimental Fair	A. Hippotherapy, 16 sessions over 8 weeks plus usual PT, 16 sessions over 8 weeks (n=16) B. Usual PT, 16 sessions over 8 weeks (n=16)	A vs. B Age: 6.4 vs. 6.1 Female: 31% vs. 38% Ambulatory: 100% GMFCS I: 25% vs. 25% GMFCS II: 75% vs. 75%	A vs. B, mean (SD), p=between groups: GMFM-66: 70.4 (7.4) to 73.7 (8.3) vs. 69.8 (8.7) to 70.1 (8.1), p=0.003 GMFM-88: 89.4 (7.3) to 91.1 (6.7) vs. 88.0 (8.3) to 88.3 (8.4), p=0.054 GMFM-88-D: 83.2 (15.5) to 83.3 (10.9) vs. 79.6 (15.5) to 79.3 (16.6), p=0.826 GMFM-88-E: 67.2 (17.5) to 74.6 (19.3) vs. 65.3 (20.0) vs. 66.9 (20.1), p=0.042 PBS: 41.7 (8.8) to 45.8 (8.6) vs. 41.0 (10.4) to 41.5 (10.6), p=0.004
Kwon, 2015[164] Balance RCT Good	A. Hippotherapy, 16 sessions over 8 weeks plus usual PT (n=46) B. Home-based aerobic exercise, 16 sessions over 8 weeks plus usual PT (n=46)	A vs. B Age: 5.7 vs. 5.9 Female: 56% vs. 37% GMFCS I: 27% vs. 26% GMFCS II: 27% vs. 26% GMFCS III: 24% vs. 26% GMFCS IV: 22% vs. 22% Spastic: 91% vs. 93% Unilateral: 9% vs. 13%	A vs. B, mean (SD), p=between groups: GMFM-66: 60.8 (14.9) to 63.5 (15.8) vs. 61.4 (14.8) to 61.8 (15.0), p<0.01 GMFM-88: 72.7 (19.2) to 75.7 (18.3) vs. 73.9 (17.9) to 74.3 (18.1), p<0.01 GMFM-88-D: 54.1 (34.2) to 59.7 (32.5) vs. 55.5 (32.2) to 54.9 (33.2), p<0.01 GMFM-88-E: 41.0 (34.1) to 45.1 (35.4) vs. 42.0 (33.2) to 43.0 (33.0), p<0.01 PBS: 25.1 (18.9) to 28.9 (18.8) vs. 26.9 (18.3) to 27.1 (18.3), p<0.01

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Lee, 2014[166] Postural control RCT Poor	A. Hippotherapy, 36 sessions over 12 weeks (n=13) B. Horseback riding simulator, 36 sessions over 12 weeks (n=13)	A vs. B Age: 10.8 vs. 10.0 Female: 38% vs. 31% Walk > 10 meters independently: 100%	A vs. B, mean (SD), p=between groups PBS: 35.6 (3.8) to 41.2 (4.7) vs. 35.8 (4.7) to 38.5 (5.3), p>0.05
Matusiak-Wieczorek, 2016[170] Postural control Quasiexperimental Poor	A. Hippotherapy, 12 sessions over 12 weeks (n=19) B. Maintain current activities (n=20)	A vs. B Age: 8.42 vs. 8.3 Female: 47% vs. 45% Ambulatory: 100% Hemiplegia: 68% vs. 75% GMFCS I: 63% vs. 55% GMFCS II: 37% vs. 45%	A vs. B, mean (SD) Sitting Assessment Scale: 14.42 (4.39) to 15.63 (3.65) vs.15.50 (3.14) to 15.75 (3.19), p=0.010
Matusiak-Wieczorek, 2020[168] Postural control RCT Fair	A. Hippotherapy, 24 sessions over 12 weeks (n=15) B. Hippotherapy, 12 sessions over 12 weeks (n=15) C. No hippotherapy (n=15)	A vs. B vs. C Age: 7.93 vs. 7.60 vs. 8.13 Female: 40% vs. 47% vs. 47% GMFCS I: 67% vs. 80% vs. 47% GMFCS II: 33% vs. 20% vs. 53%	A vs. B vs. C, mean (SD), p=between groups Sitting Assessment Scale: 10.93 (3.97) to 13.13 (3.46) vs. 15.93 (4.17) to 17.27 (2.76) vs. 14.87 (3.27) to 15.13 (3.36) A vs. C: MD 1.93, 95% CI 0.94 to 2.92, p<0.001 B vs. C: MD 1.06, 95% CI 0.61 to 1.51, p<0.001 A vs. B: MD 0.87, 95% CI 0.06 to 1.69, p=0.036
Mutoh, 2019[167] Postural control RCT Fair	A. Hippotherapy, 48 sessions over 48 weeks (n=12) B. Outdoor recreation 48 sessions over 48 weeks (n=12)	A vs. B Age: 8 vs. 9 Female: 58% vs. 50% GMFCS II: 42% vs. 42% GMFCS III: 58% vs. 58%	A vs. B, mean (SD), p=between groups GMFM-66: 56.6 (9.2) to 62.8 (10.8) vs. 57.4 (7.9) to 57.9 (9.2), p<0.05 GMFM-66-E: 45.4 (7.0) to 49.7 (7.6) vs. 46.0 (6.3) to 46.5 (6.6), p<0.05 5MWT (m/min): 31.9 (10.7) to 38.8 (13.5) vs. 31.1 (11.3) to 32.3 (11.6), p<0.05 WHOQOL (positive feelings): 3.1 (1) to 4.1 (1) vs. 3.1 (0.9) to 3.4 (1), p<0.05 WHOQOL (self-esteem): 2.9 (1.2) to 4.0 (0.7) vs. 3.3 (1.1) to 3.7 (0.7), p<0.05 WHOQOL (negative feelings): 2.9 (0.8) to 2.8 (0.7) vs. 2.8 (0.8) to 2.8 (0.8), p>0.05
Park, 2014[171] Postural control Cohort Poor	A. Hippotherapy, 16 sessions over 8 weeks (n=34) B. Waitlist control (n=21)	A vs. B Age: 6.68 vs. 7.76 Female: 56% vs. 52% Bilateral CP: 94% vs. 90% GMFCS I: 24% vs. 29% GMFCS II: 32% vs. 19% GMFCS III: 15% vs. 29% GMFCS IV: 29% vs. 24%	A vs. B, mean (SD) change from baseline, p=between groups: GMFM-66: 2.93 (3.95) vs. 1.25 (1.99), p<0.05 PEDI: 10.89 (11.94) vs. 2.00 (4.93), p<0.05

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Silva e Borges, 2011[162] Postural control RCT Fair	A. Riding simulator, 12 sessions over 6 weeks (n=20) B. Usual PT, 12 sessions over 6 weeks (n=20)	A vs. B Age: 5.65 vs. 5.77 Female: 60% vs. 55% GMFCS II: 20% GMFCS III: 40% GMFCS IV: 35% GMFCS V: 5%	A vs. B, p=between groups: <u>GMFCS reclassification indicating improved function</u>: 25% (5/20) vs. 10% (2/20), p=0.24

Abbreviations: CI = confidence interval; CP = cerebral palsy; GMFCS = Gross Motor Function Classification System; GMFM = Gross Motor Function Measure; GMFM-66 = Gross Motor Function Measure 66; GMFM-66-D = Gross Motor Function Measure 66 (standing); GMFM-66-E = Gross Motor Function Measure 66 (walking, running, jumping); GMFM-88 = Gross Motor Function Measure 88; GMFM-88-D = Gross Motor Function Measure 88 (standing); GMFM-88-E = Gross Motor Function Measure 88 (walking, running, jumping); PBS = Pediatric Balance Scale; PEDI = Pediatric Evaluation Disability Inventory; PT = physical therapy; RCT = randomized controlled trial; SD = standard deviation; WHOQOL = World Health Organization Quality of Life scale

Hippotherapy—Spinal Cord Injury

No studies were identified.

Tai Chi

Tai Chi is a form of Chinese martial arts exercise with focused movements and deep breathing that combines balance, core strength, flexibility, and meditation. It can be performed in a standing or seated position and is practiced to improve balance, flexibility, and mindfulness meditation.

Key Points

- There was insufficient evidence to determine the effect of Tai Chi on quality of life, balance, or other outcomes in participants with MS (SOE: insufficient).
- No Tai Chi studies of participants with CP were identified.
- There was insufficient evidence to determine the effect of wheelchair Tai Chi on quality of life or other outcomes in participants with SCI (SOE: insufficient).

Detailed Synthesis

Two RCTs[172,174] and one quasiexperimental study,[173] with a combined total of 106 participants, evaluated Tai Chi. These included two studies of Tai Chi versus usual care[173,174] and one trial[172] of Tai Chi plus psychological classes and PT versus psychological classes and PT without Tai Chi. Two studies[172,173] enrolled participants with MS (Table 25), and one trial was conducted in participants with SCI.[174] (Table 26). No studies met criteria for good quality, one trial was rated fair quality,[174] and two were rated poor quality and deemed to have high risk of bias due to unclear randomization and treatment allocation concealment and a lack of comparability between groups at baseline. Reported outcomes were related to quality of life (e.g., WHOQOL scale), balance (e.g., BBS), and depression (Center for Epidemiological Studies Depression Scale).

Tai Chi—Multiple Sclerosis

One poor-quality RCT[172] and one poor-quality quasiexperimental study[173] enrolled participants (n=66) with MS (Table 25). Trial mean participant ages were 35 and 43 years, mean proportion female was 69 and 100 percent, and no trials reported race. Both studies enrolled participants who could ambulate.

The RCT found twice-weekly Tai Chi plus usual care obtained similar results as usual care on balance,[172] whereas the quasiexperimental trial found twice-weekly Tai Chi compared with usual care resulted in improved balance and quality of life.[173] However, the two balance measures were very different and provided insufficient evidence to draw conclusions on the effects of Tai Chi on these outcomes (SOE: insufficient).

Neither study adequately addressed harms or adverse events. The RCT reported a participant in the Tai Chi intervention group withdrew due to unspecified health issues.[172]

Table 25. Tai Chi exercise in multiple sclerosis

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Azimzadeh, 2015[172] Postural control RCT Poor	A. Tai Chi plus usual care, 24 sessions over 12 weeks (n=16) B. Usual care (n=18)	A vs. B Age: 37.5 vs. 33 Female: 100% Ambulatory: 100%	A vs. B, mean (SD) BBS: 52.25 (3.39) to 53.94 (2.23) vs. 53.22 (2.23) to 53.61 (2.14); MD 1.39, 95% CI –0.39 to 3.17, p=0.13
Burschka, 2014[173] Postural control Quasiexperimental Poor	A. Tai Chi, 48 sessions 6 months (n=15) B. Usual care (n=17)	A vs. B Age: 42 vs. 43 Female: 66% vs. 71% Ambulatory: 100% RRMS: 93% vs. 76% SPMS: 0% vs. 24% CIS: 7% vs. 0%	A vs. B, mean (SD), p=between groups: CES-D: 12.21 (6.66) to 7.67 (5.12) vs. 13.87 (10.82) to 16.13 (11.99), p<0.05 QLS 7 item, 1–7 rating scale, maximum score 420 points): 215 (25.55) to 232.57 (25.62) vs. 204.46 to 193.81 (36.20), p<0.01 Balance (14 Balance tasks, measured 1=achieved task, 0=failed task): 8.00 (2.83) to 9.33 (2.26) vs. 6.88 (4.09) to 6.53 (4.49), p<0.05

Abbreviations: BBS = Berg Balance Scale; CES-D = Center for Epidemiologic Studies Depression Scale; CI = confidence interval; CIS = Clinically Isolated Syndrome; MD = mean difference; QLS=Questionnaire of Life Satisfaction; RCT = randomized controlled trial; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis; SD = standard deviation

Tai Chi—Cerebral Palsy

No studies of Tai Chi in participants with CP were identified.

Tai Chi—Spinal Cord Injury

One RCT enrolled 40 adults with SCI (Table 26).[174] The mean age of participants in the trial was 40 and the mean proportion female was 23 percent. All were wheelchair users. The mean baseline rating on the American Spinal Injury Association Impairment Scale was 7.5 (range 2 to 8). This trial found that treatment with wheelchair Tai Chi resulted in improved quality of life scores on the psychological subscale of the WHOQOL-BREF, but there were no differences between wheelchair Tai Chi and usual care on the physical, social, and environmental subscales (SOE: insufficient).

This study reports that there no adverse events occurred during this trial.

Table 26. Tai Chi exercise in spinal cord injury

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Qi, 2018b[174] Postural control RCT Fair	A. Wheelchair Tai Chi, 60 sessions over 6 weeks (n=20) B. Usual care control, (n=20)	A vs. B Age: 38.3 vs. 43.05 Female: 25% vs. 20% Wheelchair user: 100% C6-T1: 15% vs. 20% T2-T5: 25% vs. 30% T6-T12: 40% vs. 35% Below L1: 20% vs. 15%	A vs. B, mean (SD), p=between groups: WHOQOL-BREF (physical): 11.40 (1.25) to 11.80 (1.33) vs. 10.94 (1.15) to 11.09 (1.29), p=0.08 WHOQOL-BREF (psychological): 10.95 (1.57) to 12.23 (1.65) vs. 10.87 (1.08) to 11.20 (1.33), p=0.01 WHOQOL-BREF (social): 10.93 (1.60) to 12.40 (1.79) vs. 10.53 (1.29) to 11.27 (1.47), p=0.07 WHOQOL-BREF (environmental): 10.00 (1.72) to 10.65 (1.58) vs. 9.67 (1.51) to 10.09 (1.77), p=0.28

Abbreviations: RCT = randomized controlled trial; SD = standard deviation; WHOQOL-Bref = World Health Organization Quality of Life Assessment-BREF

Motion Gaming

Motion gaming or active video gaming is defined as technology-driven activities that require the game user to be physically active to play the game.[266]

Key Points

- Four RCTs provided low-strength evidence of improvement in function and balance with motion gaming compared with usual care in trial participants with MS (SOE: low).
- Four RCTs provided low-strength evidence of improved balance with motion gaming compared with use of a mouse, conventional balance exercises, or usual physical activity in participants with CP (SOE: low).
- One RCT found improved dynamic balance with the T-shirt test in SCI patients with motion gaming versus conventional rehabilitation, but additional evidence is needed to confirm this finding (SOE: insufficient).

Detailed Synthesis

Fourteen RCTs examined the effects of motion gaming on function, quality of life, and balance.[50,51,83,151,175-184] Twelve trials met criteria for fair quality[50,51,83,151,175-178,181-184] and two[179,180] were rated poor quality and deemed to have high risk of bias due to unclear methods of patient selection and concealment of the allocation, differences in prognostic patient factors between groups at baseline, and high attrition.

Motion Gaming—Multiple Sclerosis

Six RCTs enrolled 240 adult participants with MS,[51,83,151,175-177] with a mean age of participants between 32 and 50 years and between 64 and 90 percent female (Table 27). These trials assessed effects on balance compared with no intervention or conventional balance training.

Table 27. Motion gaming in multiple sclerosis

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Kalron, 2016[51] Postural control RCT Fair	A. Balance training using Caren Integrated Virtual Reality System with 3D visual, sound and proprioception, 12 sessions over 6 weeks (n=15) B. Static postural control, weight shifting and perturbation exercises, 12 sessions over 6 weeks (n=15)	A vs. B Age: 47.3 vs. 43.9 Female: 67% vs. 60% EDSS: 4.5 vs. 3.9	A vs. B, mean (SD), p=between groups: <u>BBS:</u> 46.8 (9.6) to 47.9 (6.4) vs. 43.3 (7.1) to 44.6 (4.9), p=0.56 <u>Four Square Step Test:</u> 16.2 (7.0) to 12.7 (6.4) vs. 14.2 (7.1) to 11.7 (5.9), p=0.361 <u>FES-I:</u> 36.4 (9/7) to 29.4 (7.8) vs. 32.9 (10.3) to 28.6 (5.8), p=0.021
Khalil, 2018[176] Postural control RCT Fair	A. Nintendo Wii balance board and VR scenarios with tasks to complete, 12 sessions over 6 weeks (n=16) B. Balance training at home, 18 sessions over 6 weeks (n=16)	A vs. B Age: 39.9 vs. 34.9 Female: 75% vs. 63% EDSS: 2.9 vs. 3.1 RRMS: 100%	A vs. B, mean difference between groups: <u>TUG:</u> 0.04, 95% CI –2.24 to 2.32, p=0.97 <u>10MWT:</u> 8.48, 95% CI –5.16 to 22.12, p=0.21 <u>3MWT</u>: –7.11, 95% CI –34.18 to 19.95, p=0.59 <u>SF-36 PCS:</u> –11.62, 95% CI –22.27 to –0.99, p=0.03 <u>SF-36 MCS:</u> –13.60, 95% CI –23.66 to –3.55, p=0.01 <u>FES-I:</u> 3.86, 95% CI –0.062 to 8.34, p=0.08 <u>BBS:</u> –4.52, 95% CI –7.90 to –1.09, p=0.01
Nilsagard, 2013[175] Postural control RCT Fair	A. Play games using Nintendo Wii Fit Plus® Balance Board for balance, yoga, strength and aerobics, 12 sessions over 6 weeks (n=42) B. No balance exercise during routine PT (n=42)	A vs. B Age: 50.0 vs. 49.4 Female: 76% vs. 76% Able to walk 100 m: 100% RRMS: 62% vs. 67% SPMS: 31% vs. 31% PPMS: 7% vs. 2% No assist device indoors: 76% vs. 88% No assist device outdoors: 52% vs. 50%	A vs. B, mean (SD) change at followup, p=between groups: <u>TUG:</u> –0.8 (2.4) vs. 0.1 (2.1), p=0.10 <u>25footWT:</u> –0.3 (1.1) vs. –0.1 (1.4), p=0.51 <u>DGI:</u> 1.78 (2.3) vs. 1.0 (2.0), p=0.21 <u>MS Walking Scale:</u> –5.9 (11.5) vs. –3.95 (18.1), p=0.76 <u>Four Square Step Test</u>: –1.6(2.1) vs. –2.0 (6.6), p=0.64
Ozkul, 2020[151] Postural control RCT Fair	A. Immersive virtual reality, 16 sessions over 8 weeks (n=13) B. Relaxation exercises at home, 16 sessions over 8 weeks (n=13)	A vs. B Age: 29 vs. 34 Female: 69% vs. 77% EDSS median: 1 vs. 2 Number of relapses: 3 vs. 2	Pre-post median (IQR): <u>BBS</u>: 52 (42.5, 56) to 54 (44.5, 56) vs. 55 (53, 56) to 56 (53.5, 56), p>0.05 <u>TUG</u>: 7.6 (6.9, 8) to 6.3 (5.7, 7.2) vs. 6.9 (6.5, 7.5) to 7.4 (6.4, 7.7), p<0.017
Tollar, 2020[83] Postural control RCT Fair	A. Xbox 360, Adventure video game, 25 sessions over 5 weeks (n=14) B. Usual PT, 25 sessions over 5 weeks (n=12)	A vs. B Age: 48.2 vs. 44.4 Female: 86% vs. 92% EDSS median: 5.0 vs. 5.0 RRMS: 50% vs. 67%	A vs. B, mean difference between groups: <u>MSIS-29</u>: –10.8 (6.09) vs. 1.0 (3.46), p<0.001 <u>6MWT</u>: 57.4 (52.09) vs. 6.3 (49.27), p=0.017 <u>BBS</u>: 6.1 (3.52) vs. –0.2 (2.62), p<0.001 <u>EQ-5 Sum score</u>:–2.3 (1.44) vs. 0.0 (1.13), p<0.001

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Yazgan, 2020[177] Postural control RCT Fair	A. Nintendo Wii Fit, 16 sessions over 8 weeks (n=15) B. Balance Trainer motion gaming, 16 sessions over 8 weeks (n=12) C. Waitlist control (n=15)	A vs. B vs. C Age: 47.5 vs. 43.1 vs. 40.7 Female: 86.7% vs. 100% vs. 86.7% EDSS: 4.16 vs. 3.83 vs. 4.06 RRMS: 73.3% vs. 66.7% vs. 93.3%	A vs. C, mean change scores: BBS: 5.8 vs. 0.93, p<0.05 TUG: –1.54 vs; 0.05, p<0.05 6MWT: 42.71 vs. 7.59 p<0.05 MusiQoL: 12.61 vs. –0.19, p<0.05 B vs. C, mean change scores: BBS: 2.66 vs. 0.93, p<0.05 TUG: –0.64 vs; 0.05, p<0.05 6MWT: 23.25 vs. 7.59 p>0.05 MusiQoL: 5.32 vs. –0.19, p<0.05 A vs. C, mean change scores: p<0.05 in favor of group A for BBS and MusiQoL

Abbreviations: 3MWT = 3-Minute Walk Test; 6MWT = 6-Minute Walk Test; 10MWT = 10-Meter Walk Test; BBS = Berg Balance Scale; CI = confidence interval; DGI = Dynamic Gait Index; EDSS = Expanded Disability Status Scale; EQ-5 = EuroQuality of Life; FES-I = Falls Efficacy Scale-International; IQR = interquartile range; MS = multiple sclerosis; MSIS-29 = Multiple Sclerosis Impact Scale; MusiQoL = Multiple Sclerosis International Quality of Live Questionnaire; SF-36 MCS = Short-Form 36 Mental Component Summary; SF-36 PCS = Short-Form 36 Physical Component Score PPMS = primary progressive multiple sclerosis; PT = physical therapy; RCT = randomized controlled trial; RRMS = relapsing-remitting multiple sclerosis; SD = standard deviation; SPMS = secondary progressive multiple sclerosis; SF-36 = Short Form-36; TUG = Timed Up and Go Test; VR = virtual reality

Four RCTs (n=177) provided low-strength evidence of improvement with motion gaming versus usual care on function in MS as measured with the 6MWT (2 studies, n=68, MD –30.90, 95% CI –49.55 to –12.25, I^2=14%) and the TUG (3 studies, n=152, MD –1.06, 95% CI –1.43 to –0.69, I^2=0%).[51,83,151,175-177] Three studies provided low-strength evidence of improvement with motion gaming on balance (n=94, MD –3.43, 95% CI –6.30 to –0.57, I^2=89%).[83,151,177] Evidence was insufficient to draw conclusions regarding the effects of motion gaming compared with different balance exercises on function, balance, and quality of life.

Three trials did not mention adverse events,[83,151,177] one trial reported that there were no harms or adverse events,[51] one trial reported that there were no serious adverse events but did not report adverse events considered not serious,[176] and one trial reported 10 falls in the exercise group compared with 14 in the control group – none occurring during balance exercises, and no other adverse events.[175]

Motion Gaming—Cerebral Palsy

Seven RCTs assessed 237 children with CP (Table 28).[50,178-183] For these trials, mean participant age ranged between 7 and 11 years old, and the proportion of girls ranged between 27 and 100 percent. Four trials primarily focused on upper extremity movements[50,179-181] while two used a balance system[178,182] and one used a virtual dance game.[183]

Table 28. Motion gaming in cerebral palsy

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Acar, 2016[179] Postural control RCT Poor	A. Nintendo Wii gaming plus neuro-developmental treatment, 12 sessions over 6 weeks (n=15) B. Neurodevelopmental treatment, 12 sessions over 6 weeks (n=15)	A vs. B Age: 9.5 vs. 9.7 Female: 47% vs. 60% GMFCS I: 40% vs. 40% GMFCS II: 60% vs. 60% Spastic hemiparesis: 100%	A vs. B, mean (SD), p=between groups WeeFIM: 46.0 (8.23) to 46.751 (7.51) vs. 48.3 (7.27) to 48.0 (7.14), p>0.05 QUEST (dissociated movement): 80.1 (7.73) to 85.6 (8.54) vs. 81.4 (10.70) to 86.4 (8.78), p>0.05 QUEST (grasp): 42.2 (18.76) to 47.1 (16.64) vs. 53.0 (16.45) to 55.7 (15.30), p>0.05 QUEST (weight bearing): 60.2 to 72.7 (19.60) vs. 75.4 (19.97) to 77.3 (15.43), p>0.05 QUEST (extension): 72.9 (14.78) to 77.0 (12.05) vs. 71.0 (23.53) to 74.0 (23.36), p>0.05
El-Shamy, 2018[181] Postural control RCT Fair	A. Arm exoskeletal + virtual reality 36 sessions over 12 weeks (n=15) B. Conventional therapy, 36 sessions over 12 weeks (n=15)	A vs. B Age: 7 vs. 7 Female 40% vs. 27% Mobile Ability Classification I: 33% vs. 40% II: 53% vs. 40% III: 13% vs. 20%	A vs. B, mean (SD), p=between groups QUEST total: 61.9 (2) to 84.6 (2.7) vs. 62.3 (1.8) to 79.1 (2); MD 5.9, 95% CI 3.7 to 7.3, p<0.05
Hsieh, 2018[50] Postural control RCT Fair	A. PC gaming using arm and trunk, 60 sessions over 12 (n=20) B. PC gaming using mouse, 60 sessions over 12 weeks (n=20)	A vs. B Age: 7.3 vs. 7.4 Female: 30% vs. 25% Quadriplegia: 55% vs. 60% Diplegia: 20% vs. 15% Athetoid: 10% vs. 10% Ataxic: 15% vs. 15%	A vs. B, mean (SD), p=between groups: TUG: 16.43 (2.12) to 17.51 (1.70) vs. 15.60 (1.10) to 15.91 (1.87), p<0.05 BBS: 44.74 (2.75) to 48.81 (4.74) vs. 44.39 (2.33) to 45.37 (2.68), p<0.05
Hsieh, 2020[182] Postural control RCT Fair	A. PC gaming using balance board, 36 sessions over 12 weeks (n=28) B. PC gaming using mouse, 36 sessions over 12 weeks (n=28)	A vs. B Age: 7.9 vs. 8.1 Female: 32% vs. 31.5% GMFCS I: 53.5% vs. 50% GMFCS II: 28.6% vs. 32.1% GMFCS III: 17.9% vs. 17.9% Deplegic: 57.1% vs. 42.9%	A vs. B, mean (SD) 2MWT: 103.4 (16.6) to 120.1 (20.2) vs. 101.4 (23.1) to 106.1 (22.8), p=0.002 PBS-total: 29.9 (5.3) to 35.8 (5.5) vs. 32.3 (7.5) to 34.4 (5.9), p=0.002
Pourazar, 2020[183] Postural control RCT Fair	A. Virtual reality Microsoft Xbox 360 Kinect, 20 sessions over 6 weeks (n=10) B. Encouraged to do typical physical activity at home (n=10)	A vs. B Age: 9.2 vs. 9.6 Female: 100% GMFCS I: 50% vs. 60% GMFCS II: 20% vs. 30% GMFCS III: 30% vs. 10%	Dynamic balance was improved in the anterior, posterolateral, and posteromedial directions with virtual reality dance game compare with the control group, p=0.001 all comparisons

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Tarakci, 2016[178] Postural control RCT Fair	A. Nintendo Wii-Fit balanced gaming, 24 sessions over 12 weeks (n=15) B. Conventional balance training, 24 sessions over 12 weeks (n=15)	A vs. B Age: 10.5 vs. 10.5 Female: 33% vs. 40% Hemiplegic: 47% vs. 47% Diplegic: 47% vs. 33% Dyskinetic: 7% vs. 20% Assist devices: 0% vs. 20%	A vs. B, mean difference between groups: TUG: –1.24, 95% CI –4.13 to 1.65, p=0.40 10MWT: –1.4, 95% CI –4.36 to 1.56, p=0.35 Sit to Stand Test: 2.07, 95% CI 0.82 to 3.32, p=0.001, favors conventional balance training 10 Step Climbing Test: –0.99, 95% CI –3.99 to 2.01, p=0.52 WeeFIM: 3.43, 95% CI –3.75 to 10.61, p=0.35 Wiibalance: 1.05, 95% CI 0.64 to 1.46, p<0.001 Tilt-table: 11.00, 95% CI 4.74 to 17.26, p=0.001 Tight-rope walking, heading in soccer, and ski slalom: p<0.001
Zoccolillo, 2015[180] Postural control RCT Poor	A. Microsoft Xbox with Kinect (3D motion capture) gaming plus neuro-developmental treatment, 16 sessions over 8 weeks (n=15) B. Neurodevelopmental treatment, 16 sessions over 8 weeks (n=16)	No demographics by group Age: 6.89 Female: NR GMFM-88: 84.6	A vs. B, mean (SD), p=between groups: QUEST: 76 (21) to 81 (20) vs. 74 (20) to 78 (20), p>0.05

Abbreviations: 10MWT = 10-Meter Walk Test; BBS = Berg Balance Scale; CI = confidence interval; FIM = Functional Independence Measure; GMFCS = Gross Motor Function Classification System; GMFM-88 = Gross Motor Function Measure 88; MD = mean difference; NR = not reported; QUEST = Quality of Upper Extremity Skills Test; RCT = randomized controlled trial; SD = standard deviation; TUG = Timed Up and Go Test; WeeFIM = Wee-Functional Independence Measure for children

Four fair-quality RCTs[50,178,182,183] provided low-strength evidence of improved balance with motion gaming, although the specific gaming interventions studied varied (Table 28). Changes in other outcomes (TUG, 10MWT, 10-Step Walking Test) after treatment were not different between groups, were inconsistent, or favored conventional balance training (SOE: insufficient).

Three trials of children with CP evaluated upper extremity function with interventions using a Wii[179,181] and a Microsoft Xbox.[180] Two trials did not show an advantage over traditional neurodevelopmental PT,[179,180] while the third (n=30) found the quality of upper extremity movement improved with virtual reality plus an exoskeleton versus conventional rehabilitation.[181] Due to low quality of included studies and small sample sizes, the evidence for improved quality of upper extremity movements is too limited to draw conclusions (SOE: insufficient).

Six RCTs did not address harms or adverse events. One RCT reported that there were no adverse events during the study.[223]

Motion Gaming—Spinal Cord Injury

One RCT (n=26) demonstrated reduced time to put on a t-shirt, as a measure of dynamic balance, after Nintendo Wii training, in conjunction with conventional therapy compared with conventional therapy alone, but additional evidence is needed to confirm these results (SOE: insufficient) (Table 29).[184]

This study did not address adverse events or harms.

Table 29. Motion gaming in spinal cord injury

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Tak, 2015[184] Postural control RCT Fair	A. Nintendo Wii, 18 sessions over 6 weeks + conventional rehabilitation (n=13) B. Conventional rehabilitation (n=13)	A vs. B Age: 50 vs. 43 Cervical: 31% vs. 38% ASIA (A): 77% vs. 77% ASIA (B): 23% vs. 23%	A vs. B mean (SD), p=between groups T-shirt test (s): 29.5 (10.95) to 22.60 (8.28) vs. 23.59 (11.35) to 22.15 (12.28), p<0.05

Abbreviations: ASIA = American Spinal Injury Association Impairment Scale; RCT = randomized controlled trial; SD = standard deviation

Whole Body Vibration

Whole body vibration is performed in a PT setting using a vibration board upon which a person can stand, sit, or lie for a set period of time, either passively or while performing active movements, depending on the ability of a participant to move on the vibration board.

There is not a standard frequency or amplitude level for vibration therapy, and more research is needed to establish what vibration frequency is most beneficial for this form of exercise.

Key Points

- Evidence for WBV on function, balance, and quality of life in patients with MS is too sparse to draw conclusions (SOE: insufficient).
- Two trials provided insufficient evidence on the effect on walking with WBV in children with CP (SOE: insufficient).
- One trial provided insufficient evidence for improved function in patients with SCI (SOE: insufficient).

Detailed Synthesis

Five RCTs evaluated the effects of WBV in participants with MS,[185,186] CP,[187,188] and SCI.[189] All trials met criteria for fair quality.

Whole Body Vibration—Multiple Sclerosis

Two RCTs (n=93) studied WBV exercise in participants with MS (Table 30).[185,186] All RCTs had intervention groups who performed exercises on the vibration board with a vibration level of 20Hz[186] or 30-40 Hz.[185] One RCT had the participants perform active exercises on the vibration board, while the control group performed the exercises on a stable surface.[185] The second RCT had a no intervention control group.[186]

One RCT provided insufficient evidence to draw conclusions on the effects of WBV versus usual care on function, including walking.[185] One RCT found improvements in quality of life using the MSQoL-54 instrument[186] but additional evidence is needed to confirm this finding (SOE: insufficient).

None of the trials addressed harms or adverse events.

Table 30. Whole body vibration exercise in multiple sclerosis

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Abbasi, 2019[186] Postural control RCT Fair	A. WBV, 18 sessions over 6 weeks (n=22) B. No intervention (n=24)	A vs. B Age: 37 vs. 39 Female: 5% vs. 17% EDSS: 1.54 vs. 1.55	A vs. B, median (IQR) followup baseline scores, p=between groups: MSQOL-54 (PCS): 4.20 (1.73, 8.40) vs. –1.26 (–3.28, 0), p<0.001 MSQOL-54 (MCS): 5.96 (2.71, 11.89) vs. –0.17 (–2.20, 0.07), p<0.001
Claerbout, 2012[185] Postural control RCT Fair	A. WBV, 10 sessions over 3 weeks plus conventional therapy (n=16) B. Whole body light vibration, 10 sessions over 3 weeks plus conventional therapy (n=14) C. Conventional therapy (n=17)	A vs. B vs. C Age: 39.1 vs. 43.8 vs. 47.6 Female: 28.6% vs. 22.2% vs. 64.7% EDSS: 5.3 vs. 5.1 vs. 5.2	A vs. B vs. C: mean (SD) change for each group, p=between groups: 3MWT: 45.0 (42.6) vs. 37.4 (34.3) vs. 20.4 (27.95), p>0.05 for all comparisons TUG: –0.8 (2.3) vs. –3.2 (4.7) vs. 0.8 (5.5), p>0.05 for all comparisons BBS: 3.9 (4.4) vs. 4.2 (6.1) vs. 0.2 (7.5), p>0.05 for all comparisons

Abbreviations: 3MWT = 3-Minute Walk Test; 6MWT = 6-Minute Walk Test; BBS = Berg Balance Scale; EDSS = Expanded Disability Status Scale; IQR = interquartile range; MSQoL = Multiple Sclerosis Quality of Life; RCT = randomized controlled trial; RRMS = relapsing-remitting multiple sclerosis; SD = standard deviation; TUG = Timed Up and Go Test; WBV = whole body vibration

Whole Body Vibration—Cerebral Palsy

Two RCTs[187,188,267] (n=50) studied WBV as an intervention for children with CP, providing insufficient evidence on improvement in walking with WBV (Table 31) due to heterogeneous outcomes reported and inconsistency in direction of findings. One[187] found improved walking speed with vibration therapy where the participants stood or squatted on a vibration board and re

ceived varying frequencies of vibration from 5-25 Hz. The second trial[188] found that walking distance was significantly improved in the control group that stood on the nonvibrating device compared with the group that received 18 minutes of standing WBV (20 to 24 Hz) per training day.[188]

The trials did not address harms or adverse events.

Table 31. Whole body vibration exercise in cerebral palsy

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Ahmadizadeh, 2020 [188] Postural control RCT Fair	A. WBV + stretching, 18 sessions over 6 weeks (n=10) B. Stretching only, 16 sessions over 6 weeks (n=10)	A vs. B Age: 6.9 vs. 8.1 Hemiplegic: 30% vs. 60% Diplegic: 60% vs. 40% Quadrapletic: 10% vs. 0%	A vs. B, mean (SD): 6MWT: 158.8 (100.24) to 189.45 (115.47) vs. 194 (78.82) to 271.5 (60.81), p=0.04
Lee, 2013[187] Postural control RCT Fair	A. WBV + PT, 24 sessions of vibration over 8 weeks (n=15) B. PT (n=15)	A vs. B Age: 10.00 vs. 9.66 Female: 60% vs. 40% Ambulatory: 100% GMFM: 78.4 vs. 79.53	A vs. B, mean (SD), p=between groups: Walking speed (meters/second): 0.37 (0.04) to 0.48 (0.06) vs. 0.39 (0.05) to 0.40 (0.05), p=0.001

Abbreviations: 6MWT = 6-Minute Walk Test; GMFM = Gross Motor Function Measure; PT = physical therapy; RCT = randomized controlled trial; SD = standard deviation; WBV = whole body vibration

Whole Body Vibration—Spinal Cord Injury

One RCT[189] (n=28) studied the effect of WBV on adults with incomplete cervical SCI. Participants were a mean of 14 months post-SCI (Table 32). All participants were ambulatory at baseline and received 80 treatments over 8 weeks in an inpatient rehabilitation setting. The intervention group performed repetitions of a semi-squatting position on a vibration board at 30Hz, while the control group received a sham treatment where they performed the movements on a nonvibrating board. Both groups also received conventional PT. While favoring WBV over usual care on improvement in function, additional studies are needed to confirm this finding (SOE: insufficient).

This trial reported that there were no serious adverse events at 30 Hz but did not address nonserious adverse events.

Table 32. Whole body vibration exercise in spinal cord injury

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
In, 2018[189] Postural control RCT Fair	A. WBV plus PT, 80 sessions over 8 weeks (n=14) B. Sham WBV plus PT, 80 sessions over 8 weeks (n=14)	A vs. B Age: 46.1 vs. 49.9 Female: 36% vs. 29% Ambulatory: 100% C6-C7: 100%	A vs. B, mean (SD), p=between groups: 10MWT: 29.3 (9.0) to 25.8 (8.1) vs. 28.8 (7.2) to 27.5 (6.3), p=0.005 TUG: 13.7 (3.1) to 11.4 (2.8) vs. 14.7 (4.5) to 13.7 (4.1), p=0.016

Abbreviations: 10MWT = 10-Meter Walk Test; PT = physical therapy; RCT = randomized controlled trial; SD = standard deviation; TUG = Timed Up and Go Test; WBV = whole body vibration

Yoga

Originating from ancient India, yoga is a group of physical, mental, and spiritual practices or disciplines. Goals of yoga practices include improving physical and mental health and in the United States yoga often involves meditation, breathing techniques, and holding specific physical postures.

Key Points

- There was low-strength evidence of no clear benefit of yoga compared with usual care on function in MS (SOE: low).
- Evidence was insufficient to draw conclusions among MS study participants on the effects of yoga versus a variety of active controls on balance, function, or quality of life (SOE: insufficient).
- There were no studies of yoga in people with CP or SCI.

Detailed Synthesis

Six RCTs, reported in nine publications,[54,120,190-197] enrolled and randomized participants to yoga versus a comparison group. The types of yoga included Hatha (postures, breathing techniques, and meditation),[191,194-196] an Iyengar approach (focus on alignment) to Hatha Yoga,[54] or was not predefined or well-delineated.[192,193,197] Comparison groups included waitlist control,[54] no intervention,[192] walking,[191,193-196] movement to music,[54] PT-led exercise,[120,192,193] fitness instructor-led exercise,[192,193] group physiotherapy,[197] and one-on-one physiotherapy.[197] Two RCTs were rated fair quality,[54,120] and the remaining were rated poor quality due to methodological limitations that included unclear methods of randomization, allocation concealment and blinding, lack of intent-to-treat analysis, and high attrition. All trials were in participants with MS. Type of MS was reported in one RCT only,[192,193] including 45 percent RRMS, 16 percent SPMS (secondary progressive multiple sclerosis), 10 percent PPMS (primary progressive multiple sclerosis), and 2 percent considered benign MS. All trials involved 8, 10, or 12 weeks of yoga.

Yoga—Multiple Sclerosis

Six RCTs enrolled 648 participants with MS with a weighted mean age of participants of 46.8 years (range 31.6 to 51.4 years) and a weighted mean proportion female of 79.6 percent (range 72.3% to 100%). Three trials enrolled only females (Table 33). Race was only reported in the U.S. study[54] and was 54 percent White, 44 percent Black, and 2 percent other. One study was conducted in participants needing bilateral support for ambulation who may need a wheelchair for longer distances,[197] and one trial enrolled participants with minimal gait impairment.[192,193] Scores on the Patient Determined Disease Steps (PDDS) (0=normal, 8=bedridden) tended toward lower disability (32% PDDS=0) in one RCT.[54]

Four trials provided low-strength evidence of no clear benefit on function with yoga compared with usual care in MS.[54,120,192,193,197] All other findings were supported by limited evidence and/or evidence that was considered to have a high risk of bias (SOE: insufficient). These included balance and quality of life in trials comparing yoga with dance,[54] aerobics,[194-196] physiotherapist-led exercises,[192,193] fitness instructor-led exercises,[192,193] group exercises,[197] and one-on-one exercises.[197] Also included was function in the trial comparing yoga with physiotherapist- and fitness instructor-led exercises[192,193] and in the trial comparing yoga with group and one-on-one exercises.[197]

Three trials did not address harms or adverse events. One RCT reported one adverse event (stroke) in the yoga group versus no adverse events in the control group.[54] Another trial excluded deaths from the analysis but did not report the incidence of death.[196]
One additional trial reports the effects of yoga on depression and is discussed in KQ2a.[70]

Table 33. Yoga exercise in multiple sclerosis

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Ahmadi, 2013[120] Postural control RCT Fair	A. Yoga, 24 sessions over 8 weeks (n=11) B. Waitlist control (n=10)	A vs. B Age: 32 vs. 37 Female: 100% EDSS: 2.00 vs. 2.25	A vs. B, mean (SD), p-value between groups: 10MWT (sec): 8.78 to 8.13 vs. 9.16 to 9.47, p<0.001 2MWT: 109 (17.44) to 120.36 (20.62) vs. 121.50 (27.73) to 119.05 (27.12), p=0.11 BBS: 47.72 (6.78) to 53.81 (3.40) vs. 44.50 (8.48) to 41.70 (8.48), p=0.07
Doulatabad, 2012[190] Najafidoulatabad, 2014[191] Postural control RCT Poor	A. Yoga, 24 sessions over 12 weeks (n=30) B. No intervention over 12 weeks (n=30)	A vs. B Age: 31.6 (18 to 45) Female: 100%	A vs. B, mean difference between groups; mean (SD), p-value within groups MSQoL-54: 2.6, 95% CI 1.64 to 3.56, p<0.001 Sexual satisfaction: A: baseline 1.8 (2.0) to 1.4 (1.5), p=0.001 B: 2.1 (1.2) to 2.1 (1.2), p>0.05
Garrett, 2013a[193] Garrett, 2013b[192] Postural control RCT Poor	A. Physiotherapist–led exercise, 10 sessions over 10 weeks (n=80)[a] B. Yoga, 10 sessions over 10 weeks (n=77) C. Fitness instructor-led exercise, 10 sessions over 10 weeks (n=86)[a] D. Usual care (n=71)	A vs. B vs. C vs. D Age: 51.7 vs. 49.6 vs. 50.3 vs. 48.8 Female: 79% vs. 70% vs. 68% vs. 87% Wheelchair user: 0% RRMS: 55% vs. 60% vs. 49% vs. 55% SPMS: 14% vs. 11% vs. 19% vs. 20% PPMS: 7% vs. 13% vs. 13% vs. 6% Benign: 0% vs. 2% vs. 5% vs. 2%	B vs. D, median (SIQR), p=between groups: 6MWT: 268 (222) to 285 (152) vs. 250 (206) to 315 (232), p=0.73 MSIS-29 (physical): 33.4 (20.0) to 29.4 (19.4) vs. 29.6 (23.0) to 29.9 (20.7), p=0.12 MSIS-29 (psychological): 33.3 (33.3) to 25.9 (33.3) vs. 22.2 (24.1) to 18.5 (38.9), p=0.04
Hasanpour-Dehkordi, 2014[196] Hasanpour-Dehkordi, 2016[195] Hasanpour-Dehkordi, 2016 (2)[194] Postural control RCT Poor	A. Yoga, 36 sessions over 12 weeks (n=20) B. Aerobics, 36 sessions over 12 weeks (n=20) C. Usual care control (n=21)	A vs. B vs. C Age: 31.9 Female: 98%	A vs. B vs. C mean difference, p=between groups on SF-36 QOL: C vs. A: 1106.41, p<0.001 B vs. A: 229.32, p=0.07 C vs. B: 877.10, p<0.001

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Hogan, 2014[197] Postural control RCT Poor	A. Group PT, 10 sessions over 10 weeks (n=48) B. 1-on-1 PT, 10 sessions over 10 weeks (n=35) C. Yoga (n=13) D. Usual care (n=15)	A vs. B vs. C vs. D Age: 57 vs. 52 vs. 58 vs. 49 Female: 63% vs. 57% vs. 62% vs. 87% RRMS: 27% vs. 20% vs. 31% vs. 33% SPMS: 42% vs. 46% vs. 38% vs. 33% PPMS: 17% vs. 31% vs. 15% vs. 33% Unknown: 15% vs. 3% vs. 15% vs. 0%	A vs. B vs. C vs. D, mean (SD/SIQR), p=between groups: 6MWT: 101 (39.5) to 121.2 (47.4) vs. 70 (30) to 45 (54.5) vs. 83.9 (39.8) to 100 (55) vs. 83.5 (44) to 90 (35), p>0.05 for all group comparisons MSIS-29 (physical): 50.5 (9.5) to 45.9 (10.5) vs. 48.3 (10.5) to 49.6 (11.6) vs. 54 (11.5) to 49.4 (12) vs. 55.3 (9.5) to 50.5 (11.3), p=NR MSIS-29 (psychological): 18 (5.5) to 15 (5.7) vs. 14 (2.2) to 15 (4) vs. 18 (5.38) to 17 (4.8) vs. 17 (4) to 15 (4.5), p>0.05 for all group comparisons BBS: 28.9 (9.5) to 34.5 (9.8) vs. 22.6 (12.6) to 27.9 (11.5) vs. 30.4 (11.6) to 34.2 (9.8) vs. 24.9 (11.6) to 21.8 (11.9), p<0.05 for all comparisons vs. control
Young, 2019[54] Postural control RCT Fair	A. Movement to Music, 36 sessions over 12 weeks (n=27) B. Adapted Yoga, 36 sessions over 12 weeks (n=26) C. Waitlist control (n=28)	A vs. B vs. C Age: 50 vs. 48 vs. 47 Female: 81% vs. 77% vs. 86% White: 44 vs. 58% vs. 61%	A vs. B vs. C, mean difference, p=between groups: TUG: A vs. C: –1.89, 95% CI –3.30 to –0.48,p=0.01 B vs. C: –1.20, 95% CI –2.58 to 0.18, p=0.09 B vs. A: 0.69, 95% CI –0.71 to 2.08, p=0.33 6MWT: A vs. C: 40.98, 95% CI 2.21 to 80, p=0.04 B vs. C: 22.83, 95%CI –16.67 to 6.2,p=0.25 B vs. A: –18.15, 95% CI –56.4 to 20.1, p=0.34 5xSit-to-Stand: A vs. C: –1.00, 95% CI –2.58 to 0.55, p=0.20 B vs. C: –0.70, 95% CI –2.17 to 0.77, p=0.34 B vs. A: 0.30, 95% –1.21 to 1.82, p=0.69

Abbreviations: 5x = five times; 6MWT = 6-Minute Walk Test; BBS = Berg Balance Scale; CI = confidence interval; EDSS = Expanded Disability Status Scale; MS = multiple sclerosis; MSIS-29 = Multiple Sclerosis Impact Scale; MSQoL = Multiple Sclerosis Quality of Life; NR = not reported; PT = physical therapy; RCT = randomized controlled trial; RRMS = relapsing-remitting multiple sclerosis; SD = standard deviation; SIQR = semi-interquartile range; SF-36 QOL = Short Form Survey (36 Item) Quality of Life; SPMS = secondary progressive multiple sclerosis; TUG = Timed Up and Go Test

[a] Not included in the sample size total in the Detailed Synthesis paragraph.

Yoga—Cerebral Palsy

No studies were identified.

Yoga—Spinal Cord Injury

No studies were identified.

Strength Exercise Interventions

Muscle Strength Exercise

Strength exercise focuses on muscle training interventions to increase muscle strength and includes exercises such as progressive resistance exercise, body weight resistance exercise, and Pilates.

Key Points

- In participants with MS, muscle strength exercise was not associated with improved function, including walking, balance, or quality of life versus usual care (SOE: low).
- In participants with CP, evidence from small trials suggest muscle strength exercise was not associated with improved walking or function when compared with usual care immediately postintervention or in the short term (SOE: low).
- In participants with SCI, there was insufficient evidence from one small trial on quality of life compared with usual care (SOE: insufficient).

Detailed Synthesis

Nineteen RCTs[52,68,83,149,198-216,218] and two quasiexperimental trials[62,217] involving 1,070 participants evaluated muscle strengthening interventions. Muscle strength exercises included progressive resistance exercises of various kinds (e.g., resistance against external weights such as leg press and hamstring curls, as well as body weight resistance such as abdominal crunches and Pilates). Most trials compared muscle strengthening to usual care, which included continuation of usual PT or rehabilitation,[52,200,201,204,205,213,216] previous activity levels,[199,202,203] or an attention control of relaxation techniques at home or massage.[198,200,201,206] Two trials included two comparator groups.[68,69,206] Pilates was compared with aquatic exercise in one trial[68,69] and progressive resistance combined with neuromuscular electrical stimulation versus neuromuscular electrical stimulation alone in another.[210] Eleven trials[52,68,69,149,198-206,215] and one quasiexperimental study[62] enrolled participants with MS (Table 34). Seven trials[207-216] and one quasiexperimental study[217] were of participants with CP (Table 35), and one trial was conducted in participants with SCI (Table 36).[218] Three trials[204,205,211,212] met criteria for good quality, twelve for fair quality,[52,83,149,198-203,207-210,214,215,218] and four trials[68,69,206,213,216] and two quasiexperimental studies[62,217] were rated poor quality. The poor-quality trials were judged to have high risk of bias due to unclear randomization and/or allocation concealment, lack of similarity between treatment groups at baseline, and unacceptable attrition. The quasiexperimental trials were deemed to have high risk of bias due to lack of similarity between treatment groups, the absence of controlling for potential confounding, and unacceptable attrition. The most frequently reported outcomes varied by condition. Most prioritized outcomes reported across conditions were walking-related (e.g., 2MWT, 6MWT, 10MWT) and few studies reported measures of functional capacity (e.g., TUG) or quality of life (e.g., SF-36). Meta-analyses of trials was conducted as appropriate.

Muscle Strength Exercise—Multiple Sclerosis

Eleven trials[52,68,69,83,149,198-206] and one quasiexperimental study[62] enrolled participants with MS (n=584) (Table 34). Weighted mean age of participants across trials was 45.7 years (range 41 to 54 years) with a weighted mean proportion female of 67.9 percent (range 29% to 100%). Race/ethnicity generally was not reported. Ambulation status varied across studies. All studies enrolled participants who could, at minimum, ambulate using bilateral assistance (i.e., crutches, canes). The EDSS at baseline was reported in four trials with a range of means or medians of 2.9 to 5.9. The weighted mean number of sessions across trials was 22.6 over a weighted mean period of 11.6 weeks.

Table 34. Muscle strength exercise in multiple sclerosis

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Bulguroglu, 2017[206] Strength RCT Poor	A. Mat Pilates, 16 sessions over 8 weeks (n=12) B. Reformer Pilates, 16 sessions over 8 weeks (n=13) C. Attention control, 16 sessions over 8 weeks (n=13)	A vs. B vs. C Age: 45 vs. 37 vs. 40 Ambulatory: 100% EDSS: 1.8 vs. 2.0 vs. 1.0	Median (IQR) **A vs. C** TUG: 6.5 (5.2 to 7.0) vs. 5.2 (4.6 to 6.1) (baseline); 5.7 (5.0 to 6.5) vs. 4.9 (4.5 to 5.3) (postintervention) MSQoL-54-MCS: 74.54 (65.43 to 83.41) vs. 75.65 (68.08 to 86.38) (baseline); 77.23 (70.72 to 84.54) vs. 78.52 (64.77 to 89.21) (postintervention) MSQoL-54-PCS: 74.54 (65.43 to 83.41) vs. 77.35 (68.17 to 88.31) (baseline);75.8 (70.83 to 86.42) vs. 82.64 (66.77 to 91.27) (postintervention) ABCS: 76.6 (62.7 to 92.7) vs. 90.6 (74.4 to 97.4) (baseline); 80.5 (71.7 to 97.3) vs. 91.9 (75.6 to 99.1) (postintervention) **B vs. C** TUG: 6.4 (5.0 to 8.9) vs. 5.2 (4.6 to 6.1) (baseline); 5.4 (4.9 to 7.1) vs. 4.9 (4.5 to 5.3) (postintervention) MSQoL-54-MCS: 74.58 (70.39 to 80.58) vs. 75.65 (68.08 to 86.38) (baseline); 69.2 (65.86 to 71.41) vs. 78.52 (64.77 to 89.21) (postintervention) MSQoL-54-PCS: 71.14 (67.26 to 74.35) vs. 77.35 (68.17 to 88.31) (baseline); 76.3 (74.39 to 83.37) vs. 82.64 (66.77 to 91.27) (postintervention) ABCS: 69.4 (52.8 to 87.8) vs. 90.6 (74.4 to 97.4) (baseline); 69.4 (52.8 to 87.8) vs. 91.9 (75.6 to 99.1) (postintervention)

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Callesen, 2019[149] Strength RCT Fair	A. Progressive resistance training (n=17): 20 sessions over 10 weeks -median number of sessions completed (range): 17 (8 to 19) B. Balance training (n=24): 20 sessions over 10 weeks -median number of sessions completed (range): 16 (6 to 20) C. Waitlist control (n=18)	A vs. B vs. C Median age: 52 vs. 51 vs. 56 years Female: 70% vs. 82% vs. 80% Race: NR Ambulatory: 100% vs. 100% vs. 100% Gait assistive devices: 17% vs. 11% vs. 10% Median duration of illness: 15 vs. 10 vs. 11 years MS type - RRMS: 70% vs. 75% vs. 65% - SPMS: 22% vs. 14% vs. 15% - PPMS: 70% vs. 9% vs. 20% Median EDSS: 4 vs. 4 vs. 3.5	Mean change scores (95% CI); mean difference between groups (95% CI) **A vs. C** <u>6MWT (meters):</u> 22.8 (4.6 to 41.0) vs. 11.3 (−6.0 to 28.5), MD 12.6 (−11.3 to 36.5), p=0.30 <u>MSWS-12:</u> −6.5 (3.0 to 10.1) vs. −1.3 (−2.2 to 4.7), MD −4.2 (−10.0 to 1.6), p=0.16 <u>MiniBEST:</u> 2.1 (0.8 to 3.4) vs. 0.9 (−0.4 to 2.2), MD 1.1 (−0.7 to 2.9), p=0.24 <u>25FWT (meters/second):</u> 0.06 (−0.01 to 0.13) vs. 0.04 (−0.03 to 0.11), MD 0.02 (−0.08 to 0.13), p=0.66 <u>SSST (seconds):</u> −0.9 (−2.0 to 0.2) vs. −0.4 (−1.5 to 0.7), MD −0.5 (−2.1 to 1.0), p=0.52 **B vs. A** <u>6MWT (meters):</u> 28.5 (13.6 to 43.4) vs. 2.8 (4.6 to 41.0), MD 4.9 (−17.5 to 27.3), p=0.67 <u>MSWS-12:</u> −9.3 (6.3 to 12.3) vs. −6.5 (3.0 to 10.1), MD −3.1 (−8.2 to 2.0), p=0.23 <u>MiniBEST:</u> 4.1 (3.0 to 5.2) vs. 2.1 (0.8 to 3.4), MD 2.2 (0.5 to 3.9), p=0.01 <u>25FWT (meters/second):</u> 0.14 (0.08 to 0.20) vs. 0.06 (−0.01 to 0.13), MD 0.08 (−0.02 to 0.18), p=0.11 <u>SSST (seconds):</u> −2.6 (−3.6 to –1.7) vs. −0.9 (−2.0 to 0.2), MD −1.7 (−3.1 to –0.2), p=0.02
Dalgas, 2009[202] Dalgas, 2010[203] Strength RCT Fair	A. Progressive resistance, 24 sessions over 12 weeks (n=15) B. Waitlist control (n=16)	A vs. B Age: 45 vs. 48 Female: 63% vs. 67% Ambulatory to 100m: 100% RRMS: 100%	A vs. B, mean (95% CI), p=between groups: <u>6MWT</u>: 15.3% (9.8% to 20.9%) vs. 3.9% (−1.2% to 8.9%), p<0.05 <u>10MWT</u>: −12.3% (−16.8% to −7.9%) vs. 6.7% (−0.7% to 14.1%), p<0.05 <u>SF-36 MCS</u>: 54.3 (50.4 to 58.2) vs. 55.0 (50.5 to 59.5) (baseline); 56.8 (52.4 to 61.2) vs. 53.1 (49.3 to 56.8) (postintervention), p>0.05 <u>SF-36 PCS</u>: 41.4 (37.5 to 45.3) vs. 42.6 (38.5 to 46.6) (baseline); 44.9 (40.9 to 48.9) vs. 41.6 (37.8 to 45.4) (postintervention), p<0.05 <u>EDSS:</u> 3.9% (−3.4% to 11.2%) vs. −0.7% (−9.3% to 7.9%), p>0.05

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Dodd, 2011[204] Strength RCT Good	A. Progressive resistance, 20 sessions over 10 weeks (n=36) B. Attention control (social program), 10 sessions over 10 weeks (n=35)	A vs. B Age: 47.7 vs. 50.4 Female: 72% vs. 74% Ambulation index: 2 (mild): 47% vs. 54% 3 (moderate): 39% vs. 26% 4 (severe): 14% vs. 20% Gait aid use (yes): 33% vs. 37%	A vs. B, mean difference 2MWT: MD 2.6, 95% CI −4.0 to 9.1, p>0.05 (post-pre change); MD −3.4 (95% CI −9.5 to 2.7), p>0.05 (week 22 followup) WHO-QOL: MD 0.3, 95% CI −0.1 to 0.6, p>0.05 (post-pre change); MD −0.2, 95% CI −0.6 to 0.3, p>0.05 (week 22 followup)
Duff, 2018[198] Strength RCT Fair	A. Pilates plus massage, 24 sessions of Pilates and 12 massages over 12 weeks (n=15) B. Attention control (massage), 12 massages over 12 weeks (n=15)	A vs. B Age: 45.7 vs. 45.1 Female: 80% vs. 73% Ambulatory: 100% Wheelchair user: 0% RRMS: 93% vs. 73% SPMS: 0% vs. 13% PPMS: 7% vs. 13%	A vs. B, mean difference (95% CI), p=between groups TUG left turn: −1.5 (–2.7 to –0.4) vs. 0.3 (95% CI –0.9 to 1.4), p=0.03 TUG right turn: –1.1 (95% CI –2.1 to –0.1) vs. 0.3 (–0.7 to 1.4), p=0.6 6MWT: 52.4 (32.7 to 72.1) vs. 15.0 (–4.7 to 34.7), p=0.01 MSQoL-54-PCS: 4.6 (–1.3 to 10.5) vs. 2.4 (–3.5 to 8.3), p=0.60 MSQoL-54-MCS: 5.9 (–0.5 to 12.2) vs. 4.2 (–2.1 to 10.6), p=0.71 FABS: 2.3 (0.3 to 4.3) vs. 2.2 (0.2 to 4.2), p=0.96
Fox, 2016[200] Freeman, 2012[201] Strength RCT Fair	A. Pilates, 12 sessions over 12 weeks (n=33) B. Usual PT, 12 sessions over 12 weeks (n=35) C. Relaxation, 3 sessions over 12 weeks (n=32)	A vs. B vs. C Age: 53.97 vs. 54.60 vs. 53.78 Female: 85% vs. 71% vs. 66% Ambulatory to 20 m: 100% RRMS: 39% vs. 37% vs. 38% SPMS: 24% vs. 31% vs. 34% PPMS: 36% vs. 31% vs. 25% Benign: 0% vs. 0% vs. 3%	Mean difference (95% CI), p=between groups: **A vs. B** 10MWT: −3.71 (−7.79 to 0.37), p>0.05 (postintervention); −1.96 (−6.04 to 2.13), p>0.05 (4-week followup) MSWS-12: −15.65 (−29.50 to −1.79), p<0.05 (postintervention); −15.97 (−29.83 to −2.12), p<0.05 (4-week followup) ABCS: 0.98 (−0.24 to 2.21), p>0.05 (postintervention); 0.95 (−0.28 to 2.17), p>0.05 (4-week followup) **A vs. C** 10MWT: −0.50 (−4.68 to 3.69), p>0.05 (postintervention); −0.50 (−4.68 to 3.69), p>0.05 (4-week followup) MSWS-12: −4.90 (−19.11 to 9.32), p>0.05 (postintervention); −3.71 (−17.93 to 10.50), p>0.05 (4-week followup) ABCS: 0.49 (−0.76 to 1.74), p>0.05 (postintervention); 0.31 (−0.94 to 1.56), p>0.05 (4-week followup)

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Kalron, 2017[52] Strength RCT Fair	A. Pilates, 12 sessions over 12 weeks (n=22) B. Usual physical therapy, 12 sessions over 12 weeks (n=23)	A vs. B Age: 42.9 vs. 44.3 Female: 60.9% vs. 68.2% Ambulatory to 100m: 100% EDSS: 4.1 vs. 4.6 RRMS: 100%	A vs. B, mean change (SD), p=between group TUG: −1.8 (2.1) vs. −1.7 (2.1), p=0.422 6MWT: 39.1 (78.3) vs. 25.3 (67.2), p=0.341 2MWT: 14.5 (25.8) vs. 12.7 (23.0), p=0.872 MSWS-12: 2.8 (6.3) vs. 2.4 (5.9), p=0.924 BBS: 1.1 (4.2) vs. 1.3 (5.2), MD –0.20, 95% CI –2.888 to 2.488, p=0.561
Kara, 2017[62] Strength Quasiexperimental Poor	A. Pilates, 16 sessions over 8 weeks (n=27) B. Multimodal exercise (focus on aerobic), 16 sessions over 8 weeks (n=28)	A vs. B Age: 50 vs. 43 Female: 67% vs. 65% EDSS: 2.85 vs. 3.2	A vs. B, mean difference (95% CI), p=between groups: TUG right: –0.47 (–2.98 to 2.04), p=0.71 TUG left: –3.07 (–6.34 to 0.20), p=0.07 BBS: –0.67 (–10.56 to 9.22), p=0.89
Kjolhede, 2016[199] Strength RCT Fair	A. Progressive resistance, 48 sessions over 24 weeks (n=17) B. Usual care (habitual lifestyle) (n=18)	A vs. B Age: 44.6 vs. 42.2 Female: 75% vs. 75% EDSS: 2.9 vs. 2.9 RRMS: 100%	A vs. B, mean (95% CI), p=between group: 2MWT (m/s): 1.61 (1.4 to 1.8) vs. 1.66 (1.5 to 1.8) (baseline); 1.77 (1.6 to 2.0) vs. 1.69 (1.5 to 1.9) (postintervention), p=0.011 2MWT (meters): 193.2 (168 to 216) vs. 199.2 (180 to 216) (baseline); 212.2 (192 to 240) vs. 202.8 (180 to 228) (postintervention) 25FWT (m/s): 1.66 (1.5 to 1.8) vs. 1.79 (1.6 to 2.0) (baseline); 1.82 (1.7 to 2.0) vs. 1.80 (1.6 to 2.0) (postintervention), p=<0.001
Marandi, 2013[68,69] Strength RCT Poor	A. Pilates, 36 sessions over 12 weeks (n=15) B. Aquatics, 36 sessions over 12 weeks (n=15) C. Usual care (n=15)	A vs. B vs. C Age: NR Female: 100% Ambulatory: 100% Wheelchair user: 0%	Mean difference (SE), p=between groups: **A vs. C** **A vs. C** Right leg SSST: −5.96 (1.4), p=0.000 Left leg SSST: −6.23 (1.2), p=0.000 **A vs. B** Right leg SSST: −0.08 (1.4), p=0.955 Left leg SSST: 0.00 (1.2), p=0.997

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Ortiz-Rubio, 2016[205] Strength RCT Good	A. Upper extremity strength plus coordination, 16 sessions over 8 weeks (n=19) B. Booklet with exercise info (n=18)	A vs. B Age: 42.21 vs. 44.89 Female: 26% vs. 33% MS type: RRMS: 21% vs. 22% PPMS: 16% vs. 11% SPMS: 63f% vs. 67% EDSS: 5.71 vs. 6.04	A vs. B, mean difference (95% CI), p=between groups: <u>ARAT most affected upper limb:</u> 2.21 (−2.95 to −1.46) vs. 0.16 (−0.29 to 0.62), p=<0.001 <u>ARAT least affected upper limb:</u> 0.68 (−1.28 to −0.08) vs. 0.16 (−0.08 to 0.42), p<0.001
Tollar, 2020[83] **Strength**: proprioceptive neuromuscular facilitation RCT Fair	A. Proprioceptive neuromuscular facilitation, 25 sessions over 5 weeks (n=14) B. Usual care, 25 sessions over 5 weeks (n=12)	Age: 47 vs. 44 Female: 93% vs. 92% Ambulatory: 100% RRMS: 64% vs. 66% PPMS: 36% vs. 34% Median EDSS score: 5.0 vs. 5.0	A vs. B, mean (SD) <u>MSIS-29:</u> 109.8 (10.67) vs. 109.8 (10.67) (baseline) –1.9 (2.8) vs. 1.0 (3.46), MD –2.9 (95% CI –5.4 to –0.4) (pre-post change) <u>EQ-5D sum score:</u> 13.9 (1.44) vs. 13.3 (0.89) (baseline) –0.5 (1.16) vs. 0.0 (1.3), MD –0.5 (95% CI –1.5 to 0.5) (pre-post change) <u>BDI:</u> 12.3 (2.55) vs. 14.3 (3.22) (baseline) –0.6 (1.87) vs. –0.4 (2.94), MD –0.2 (95% CI –2.2 to 1.8) (pre-post change) <u>BBS:</u> 21.1 (1.51) vs. 22.5 (4.38) (baseline) 1.6 (3.52) vs. –0.2 (2.62), MD 1.8 (95% CI –0.7 to 4.3) (pre-post change) <u>6MWT:</u> 244.3 (52.98) vs. 243.3 (39.56) (baseline) 5.5 (34.64) vs. 6.3 (49.27), MD –0.8 (95% CI –34.9 to 33.3) (pre-post change)

Abbreviations: 2MWT = 2-Minute Walk Test; 6MWT = 6-Minute Walk Test; 10MWT = 10-Meter Walk Test; 25FWT = 25-Foot Walk Test; ABCS = Activities-specific Balance Confidence Scale; AC = attention control; AE = adverse event; ARAT = Action Research Arm Tests; BBS = Berg Balance Scale; BDI = Beck Depression Index; CI = confidence interval; EDSS = Expanded Disability Status Scale; EPC = Evidence-based Practice Center; EQ-5D = EuroQOL-5 Dimension Questionnaire; FABS = Fullerton Advanced Balance Scale; IQR = interquartile range; MD = mean difference; MiniBEST = Mini Balance Evaluation System Test; MS = multiple sclerosis; MSIS-29 = Multiple Sclerosis Impact Scale; MSQoL-MCS = Multiple Sclerosis Quality of Life–54 instrument Mental Component Score; MSQoL-PCS = Multiple Sclerosis Quality of Life–54 instrument Physical Component Score; MSWS-12 = Multiple Sclerosis Walking Scale-12; MD = mean difference; NR = not reported; PPMS = primary progressive multiple sclerosis; PT = physical therapy; QOL = quality of life; RCT = randomized controlled trial; RRMS = relapsing-remitting multiple sclerosis; SD = standard deviation; SE = standard error; SF-36 MCS = Short-Form 36 Mental Component Summary; SF-36 PCS = Short-Form 36 Physical Component Score; SPMS = secondary progressive multiple sclerosis; SSST = Six Spot Step Test; TUG = Timed Up and Go Test; WHOQoL = World Health Organization Quality of Life

Walking Measures

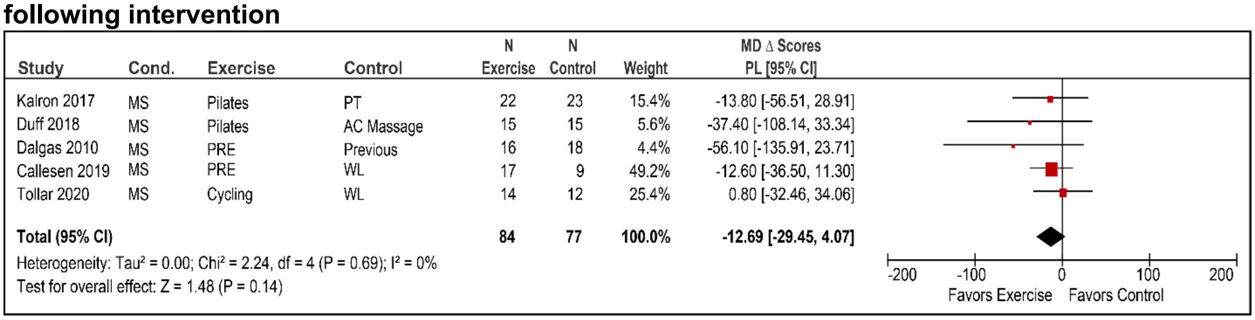
Walking-related outcome measures were most commonly reported. Strengthening exercises were generally not clearly associated with improved walking ability across measures compared with attention control (massage or social program), continuation of previous exercise, or PT

immediately postintervention, based on pooled differences in changed scores (6MWT [Figure 9, 5 trials[83]]; 2MWT [Figure 10, 3 trials[52,199,204]]; 10MWT [Figure 11, 2 trials with 3 comparisons[200-203]]; and multiple sclerosis walking scale MSWS-12 [Figure 12, 0-100 scale, 3 trials with 3 comparisons [52,149,200,201]]). Study results were generally homogeneous across trials for all walking measures despite variability in type, duration, and intensity of the strengthening exercises, and differences in the baseline activity level in the control groups. Two trials also reported no difference in walking speed in the strengthening group versus previous activity level or waitlist controls for the 25FWT[149,199] (2 trials, MD −0.07 seconds, 95% CI −0.19 to 0.05, I^2=47%) (Figure 13).

There was limited evidence for a strengthening exercise effect beyond immediate posttreatment. There was no clear improvement in walking ability (10MWT) at short-term followup for strengthening exercises versus a relaxation attention control or PT (2 trials with 3 comparisons,[200-203] MD −1.3, 95% CI −2.75 to 0.22) (Figure 11).

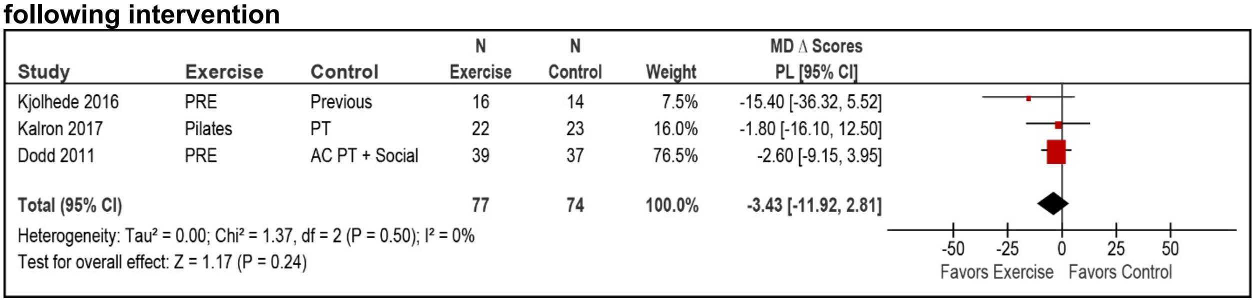
These trials provided low-strength evidence of no clear benefit on walking with muscle strength exercises compared with usual care immediately postintervention and at short-term followup.

Figure 9. Muscle strength exercise versus usual care in multiple sclerosis: 6MWT immediately following intervention



Abbreviations: Δ = change; 6MWT = 6-Minute Walk Test; AC = attention control; CI = confidence interval; MD = mean difference; PL = profile likelihood; PRE = progressive resistance exercise; PT = physical therapy

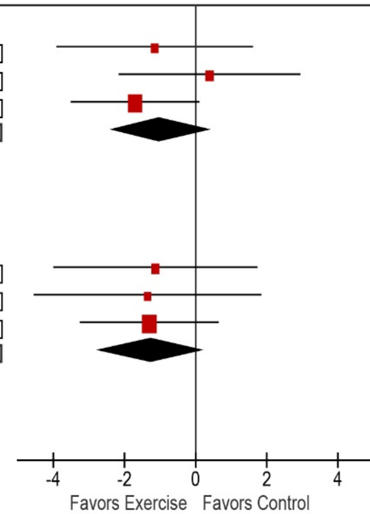
Figure 10. Muscle strength exercise versus usual care in multiple sclerosis: 2MWT immediately following intervention



Abbreviations: Δ = change; 2MWT = 2-Minute Walk Test; AC = attention control; CI = confidence interval; MD = mean difference; PL = profile likelihood; PRE = progressive resistance exercise; PT = physical therapy

Figure 11. Muscle strength exercise versus usual care in multiple sclerosis: 10MWT immediately following intervention and during the short-term followup

Study	Exercise	Control	N Exercise	N Control	Weight	MD Δ Scores PL [95% CI]
IP						
Fox 2016 (AC)	Pilates	AC Relaxation	16	29	22.1%	-1.15 [-3.89, 1.59]
Fox 2016 (PT)	Pilates	PT	17	32	25.9%	0.39 [-2.14, 2.92]
Dalgas 2010	PRE	Previous	16	18	52.0%	-1.70 [-3.49, 0.09]
Subtotal (95% CI)			**49**	**79**	**100.0%**	**-1.04 [-2.48, 0.69]**
Heterogeneity: Tau² = 0.00; Chi² = 1.76, df = 2 (P = 0.42); I² = 0%						
Test for overall effect: Z = 1.58 (P = 0.11)						
Short						
Fox 2016 (AC)	Pilates	AC Relaxation	16	29	25.1%	-1.13 [-3.98, 1.72]
Fox 2016 (PT)	Pilates	PT	17	32	20.2%	-1.35 [-4.52, 1.82]
Dalgas 2010	PRE	Previous	15	16	54.7%	-1.30 [-3.23, 0.63]
Subtotal (95% CI)			**48**	**77**	**100.0%**	**-1.27 [-2.75, 0.22]**
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 2 (P = 0.99); I² = 0%						
Test for overall effect: Z = 1.74 (P = 0.08)						

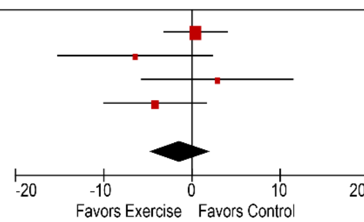


Abbreviations: Δ = change; 10MWT = 10-Meter Walk Test; AC = attention control; CI = confidence interval; MD = mean difference; PL = profile likelihood; PRE = progressive resistance exercise; PT = physical therapy

Figure 12. Muscle strength exercise versus usual care in multiple sclerosis: MSWS-12 immediately following intervention

Figure 12 is a forest plot examining 12 minute walking test scores comparing muscle strength exercise with usual care. The pooled mean difference for the four studies is -1.36 (95% confidence interval -4.83 to 2.10), favoring exercise, with an I-squared value of 26% and a p-value of 0.44.

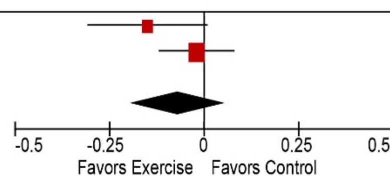
Study	Cond.	Exercise	Control	N Exercise	N Control	Weight	MD Δ Scores PL [95% CI]
Kalron 2017	MS	Pilates	PT	22	23	46.8%	0.40 [-3.17, 3.97]
Fox 2016 (AC)	MS	Pilates	AC Relaxation	16	29	13.5%	-6.44 [-15.18, 2.30]
Fox 2016 (PT)	MS	Pilates	PT	17	32	13.9%	2.88 [-5.69, 11.45]
Callesen 2019	MS	PRE	WL	17	9	25.8%	-4.20 [-10.00, 1.60]
Total (95% CI)				**72**	**93**	**100.0%**	**-1.36 [-4.83, 2.10]**
Heterogeneity: Tau² = 3.37; Chi² = 4.04, df = 3 (P = 0.26); I² = 26%							
Test for overall effect: Z = 0.77 (P = 0.44)							



Abbreviations: AC = attention control; CI = confidence interval; MD = mean difference; MSWS-12 = Multiple Sclerosis Walking Scale-12; PL = profile likelihood; PT = physical therapy

Figure 13. Muscle strength exercise versus usual care in multiple sclerosis: 25FWT immediately following intervention

Study	Cond.	Exercise	Control	N Exercise	N Control	Weight	MD Δ Scores PL [95% CI]
Kjolhede 2016	MS	PRE	Previous	16	14	38.5%	-0.15 [-0.31, 0.01]
Callesen 2019	MS	PRE	WL	17	18	61.5%	-0.02 [-0.12, 0.08]
Total (95% CI)				**33**	**32**	**100.0%**	**-0.07 [-0.19, 0.05]**
Heterogeneity: Tau² = 0.00; Chi² = 1.90, df = 1 (P = 0.17); I² = 47%							
Test for overall effect: Z = 1.11 (P = 0.27)							

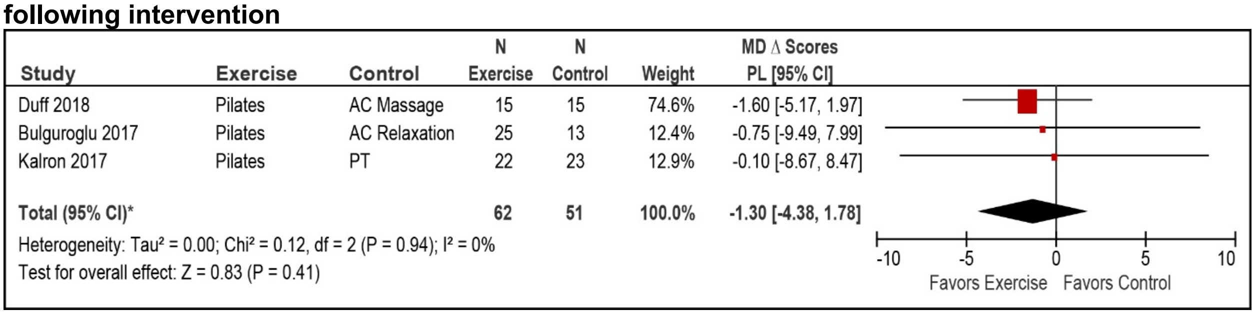


Abbreviations: Δ = change; 25FWT = 25-Foot Walk Test; CI = confidence interval; MD = mean difference; MS = multiple sclerosis; PL = profile likelihood; PRE = progressive resistance exercise; WL = waitlist

Functional Capacity Measures

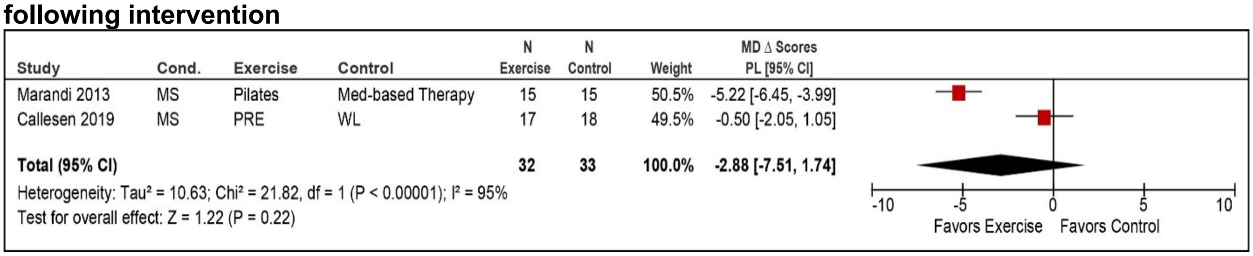
Muscle strengthening exercises resulted in no difference in improvement in functional capacity based on the TUG immediately postintervention compared with usual care or attention control (3 trials[52,198,206] MD −1.3 seconds, 95% CI −4.38 to 1.78, I^2=0%) (Figure 14). Exclusion of the poor-quality trial[206] resulted in a smaller but more precise effect estimate, however the difference did not reach statistical significance (2 trials, MD −0.61 seconds, 95% CI −2.00 to 0.78, I^2=33%). One poor-quality study of Pilates versus aerobics found no difference between groups for the right or left TUG.[62] Two trials (1 fair and 1 poor quality)[68,69,149] found no improvement in the Six Spot Step Test (SSST), with strengthening exercises compared with usual care (2 trials, MD −2.88 seconds, 95% CI −7.51 to 1.74, I^2=95%) (Figure 15). Additionally, there was no difference in the SSST compared with aquatic exercise in one trial.[68,69] Results provided low-strength evidence of no clear benefit on function with strength exercises alone compared with usual care.

Figure 14. Muscle strength exercise versus usual care in multiple sclerosis: TUG immediately following intervention



Abbreviations: Δ = change; AC = attention control; CI = confidence interval; MD = mean difference; PL = profile likelihood; PT = physical therapy; TUG = Timed Up and Go Test

Figure 15. Muscle strength exercise versus usual care in multiple sclerosis: SSST immediately following intervention



Abbreviations: Δ = change; CI = confidence interval; MD = mean difference; MS = multiple sclerosis; PL = profile likelihood; PRE = progressive resistance exercise; SSST = Six Spot Step Test; WL = waitlist

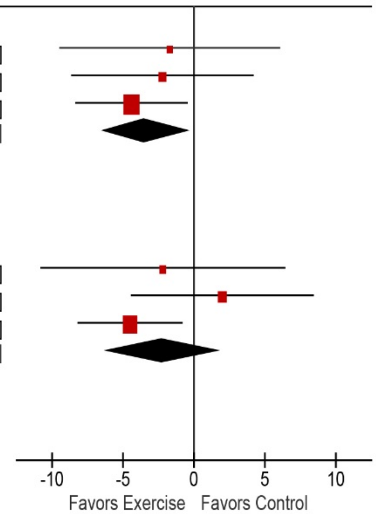
Quality of Life Measures

Quality of life based on the Mental Component Summary (MCS) and Physical Component Summary (PCS) of either the SF-36 or MSQoL (0-100 scales) was reported in three trials.[198,202,203,206] A small improvement in MCS was seen for muscle strengthening exercises versus attention control or massage (3 trials,[198,202,203,206] MD −3.5, 95% CI −6.61 to −0.27, I^2=0%) (Figure 16). Exclusion of the poor-quality trial[206] had a negligible impact on the effect size (MD -3.85, 95% CI -7.33 to -0.37, I^2=0%). It is unclear whether this small difference represents a clinically meaningful improvement. There was no difference between groups for PCS across all three trials[198,202,203,206] (MD −2.8, 95% CI −6.68 to 3.12, I^2=34%) (Figure 16). However, exclusion of the poor-quality trial[206] resulted in a small improvement favoring muscle strengthening exercise (2 trials, MD −4.2, 95% CI −7.51 to −0.79, I^2=0%). Again, it is unclear

whether this small difference represents a clinically meaningful improvement. Two additional trials found no difference in overall quality of life based on the WHOQOL immediately postintervention or 12 weeks after the intervention (difference 0.3, 95% CI −0.1 to 0.6, and difference −0.2, 95% CI −0.6 to 0.3, respectively),[83,204] or the EuroQOL-5 Dimension Questionnaire (EQD-5) immediately postintervention (difference –0.5, 95% CI –1.5 to 0.5).[83] Together these studies found low-strength evidence of no clear benefit with strength exercises alone on quality of life compared with usual care.

Figure 16. Muscle strength exercise versus usual care in multiple sclerosis: MSQOL/SF-36 MCS and PCS immediately following intervention

Study	Exercise	Control	N Exercise	N Control	Weight	MD Δ Scores PL [95% CI]
MCS						
Duff 2018	Pilates	AC Massage	15	15	15.6%	-1.70 [-9.42, 6.02]
Bulguroglu 2017	Pilates	AC Relaxation	25	13	23.0%	-2.22 [-8.59, 4.15]
Dalgas 2010	PRE	Previous	16	18	61.4%	-4.40 [-8.30, -0.50]
Subtotal (95% CI)			**56**	**46**	**100.0%**	**-3.48 [-6.61, -0.27]**
Heterogeneity: Tau² = 0.00; Chi² = 0.57, df = 2 (P = 0.75); I² = 0%						
Test for overall effect: Z = 2.23 (P = 0.03)						
PCS						
Duff 2018	Pilates	AC Massage	15	15	18.3%	-2.20 [-10.78, 6.38]
Bulguroglu 2017	Pilates	AC Relaxation	25	13	28.5%	2.00 [-4.38, 8.38]
Dalgas 2010	PRE	Previous	16	18	53.3%	-4.50 [-8.15, -0.85]
Subtotal (95% CI)			**56**	**46**	**100.0%**	**-2.77 [-6.68, 3.12]**
Heterogeneity: Tau² = 4.73; Chi² = 3.03, df = 2 (P = 0.22); I² = 34%						
Test for overall effect: Z = 1.07 (P = 0.29)						



Abbreviations: Δ = change; AC = attention control; CI = confidence interval; MD = mean difference; MSQOL = Multiple Sclerosis Quality of Life; PL = profile likelihood; PRE = progressive resistance exercise; SF-36 MCS/PCS = Short-Form 36 Mental Component Summary/Physical Component Summary

Other Outcome Measures

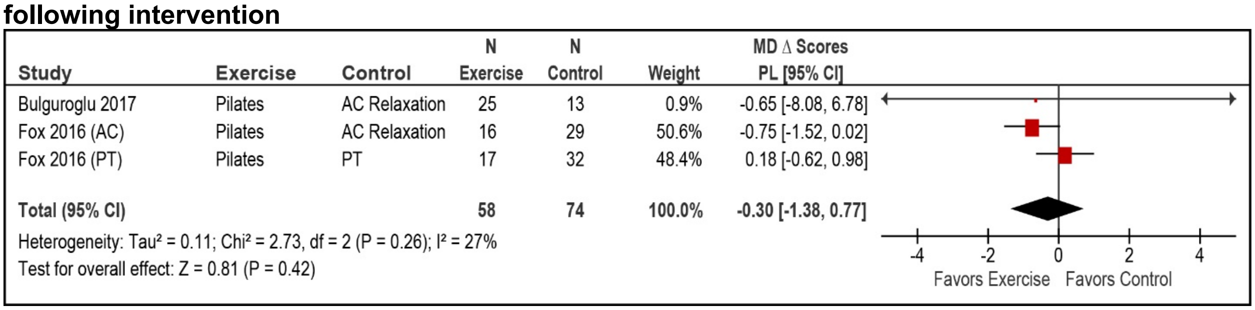
Across five trials comparing strengthening exercises with usual care, previous activity, or attention control, different measures of balance were used. Two trials with three comparisons assessed balance immediately postintervention using the Activities-specific Balance Confidence Scale (ABCS) (0-100 scale). Strengthening exercises were not associated with improved balance immediately postintervention (MD –1.33, 95% CI −4.95 to 2.60, I^2=39%) (Figure 17).[149,200,201,206] There was no difference in balance improvement immediately postintervention in three other fair-quality trials, one using the Fullerton Advanced Balance Scale (scale 0-4, difference in change score MD 0.1, 95% CI −5.43 to 5.63)[198] and two the BBS (scale 0-56, Figure 18, 2 trials[52,83]). One poor-quality trial[62] comparing strengthening to aerobic exercise found no difference in balance as assessed by the BBS immediately postintervention (difference in change score, MD 0.7, 95% CI −5.93 to 7.23). These studies provided low-strength evidence for no benefit on balance between strength exercises and usual care, previous activity, or attention control.

Disability status was assessed in one fair-quality trial that compared strengthening exercises to previous activity level using the EDSS (0-10 scale). Strengthening exercises were not associated with an improvement in disability immediately postintervention (difference 0.1, 95% CI −0.43 to 0.63).[202,203]

Two fair-quality trials assessed depression immediately following 12 weeks of progressive resistance training (PRT)[202,203] or 5 weeks of proprioceptive neuromuscular facilitation (PNF)[83] using the Major Depression Inventory and Beck Depression Inventory, respectively. There was no difference comparing the strengthening exercise groups versus standard care (Figure 19, 2 trials[83,202,203]). In the trial assessing PNF, the scores on the MSIS-29 improved slightly compared with usual care (MD −2.9, 95% CI −5.4 to −0.4).

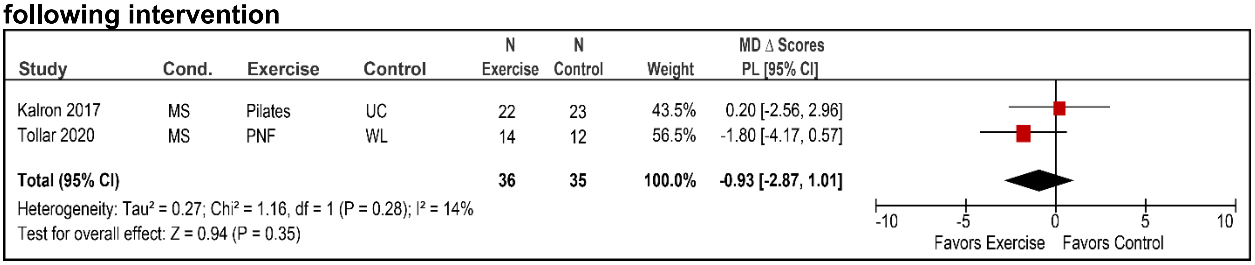
Upper extremity strengthening exercises were associated with a small functional improvement for both the more and the less affected upper extremity compared with attention control immediately postintervention based on the Action Research Arm Tests (ARAT) (scale 0-57, difference in change score, 2.1, 95% CI 1.54 to 2.56 and 0.5, 95% CI 0.23 to 0.81, respectively).[205] However, it is not clear whether these small changes represent clinically important differences.

Figure 17. Muscle strength exercise versus usual care in multiple sclerosis: ABCS immediately following intervention



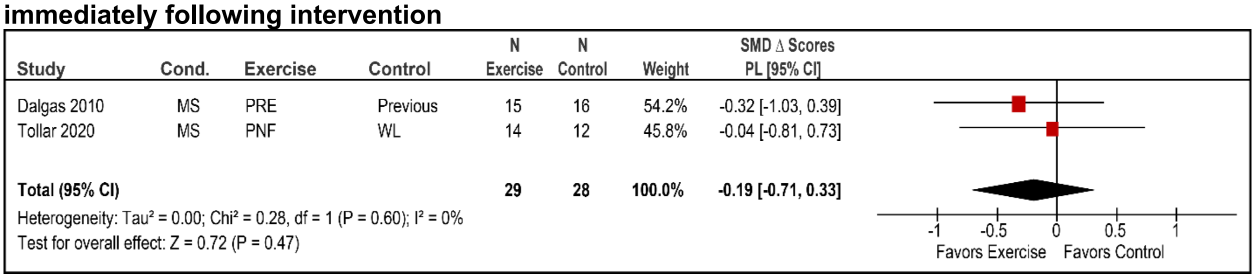
Abbreviations: Δ = change; ABCS = Activities-specific Balance Confidence Scale; AC = attention control; CI = confidence interval; MD = mean difference; PL = profile likelihood; PT = physical therapy

Figure 18. Muscle strength exercise versus usual care in multiple sclerosis: BBS immediately following intervention



Abbreviations: Δ = change; BBS = Berg Balance Scale; CI = confidence interval; MD = mean difference; PL = profile likelihood; SE = standard error

Figure 19. Muscle strength exercise versus usual care in multiple sclerosis: BDI depression immediately following intervention



Abbreviations: Δ = change; BDI = Beck Depression Inventory; CI = confidence interval; MD = mean difference; MDI = Major Depression Inventory; PL = profile likelihood; SE = standard error

Six trials did not address harms or adverse events. Three trials reported no adverse events;[52,198,205] one trial reported no intervention-related adverse events but four events unrelated to the intervention (1 fractured ankle from falling in the snow in the Pilates group, 1 fractured humerus from falling in the snow in the PT group, and 1 pneumonia and 1 pancreatitis in the relaxation group);[200,201] and one trial reported short-term muscle soreness in 25 (69%) participants in the strengthening exercise group,[204] however, no training sessions were missed due to any injury.

Muscle Strength Exercise—Cerebral Palsy

Seven trials[207-216] and one quasiexperimental study[217] enrolled participants with CP (n=388) (Table 35). Weighted mean age of participants across trials was 9.9 years (range, 5.9 to 18.4 years) with weighted mean proportion female of 45 percent (range, 38% to 53%). No study provided data on race. Six studies enrolled participants who could, at minimum, ambulate using bilateral assistance (i.e., crutches, canes),[207-212,215-217] while one enrolled children who could sit for 10 seconds with back unsupported and feet supported,[213] and one did not report data on ambulatory status.[214] The weighted mean baseline GMFM was 61.2 (range, 44.3 to 80.2). Seventeen percent of patients in the quasiexperimental study were wheelchair users; no other study provided data on wheelchair use.[217] Six trials compared strengthening exercises with usual PT,[207-209,211-216] and the remaining trial compared strengthening combined with neuroelectrical stimulation versus neuroelectrical stimulation alone.[210] One quasiexperimental study compared strengthening exercise of the lower extremity and trunk with a nontraining group.[217]

Table 35. Muscle strength exercise in cerebral palsy

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Cho, 2020[216] Strength RCT Poor	A. FPRE, 12 sessions over 6 weeks (n=13) B. Conventional therapy, 18 sessions over 6 weeks (n=12)	A vs. B Age (mean years): 5.54 vs. 7.17 Female: 9 (69%) vs. 4 (33%) Ambulatory: 100% GMFCS: 2.08 vs. 2.33	A vs. B, mean (SD) GMFM-88 score 69.98 (21.55) vs. 68.15 (27.15) (baseline) 71.78 (21.05) vs. 63.48 (27.48) (postintervention), p=0.019 for group A and 0.375 for group B for change from baseline Increase pre-post for FPRE group p=0.019; control group showed no significant difference, p=0.375.
Elnaggar 2019[215] Strength RCT Fair	A. Plyometric training, 16 sessions over 8 weeks (n=19) B. Usual care (n=20)	Age: 9.5 vs. 10.3 Female: 32% vs. 45% Ambulatory: 100% All patients were considered to have mild spastic CP	A vs. B, mean (SD) <u>10MWT (m/s):</u> 1.18 (0.08) vs. 1.21 (0.09) (baseline) 1.29 (0.06) vs. 1.25 (0.05) (postintervention) 0.11 (0.05) vs. 0.04 (0.06), MD 0.07 (95% CI 0.04 to 0.10) (pre-post change score)
Kara, 2020[214] Strength RCT Fair	A. Strength and power training, 36 sessions over 12 weeks (n=15) B. Usual care occupational therapy, 36 sessions over 12 weeks (n=15)	A vs. B Age: 12.3 vs. 11.8 Female: 53% vs. 53% MACS Level I: 47% vs. 40% II: 27% vs. 33% III: 27% vs. 27% GMFCS Level I: 87% vs. 87% II: 13% vs. 13%	A vs. B, mean (SD), p-value for between group difference <u>QUEST total:</u> 8.88 (6.51) vs. 2.22 (4.74), MD 6.65 (95% CI 2.4 to 10.9), p=0.001 (pre-post change) <u>COPM total:</u> 6.12 (2.33) vs. 0.41 (1.56), MD 5.71 (95% CI 4.2 to 7.2), p<0.001 (pre-post change)

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Scholtes, 2010[209] Scholtes, 2012[207] Scholtes, 2008[208] Strength RCT Fair	A. Progressive resistance, 36 sessions over 12 weeks (n=24) B. Usual care (n=25)	A vs. B Age: 10.33 vs. 10.25 Female: 33% vs. 50% Ambulatory: 100% Bilateral: 71% vs. 60% GMFM I: 54% vs. 48% GMFM II: 33% vs. 36% GMFM III: 13% vs. 16%	A vs. B, Regression effect size (95% CI), p=between groups: GMFM-66: −0.56 (−2.11 to 0.99), p=0.48 (postintervention); 0.26 (−1.23 to 1.76), p=0.73 (6 weeks postintervention) 10MWT: −0.04 (−0.18 to 0.10), p=0.56 (postintervention); −0.06 (−0.17 to 0.04), p=0.25 (6 weeks postintervention) Sit-to-Stand (reps): −0.47 (−2.28 to 1.33), p=0.61 (postintervention); −0.75 (−2.21 to 0.72), p=0.32 (6-weeks postintervention) Lateral step-up test (reps): 0.48 (−1.45 to 2.40), p=0.63 (postintervention); 0.13 (−1.84 to 2.10), p=0.9 (6 weeks postintervention) 1-minute fast walking test (m/s): 0.04 (−0.04 to 0.12), p=0.30 (postintervention); −0.01 (−0.08 to 0.06), p=0.78 (6 weeks postintervention) Timed Stair Test (s): 0.83 (−2.64 to 4.30), p=0.64 (postintervention); 2.87 (−2.41 to 8.16), p=0.29 (6 weeks postintervention)
Taylor, 2013[211] Bania, 2016[212] Strength RCT Good	A. Progressive resistance, 24 sessions over 12 weeks (n=23) B. Usual care (n=25)	A vs. B Age: 18.17 vs. 18.58 Female: 44% vs. 48% No gait aid 57% vs. 60% GMFM II: 57% vs. 64% GMFM III: 43% vs. 36%	A vs. B, mean difference (95% CI) between groups: GMFM-66-D: –1.3 (–4.9 to 2.4), p>0.05 (postintervention); 2.5 (–1.8 to 6.9), p>0.05 (12 weeks postintervention) GMFM-66-E: 0.9 (–3.0 to 4.7), p>0.05 (postintervention); 1.0 (–2.6 to 4.5), p>0.05 (12 weeks postintervention) 6MWT: 0.1 (–20.6 to 20.9), p>0.05 (postintervention); –12.3 (–34.8 to 10.2), p>0.05 (12 weeks postintervention) Timed Stair Test (s): –0.9 (–4.7 to 2.9) (postintervention); –0.6 (–4.2 to 3.0) (12 weeks postintervention) Gait Profile Score (°): 0.2 (–0.6 to 0.9), p>0.05 (postintervention); 0.2 (–0.8 to 1.2), p>0.05 (12 weeks postintervention)
Kirk, 2016[217] Strength Quasiexperimental Poor	A. Progressive resistance, 36 sessions over 12 weeks (n=12) B. Usual care (n=23)	A+B Age: 36.5 Female: 43% Wheelchair user: 17%	A vs. B, mean (SD), p=between groups: 10MWT: 7.76 (1.23) to 7.49 (1.10) vs. 8.83 (0.78) to 8.47 (0.86), p>0.05 6MWT: 481 (30) to 510 (33) vs. 400 (32) to 416 (33) p>0.05 Timed Stair Test (s): 30.69 (4.92) to 29.15 (4.62) vs. 49.82 (7.27) to 45.01 (6.57), p>0.05
Qi, 2018a[210] Strength RCT Fair	A. Strength exercises + neuromuscular electrical stimulation, 30 sessions over 6 weeks (n=50) B. Neuromuscular electrical stimulation, 30 sessions over 6 weeks (n=50)	A vs. B Age: 5.8 vs. 6.0 Female: 48% vs. 46% Spastic CP: 100%	A vs. B, mean (SD) GMFM-D/E: 44.5 (13.2) vs. 44 (12.6), p>0.05 (baseline) 70.6 (15.2) vs. 56.7 (14.3), p<0.05 (postintervention) MD 13.4, 95% CI 7.94 to 18.86, p<0.001 71.0 (16.4) vs. 58.0 (15.6), p<0.05 (6 weeks postintervention) MD 12.5, 95% CI 6.74 to 18.26, p<0.001

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Tedla, 2014[213] Strength RCT Poor	A. Strength training 18 sessions over 6 weeks + conventional PT (n=31) B. Conventional PT 3-5 sessions per week for 6 weeks (n=31)	A vs. B (data are for completers only; n=30 vs. 30) Age: 9.1 vs. 8.9 years Female: 33% vs. 33% Gross motor function classification system: I: 7% vs. 3% II: 20% vs. 27% III: 37% vs. 27% IV: 37% vs. 43%	A vs. B, mean change from baseline (SD): PBS total score 7.23 (3.350) vs. 1.87 (1.074), p<0.001 GMFM-total score 9.9 (NR) vs. 2.2 (NR), p=NR

Abbreviations: 6MWT = 6-Minute Walk Test; 10MWT = 10-Meter Walk Test; AE = adverse event; COPM = Canadian Occupational Performance Measure; CI = confidence interval; COPM = Canadian Occupational Performance Measure; CP = cerebral palsy; EPC = Evidence-based Practice Center; FPRE = functional progressive resistance exercise; GMFM = Gross Motor Function Measure; GMFM-66 = Gross Motor Function Measure 66; GMFM-66-D = Gross Motor Function Measure 66 (standing); GMFM-66-E = Gross Motor Function Measure 66 (walking, running, jumping); MACS = manual ability classification system; MD = mean difference; NR = not reported; PBS = Pediatric Balance Scale; PT = physical therapy; QUEST = Quality of Upper Extremity Skill Test; RCT = randomized controlled trial; SD = standard deviation

Walking Measures

There were no differences between strengthening exercise compared with usual PT care in one good-quality[211,212] and one fair-quality trial[207-209] immediately post-12-week treatment in the 1MWT,[207-209] the 6MWT,[211,212] and the 10MWT (Figure 20, 2 trials[207-209,215]). In one trial,[211,212] there was no improvement in gait profile scores following strength exercises versus PT in immediate- or short-term followup. One quasiexperimental study also reported no difference on 6MWT and 10MWT comparing strengthening with active training.[217] At short-term followup, no difference was reported in walking ability between groups in the two trials (1 minute fast walking test),[207-209] the 6MWT ,[211,212] and the 10MWT.[207-209] These studies provided low-strength evidence of no clear benefit on walking with strength exercises alone compared with usual care immediately postintervention and at short-term followup.

Functional Capacity Measures

Evidence on functional outcomes with strengthening exercise in children with CP was based on one good-quality,[211,212] one fair-quality,[207-209] and two poor-quality studies[213,216] (Table 35) and provided low-strength evidence of no clear benefit of strengthening exercise on function versus control groups using the GMFM immediately, 6 weeks, or 12 weeks following treatment. One fair-quality trial[207-209] also reported no difference between groups in the 30-second lateral step-up test in immediate and short-term followup.

In one fair-quality trial,[210] strength exercises combined with neuroelectrical stimulation versus neuroelectrical stimulation alone resulted in improved functional capacity based on the GMFM in immediate- and short-term followup (difference in change scores −13.4, 95% CI −16.90 to −9.90; and −12.5, 95% CI −16.26 to −8.74, respectively). Due to study limitations, lack of corroborating evidence, and imprecision in the estimates, this evidence was insufficient to draw conclusions.

Other Outcome Measures

Across two trials (1 good and 1 fair quality), there was no improvement in the timed stair test with strengthening versus usual PT immediately postintervention and at short-term followup.[207-

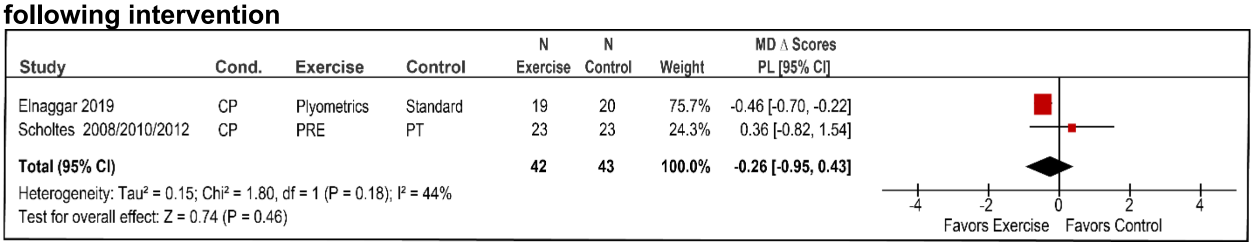
[209,211,212] The one poor-quality quasiexperimental study reported no difference immediately posttreatment between strength exercises and usual care in the timed stair test.[217] Strengthening compared with usual PT did not improve 30-second sit-to-stand in one trial in the immediate- or short-term followup.[207-209]

Strengthening compared with usual PT improved balance immediately after the intervention as measured by the PBS in one poor-quality trial[213] (differences in change scores 7.23, standard deviation (SD) 3.35 and 1.87, SD 1.07, p<0.001) and in the Forward and Side Functional Reach Test (before-after change, p<0.005) in another poor-quality trial.[216]

One fair-quality trial (n=30) found the quality of upper extremity movement, and both activity performance and satisfaction improved, with strength and power training versus usual occupational therapy.[214] Due to the risk of bias and small sample size, the evidence for improved upper extremity movements is too limited to draw conclusion. None of the trials reported on quality of life measures.

Adverse events were reported in one RCT and in one quasiexperimental study. In the RCT,[211,212] short-term muscle soreness was reported by most participants in the strength exercise group. Additionally, one minor calf strain and one minor discomfort due to plantar fasciitis occurred in the same group. In the quasiexperimental study, most subjects in the exercise group reported muscle soreness and three subjects reported irritation in tendon tissue surrounding the knee.[217] One trial reported no adverse events in either treatment arm[214] and the remaining four RCTs did not address harms or adverse events.

Figure 20. Muscle strength exercise versus usual care in cerebral palsy: 10MWT immediately following intervention



Abbreviations: Δ = change; 10MWT = 10-meter Walk Test; CI = confidence interval; MD = mean difference; PL = profile likelihood.

Muscle Strength Exercise—Spinal Cord Injury

One fair-quality trial[218] enrolled adult males (n=98) with SCI (Table 36). The mean age of participants was 63 years; all participants were paraplegic. Limited evidence suggested 12 months of breathing and upper limb strength exercises improved quality of life as measured on four of five SF-36 subscales (0-100 scale) immediately after the intervention: physical function (26.7, 95% CI 24.61 to 28.79); social function (28.9, 95% CI 26.06 to 31.74); role emotional (22.0, 95% CI 20.11 to 23.89); and mental health (21.0, 95% CI 19.10 to 22.90). There were no differences between groups in any of the SF-36 subscales after 4 weeks of intervention. However, the evidence was considered too limited to draw firm conclusions on the effectiveness of strength training on quality of life (SOE: insufficient).[218]

This trial did not address harms or adverse events.

Table 36. Muscle strength exercise in spinal cord injury

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Prioritized Outcomes
Chen, 2016[218] Strength RCT Fair	A. Pulmonary rehabilitation, 365 sessions over 52 weeks (n=49) B. Usual care (n=49)	A vs. B Age: 62.3 vs. 63.1 Female: 0% T1–2: 35% vs. 35% T3–4: 33% vs. 33% T5–6: 33% vs. 33%	A vs. B, mean (SD): <u>SF-36 Subscale - physical function:</u> 54.2 (7.8) vs. 54.2 (7.8), p>0.05 (baseline) 81.1 (3.1) vs. 54.4 (7.7), p<0.05 (postintervention) 54.4 (8.0) vs. 54.6 (7.9), p>0.05 (4-week followup) <u>SF-36 Subscale - social function:</u> 50.6 (11.8) vs. 50.6 (11.8), p>0.05 (baseline) 80.1 (9.4) vs. 51.2 (11.0), p<0.05 (postintervention) 51.2 (11.0) vs. 50.6 (11.8), p>0.05 (4-week followup) <u>SF-36 Subscale - role emotional:</u> 54.3 (7.85 vs. 5.3 (6.9), p>0.05 (baseline) 76.3 (7.3) vs. 54.3 (7.8), p<0.05 (postintervention) 54.2 (7.8) vs. 54.4 (7.7), p>0.05 (4-week followup) <u>SF-36 Subscale - mental health:</u> 54.1 (7.7) vs. 54.2 (7.8), p>0.05 (baseline) 75.1 (6.8) vs. 54.2 (7.8), p<0.05 (postintervention) 54.2 (7.8) vs. 54.2 (7.8), p>0.05 (4-week followup)

Abbreviations: RCT = randomized controlled trial; SD = standard deviation; SF-36=Short-Form 36

Multimodal Interventions

Progressive Resistance or Strengthening Combination Exercises

Multimodal exercises provide information on the benefit of combining different types of interventions. Unlike single exercise interventions, multimodal exercise blends various types of exercises by linking progressive resistance exercise and/or strengthening exercises with at least one component of aerobic exercises, balance exercises, or other interventions.

Key Points

- In participants with MS, across measures of walking ability (6MWT and 10MWT), multimodal exercise was associated with improved walking ability and balance compared with usual care at the end of treatment (SOE: low). Evidence was insufficient to draw conclusions from one small trial of group versus home-based exercise with regard to walking ability or balance.
- Evidence was limited in MS on functional capacity and quality of life (SOE: insufficient).
- In participants with CP, there was low-strength evidence of no clear benefit in functional capacity or quality of life with multimodal exercises. Evidence was insufficient to draw conclusions regarding the impact of multimodal exercise on walking.
- In participants with SCI, evidence from small trials was insufficient to draw conclusions regarding the impact of exercise on walking or functional capacity (SOE: insufficient).

Detailed Synthesis

Seventeen RCTs,[220-223,225,226,228-230,232,234-242,244-248] one quasiexperimental study,[233] and one cohort study[250] in 911 participants evaluated multimodal exercise. Multimodal exercises included progressive resistance exercises/strengthening exercises in combination with aerobic exercise. Some also included balance exercises. Most trials compared multimodal exercise to usual care. Usual care included maintaining previous activity levels (5 trials, 1 quasiexperimental

study),[222,223,225,226,228,233] inclusion of an attention control (2 trials),[221,232] PT (4 trials),[234-242] self-regulated exercise (1 study),[250] or waitlist (2 trials).[230,231,246,247] Additional trials compared multimodal exercise with aerobic exercise,[220] or a different combination of multimodal exercises.[244,245,248] Ten trials[220-223,225,226,228,230-232] and one quasiexperimental study[233] enrolled participants with MS (Table 37), four trials[234-242] were in participants with CP (Table 38), and four studies (3 RCTs, 1 cohort study)[244-248,250] were conducted in participants with SCI (Table 39). Twelve[220-223,230-232,234-242,244,245,248] trials met criteria for fair quality and four[225,226,228,246,247] were rated poor quality and deemed to have high risk of bias due to unclear randomization and/or allocation concealment, lack of similarity between treatment groups at baseline, and unacceptable attrition. The quasiexperimental and cohort studies were considered to be fair quality.[233,250] The most frequently prioritized outcomes reported were walking-related measures (e.g., 6MWT, 10MWT) and quality of life (e.g., SF-36); few studies reported on functional capacity measures (e.g., TUG). Measures reported varied by condition. Differences in change scores (mean difference) between treatment groups were reported unless otherwise noted.

Multimodal Exercises—Multiple Sclerosis

Ten trials[220-223,225,226,228,230-232] and one quasiexperimental study[233] enrolled participants (n=540) with MS (Table 37). Weighted mean age of participants across trials was 39.76 years (range 32.7 to 52.0 years) with weighted mean proportion female of 73.9 percent (range 55.9% to 100%). No study provided data on race. All studies enrolled participants who could, at minimum, ambulate using bilateral assistance (i.e., crutches or canes), and the weighted mean baseline EDSS (across 4 studies)[222,223,228,232] was 4.9 (range 1.61 to 8.7).

Table 37. Multimodal exercise in multiple sclerosis

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Cakit, 2010[225] Multimodal exercise RCT Poor	A. Progressive resistance cycling plus balance exercises (lower extremity strengthening), 16 sessions over 8 weeks (n=14) B. Usual care (n=9)	A vs. B Age: 36.4 vs. 35.5 Female: 64% vs. 67% RRMS or SPMS: 100% Assistive device: 28.5% vs. 37.5%	A vs. B, mean (SD) change, p=between groups: TUG : –1.3 (1.2) vs. –0.2 (0.8), p<0.05 10MWT: –1.9 (1.2) vs. 0.1 (0.8), p<0.05 DGI: 2.7 (0.5) vs. 0.4 (0.4), p<0.01 Falls Efficiency Scale: –11.3 (7.8) vs. –2.6 (3.1), p<0.01 SF-36 Physical Function: 21.2 (14.4) vs. 7.7 (7.4), p>0.05 SF-36 Role-Physical Function: 34.0 (30.1) vs. 5.0 (44.7), p>0.05 SF-36 General Health: 4.3 (8.4) vs. 3.2 (11.7), p>0.05 SF-36 Vitality: 9.0 (19.3) vs. 11.0 (20.4), p>0.05 SF-36 Social Functioning: 3.4 (23.1) vs. 5.0 (16.7), p>0.05 SF-36 Role-Emotional Function: 24.2 (49.6) vs. 19.9 (50.5), p>0.05 SF-36 Mental Health: 7.2 (13.4) vs. 7.0 (6.7), p>0.05

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Ebrahimi, 2015[228] Multimodal exercise RCT Poor	A. Whole body vibration + low-intensity exercise, 30 sessions over 10 weeks (n=17) B. Usual care (n=17)	A vs. B Age: 37.06 vs. 40.75 Female: 69% vs. 86% Ambulatory: 100% EDSS: 3.12 vs. 3.10	A vs. B, mean (SD), p=between groups: TUG: 11.32 (5.21) to 11.16 (8.82) vs. 14.43 (3.20) to 14.57 (4.02), p=0.05 10MWT: 17.67 (8.92) to 13.37 (4.59) vs. 21.16 (6.36) to 19.39 (6.52), p=0.56 6MWT: 184.01 (101.04) to 272.32 (105.60) vs. 150.37 (65.18) to 162.80 (60.57), p=0.01 MSQoL-54 PCS: 45.80 (9.70) to 53.36 (11.9) vs. 43.38 (15.43) to 45.53 (7.30), p=0.40 MSQoL-54 MCS: 50.87 (15.46) to 58.34 (14.89) vs. 41.66 (17.07) to 50.10 (14.72), p=0.42 EDSS: 3.12 (1.19) to 2.65 (1.20) vs. 3.10 (0.76) to 3.03 (0.69), p=0.01 BBS: 40.37 (9.97) to 46.43 (8.34) vs. 34.00 (9.13) to 35.85 (7.22), p=0.01
Faramarzi, 2020[230] Has companion: Banitalebi, 2020[231] Multimodal Exercise Immediately Postintervention, 12 weeks RCT Fair	A. Resistance + endurance + Pilates + balance + stretch), 36 sessions over 12 weeks (n=23) B. Combined exercise - Moderate disability group (4.5 ≤ EDSS ≤ 6) 36 sessions (3 per week) over 12 weeks (n=13) C. Combined exercise - High disability group (EDSS ≥ 6.5) 36 sessions (3 per week) over 12 weeks (n=11) D. Waitlist control Low (n=23) E. Waitlist control Moderate (n=13) F. Waitlist control High (n=11)	A vs. B vs. C vs. D Age: NR (between 18 and 50 years) Female: 100% Ambulatory: 100% EDSS score: EDSS < 4.5: A. 23 (24%) vs. D. 23 (24%) EDSS ≤ 4.5 to ≤ 6: B.13 (14%) vs. D. 13 (14%) EDSS ≥ 6.5: C.11 (12%) vs. D. 11 (12%)	A vs. B vs. C vs. D vs. E vs. F, Mean change from baseline (95% CI) [change value calculated by EPC from figures] 6MWT: A vs. D 63.1 (95% CI -15.6 to 139.5) vs. -11.1 (95% CI -44.6 to 21.7) B vs. E 49.7 (95% CI 1.5 to 97.83) vs. -1.9 (95% CI -35.0 to 32.4) C vs. F 64.1 (95% CI 39.2 to 88.6) vs. -13.1 (95% CI -42.8 to 17.4) TUG: A vs. D -1.5 (95% CI -4.1 to 1.2) vs. 0.72 (95% CI -0.34 to 1.8) B vs. E -1.6 (95% CI -3.6 to 0.37) vs. -0.3 (95% CI -4.9 to 4.5) C vs. F -1.9 (95% CI -3.9 to 0.03) vs. 1.4 (95% CI 0.05 to 2.6) Author tests for interactions between disability levels were not statistically significant. VO_2-peak change (mL/kg/min): Significant positive correlation between changes (Vo_2 peak) with exercise, p=0.041 There was a significant condition main effect on change in VO_2 peak, p=0.004

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Kerling, 2015[220] Multimodal exercise RCT Fair	A. Full body progressive resistance + aerobic training, 36 sessions over 12 weeks (n=30) B. Aerobic training, 36 sessions over 12 weeks (n=30)	A vs. B Age: 42.3 vs. 45.6 Female: 80% vs. 67% EDSS: 2.6 vs. 3.1	A vs. B, mean (SD), p=between groups: SF-36 PCS: 44.9 (9.1) to 46.2 (9.1) vs. 39.0 (10.8) to 39.6 (11.3), p=0.56 SF=36 MCS: 44.9 (13.6) to 45.4 (13.4) vs. 46.7 (11.7) to 51.4 (8.6), p=0.01
Ozkul, 2020b[232] Multimodal Exercise RCT Fair	A. Aerobics + Pilates, 24 sessions over 8 weeks (n=17) B. Control group, relaxation exercise at home, 24 sessions over 8 weeks (n=17)	A vs. B Age: 35.8 vs. 36.7 Female: 76% vs. 76% Ambulatory: 100% EDSS: 1.5 vs. 1.71	A vs. B, Mean (SD), change mean (SD), p=within groups 6MWT (meters): 539.94 (50.21) vs. 513.82 (50.96) (baseline) 587.92 (51.44) vs. 502.75 (53.54) (postintervention); change mean (SD) 47.98 (23.34) vs. −11.07 (36.40), p<0.001 MSQOL-54-MCS: 62.74 (19.37) vs. 56.29 (16.47) (baseline) 74.24 (14.83) vs. 50.91 (20.42) (postintervention) change mean (SD) 11.50 (15.94) vs. −5.38 (17.37), p=0.006 MSQOL-54-PCS: 120.54 (29.32) vs. 109.67(27.89) (baseline) 140.08 (18.42) vs. 97.83 (35.58) (postintervention) change mean (SD) 19.54 (14.42) vs. −11.84 (28.36), p<0.001 52
Roppolo, 2013[233] Multimodal exercise Quasiexperimental Fair	A. Combination therapy (aerobic + strength training), 24 sessions over 12 weeks (n=17) B. Usual care (n=18)	A vs. B Age: 40 vs. 40 years Female: 100% vs. 100% EDSS: 1.5 vs. 2.0	A vs. B, mean (SD) MSQOL-54 202.7 (7.9) vs. 139.3 (32.4), MD 63.4 (7.86) (95% CI 47.43 to 79.4), p<0.001 (postintervention); 29.5 (36.17) vs. −22.5 (55.57), MD 52.0, 95% CI 20.8 to 83.2, p=NR (pre-post change)
Sandroff, 2017[221] Multimodal exercise RCT Fair	A. Resistance + aerobics + balance, 72 sessions over 24 weeks. (n=43) B. Usual care-stretching and toning, 72 sessions over 24 weeks (n=40)	A vs. B Age: 49.8 vs. 51.2 Female: 83.7% vs. 87.5% EDSS 4-6: 100% Walking difficulties: 100%	A vs. B mean (SD), p=between groups: 6MWT: 1073.1 (529.0) vs. 1097.5 (493.3) (baseline); 1185.5 (600.5) vs. 1115.1 (512.7) (postintervention), p=0.05 25 foot WT: 3.7 (1.8) vs. 4.0 (1.4) (baseline); 4.0 (1.9) vs. 4.0 (1.5) (postintervention), p>0.11 MSWS-12: 64.8 (24.7) vs. 51.8 (24.7) (baseline); 59.0 (23.4) vs. 49.3 (27.1) (postintervention), p=0.98

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Sangelaji, 2014[226] Multimodal exercise RCT Poor	A. Strength + aerobics + balance, 30 sessions over 10 weeks (n=29) B. Usual care (previous activity level) (n=22)	A vs. B Age: 33.05 vs. 7.68 Female: 61.5% vs. 68.2% EDSS 0-4: 100%	A vs. B, mean difference (SD), p=between groups: 6MWT: 137.2 (24.54), p<0.0001; 184.3 (51.1), p=0.001 (1-year followup) MSQoL-PCS: 12.17 (3.62), p=0.001; 10.90 (4.55), p=0.02 (1-year followup) MSQoL-MCS: MD 16.36 (4.46), p=0.001; 13.54 (5.37), p=0.02 (1-year followup) EDSS: –0.13 (0.23), p=0.60; –0.28 (0.29), p=0.35 (1 year followup) BBS: 3.34 (0.87), p<0.0001; 3.21 (1.44), p=0.03 (1-year followup)
Sangelaji, 2016[222] Multimodal exercise RCT Fair	A. 1 aerobic + 3 resistance training, 32 sessions over 8 weeks (n=10) B. 2 aerobic + 2 resistance training, 32 sessions over 8 weeks (n=10) C. 3 aerobic + 1 resistance training, 32 sessions over 8 weeks (n=10) D. No intervention control (n=10)	A vs. B vs. C vs. D Age: 36 vs. 31 vs. 34 vs. 34 Female: 60% vs. 60% vs. 60 vs. 60% Baseline EDSS: 1.33 vs. 2.06 vs. 1.95 vs. 1.81	Mean difference (SE), p=vs. control group: A vs. D 10MWT: 2.31 (1.04), p=0.030 6MWT: −75.22 (28.21), p=0.010 BBS: –5.88 (1.80), p<0.001 B vs. D 10MWT: 1.45 (1.07), p=0.190 6MWT: −63.00 (29.03), p=0.040 BBS: –1.25 (1.85), p=0.500 C vs. D 10MWT: 1.83 (1.01), p=0.080 6MWT: −27.50 (27.54), p=0.330 BBS: –3.10 (1.75), p=0.090
Tarakci, 2013[223] Multimodal exercise RCT Fair	A. Exercise (e.g., ROM, strength, flexibility, balance, core stability), 36 sessions over 12 weeks (n=51) B. Waitlist control (n=48)	A vs. B Age: 41.5 vs. 39.7 Female: 67% vs. 63% EDSS: 9.0 vs. 8.4 RRMS: 63% vs. 69% PPMS: 20% vs. 17% SPMS: 18% vs. 15%	A vs. B, mean (SD), p=between groups: 10MWT: 17.97 (2.89) vs. 17.17 (3.89) (baseline) 15.24 (2.51) vs. 18.62 (4.21), MD 0.98 (postintervention), p<0.001 MusiQoL: 74.41 (9.20) vs. 73.42 (9.73) (baseline) 76.39 (9.53) vs. 73.02 (10.30), MD 0.34 (postintervention), p=0.02 BBS: 37.68 (9.91) vs. 36.94 (12.55) (baseline) 42.01 (9.32) vs. 34.81 (12.85), MD 0.64 (postintervention), p=0.003 Stair Climbing Test: 12.00 (3.57) vs. 13.92 (4.54) 9.53 (3.49) vs. 18.46 (16.34), MD 0.290 (postintervention), p<0.001

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Williams, 2020[229] Multimodal exercise RCT Fair	A. Center-based group strength + endurance + balance, 16 sessions over 8 weeks (n=26) B. Home-based exercise strength + endurance + balance exercises, 16 sessions over 8 weeks (n=24)	Age: 53 vs. 51 Female: 65% vs. 88% Ambulatory: 100% Aid use None: 27% vs. 58% Unilateral: 42% vs. 29% Bilateral: 31% vs. 13% Type of MS RRMS: 58% vs. 67% PPMS: 19% vs. 8% SPMS: 15% vs. 8% Benign: 4% vs. 8% Unknown/NR: 4% vs. 8%	A vs. B, mean (SD): All patients 0.83 (0.5) vs. 1.1 (0.4) (baseline) 0.95 (0.5) vs. 1.25 (0.5) (postintervention) MD 0.01 (95% CI −0.36 to 0.37) (pre-post change) 0.86 (0.4) vs. 1.2 (0.4) (8 weeks postintervention) MD –0.07 (95% CI –0.22 to 0.08) (pre-8 week postintervention change) Low disability patients (Disease Step Rating Scale 0-2) 1.37 (0.38) vs. 1.37 (0.32) (baseline) 1.28 (0.33) vs. 1.52 (0.46) (postintervention) MD 0.24 (95% CI −0.61 to 1.08) (pre-post change) 1.22 (0.06) vs. 1.41 (0.37) (8 weeks postintervention) MD –0.19 (95% CI –0.41 to 0.03) (pre-8 week postintervention change) High disability patients (Disease Step Rating Scale 3-5) 0.71 (0.39) vs. 0.81 (0.28) (baseline) 0.86 (0.46) vs. 0.89 (0.36) (postintervention) 0.16 (0.59) vs. 0.07 (0.85) MD 0.8 (95% CI −0.47 to 0.64) (pre-post change) 0.76 (0.41) vs. 0.92 (0.33) (8 weeks postintervention) MD –0.06 (95% CI –0.24 to 0.12) (pre-8 week postintervention change) 6MWT (meters): 216.4 (128.4) vs. 301.3 (108.4) (baseline) 248.7 (125.3) vs. 312.3 (121.9) (immediately postintervention) MD 18.67 (95% CI −78.22 to 115.56) (pre-post change) 236.3 (115.2) vs. 300.7 (119.4) (8 weeks postintervention) MD -20.5 (95% CI –60.21 to 19.21) (pre-8 week postintervention change) Low disability patients: 372.5 (61.5) vs. 359.36 (85.6) (baseline) 378 (63.3) vs. 382.4 (103) (postintervention) 5.5 (248.8) vs. 23.1 (151.5), MD 17.6 (95% CI −184.2 to 219.26) (pre-post change) 352 (67.2) vs. 367 (97.4) (8 weeks postintervention) MD 28.14 (95% CI –8.26 to 64.54) (pre-8 week postintervention change)

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Williams, 2020 (Continued)			High disability patients: 178.6 (102.1) vs. 216.5 (84.6) (baseline) 214.5 (111.5) vs. 221.2 (93.7) (postintervention) 35.9 (151.7) vs. 4.7 (211.80), MD 31.17 (95% CI −108.37 to 170.72) (pre-post change score) 204.1 (105.2) vs. 212.2 (85.1) (8 weeks postintervention) MD –29.8 (95% CI –77.21 to 17.61) (pre-8 week postintervention change) BBS: 42 (16.7) vs. 50.9 (6) (baseline) 43.5 (14.9) vs. 50.7 (7.9) (postintervention) 1.5 (17.02) vs. −0.18 (17.37), MD 1.70 (95% CI −8.4 to 11.80) (pre-post change) 44 (15.4) vs. 51 (6.9) (8 weeks postintervention) MD –1.9 (–6.44 to 2.64) (pre-8 week postintervention change) Low disability patients: 53.8 (0.8) vs. 53.3 (3.6) (baseline) 54.2 (1.9) vs. 53.8 (3.5) (immediately postintervention) MD 0.2 (95% CI −7.69 to 8.01) (pre-post change) 54 (1.9) vs. 53.5 (3.9) (8 weeks postintervention) 0.20 (1.35) vs. 0.20 (2.39), MD 0.0 (–1.37 to 1.37) (pre-8 week postintervention change) High disability patients: 39.1 (17.5) vs. 47.6 (7.3) (baseline) 40.7 (15.5) vs. 46.7 (10.2) (immediately postintervention) MD 2.54 (95% CI −18.01 to 23.08) (pre-post change) 41.2 (16.4) vs. 47.7 (8.7) (8 weeks postintervention) MD –2.0 (95% CI –9.31 to 5.31) (pre-8 week postintervention change)

Abbreviations: 6MWT = 6-Minute Walk Test; 10MWT = 10-Meter Walk Test; AE = adverse event; BBS = Berg Balance Scale; BDI = Beck Depression Inventory; CI = confidence interval; DGI = Dynamic Gait Index; EDSS = Expanded Disability Status Scale; EPC = Evidence-based Practice Center; MD = mean difference; MS = multiple sclerosis; MSQoL-MCS = Multiple Sclerosis Quality of Life–54 instrument Mental Component Score; MSQoL-PCS = Multiple Sclerosis Quality of Life–54 instrument Physical Component Score; MSWS-12 = Multiple Sclerosis Walking Scale-12; MusiQoL = Multiple Sclerosis International Quality of Life questionnaire; NR = not reported; PPMS = primary progressive multiple sclerosis; QOL = quality of life; RCT = randomized controlled trial; RRMS = relapsing-remitting multiple sclerosis; SD = standard deviation; SE = standard error; SF-36 MCS = Short-Form 36 Mental Component Summary; SF-36 PCS = Short-Form 36 Physical Component Score; SF-36 = Short-Form 36 Quality of Life; SPMS = secondary progressive multiple sclerosis; TUG = Timed Up and Go Test; VO_2 peak = highest value of VO_2 attained

Walking Measures

There was low strength of evidence that multimodal exercise was generally associated with improved walking ability across measures, compared with attention control (stretching) or continuation of previous activity based on pooled difference in change scores (6MWT, 6 trials, MD –67.7 meters, 95% CI -85.6 to -49.9, I^2=58%;[221,222,226,228,230,232] 10MWT, 4 trials, MD –2.7 seconds, 95% CI –4.2 to –1.2, I^2=80%[222,223,225,228]) immediately posttreatment (Figures 21 and 22). Substantial heterogeneity in pooled estimates for both measures was noted; all but one trial favored multimodal exercise and all had different magnitudes of effect and variability. This may in part be due to differences in baseline measure values across studies and may also be related to

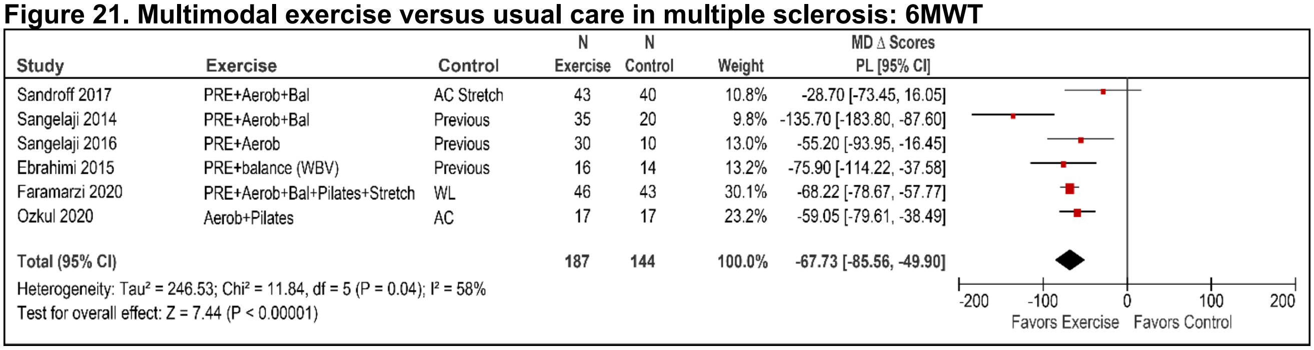
differences in intervention. Isolated studies reported ambulatory ability or use of assistive devices, duration of MS, or status (e.g., progressive, remitting), precluding evaluation of these as sources of heterogeneity. For the 6MWT, exclusion of two poor-quality trials only slightly attenuated the effect size and but did substantially reduce heterogeneity (4 trials, MD –66.3 meters, 95% CI -75.1 to -38.5, I^2=0%)[221,222,230,232] and exclusion of an outlier trial resulted in a decrease in effect size and substantially reduced heterogeneity (4 trials, MD –64.9 meters, 95% CI –73.5 to -56.2 , I^2=0%),[221,222,228] maintaining an effect size that may be clinically meaningful. These trials provided low-strength evidence for improved walking with multimodal exercises compared with usual care, previous activity, or attention control. Authors of one trial reported that results did not statistically differ based on disability status based on EDSS scores considered low (<4.5), moderate (4.5 to ≤6), or high (≥6.5).[230] Interestingly, the trial with the longest intervention length (72 sessions over 24 months) showed no difference between treatment groups and had smallest effect size;[221] the other trials involved 30 to 36 sessions over 8 to 12 weeks. For the 10MWT, exclusion of poor-quality trials had negligible impact on either effect size and increased heterogeneity (2 trials, MD 3.1 seconds, 95% CI –5.4 to –0.8, I^2=87%).[222,223] However, exclusion of an outlier trial resulted in a slightly smaller but more precise effect size and substantially reduced heterogeneity (3 trials MD –1.99 seconds, 95% CI –2.8 to –1.2, I^2=0%).[222,225,228] The differences between groups may not be not clinically meaningful for this outcome. The mean baseline EDSS of the excluded trial was ~4.3 compared with a mean of ~2 in the only other trial reporting this measure.

In one trial[221] there was no difference in walking ability on the Multiple Sclerosis Walking Scale-12 (difference –3.3, 95% CI –10.2 to 3.6, 0-100 scale) or on a timed 25FWT (difference 0.30, 95% CI –0.2 to 0.8 feet/second) immediately posttreatment.

One poor-quality trial[226] reported that improvement in the 6MWT persisted long- term (42 weeks) posttreatment (MD 184.3 ± 51.1 meters, p=0.03) following multimodal exercise (strength, aerobics and balance exercises) versus usual care.

One small fair-quality trial[229] found no difference in walking ability between multimodal exercise performed in a group setting or home setting based on 6MWT immediately after the 8-week intervention or at the subsequent 8-week followup, or for 10MWT at either time. Authors reported higher percentage of completed sessions in the group exercise arm (83% versus 45%). No differences between groups in either walking measure were observed based on disability level measured via the Disease Step Rating Scale (0-6 overall score with scores 0-2 for low and 3-6 for high disability) at either time frame (Table 37).

Figure 21. Multimodal exercise versus usual care in multiple sclerosis: 6MWT

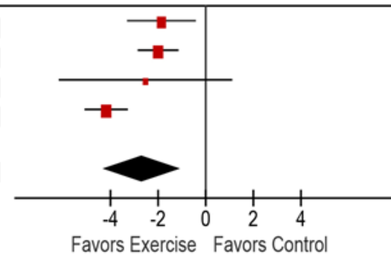


Abbreviations: Δ = change; 6MWT = 6-Minute Walk Test; AC = attention control; CI = confidence interval; MD = mean difference; PA = previous activity; PL = profile likelihood; PRE = progressive resistance exercise

Figure 22. Multimodal exercise versus usual care in multiple sclerosis: 10MWT

Study	Exercise	Control	N Exercise	N Control	Weight	MD Δ Scores PL [95% CI]
Sangelaji 2016	PRE+Aerob	PA	30	10	26.3%	-1.86 [-3.27, -0.45]
Cakit 2010	PRE+Aerob+Bal	PA	14	9	31.8%	-2.00 [-2.82, -1.18]
Ebrahimi 2015	PRE+Bal	PA	16	14	10.7%	-2.53 [-6.13, 1.07]
Tarakci 2013	PRE+Bal	PA	55	55	31.3%	-4.18 [-5.05, -3.31]
Total (95% CI)			**115**	**88**	**100.0%**	**-2.73 [-4.15, -1.22]**

Heterogeneity: Tau² = 1.46; Chi² = 15.02, df = 3 (P = 0.002); I² = 80%
Test for overall effect: Z = 3.75 (P = 0.0002)



Abbreviations: Δ = change; 10MWT = 10-Meter Walk Test; AC = attention control; CI = confidence interval; MD = mean difference; PA = previous activity; PL = profile likelihood; PRE = progressive resistance exercise= profile likelihood; PRE = progressive resistance exercise; TUG = Timed Up and Go Test

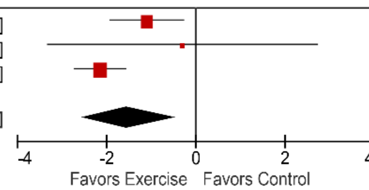
Functional Capacity Measures

Improvement in functional capacity based on TUG was seen immediately postmultimodal exercise intervention across two small poor-quality trials and one larger fair-quality trial (3 trials, MD –1.65 seconds, 95% CI –2.6 to –0.4; I^2=62%)[225,228] compared with previous activity but may not be clinically meaningful. Evidence was considered insufficient (Figure 23).

Figure 23. Multimodal exercise versus usual care in multiple sclerosis: TUG

	Exercise	Control	N Exercise	N Control	Weight	MD Δ Scores PL [95% CI]
	PRE+Aero+Bal	Previous	14	9	41.8%	-1.10 [-1.92, -0.28]
)15	PRE+Balance(WBV)	Previous	16	14	8.4%	-0.30 [-3.32, 2.72]
2020	PRE+Aerob+Bal+Pilates+Stretch	WL	46	43	49.8%	-2.15 [-2.72, -1.58]
CI)			**76**	**66**	**100.0%**	**-1.65 [-2.59, -0.36]**

›ity: Tau² = 0.38; Chi² = 5.21, df = 2 (P = 0.07); I² = 62%
›rall effect: Z = 3.23 (P = 0.001)



Abbreviations: Δ = change; AC = attention control; CI = confidence interval; MD = mean difference; PA = previous activity; PRE = progressive resistance exercise; PL = profile likelihood; TUG = Timed Up and Go Test

Quality of Life Measures

Quality of life evidence, based on MSQOL-54 MCS and PCS (0 to 100 scales) across two poor-quality trials and one fair-quality trial postintervention was considered insufficient to draw firm conclusions (Figure 24).[226,228] For MCS, there was substantial heterogeneity for the pooled difference (3 trials, MD –10.7, 95% CI –22.6 to 1.24, I^2= 91%). Two trials favored exercise[226] versus maintenance of usual activity but a third showed no difference between treatment groups (0.97, 95% CI –6.2 to 8.1).[228] All trials reported improvement on the PCS (3 trials, MD –13.7, 95% CI –21.64 to –4.9 I^2=81%) but only one reached statistical significance; substantial heterogeneity was noted although estimates tended to favor exercise. Author-reported data for one trial appeared to be out of the expected range for this measure; exclusion of it slightly reduced the effect size and heterogeneity for PCS (2 poor -quality trials, MD –12.0, 95% CI 13.8 to –5.0, I^2=75%). It is unclear if this was a clinically meaningful difference.

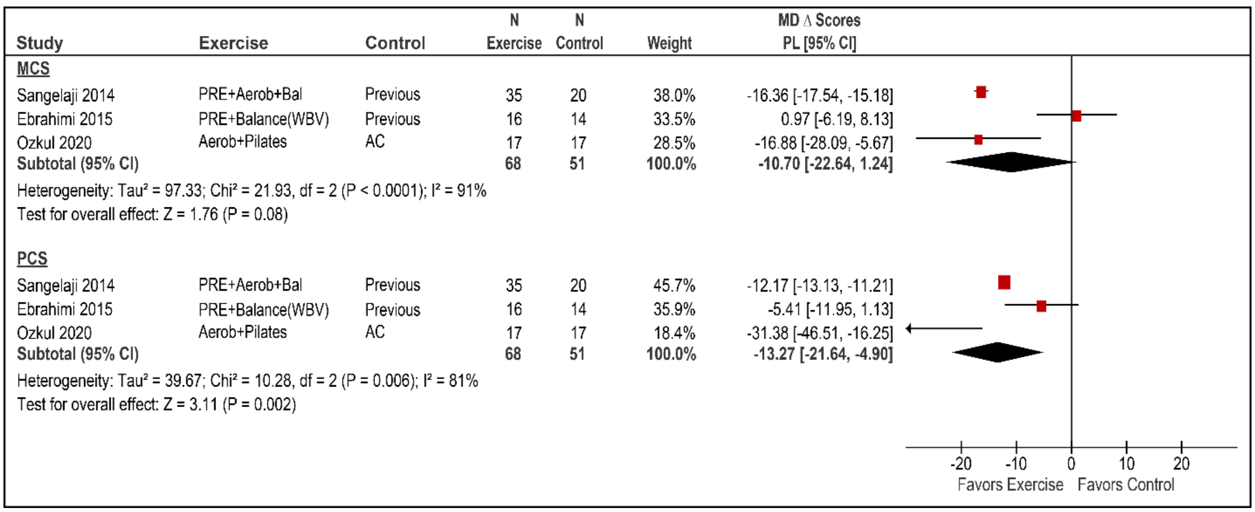
Improved quality of life based on the Multiple Sclerosis International Quality of Life questionnaire (MusiQoL) (0-100 scale) was seen in an additional fair-quality trial (difference –2.4, 95% CI –4.7 to –0.1).[223] In one fair-quality prospective quasiexperimental study,[233] exercise significantly improved MSQOL-54 total scores postintervention compared with usual care (difference 52.0, 95% CI 20.8 to 83.2).

In one poor-quality trial, individual SF-36 domain scores that improved with exercise were physical functioning and bodily pain; no differences between groups were seen for the other domains (Table 38).[225]

In the only trial (poor-quality) that reported long-term outcomes (42 weeks) posttreatment, improvement on both the PCS and MCS of the MSQOL persisted long term (PCS difference 10.9 ± 4.55, p=0.02, MCS difference 13.5 ± 5.4, p=0.02, 0-100 scale) for multimodal exercise versus usual care.[226]

In one trial, the control condition of aerobic exercise was associated with improvement in the SF-36 MCS compared with multimodal exercise (difference 4.2, 95% CI 0.2 to 8.2, 0-100 scale) but there was no difference between groups on SF-36 PCS (difference –0.7, 95% CI –3.9 to 2.2, 0-100 scale) in one trial.[220]

Figure 24. Multimodal exercise versus usual care in multiple sclerosis: MSQOL MCS and MSQOL PCS



Abbreviations: Δ = change; AC = attention control; CI = confidence interval; MD = mean difference; MCS = mental component score; MSQOL = Multiple Sclerosis Quality of Life; PA = previous activity; PCS = physical component score; PL = profile likelihood; PRE = progressive resistance exercise

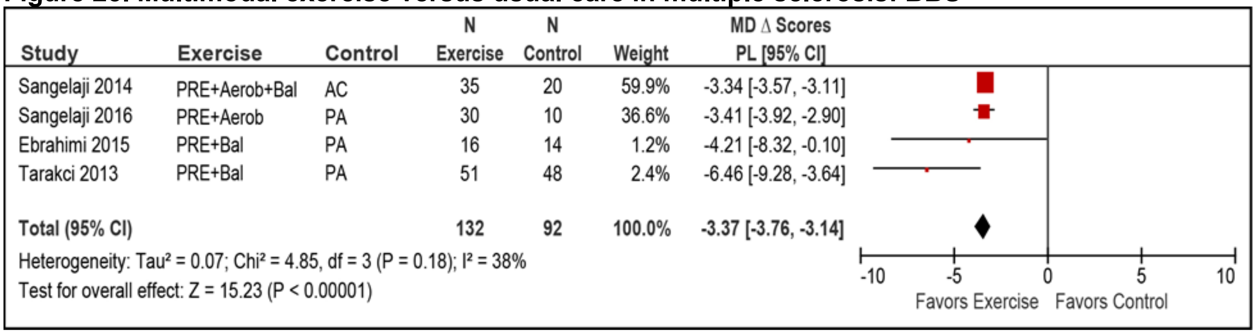
Functional capacity was improved with multimodal exercise based on a timed climbing test in one fair-quality trial (difference –7.0 seconds, 95% CI –10.5 to –3.5)[223] and based on the Dynamic Gait Index (DGI) (difference 0.20, 95% CI 1.9 to 2.7) and Falls Efficacy Scale (difference –8.7, 95% CI –14.4 to –3.0) in another poor-quality trial.[225]

Balance improved with multimodal exercise compared with continuation of previous activity (4 trials, MD –3.4, 95% CI –3.8 to –3.1, I^2=38%, BBS, 0-56 scale);[222,223,226,228] individually all trials favored exercise but the magnitude of effect size varied (range –3.3 to –6.5) (Figure 25). Analysis excluding one outlier had no impact on effect size but substantially reduced heterogeneity (3 trials, MD –3.4, 95% CI –3.6 to –3.1, I^2=0%).[222,226,228] These trials provided low-strength evidence of improved balance scores with multimodal exercises. However, no difference in balance (BBS 0-56 scale) between group and home-based multimodal exercise in one trial[229] was observed immediately after the intervention or at 8-week followup. Similarly, there were no differences between groups observed based on disability level (low or high) at either timeframe in this trial (Table 37).

No clear difference in disability immediately posttreatment was reported across two poor-quality trials based on the EDSS (0-10 scale, 2 trials, MD –0.1, 95% CI –0.3 to 0.1, I^2=42%)

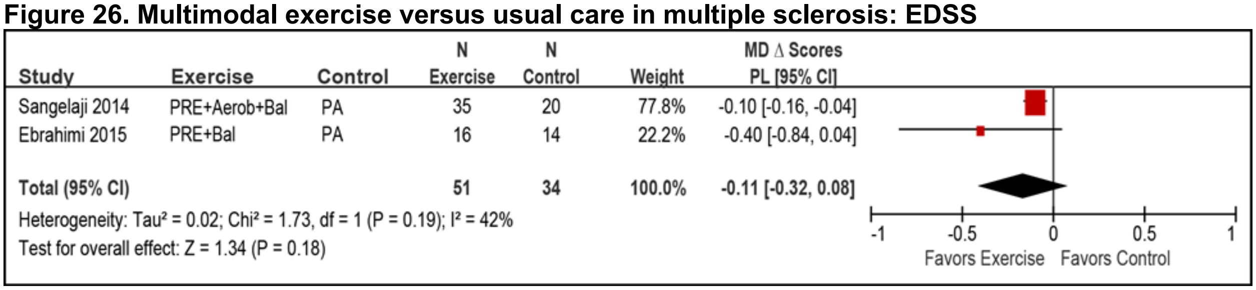
(Figure 26).[226,228] One of the trials reported no difference in EDSS at long term (42 weeks) between multimodal exercises and usual care.[226]

Figure 25. Multimodal exercise versus usual care in multiple sclerosis: BBS



Abbreviations: Δ = change; AC = attention control; BBS = Berg Balance Scale; CI = confidence interval; MD = mean difference; PA = previous activity; PL = profile likelihood; PRE = progressive resistance exercise

Figure 26. Multimodal exercise versus usual care in multiple sclerosis: EDSS



Abbreviations: Δ = change; CI = confidence interval; EDSS = Expanded Disability Status Scale; MD = mean difference; PA = previous activity; PL = profile likelihood; PRE = progressive resistance exercise

Six RCTs did not address harms or adverse events. Two RCTs reported that no adverse events occurred.[223,229]

Multimodal Exercises—Cerebral Palsy

Four trials enrolled participants (n=177) with CP (Table 38).[234-240] Weighted mean age of participants across trials was 13.5 years (range 9.75 to 20 years) with weighted mean proportion female of 48.5 percent (range 42% to 52.6%). No study provided data on race. Weighted mean proportion of participants who could ambulate was 96.3 percent (range 92.3% to 100%) and level I, II, III, and IV GMFCS levels were 56, 31, 13, and 3 percent, respectively.

Table 38. Multimodal exercise in cerebral palsy

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Fosdahl, 2019b[241] Multimodal exercise RCT Fair	A. Strength training (progressive resistance exercise) + stretching, 48 sessions over 16 weeks (n=17) B. Usual care (n=20)	A vs. B Age: 10.4 vs. 10.0 Female: 59% vs. 30% Ambulatory: 100% GMFM: I: 59% vs. 60% II: 41% vs. 35% III: 0% vs. 5%	A vs. B, mean change score (SD) <u>6MWT (meters):</u> −45.7 (55.4) vs. −55.4 (55.5), adj. MD 10.6 (95% CI −29.3 to 50.6), p=0.590 (pre-post change) −51.1 (72.8) vs. −56.6 (59.6), adj. MD 7.2 (95% CI −43.3 to 57.7), p=0.772 (16-week change) <u>GDI:</u> −0.4 (4.4) vs. −0.8 (7.14), adj. MD −1.0 (95% CI −5.3 to 3.3), p=0.650 (pre-post change) −0.7 (6.0) vs. 1.01 (5.9), adj. MD −1.4 (95% CI −5.6 to 2.8), p=0.504 (16-week change)
Kaya Kara, 2019[242] Multimodal exercise RCT Fair	A. Strength training (progressive resistance exercise) + balance, 36 sessions over 12 weeks (n=17) B. Usual care, 36 sessions over 12 weeks (n=16)	A vs. B Age: 11.8 vs. 11.3 Female: 53% vs. 60% Ambulatory: 100% Manual ability classification system level: I: 47% vs. 47% II: 33% vs. 27% III: 20% vs. 27%	A vs. B, mean change from baseline (SD) (data are for completers only; n=15 vs. 15) <u>GMFM-88D:</u> 0.17 (0.67) vs. 0.32 (1.42), MD −0.15 (95% CI −0.93 to 0.63), p=0.632; effect size 0.13 <u>GMFM-88E:</u> 2.31 (2.20) vs. −0.37 (2.59), MD 2.68 (95% CI 0.98 to 4.38), p=0.004; effect size 1.11 <u>1MWT:</u> 7.76 (7.03) vs. 0.53 (3.37), MD 7.23 (95% CI NR), p=0.001; effect size 1.31 <u>TUG:</u> −1.02 (0.45) vs. 0.08 (0.45), MD −1.10 (95% CI −1.42 to −0.78), p<0.001; effect size 2.42
Slaman, 2015[237] Slaman, 2015[234] Slaman, 2014[235] Slaman, 2010[236] Multimodal exercise RCT Fair	A. Strength training + aerobic fitness, 48 sessions over 3 months plus 8-10 counseling sessions on physical activity and sports participation over 3 months: (n=28) B. Usual care (n=29)	A vs. B Age: 20 vs. 20 Female: 48.3% vs. 57.1% Ambulatory: 97% vs. 89% Wheelchair user: 3.3% vs. 10.7% Unilateral CP: 52% vs. 50% GMFM I: 61% vs. 55% GMFM II: 32% vs. 31% GMFM III: 7% vs. 10% GMFM IV: 0% vs. 3%	A vs. B, mean difference (95% CI), p=between groups: <u>GMFM-66</u>: –1.94 (–4.69 to 0.82), p>0.05 (postintervention); –0.08 (–1.99 to 1.83), p>0.05 (1-year followup) <u>SF-36 Physical Functioning</u>: 3.11 (95% CI –8.31 to 14.53), p>0.05 (postintervention); 5.45 (–5.13 to 16.04), p>0.05 (1 year followup) <u>SF-36 Role Physical</u>: 4.15 (–15.10 to 23.40), p>0.05 (postintervention); 16.27 (–8.65 to 41.20), p>0.05 (1-year followup) <u>SF-36 General Health:</u> 7.41 (–3.81 to 18.62), p>0.05 (postintervention); 10.28 (–1.42 to 21.98), p>0.05 (1 year followup) <u>SF-36 Vitality</u>: 1.64 (–4.96 to 8.23), p>0.05 (postintervention); −0.40 (–6.92 to 7.71), p>0.05 (1-year followup) <u>SF-36 Social Functioning:</u> 1.76 (–5.88 to 9.41), p>0.05 (postintervention); −3.08 (–12.64 to 6.49), p>0.05 (1-year followup) <u>SF-36 Role Emotional</u>: 5.94 (–5.01 to 16.90), p>0.05 (postintervention); 11.09 (–1.22 to 23.39), p>0.05 (1 year followup) <u>SF-36 Mental Health</u>: 8.00 (0.96 to 15.05), p<0.05 (postintervention); 8.80 (0.99 to 16.61), p<0.05 (1-year followup)

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Van Wely, 2014a[238] Van Wely, 2014b[239] Van Wely, 2010[240] Multimodal exercise RCT Fair[a]	A. Strength plus aerobics 24 sessions over 4 months plus PT and counseling over 6 months plus usual PT from months 4-12 (n=25) B. Usual PT months 0-12 (n=25)	A vs. B Age: 9.5 vs. 10.0 Female: 52% vs. 33% Ambulatory: 100% Wheelchair user for long distances: 20%) vs. (21% GMFCS I: 60% vs. 54% GMFCS II: 24% vs. 25% GMFCS III: 16% vs. 21% Bilateral: 52% vs. 54%	A vs. B, mean difference (95% CI), p=between groups: GMFM-66: 2.8 (0.2 to 5.4), p=0.03 (month 6); −0.9 (−3.3 to 1.4), p>0.05 (month 12) 1MWT: 5.0 (0.0 to 9.0), p=0.06 (month 4); 2.0 (−4.0 to 9.0), p>0.05 (month 6); 3.0 (−43.0 to 10.0), p>0.05 (month 12) CPQoL Social Well-Being & Acceptance: –3.1 (–7.9 to 1.7), p=0.19 (month 12) CPQoL Functioning: –2.5 (–7.3 to 2.3), p=0.30 (month 12) CPQoL Participation & Physical Health: –0.8 (–5.7 to 4.1), p=0.75 (month 12) CPQoL Emotional Well-Being and Self-Esteem: –0.3 (–5.3 to 4.7), p=0.90 (month 12) CPQoL pain and impact on disability: 5.0 (–5.2 to 15.2), p=0.33 (month 12)

Abbreviations: 1MWT = One-Minute Walk Test; 6MWT = 6-Minute Walk Test; adj. = adjusted; CI = confidence interval; CPQoL = Cerebral Palsy Quality of Life questionnaire; GDI = Gait Deviation Index; GMFCS = Gross Motor Function Classification System; GMFM = Gross Motor Function Measure; GMFM-88D = Gross Motor Function Measure-88D (standing); GMFM-88E = Gross Motor Function Measure E (walking, running, jumping); MD = mean difference; NR = not reported; PT = physical therapy; RCT = randomized controlled trial; SD = standard deviation; SF-36 = Short-Form 36 Quality of Life; TUG = Timed Up and Go Test

[a] Van Wely was considered a fair-quality trial based on the 2014a publication which reported primary outcomes of interest; the 2014b publication reported secondary outcomes (quality of life) and the 2010 publication is the trial protocol (LEARN 2 MOVE 7-12).

Walking outcomes were reported in three RCTs.[238-242] Evidence was considered insufficient to draw firm conclusions on the impact of exercise on walking. There was no improvement in 6MWT versus usual care either immediately post-16-week intervention or at 16 weeks postintervention.[241] Similarly, there was no improvement in Gait Deviation Index (GDI) at either time in the same trial.[241] There was improvement on the 1MWT with multimodal exercise versus usual care immediately post-12- to 16-week treatment across two trials (MD –5.3, 95% CI –10.24 to –0.33, I^2=45) (Figure 27). There was no difference between multimodal exercise and usual care in one trial at 26 weeks or 52-week followup.[238-240]

There was low-strength evidence of no clear benefit to exercise on functional capacity based on GMFM-66 compared with usual care immediately posttreatment. Results across two trials reporting GMFM-66 (0-100 scale) were inconsistent with the pooled differences, showing no difference between multimodal exercise versus usual care (2 trials, MD −1.5, 95% CI −6.4 to 4.7, I^2=71%) (Figure 28).[234-240] No difference between groups was seen in one trial (difference 1.6, 95% CI −2.7 to 5.9)[234-237] while the other trial favored the combination of strength training, aerobics, and PT over usual care (difference −3.1, 95% CI −5.7 to −0.6).[238-240] In addition to variation in interventions, differences in patient populations may have contributed to the inconsistency: the first study enrolled older participants (mean age 20 years vs. 10 years) and more participants with GMFCS level II (32% vs. 24.5%). It was unclear whether the effect sizes are clinically meaningful. In one small trial, there was no difference between exercise and usual care on the GMFM-88-D but some improvement in GMFM-88-E (difference 2.7, 95%CI 1.0 to 4.4).[242] In the same trial, TUG improved with exercise (difference −1.1, 95% CI −1.4 to −0.78) compared with usual care, but evidence was considered insufficient for this outcome.

No improvement in quality of life for any CPQoL domain was reported in one trial following multimodal exercise (strength training combined with cardiopulmonary fitness exercise) versus usual care.[238-240] The other trial reported no improvement for any SF-36 domain scores immediately postintervention with multimodal exercise versus usual care; only the bodily pain subscale was improved at intermediate-term (24 weeks) followup (Table 38).[234-237] These trials provided low-strength evidence of no clear benefit of multimodal exercises function or quality of life.

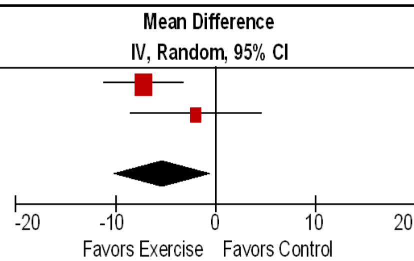
Functional muscle strength measured as the number of lateral step-ups and sit-to-stands in 30 seconds was not different between the multimodal exercise and usual care groups immediately after the 16-week intervention or at 24 weeks followup.[238-240]

One RCT reported that there were no adverse events.[234] Another RCT indicated that two participants were lost to followup due to medical reasons, but did not specify the medical reasons or otherwise address harms or adverse events.[238] A third trial reported that no adverse events were associated with the training protocol, but that one participant in the exercise group had ankle pain following a fall while playing basketball.[242] A fourth trial did not report on adverse events.[241]

Figure 27. Multimodal exercise versus usual care in cerebral palsy: 1MWT[a]

Study or Subgroup	Mean Difference	SE	Exercise Total	Control Total	Weight	Mean Difference IV, Random, 95% CI
Kaya Kara 2019	-7.23	2.01	15	15	62.8%	-7.23 [-11.17, -3.29]
Van Wely 2014	-2	3.32	25	25	37.2%	-2.00 [-8.51, 4.51]
Total (95% CI)			**40**	**40**	**100.0%**	**-5.28 [-10.24, -0.33]**

Heterogeneity: Tau² = 6.15; Chi² = 1.82, df = 1 (P = 0.18); I² = 45%
Test for overall effect: Z = 2.09 (P = 0.04)



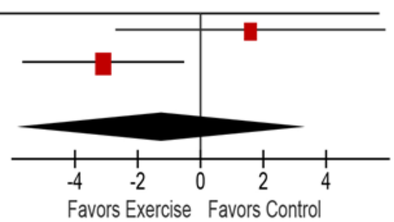
Abbreviations: Δ = change; 1MWT = 1-Minute Walk Test; CI = confidence interval; IV = weighted mean difference; SE = standard error

[a] This figure reflects Dersimonian Laird estimates as the Profile Likelihood model did not converge.

Figure 28. Multimodal exercise versus usual care in cerebral palsy: GMFM-66

Study	Exercise	Control	N Exercise	N Control	Weight	MD Δ Scores PL [95% CI]
Slaman 2015	PRE+Areob	PT	28	27	43.0%	1.59 [-2.68, 5.86]
Van Wely 2014	PRE+Aerob+PT	PT	25	25	57.0%	-3.10 [-5.65, -0.55]
Total (95% CI)			**53**	**52**	**100.0%**	**-1.48 [-6.37, 4.66]**

Heterogeneity: Tau² = 7.78; Chi² = 3.41, df = 1 (P = 0.06); I² = 71%
Test for overall effect: Z = 0.47 (P = 0.64)



Abbreviations: Δ = change; AC = attention control; CI = confidence interval; GMFM-66 = Gross Motor Function Measure 66; MD = mean difference; PA = previous activity; PL = profile likelihood; PRE = progressive resistance exercise

Multimodal Exercises—Spinal Cord Injury

Three RCTs[244-248] and one cohort study[250] enrolled participants (n=228) with SCI (Table 39). Weighted mean age of participants across trials was 35.3 (range 36.8 to 41.4 years) with weighted mean proportion female of 17.6 percent (range 1% to 15.5%). No study provided data on race or ambulatory abilities. Evidence was considered insufficient for all outcomes based on single trials for each comparison, study quality, and imprecision of effect sizes.

Table 39. Multimodal strength exercise in spinal cord injury

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Galea, 2018[245] Multimodal exercise RCT Fair	A. Whole body strength + aerobics, 36 sessions over 12 weeks (n=60) B. Upper body strength + aerobics, 36 sessions over 12 weeks (n=56)	A vs. B Age: 40.1 vs. 42.8 Female: 15% vs.16% ASIA A: 48% vs. 50% ASIA B: 15% vs. 14% ASIA C: 12% vs. 9% ASIA D: 25% vs. 27% C2-C8: 48% vs. 59% T1-T6: 30% vs. 23% T7-T12: 22% vs. 18%	A vs. B, mean difference (95% CI) between groups: 6MWT: –18.36 (–68.57 to 31.84), p=0.45 (12 weeks); 27.12 (–12.69 to 66.94), p=0.168 (6 months) 10MWT (m•sec^{-1}): –0.01 (–0.1 to 0.08), p=0.818 (12 weeks); –0.72 (–2.41 to 0.98), p=0.382 (6 months) ASIA-UEMS: –0.04 (–1.12 to 1.04), p=0.94 ASIA-LEMS: 0.90 (–0.48 to 2.27), p=0.20
Harness, 2008[250] Multimodal exercise Cohort study Fair	A. Strength + cycling + vibration, mean 56 days over 6 months (n=22) B. Usual care (self-regulated exercise), mean 98 days over 6 months (n=9)	A vs. B Age: 37.8 vs. 34.5 Female: 13.6% vs. 0% ASIA-UEMS: 31.0 vs. 38.0, p=0.37 ASIA-LEMS: 8 vs. 4	A vs. B, mean change (SE), p=between groups: EQ-5D: 14.0 (5.0) vs. 3.0 (5.0), p=0.14 LEMS: 3.3 (0.9) vs. 0 (0.2), p=0.035 ASIA Total Motor: 4.8 (1.0) vs. –0.1 (0.5), p<0.001 CHART: 12.0 (15.0) vs. 0.1 (18.0), p=0.60
Jones, 2014a[247] 2014b[246] Multimodal exercise RCT Poor	A. Activity-based therapy, 72 sessions over 24 weeks (n=20) B. Waitlist (n=21)	A vs. B Age: 42 vs. 34 Female: 5% vs. 48% Tetraplegia: 75% vs. 76% AIS C: 35% vs. 52% AIS D: 65% vs. 48%	A vs. B, mean change (SD), p=between groups: 10MWT (m/s): 0.096 (0.140) vs. 0.027 (0.104), p=0.036 6MWT: 35.97 (48.15) vs. 3.0 (25.51), p=0.002 TUG: –37.2 (81.3) vs. –6.2 (18.1), p=0.267 Reintegration to normal living index: 4.6 (13.87) vs. –2.0 (10.01), p=0.087 SCI-FAI: 5.0 (8.03) vs. –0.21 (2.83), p=0.031 SCIM-III: 1.35 (5.2) vs. 0.0 (4.53), p=0.393
Liu, 2019[248] Multimodal exercise RCT Fair	A. Strength exercise + treadmill + core stability training on a stable support surface, 60 sessions over 12 weeks (n=20) B. Strength exercise + treadmill + core stability training on an unstable support surface, 60 sessions over 12 weeks (n=20)	A vs. B (data are for completers only; n=14 vs. 15) Age: 43 vs. 46 Female: 21% vs. 27% Ambulatory: 100% -paraplegia: 36% vs. 40% -tetraplegia: 64% vs. 60%	A vs. B, mean (SD), data for completers only: Stride length (units NR): 0.564 (0.189) vs. 0.454 (0.173), p=0.025 (postintervention) 0.09 (0.26) vs. 0.06 (0.24), MD 0.03 (95% CI –0.16 to 0.22), p=NR (pre-post change) Walking speed (units NR): 0.350 (0.226) vs. 0.209 (0.171), p=0.0196 (postintervention) 0.09 (0.30) vs. 0.03 (0.23), MD 0.06 (95% CI –0.14 to 0.26), p=NR (pre-post change)

Abbreviations: 6MWT = 6-Minute Walk Test; 10MWT = 10-Meter Walk Test; AE = adverse event; AIS = ASIA Impairment Scale; ASIA-LEMS = American Spinal Injuries Association Impairment Scale - Lower Extremity Motor Score; ASIA-UEMS = American Spinal Injuries Association Impairment Scale - Upper Extremity Motor Score; CHART = Craig Handicap Assessment and Reporting Technique; CI = confidence interval; EQ-5D = European Quality of Life 5 dimensions; MD = mean difference; NR = not reported; RCT = randomized controlled trial; SCI = spinal cord injury; SCIM = Spinal Cord Independence Measure; SD = standard deviation; SE = standard error; SEM = standard error mean; TUG = Timed Up and Go Test; UEMS = Upper Extremety Motor Score

Evidence from small trials was insufficient to draw conclusions regarding the impact of multimodal exercise on functional capacity or walking in participants with SCI.

Two studies, one RCT[246,247] and one cohort study,[250] compared multimodal exercise with usual care. Multimodal exercise (which consisted of progressive resistance exercise and locomotor training using manual or robot-assisted gait and aquatic exercise) was associated with improved walking ability compared with waitlist immediately postintervention in the RCT (at 24 weeks), based on the 6MWT (36.0 ± 48.2 vs. 3.0 ± 25.5 meters, p=0.002), the 10MWT (0.1 ± 0.1 vs. 0.03 ± 0.1 meters per second; p=0.036), and the Spinal Cord Injury Function Ambulation Index (SCI-FAI, scale not provided) (5.0 ± 8.0 vs. –0.2 ± 2.8, p=0.031). It is not clear if differences are clinically meaningful. Multimodal exercise was not associated with improved functional capacity based on the TUG test in the RCT.[247]

The fair-quality cohort study found no difference between multimodal exercise (consisting of progressive resistance exercise, aerobic exercise, and balance training) versus self-regulated exercise in quality of life using the EQ-5D immediately posttreatment (26 weeks) change scores (14.0 ± 5.0 vs. 3.0 ± 5.0, respectively, p=0.14).[250]

Another trial compared whole-body (progressive resistance exercise for the trunk and upper and lower extremity, locomotor training, and functional electrical stimulation assisted cycling) versus upper body (circuit-based strength and aerobic training) multimodal exercise programs.[244,245] Walking measures were only reported for the small subset of participants who could walk (n=26). There was no difference immediately following the 12-week intervention (6MWT difference –12.30 meters, 95% CI –68.01 to 43.41; 10MWT difference –0.10 m•sec^{-1}, 95% CI –0.30 to 0.10). At 12-week followup, whole body exercise was associated with improvement in the 6MWT (difference –88.0 meters, 95% CI –143.71 to –32.29) but not the 10MWT (difference –0.80 m•sec^{-1}, 95% CI –2.3 to 0.70) versus upper body exercise. Evidence was considered insufficient to draw firm conclusions.

One trial compared trunk stabilization exercises done on an unstable surface to exercises performed on a stable surface.[248] There were no differences between treatment groups for either walking speed or stride length immediately after the 12-week intervention. (Authors did not provide units of measure.)

One RCT comparing multimodal exercise with usual care (waitlist) found no differences in change scores between groups in disability or activities of daily life immediately posttreatment (12 weeks): Spinal Cord Independence Measure, version III (SCIM-III) (1.4 ± 5.2 vs. 0.0 ± 4.5, p=0.393) and Reintegration to Normal Living (4.6 ± 13.9 vs. –2.0 ± 10.0, p=0.087), respectively.[244,245] The cohort study reported no differences in disability between multimodal exercise and usual care based on the Craig Handicap and Assessment Reporting Technique (CHART).[250]

Withdrawals due to injuries related to participation in intensive exercise versus usual care were reported in one trial (7.7% vs. 0%).[246,247] In the trial comparing whole body versus upper body multimodal exercise, withdrawal due to adverse events was similar (3.3% vs. 1.8%) even though the reporting of any definite or probable intervention-related event was more common with whole body strengthening and aerobics versus the upper body intervention.[244,245] Skin abrasion/bruising was the most common (Table 39). The study comparing trunk stabilization exercise on an unstable support surface versus the exercises done on a stable surface reported that no adverse events occurred.[248]

All Exercise

The outcomes with sufficient data were analyzed using meta-analysis across all trials combined to determine a general exercise effect that was not dependent on patient population or

intervention modality(s). The comparison group consisted of no treatment or waitlist controls, or control groups with low-intensity usual care. Usual care arms of higher intensity (e.g., 48 sessions over 12 weeks of strength, aerobic, balance, and coordination exercises) were excluded from the analysis, due to concern that they may confer some level of treatment. The analysis included the difference in outcome from before treatment (baseline) to immediately postintervention. Only RCTs were included in these meta-analyses due to the overall lower quality of nonrandomized studies in this body of evidence. Sensitivity analyses removing trials rated poor quality from the meta-analyses in this section yielded results similar to the primary analyses, with the exception of the TUG test, which was no longer statistically significant after the removal of poor quality studies.

Key Points

- Across different interventions in trials of participants with MS, there was evidence that physical exercise improves walking ability (SOE: high).
- Across different interventions in trials of participants with MS, there was evidence that physical exercise improves balance (SOE: moderate).
- There was moderate-strength evidence of no clear benefit of physical activity on function in participants with MS (SOE: moderate).
- Across different interventions in trials of participants with CP, there was low-strength evidence that physical activity improves function (SOE: low).
- Across different interventions in trials of participants with SCI, there was low-strength evidence that physical activity improves function (SOE: low).

Detailed Synthesis

Walking Ability

In order to determine if walking ability improves with any physical activity intervention, RCTs that assessed performance on the 6MWT, the 10MWT, and/or the MSWS-12 versus no or low-intensity usual care were pooled. Twenty-seven total RCTs were included (23 RCTs for the 6MWT, 14 RCTs for 10MWT, 9 RCTs for MSWS-12). Most trials enrolled participants with MS (25 RCTs, n=1,343). Seven RCTs enrolled participants with CP (n=234)[126,129,188,207,211,215,241] and two enrolled participants with SCI (n=69).[189,247]

6-Minute Walk Test

Twenty-five RCTs (n=1,196) were included in the 6MWT analysis[52,54,66,77,80,83,126,129,149,160,177,188,192,193,197,198,203,211,221,222,226,228,230,232,241,246,247] (Figure 29). Most trials were rated fair quality, one trial was rated good quality,[211] and eight RCTs were rated poor quality.[188,192,193,197,226,228,246,247] Nineteen trials were in participants with MS,[52,54,66,77,80,83,149,160,177,192,193,197,198,203,221,222,226,228,230,232] five RCTs enrolled participants with CP,[126,129,188,211,241] and one was in participants with SCI.[247] Aerobic interventions included cycling, aquatics, dance, motion gaming, and treadmill training; strength interventions included Pilates and progressive resistance exercises; and multimodal interventions generally included strength training along with aerobic and/or balance training. One study included balance and motor control training as an intervention.[149]

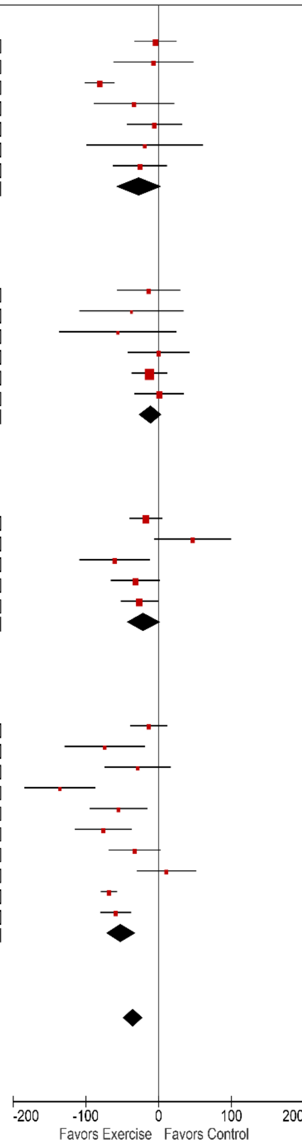
In pooled analysis, participants in the intervention groups walked a mean of almost 33 more meters than those in the control groups after controlling for baseline walking distance (MD

–32.94, 95% CI –46.07 to –19.81, I^2=78%, p<0.001) (Figure 29). The treatment effect was stronger and significant in trials of multimodal interventions (MD, –51.70, 95% CI –71.92 to –31.48, p<0.001) for a significant difference based on exercise modality subgroup (i.e., aerobic, vs. strength, vs. postural control vs. multimodal exercises, p=0.02).

In pooled analysis of the 19 trials that enrolled participants with MS, results also favored physical activity (MD –42.70, 95% CI –57.05 to –28.35, I^2=75%). This was not the case in the four trials that enrolled participants with CP where distance walked was similar in the intervention and control groups (MD 6.85, 95% CI –13.39 to 27.08, I^2=0%), or in the one SCI trial (MD –32.97, 95% CI -68.17 to 2.23).

Figure 29. 6MWT meta-analysis of all randomized controlled trials versus no treatment/usual care

Study	Cond.	Exercise	Control	N Exercise	N Control	Weight	MD Δ Scores PL [95% CI]
Aerobic ex							
Baquet 2018	MS	Cycling	WL	34	34	17.1%	-4.40 [-32.74, 23.94]
Hebert 2011*	MS	Cycling	WL	13	13	12.4%	-7.19 [-61.42, 47.04]
Kargarfard 2018	MS	Aqua	WL	17	15	18.4%	-81.00 [-100.72, -61.28]
Young 2018	MS	Movement to music	WL	20	19	12.4%	-33.70 [-88.09, 20.69]
Kim 2015	CP	Treadmill	PT	14	7	15.4%	-5.71 [-43.18, 31.76]
Bahrami 2019	CP	Treadmill	PT	15	14	8.7%	-19.03 [-98.40, 60.34]
Tollar 2020	MS	Cycling	WL	14	12	15.6%	-25.80 [-62.16, 10.56]
Subtotal (95% CI)				**127**	**114**	**100.0%**	**-27.30 [-58.36, 3.76]**
Heterogeneity: Tau² = 1261.16; Chi² = 28.14, df = 6 (P < 0.0001); I² = 79%							
Test for overall effect: Z = 1.72 (P = 0.08)							
Strength ex							
Kalron 2017	MS	Pilates	PT	22	23	13.2%	-13.80 [-56.51, 28.91]
Duff 2018	MS	Pilates	AC Massage	15	15	4.8%	-37.40 [-108.14, 33.34]
Dalgas 2010	MS	PRE	Previous	16	18	3.8%	-56.10 [-135.91, 23.71]
Taylor 2013	CP	PRE	PT	23	25	14.0%	0.00 [-41.59, 41.59]
Callesen 2019	MS	PRE	WL	17	9	42.3%	-12.60 [-36.50, 11.30]
Tollar 2020	MS	PRE	WL	14	12	21.8%	0.80 [-32.46, 34.06]
Subtotal (95% CI)				**107**	**102**	**100.0%**	**-10.92 [-27.12, 4.65]**
Heterogeneity: Tau² = 0.00; Chi² = 2.55, df = 5 (P = 0.77); I² = 0%							
Test for overall effect: Z = 1.38 (P = 0.17)							
Postural Control ex							
Callesen 2019	MS	Bal. Training	WL	24	9	27.3%	-17.50 [-39.15, 4.15]
Ahmadizadeh 2019	CP	WBV + stretching	AC	10	10	12.6%	46.85 [-5.38, 99.08]
Moraes 2020	MS	Hippotherapy	WL	17	16	14.1%	-60.40 [-108.13, -12.67]
Tollar 2020	MS	Exergaming or Bal.	WL	28	12	20.7%	-32.00 [-65.03, 1.03]
Yazgan 2019	MS	Exergaming	WL	27	15	25.4%	-26.47 [-51.28, -1.66]
Subtotal (95% CI)				**106**	**62**	**100.0%**	**-20.72 [-43.70, 2.26]**
Heterogeneity: Tau² = 381.92; Chi² = 9.80, df = 4 (P = 0.04); I² = 59%							
Test for overall effect: Z = 1.77 (P = 0.08)							
Multimodal ex							
Hogan 2014*	MS	PT-led community	Previous	48	15	11.9%	-13.70 [-38.40, 11.00]
Garret 2012ab*	MS	PT-led community	Previous	63	49	7.0%	-74.00 [-128.62, -19.38]
Sandroff 2017	MS	PRE+Aerob+Bal	AC Stretch	43	40	8.5%	-28.70 [-73.45, 16.05]
Sangelaji 2014	MS	PRE+Aerob+Bal	Previous	35	20	7.9%	-135.70 [-183.80, -87.60]
Sangelaji 2016	MS	PRE+Aerob	Previous	30	10	9.4%	-55.20 [-93.95, -16.45]
Ebrahimi 2015	MS	PRE+balance (WBV)	Previous	16	14	9.5%	-75.90 [-114.22, -37.58]
Jones 2014a	SCI	PRE+Locomotor+Aquatics	WL	20	21	10.0%	-32.97 [-68.17, 2.23]
Fosdahl 2019	CP	PRE+Stretch	UC	15	16	9.2%	10.60 [-29.35, 50.55]
Faramarzi 2020	MS	PRE+Aerob+Bal+Pilates+Stretch	WL	46	43	13.9%	-68.22 [-78.67, -57.77]
Ozkul 2020	MS	Aerob+Pilates	AC	17	17	12.6%	-59.05 [-79.61, -38.49]
Subtotal (95% CI)				**333**	**245**	**100.0%**	**-51.70 [-71.92, -31.48]**
Heterogeneity: Tau² = 737.25; Chi² = 42.17, df = 9 (P < 0.00001); I² = 79%							
Test for overall effect: Z = 5.01 (P < 0.00001)							
Total (95% CI)				**673**	**523**	**100.0%**	**-32.94 [-46.07, -19.81]**
Heterogeneity: Tau² = 849.22; Chi² = 122.91, df = 27 (P < 0.00001); I² = 78%							
Test for overall effect: Z = 4.92 (P < 0.00001)							
Test for subgroup differences: Chi² = 10.00, df = 3 (P = 0.02), I² = 70.0%							



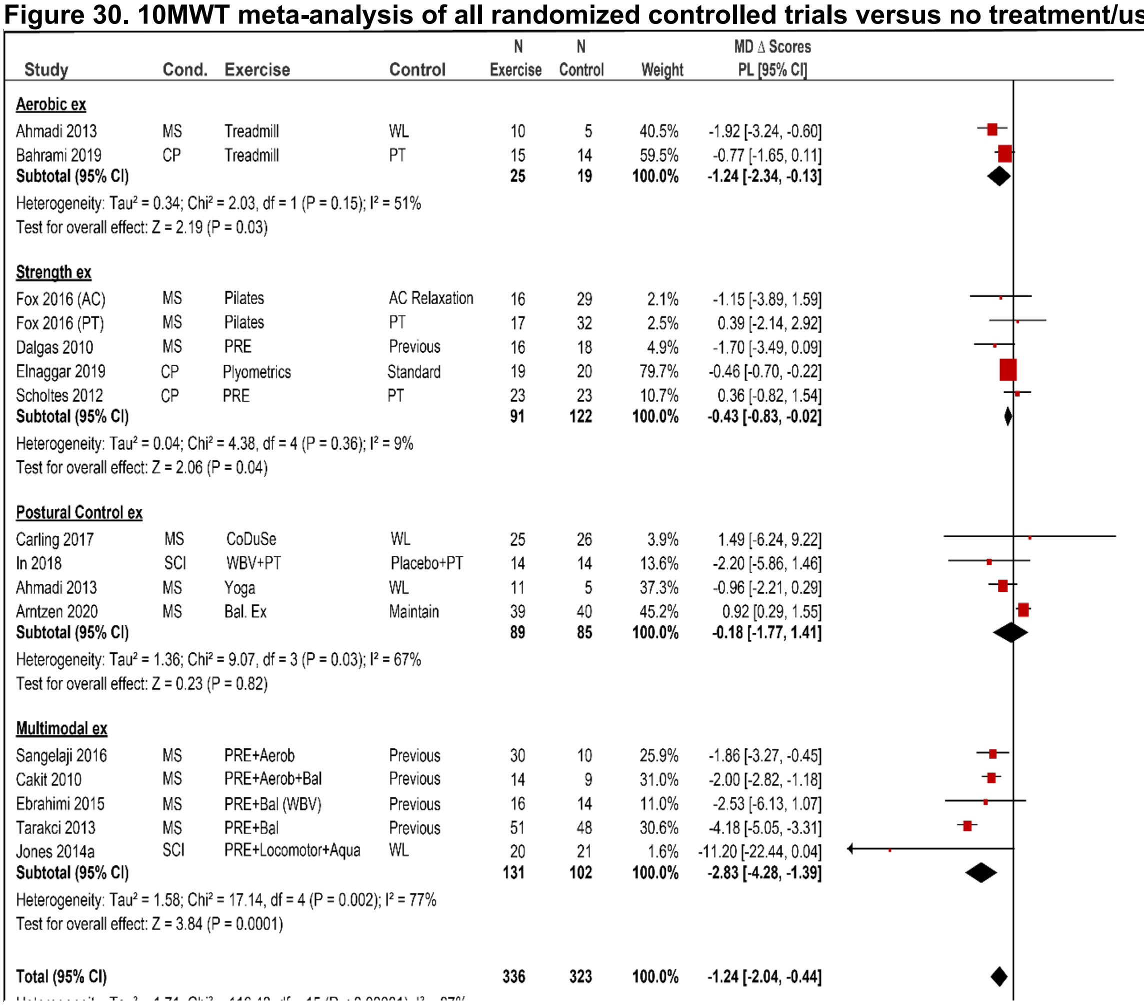
Abbreviations: Δ = change; 6MWT = 6-Minute Walk Test; AC = attention control; Aerob = aerobic exercise; Aqua = aquatic exercise; Bal = balance training; CI = confidence interval; Cond. = condition; CP = cerebral palsy; ex = exercise; MD = mean difference; MS = multiple sclerosis; PL = profile likelihood; PRE = progressive resistance exercise; Previous = continuation of previous activities; PT = physical therapy; SCI = spinal cord injury; Stretch = stretching exercise; UC = usual care (not otherwise specified); WL = waitlist

10-Meter Walk Test

Fourteen RCTs (n=659)[120,129,143,150,189,200,203,207,215,222,223,225,228,247] were included in the analysis of 10MWT. Nine trials were of participants with MS,[120,143,150,200,203,222,223,225,228] two trials were of participants with CP,[129,207,215] and two trials enrolled participants with SCI.[189,247] Ten trials were rated fair quality and three were rated poor quality.[225,228,247] Strength exercises consisted of Pilates and progressive resistance exercises, balance exercises included CoDuSe and PT along with WBV, and multimodal exercises included strength exercises plus aerobic and/or balance exercises. The physical activity intervention was associated with improved time on the 10MWT by 1.24 seconds compared with controls (MD –1.24, 95% CI –2.04 to –0.44, I^2=87%) (Figure 30).

In pooled analysis of the nine MS RCTs, participants in the physical activity groups walked faster than participants in the control groups (MD –1.44, 95% CI –2.74 to –0.13, I^2=90%). There were no differences between the intervention and control groups in the pooled analysis of the three CP trials (MD –0.46, 95% CI –1.55 to 0.63) or in pooled analysis of the two trials that enrolled participants with SCI (MD –5.07, 95% CI –13.29 to 3.15, I^2=55%).

Figure 30. 10MWT meta-analysis of all randomized controlled trials versus no treatment/usual care



Abbreviations: Δ = change; 10MWT = 10-Meter Walk Test; AC = attention control; Aerob = aerobic exercise; Aqua = aquatic exercise; Bal = balance training; CI = confidence interval; CoDuSe = core stability, dual task and sensorimotor challenges; Cond. = condition; CP = cerebral palsy; ex = exercise; MD = mean difference; MS = multiple sclerosis; PL = profile likelihood; PRE =

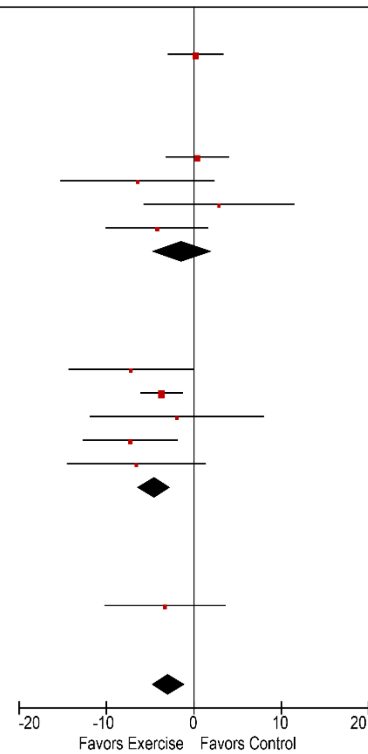
progressive resistance exercise; Previous = continuation of previous activities; PT = physical therapy; SCI = spinal cord injury; WBV = whole body vibration; WL = waitlist

Multiple Sclerosis Walking Scale-12

Eight fair-quality RCTs[52,77,143,144,149,150,175,200] (n=632) assessed the effect of physical activity on walking ability in participants with MS using the MSWS-12 (Figure 31). Cycling was the intervention in the aerobic exercise RCT; strength interventions were Pilates; the balance interventions included CoDuSe, balance and motor control training, and supervised Wii training using virtual reality; and the multimodal intervention consisted of strength and aerobic and/or balance exercises. Physical activity was associated with improved scores on the MSWS-12 (MD –2.88, 95% CI –4.80 to –0.96, I^2=33%). Although there were no differences between subgroups based on intervention category (i.e., aerobic vs. strength vs. balance vs. multimodal exercise, p=0.06), pooled analysis of the five RCTs that focused on balance training did show improvement versus control with balance exercise on self-reported walking ability in participants with MS (n=316, MD –4.56, 95% CI –6.51 to –2.60, I^2=0%).

Figure 31. MSWS-12 meta-analysis of all RCTs versus no treatment/usual care

Study	Cond.	Exercise	Control	N Exercise	N Control	Weight	MD Δ Scores PL [95% CI]
Aerobic ex							
Baquet 2018	MS	Cycling	WL	34	34	17.2%	0.20 [-2.91, 3.31]
Test for overall effect: Z = 0.13 (P = 0.90)							
Strengh ex							
Kalron 2017	MS	Pilates	PT	22	23	15.1%	0.40 [-3.17, 3.97]
Fox 2016 (AC)	MS	Pilates	AC Relaxation	16	29	4.2%	-6.44 [-15.18, 2.30]
Fox 2016 (PT)	MS	Pilates	PT	17	32	4.3%	2.88 [-5.69, 11.45]
Callesen 2019	MS	PRE	WL	17	9	8.1%	-4.20 [-10.00, 1.60]
Subtotal (95% CI)				**72**	**93**	**31.7%**	**-1.36 [-4.83, 2.10]**
Heterogeneity: Tau² = 3.37; Chi² = 4.04, df = 3 (P = 0.26); I² = 26%							
Test for overall effect: Z = 0.77 (P = 0.44)							
Postural Control ex							
Carling 2017	MS	CoDuSe	WL	25	26	6.0%	-7.21 [-14.27, -0.15]
Forsberg 2016	MS	CoDuSe	WL	35	38	21.4%	-3.70 [-6.05, -1.35]
Nilsagard 2012	MS	PT w/Wii	WL	41	39	3.4%	-1.95 [-11.85, 7.95]
Callesen 2019	MS	Bal Training	WL	24	9	9.1%	-7.30 [-12.65, -1.95]
Arntzen 2020	MS	Bal Training	Maintain	39	40	5.0%	-6.58 [-14.46, 1.30]
Subtotal (95% CI)				**164**	**152**	**44.8%**	**-4.56 [-6.51, -2.60]**
Heterogeneity: Tau² = 0.00; Chi² = 2.58, df = 4 (P = 0.63); I² = 0%							
Test for overall effect: Z = 4.57 (P < 0.00001)							
Multimodal ex							
Sandroff 2017	MS	PRE+Aerob+Bal	AC Stretching	43	40	6.3%	-3.30 [-10.16, 3.56]
Test for overall effect: Z = 0.94 (P = 0.35)							
Total (95% CI)				**313**	**319**	**100.0%**	**-2.88 [-4.80, -0.96]**
Heterogeneity: Tau² = 3.05; Chi² = 14.91, df = 10 (P = 0.14); I² = 33%							
Test for overall effect: Z = 2.94 (P = 0.003)							
Test for subgroup differences: Chi² = 7.36, df = 3 (P = 0.06), I² = 59.2%							



Abbreviations: Δ = change; AC = attention control; Aerob = aerobic exercise; Bal = balance training; CI = confidence interval; CoDuSe = core stability, dual task, and sensorimotor challenges; ex = exercise; MD = mean difference; MS = multiple sclerosis; MSWS-12 = Multiple Sclerosis Walking Scale-12; PL = profile likelihood; PRE = progressive resistance exercise; PT = physical therapy; WL = waitlist

Other Function Outcomes

Ten RCTs[85-87,101,102,161,165,167,209,211,212,234,238] provided evidence for exercise on the GMFM or on the D (standing) and/or E (walking, running, jumping) subscales of the GMFM-66 (Figures 32-34). All trials were conducted in participants with CP. All RCTs enrolled children (8 trials

with mean ages between 8.5 and 14) or young adults (2 trials with mean ages between 18 and 20).[167,211,212,234-237] Eighteen trials[50,52-54,95,143,144,151,175,177,185,189,198,206,225,228,242,246,247] examined the effect of physical activity on the TUG (Figure 35).

GMFM-66

Eight RCTs in participants with CP[85-87,161,165,167,209,211,212,234,238] (n=377) measured gross motor function with the GMFM-66 and provided the total scores pre- and post-exercise (Figure 32). One trial was rated poor quality[165] and the remainder were judged to be fair quality. Aerobic exercises included cycling and treadmill training; strength exercises used progressive resistance; balance training used horses (hippotherapy), and multimodal exercises included strength training along with aerobic activity.

There was no change in GMFM-66 scores attributable to physical exercise (MD –0.58, 95% CI –1.62 to 0.45, p=0.27) (Figure 32). There were subgroup differences based on the exercise category of the intervention (p=0.001). The results from the single trial of strength training[209] significantly favored the control group (MD 1.30, 95% CI 0.67 to 1.93, p<0.001). In this trial children in the control group received usual care, which consisted of one to three sessions per week of conventional PT. The intervention group underwent three sessions per week of functional progressive resistance exercise training to improve walking ability. Although strength measures were improved with strength training, GMFM-66 scores were not.

GMFM-66-D

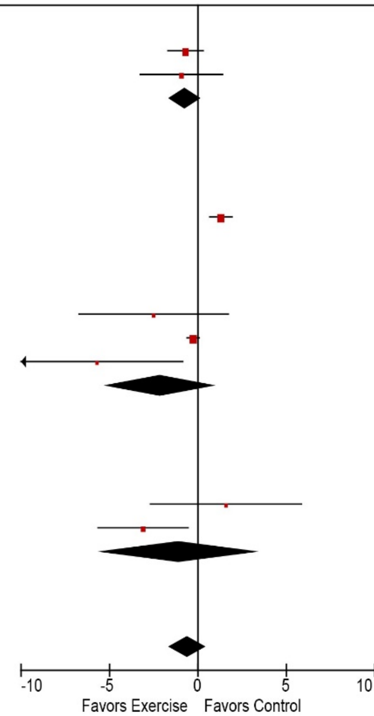
The GMFM-66-D subscale is concerned with standing ability. Two RCTs (n=78), one rated good quality[211,212] and one poor quality,[101,102] presented evidence for the D subscale and found no differences between RAGT or muscle strength exercises and usual care (MD –0.89, 95% CI –7.33 to 5.55, p=0.79) (Figure 33). There were no subgroup differences (p=0.11). Excluding the poor-quality RCT did not alter the findings.

GMFM-66-E

Four RCTs[101,165,167,211,212] (n=175) reported GMFM-66-E subscale scores, which examine walking, running, and jumping ability (Figure 34). One trial was rated good quality,[211,212] one fair quality,[167] and the other two were considered poor quality.[102,165] Included interventions were RAGT, muscle strength exercises, and hippotherapy. Pooled analysis found a significant improvement with exercises versus usual care (MD –3.73, 95% CI –5.78 to –1.67, p<0.001).

Figure 32. GMFM-66 meta-analysis of all randomized controlled trials versus no treatment/usual care

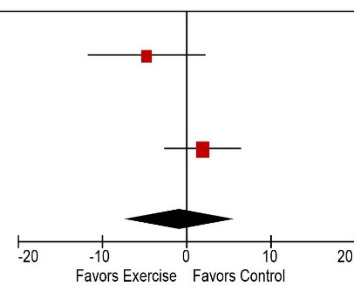
Study	Cond.	Exercise	Control	N Exercise	N Control	Weight	MD Δ Scores PL [95% CI]
Aerobic ex							
Fowler 2010/Demuth 2012	CP	Cycling	Previous	29	29	19.9%	-0.70 [-1.69, 0.29]
Bryant 2012	CP	Bike+Treadmill	PT	20	10	10.9%	-0.93 [-3.25, 1.39]
Subtotal (95% CI)				**49**	**39**	**30.8%**	**-0.74 [-1.97, 0.42]**
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.86); I² = 0%							
Test for overall effect: Z = 1.58 (P = 0.11)							
Strength ex							
Scholtes 2010	CP	PRE	PT	24	25	22.3%	1.30 [0.67, 1.93]
Test for overall effect: Z = 4.05 (P < 0.0001)							
Postural Control ex							
Deutz 2017	CP	Hippotherapy	WL	35	38	4.8%	-2.50 [-6.71, 1.71]
Herrero 2012	CP	Hippotherapy	Placebo	19	19	23.7%	-0.27 [-0.61, 0.07]
Mutoh 2019	CP	Hippotherapy	Outdoor Rec	12	12	3.8%	-5.70 [-10.54, -0.86]
Subtotal (95% CI)				**66**	**69**	**32.3%**	**-2.12 [-5.27, 1.04]**
Heterogeneity: Tau² = 5.12; Chi² = 5.86, df = 2 (P = 0.05); I² = 66%							
Test for overall effect: Z = 1.32 (P = 0.19)							
Multimodal ex							
Slaman 2015	CP	PRE+Aerob	PT	28	27	4.7%	1.59 [-2.68, 5.86]
Van Wely 2014	CP	PRE+Aerob+PT	PT	25	25	9.8%	-3.10 [-5.65, -0.55]
Subtotal (95% CI)				**53**	**52**	**14.5%**	**-1.48 [-6.37, 4.66]**
Heterogeneity: Tau² = 7.78; Chi² = 3.41, df = 1 (P = 0.06); I² = 71%							
Test for overall effect: Z = 0.47 (P = 0.64)							
Total (95% CI)				**192**	**185**	**100.0%**	**-0.58 [-1.62, 0.45]**
Heterogeneity: Tau² = 1.14; Chi² = 34.06, df = 7 (P < 0.0001); I² = 79%							
Test for overall effect: Z = 1.11 (P = 0.27)							
Test for subgroup differences: Chi² = 16.34, df = 3 (P = 0.0010), I² = 81.6%							



Abbreviations: Δ = change; Aerob = aerobic exercise; CI = confidence interval; CP = cerebral palsy; ex = exercise; GMFM = gross motor function measure; MD = mean difference; Outdoor Rec = outdoor recreation; PL = profile likelihood; PRE = progressive resistance exercise; Previous = continuation of previous activities; PT = physical therapy; WL = waitlist

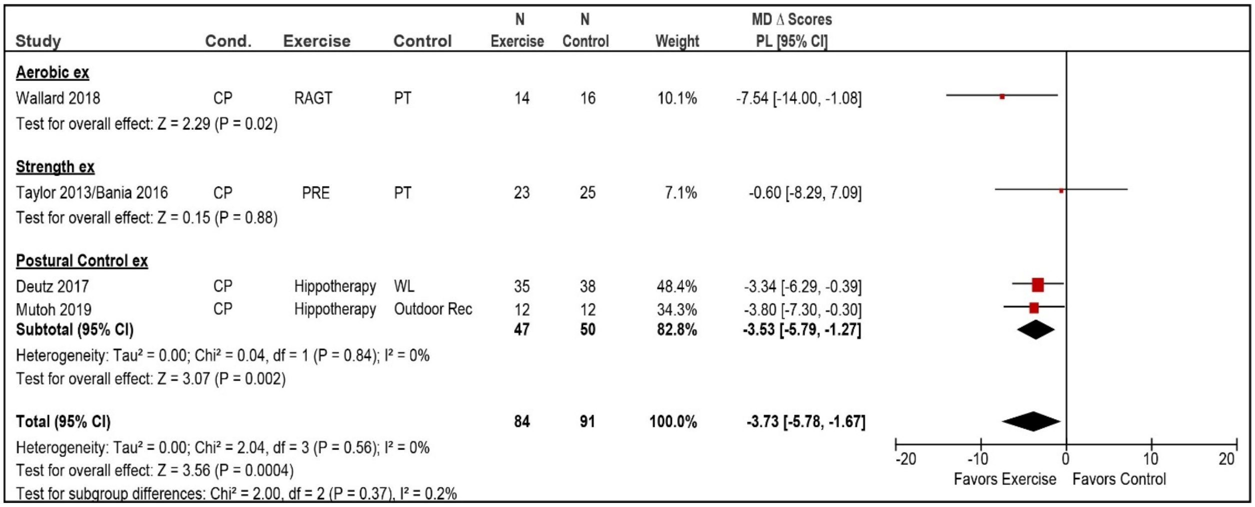
Figure 33. GMFM-66-D meta-analysis of all randomized controlled trials versus no intervention/usual care

Study	Cond.	Exercise	Control	N Exercise	N Control	Weight	MD Δ Scores PL [95% CI]
Aerobic ex							
Wallard 2018	CP	RAGT	PT	14	16	41.9%	-4.76 [-11.65, 2.13]
Test for overall effect: Z = 1.35 (P = 0.18)							
Strength ex							
Taylor 2013/Bania 2016	CP	PRE	PT	23	25	58.1%	1.90 [-2.58, 6.38]
Test for overall effect: Z = 0.83 (P = 0.41)							
Total (95% CI)				**37**	**41**	**100.0%**	**-0.89 [-7.33, 5.55]**
Heterogeneity: Tau² = 13.38; Chi² = 2.52, df = 1 (P = 0.11); I² = 60%							
Test for overall effect: Z = 0.27 (P = 0.79)							
Test for subgroup differences: Chi² = 2.52, df = 1 (P = 0.11), I² = 60.4%							



Abbreviations: Δ = change; CI = confidence interval; Cond. = condition; CP = cerebral palsy; ex = exercise; GMFM-D = gross motor function measure, subscale D (standing); MD = mean difference; PL = profile likelihood; PRE = progressive resistance exercise; PT = physical therapy; RAGT = robotic assisted gait training

Figure 34. GMFM-66-E meta-analysis of all randomized controlled trials versus no intervention/usual care



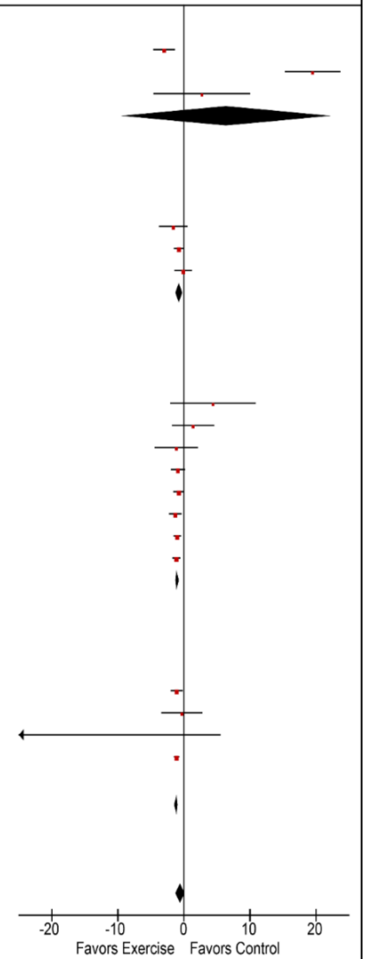
Abbreviations: Δ = change; CI = confidence interval; CP = cerebral palsy; ex = exercise; GMFM-E = Gross Motor Function Measure 66, subscale E (walking, running, jumping); MD = mean difference; Outdoor Rec = outdoor recreation; PL = profile likelihood; PRE = progressive resistance exercise; PT = physical therapy; RAGT = robotic assisted gait training; SE = standard error; WL = waitlist

Timed Up and Go Test

Nineteen trials[50,52-54,95,143,144,151,175,177,185,189,198,206,225,228,230,242,246,247] (n=793) examined the effect of physical activity on the TUG (Figure 35). Two studies enrolled participants with CP,[50,242] two enrolled participants with SCI,[189,246,247] and the remainder were conducted in participants with MS. Aerobic interventions included interval exercises, RAGT, and movement to music; balance exercises included motion gaming, WBV, and CoDuSe; and strength and multimodal interventions included Pilates and progressive resistance training, along with aerobic exercise or balance exercises. Physical activity was associated with improvement on the TUG (MD –0.66, 95% CI –1.28 to -0.04, I^2=85%). However, the results were no longer statistically significant after the removal of the poor quality trials in a sensitivity analysis (n=15 studies, MD -0.55, 95% CI -1.29 to 0.19, I^2=89%). Results were also not significant when the fifteen trials that enrolled participants with MS were pooled (MD –0.30, 95% CI –1.18 to 0.59, I^2=89%). There was also no difference between all exercise versus usual care when the two trials in participants with SCI were pooled (MD –10.33, 95% CI –37.10 to 16.45, I^2=61%). However, pooled analysis of the two trials in participants with CP found improved TUG with all exercise (MD –1.05, 95% CI –1.35 to –0.76, I^2=0%).

Figure 35. Timed Up and Go Test versus no intervention or usual care

Study	Cond.	Exercise	Control	N Exercise	N Control	Weight	MD Δ Scores PL [95% CI]
Aerobic ex							
Negaresh 2018	MS	Interval Exercises	No exercise	34	27	6.2%	-3.00 [-4.56, -1.44]
Russo 2018	MS	RAGT+Conv. Rehab	Conv. Rehab	30	15	2.0%	19.50 [15.40, 23.60]
Young 2018	MS	Movement to music	WL	20	22	0.7%	2.70 [-4.53, 9.93]
Subtotal (95% CI)				**84**	**64**	**8.1%**	**6.39 [-9.44, 22.23]**
Heterogeneity: Tau² = 189.77; Chi² = 101.47, df = 2 (P < 0.00001); I² = 98%							
Test for overall effect: Z = 0.79 (P = 0.43)							
Strengh ex							
Duff 2018	MS	Pilates	AC massage	15	15	4.9%	-1.60 [-3.67, 0.47]
Bulguroglu 2017	MS	Pilates	AC	25	13	8.7%	-0.75 [-1.43, -0.07]
Kalron 2017	MS	Pilates	PT	22	23	7.1%	-0.10 [-1.33, 1.13]
Subtotal (95% CI)				**62**	**51**	**19.0%**	**-0.67 [-1.24, -0.10]**
Heterogeneity: Tau² = 0.00; Chi² = 1.66, df = 2 (P = 0.44); I² = 0%							
Test for overall effect: Z = 2.32 (P = 0.02)							
Postural Control ex							
Carling 2017	MS	CoDuSe	WL	25	26	0.9%	4.41 [-1.97, 10.79]
Forsberg 2016	MS	CoDuSe	WL	35	38	3.0%	1.40 [-1.70, 4.50]
Claerbout 2012	MS	WBV-light+PT	PT	38	17	2.9%	-1.15 [-4.33, 2.03]
Nilsagard 2012	MS	PT w/Wii	WL	41	39	7.8%	-0.90 [-1.89, 0.09]
Hsieh 2018	CP	PC games Platform	PC games Mouse	20	20	8.5%	-0.77 [-1.53, -0.01]
In 2018	SCI	WBV+PT	Placebo + PT	14	14	8.2%	-1.30 [-2.16, -0.44]
Ozkul 2020	MS	Bal+Exergaming	AC	26	13	9.1%	-1.01 [-1.48, -0.54]
Yazgan 2019	MS	Exergaming	WL	27	15	9.1%	-1.14 [-1.65, -0.63]
Subtotal (95% CI)				**226**	**182**	**45.5%**	**-1.01 [-1.29, -0.73]**
Heterogeneity: Tau² = 0.00; Chi² = 6.22, df = 7 (P = 0.51); I² = 0%							
Test for overall effect: Z = 7.05 (P < 0.00001)							
Multimodal ex							
Cakit 2010	MS	PRE+Aero+Bal	Previous	14	9	8.3%	-1.10 [-1.92, -0.28]
Ebrahimi 2015	MS	PRE+Balance(WBV)	Previous	16	14	3.1%	-0.30 [-3.32, 2.72]
Jones 2014a	SCI	PRE+Locomotor+Aqua	WL	20	21	0.0%	-31.00 [-67.46, 5.46]
Kaya Kara 2019	CP	PRE	Loco+SBWDT+Stretch	15	15	9.4%	-1.10 [-1.42, -0.78]
Faramarzi 2020	MS	PRE+Aero+Bala+Pilates+Stretch	WL	46	43	8.2%	-2.15 [-2.72, -1.58]
Subtotal (95% CI)				**111**	**102**	**27.4%**	**-1.41 [-2.13, -0.68]**
Heterogeneity: Tau² = 0.00; Chi² = 2.85, df = 3 (P = 0.42); I² = 0%							
Test for overall effect: Z = 7.20 (P < 0.00001)							
Total (95% CI)				**483**	**399**	**100.0%**	**-0.66 [-1.28, -0.04]**
Heterogeneity: Tau² = 1.15; Chi² = 115.58, df = 17 (P < 0.00001); I² = 85%							
Test for overall effect: Z = 1.60 (P = 0.11)							
Test for subgroup differences: Chi² = 2.48, df = 3 (P = 0.48), I² = 0%							



Abbreviations: Δ = change; AC = attention control; Aerob = aerobic exercise; Aqua = aquatics; Bal = balance; Conv Rehab = conventional rehabilitation; CP = cerebral palsy; loco = locomotor; MS = multiple sclerosis; PRE = progressive resistance exercise; PT = physical therapy; RAGT = robot-assisted gait training; SBWDT = weight-bearing symmetry; SCI = spinal cord injury; WBV = whole body vibration; WL = waitlist

Balance

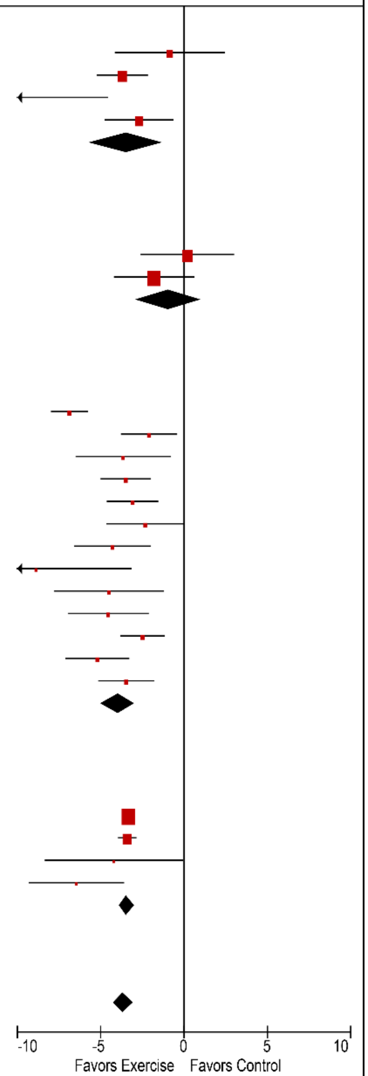
Twenty RCTs[50,52,66,83,117,120,141,143-146,151,156-158,177,222,223,226,228] (n=1,011) that compared a physical exercise intervention with no activity or low-intensity usual care included the BBS to assess balance prior to the intervention and immediately after treatment (Figure 36). All RCTs enrolled participants with MS except for three trials, one conducted in participants with CP (n=40)[50] and two conducted in SCI (n=60).[156,157] One trial was considered good quality,[145] two trials were rated poor quality,[226,228] and the remainder were rated fair quality. Aerobic interventions included treadmill training and aquatic exercise; balance interventions included CoDuSe, Cawthorne/Cooksey exercises, balance training with sensory integration, computer games using a platform, and hippotherapy; and multimodal interventions included strength plus balance and/or aerobics.

Physical activity was associated with significantly improved scores on the BBS by over 3 points (MD –3.64, 95% CI –4.23 to –3.04, I^2=68%). Trials of aerobic exercise, balance (postural control) exercises, and trials of multimodal exercises reported significant effects (MD –3.48,

95% CI –5.68 to –1.28, p=0.002; MD –3.97, 95% CI –5.00 to –2.94, p<0.001; MD –3.45, 95% CI –3.89 to –3.01, p<0.001, respectively) although there was no subgroup effect based on intervention category (i.e., aerobic vs. strength vs. balance vs. multimodal exercise, p=0.06). The overall results were similar when only the MS trials were analyzed (MD –3.56, 95% CI –4.58 to –2.54, I^2=77%).

Figure 36. BBS meta-analysis of all randomized controlled trials versus no intervention/usual care

Study	Cond.	Exercise	Control	N Exercise	N Control	Weight	MD Δ Scores PL [95% CI]
Aerobic ex							
Gervasoni 2013	MS	Treadmill	Conv. Rehab	15	15	22.1%	-0.86 [-4.12, 2.40]
Kargarfard 2018	MS	Aqua	Previous	17	15	35.7%	-3.70 [-5.19, -2.21]
Ahmadi 2013	MS	Treadmill	WL	10	5	10.8%	-10.40 [-16.20, -4.60]
Tollar 2020	MS	Cycling	WL	14	12	31.4%	-2.70 [-4.72, -0.68]
Subtotal (95% CI)				**56**	**47**	**100.0%**	**-3.48 [-5.68, -1.28]**
Heterogeneity: Tau² = 2.96; Chi² = 8.52, df = 3 (P = 0.04); I² = 65%							
Test for overall effect: Z = 3.10 (P = 0.002)							
Strength ex							
Kalron 2017	MS	Pilates	UC	22	23	43.5%	0.20 [-2.56, 2.96]
Tollar 2020	MS	PNF	WL	14	12	56.5%	-1.80 [-4.17, 0.57]
Subtotal (95% CI)				**36**	**35**	**100.0%**	**-0.93 [-2.87, 1.01]**
Heterogeneity: Tau² = 0.27; Chi² = 1.16, df = 1 (P = 0.28); I² = 14%							
Test for overall effect: Z = 0.94 (P = 0.35)							
Postural Control ex							
Afrasiabifar 2018	MS	Cawthrone+Frankel	NOS	47	50	10.2%	-6.87 [-7.95, -5.79]
Forsberg 2016	MS	CoDuSe	WL	35	38	8.8%	-2.10 [-3.75, -0.45]
Carling 2017	MS	CoDuSe	WL	25	26	6.1%	-3.65 [-6.47, -0.83]
Gandolfi 2015	MS	Sensory Bal	Conv. Rehab	39	41	9.3%	-3.50 [-4.97, -2.03]
Hsieh 2018	MS	Hippotherapy	Previous	20	20	9.2%	-3.09 [-4.60, -1.58]
Vermohlen 2018	CP	PC games Platform	PC games mouse	30	37	7.3%	-2.33 [-4.63, -0.03]
Brichetto 2015	MS	Tailored ex	Traditional ex	16	16	7.4%	-4.30 [-6.55, -2.05]
Ahmadi 2013	MS	Yoga	WL	11	5	2.5%	-8.89 [-14.59, -3.19]
Norouzi 2019	SCI	Vestibular Stimulation	C&C Ex	10	10	5.3%	-4.50 [-7.75, -1.25]
Hota 2020	SCI	Balance Ex	UC	20	20	7.1%	-4.55 [-6.94, -2.16]
Ozkul 2020	MS	Exergaming	AC	26	13	9.7%	-2.50 [-3.79, -1.21]
Tollar 2020	MS	Exergaming	WL	28	12	8.3%	-5.20 [-7.08, -3.32]
Yazgan 2019	MS	Exergaming	WL	27	15	8.8%	-3.47 [-5.12, -1.82]
Subtotal (95% CI)				**334**	**303**	**100.0%**	**-3.97 [-5.00, -2.94]**
Heterogeneity: Tau² = 2.41; Chi² = 46.53, df = 12 (P < 0.00001); I² = 74%							
Test for overall effect: Z = 7.56 (P < 0.00001)							
Multimodal ex							
Sangelaji 2014	MS	PRE+Aerob+Bal	Previous	35	20	59.9%	-3.34 [-3.57, -3.11]
Sangelaji 2016	MS	PRE+Aerob	Previous	30	10	36.6%	-3.41 [-3.92, -2.90]
Ebrahimi 2015	MS	PRE+Bal (WBV)	Previous	16	14	1.2%	-4.21 [-8.32, -0.10]
Tarakci 2013	MS	PRE+Bal	Previous	51	48	2.4%	-6.46 [-9.28, -3.64]
Subtotal (95% CI)				**132**	**92**	**100.0%**	**-3.45 [-3.89, -3.01]**
Heterogeneity: Tau² = 0.07; Chi² = 4.85, df = 3 (P = 0.18); I² = 38%							
Test for overall effect: Z = 15.23 (P < 0.00001)							
Total (95% CI)				**558**	**448**	**100.0%**	**-3.64 [-4.23, -3.04]**
Heterogeneity: Tau² = 0.87; Chi² = 69.52, df = 22 (P < 0.00001); I² = 68%							
Test for overall effect: Z = 11.98 (P < 0.00001)							
Test for subgroup differences: Chi² = 7.29, df = 3 (P = 0.06), I² = 58.8%							



Abbreviations: Δ = change; Aerob = aerobic exercise; Aqua = aquatic exercise; BBB = Berg Balance Scale; Bal = balance training; C&C = Cawthorne and Cooksey exercises; CI = confidence interval; CoDuSe = core stability, dual task and sensorimotor challenges; Cond. = condition; Conv. = conventional; CP = cerebral palsy; ex = exercise; MD = mean difference; MS = multiple sclerosis; NOS = not otherwise specified; PC = personal computer; PL = profile likelihood; PNF = proprioceptive neuromuscular facilitation; PRE = progressive resistance exercise; Previous = continuation of previous activities; Rehab = rehabilitation; SCI = spinal cord injury; WL = waitlist

KQ2a: Clinical Outcomes

Cardiometabolic Disease

No studies were identified that assessed the long-term (or short-term) benefits of physical exercise on the primary, secondary, or tertiary prevention of cardiovascular disease and diabetes. Although some studies did examine the effect of exercise on intermediate outcomes such as resting heart rate, lipid levels, and serum glucose (discussed in KQ2b), there were no included studies that reported prevention of myocardial infarction, stroke, or the development of diabetes. A history of cardiovascular or metabolic disorders was often used as exclusion criteria in trials enrolling adults with MS and SCI. This prevented examination of the effects of exercise on improvement in cardiovascular disease or diabetes symptoms. (CP trials were mostly in children and adolescents and did not typically address cardiometabolic disease.)

Obesity

No included studies provided evidence for the development of obesity or overweight or the proportion of patients who were no longer overweight or obese following an intervention.

Depression and Anxiety

While there was a lack of evidence on cardiometabolic disease and exercise, multiple trials addressed mental health and administered validated self-report mental health instruments (e.g., Beck Depression Inventory [BDI], Hospital Anxiety and Depression Scale [HADS]) before and after physical exercise. Most trials were in participants with MS (17 RCTs, 4 quasiexperimental trials, total n=973) (Table 40). Three RCTs enrolled participants with SCI (n=171) (Table 41).

Multiple Sclerosis

The best quality evidence in MS patients was in RAGT (3 good-quality RCTs,[96-98] 1 fair-quality RCT,[95] 209 studies), followed by cycling studies (3 fair-quality RCTs,[53,77,80] n=169) and aqua therapy (2 good-quality RCTs,[70,71] n=109). Other interventions in trials with evidence for mental health in participants with MS included treadmill training, calisthenics, Tai Chi, Pilates, aquatics, yoga, and progressive resistance training, and multimodal exercises (Table 40). All but one trial[117] enrolled more females than males, with most adults in their 30s and 40s.

In the four RAGT RCTs (one with virtual reality) in participants with MS, two studies used the Hamilton Rating Scale for Depression[95,96] (HRSD, also called the Hamilton Depression Rating Scale, abbreviated HDRS or HAM-D) and two trials used the Patient Health Questionnaire-9 (PHQ-9).[97,98] Comparison groups were usual rehabilitation exercises, walking therapy without RAGT, and RAGT without virtual reality. Comparisons between RAGT and control groups indicated improved depression scores after exercise, with no differences between exercise groups.

The instruments used in the three MS cycling RCTs were the Inventory of Depressive Symptomatology Self Report 16 item (IDS-16-SR), the BDI, and the BDI-II. All trials had a usual care or waitlist control arm and one trial also had a vestibular rehabilitation comparison group. In two RCTs[53,77] exercise was associated with improved baseline to postintervention depression scores that were statistically significant, whereas the usual care arms did not show significant improvement, but between group differences failed to reach significance. The third RCT found no differences between either cycling or vestibular rehabilitation and control.[80]

Table 40. Effects of exercise on depression in participants with multiple sclerosis

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Ahmadi, 2013[120] Aerobic/ Postural control RCT Fair	A. Treadmill, 24 sessions over 8 weeks (n=10) A. Yoga, 24 sessions over 8 weeks (n=11) B. Waitlist control (n=10)	A vs. B vs. C Age: 37 vs. 32 vs. 37 Female: 100% EDSS: 2.40 vs. 2.00 vs. 2.25	A vs. B vs. C, mean (SD), p=between groups: BDI: 8.50 (3.06 to 5.60 (3.40) vs. 17.36 (12.42) to 11.09 (12.46) vs. 11.90 (9.39) to 12.50 (8.1) A vs. B, p=0.11 A vs. C, p=0.11 B. vs. C, p=p=0.001 BAI: 7.90 (5.91) to 6.10 (4.95) vs. 12.45 (4.54) to 6.45 (3.61) vs. 7.50 (6.77) to 8.20 (7.39) A vs. B, p=0.01 A vs. C, p=0.22 B vs. C, p=0.001
Aydin, 2014[59] Aerobics RCT Fair	A. Callisthenic exercises (in clinic): 60 sessions, over 12 weeks, (n=16) B. Callisthenic exercises (home-based): 60 sessions, over 12 weeks, (n=20)	A vs. B Age: 32.6 vs. 33 Female: 56% vs. 55% EDSS: 3.6 vs. 3.4	A vs. B, mean (SD) HADS-A: 10.63 (7.33) vs. 11.05 (5.73), p=0.762 (baseline) 8.69 (6.11) vs. 10.00 (5.36), p=0.482 (postintervention) Pre-post exercise intra-group comparison: Difference –1.94 (2.35) –1.05 (1.32), p=0.412 HADS-D: 8.50 (3.74) vs. 6.75 (3.23), p=0.212 (baseline) 6.13 (3.26) vs. 8.60 (2.41), p=0.011 (postintervention) Pre-post exercise intra-group comparison: Difference –1.94 (2.35) vs. 1.85 (1.60), p=<0.001
Baquet, 2018[77] Aerobic exercise RCT Fair	A. Bicycle ergometry, 24-36 sessions over 12 weeks (n=34) B. Waitlist control group (n=34)	A vs. B Age: 38.2 vs. 39.6 Female: 62% vs. 74% EDSS: 1.7 vs. 1.8 RRMS: 100%	A vs. B, mean difference between groups: IDS16-SR: 0.5, 95% CI –0.8 to 1.9, p=0.44
Burschka, 2014[173] Postural control Quasiexperimental Poor	A. Tai Chi, 48 sessions 6 months (n=15) B. Usual care (n=17)	A vs. B Age: 42 vs. 43 Female: 66% vs. 71% Ambulatory: 100% RRMS: 93% vs. 76% SPMS: 0% vs. 24% CIS: 7% vs. 0%	A vs. B, mean (SD), p=between groups: CES-D: 12.21 (6.66) vs. 13.87 (10.82) (baseline) 7.67 (5.12) vs. 16.13 (11.99) (postintervention) Tai Chi resulted in greater improvement in CES-D scores than usual care, p<0.05
Cakit, 2010[225] Multimodal exercise RCT Poor	A. Progressive resistance cycling plus balance exercises (lower extremity strengthening),16 sessions over 8 weeks (n=14) B. Usual care (n=9)	A vs. B Age: 36.4 vs. 35.5 Female: 64% vs. 67% RRMS or SPMS: 100% Assistive device: 28.5% vs. 37.5% Fall frequency last year: 2.0 vs. 2.4	A vs. B, mean (SD), p=between groups: BDI: 22.8 (12.7) vs. 27.0 (17.6) (baseline) 17.2 (12.3) vs. 25.4 (22.8) (postintervention) –5.5 (5.3) vs. –1.6 (6.0), p=<0.05 (pre-post change)

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Calabro, 2017[96] Aerobic exercise RCT Good	A. Lokomat-Pros (RAGT + VR), 40 sessions over 8 weeks (n=20) B. Lokomat-Nanos (RAGT), 40 sessions over 8 weeks (n=20)	A vs. B Age: 44 vs. 41 Female: 65% vs. 60% EDSS: 4.40 vs. 4.75	HRSD median change score, p=between groups: –0.062, 95% CI –4.932 to 4.808, p=0.90
Castro-Sanchez, 2012[71] Aerobic Exercise RCT Good	A. Ai-Chi aqua therapy with Tai-Chi music, 40 sessions over 20 weeks (n=36) B. Relaxation exercises on exercise mat without music, 40 sessions over 20 weeks (n=37)	A vs. B Age: 46 vs. 50 Female: 72% vs. 65% EDSS: 6.3 vs. 5.9 PPMS: 17% vs. 24% SPMS: 25% vs. 32%	A vs. B, median (SD), p-value=between groups: BDI: 14 (7.72) to 5 (3.2) vs. 15 (8.68) to 13 (5.91), p<0.05 Differences in depression scores were maintained at 24 weeks (4 weeks postintervention) but there was no difference between groups at 30 weeks
Dalgas, 2009[202] Dalgas, 2010[203] Strength RCT Fair	A. Progressive resistance, 24 sessions over 12 weeks (n=15) B. Waitlist control (n=16)	A vs. B Age: 45 vs. 48 Female: 63% vs. 67% Ambulatory to 100m: 100% RRMS: 100%	A vs. B, mean (SD), p=between groups: MDI (20 to 24, mild depression; 25 to 29, moderate depression; >29, major depression): 10.3, 95% CI 7.0 to 13.5 vs. 8.8, 95% CI 6.4 to 11.3 (baseline) 7.9, 95% CI 5.2 to 10.6 vs. 9.9, 95% CI 7.4 to 12.5 (postintervention) Mean change between group NR, p=0.01
Gervasoni, 2014[117] Aerobic Exercise RCT Fair	A. 30 minutes conventional therapy + 15 minutes treadmill training, 12 sessions over 2 weeks (n=15) B. 45 minutes conventional therapy, 12 sessions over 2 weeks (n=15)	A vs. B Age: 49.6 vs. 45.7 Female: 40% Able to walk 6 meters with or without assist device EDSS: 5.25 (3.0 to 6.5) RRMS: 47.6% PPMS: 19.0% SPMS: 33.3%	Median change scores, p=between groups: PANAS positive: 1.0 vs. 5.0, p=0.86 PANAS negative –5.0 vs. –2.0, p=0.48
Hebert, 2011[80] Aerobic Exercise RCT Fair	A. Bicycle Ergometry, 12 sessions for 6 weeks (n=12) B. Vestibular rehab (n=13) C. Waitlist control (n=13)	A vs. B vs. C Age: 46.8 vs. 42.6 vs. 50.2 Female: 75% vs. 85% vs. 85% Ambulatory: 100%	Mean difference between groups: BDI-II: A vs. B: 4.4, 95% CI –3.0 to 11.9, p=0.431 A vs. C: 5.0, 95% CI –2.5 to 12.4, p=0.307 B vs. C: 0.6, 95% CI –6.8 to 7.8, p=1.00

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Kara, 2017[62] Strength Quasiexperimental Poor	A. Pilates, 16 sessions over 8 weeks (n=27) B. Multimodal exercise (focus on aerobic), 16 sessions over 8 weeks (n=28)	A vs. B Age: 50 vs. 43 Female: 67% vs. 65% EDSS: 2.85 vs. 3.2	A vs. B, mean (SD), p=between groups: BDI: 11.44 (6.52) vs. 8.92 (6.49), p=0.001 (baseline) 9.77 (5.26) vs. 7.15 (6.35), p=0.156 (postintervention) Mean change between groups: 0.1, 95% CI –0.4.53 to 4.73, p=0.97
Keser, 2011[63] Aerobic exercise Quasiexperimental Poor	A. Calisthenics, 18 sessions over 6 weeks (n=15) B. Routine neuro-rehab (strength, balance, coordination, spasticity exercises), 18 sessions over 6 weeks (n=15)	A vs. B Age: 36 vs. 35 Female: 53% vs. 47% EDSS: 2.9 vs. 2.8	A vs. B, p=between groups: HADS Anxiety: scores not provided HADS Depression: scores not provided Differences between groups were not significant, p>0.05
Negaresh, 2019[53] Aerobic exercise RCT Fair	A. Normal BMI cycling UE/LE, 24 sessions over 8 weeks (n=18) B. Normal BMI control (n=15) C. Overweight cycling UE/LE, 24 sessions over 8 weeks (n=17) D. Overweight control (n=13)	A vs. B vs. C vs. D Age: 31.2 vs. 29.1 vs. 32.1 vs. 2.1 Female: 64% vs. 64% vs. 64% vs. 69% RRMS: 100%	A vs. B vs. C vs. D (scores are estimates from graph) BDI change score from baseline: –4.8 vs. 0.1 vs. –2.5 vs. –0.1, p=0.005 Interaction between Weight and Exercise p=0.14
Ozkul, 2020b[232] Multimodal exercise RCT Fair	A. Aerobic exercise + Pilates, 24 sessions over 8 weeks (n=17) B. Relaxation exercises, 24 sessions over 8 weeks (n=17)	A vs. B Age: 35.88 vs. 36.76 Female: 76% vs. 76% RRMS: 100% EDSS: 1.50 vs. 1.71	A vs. B, mean change (SD), p=between groups BDI: Mean change -1.88 (5.35) vs. 3.24 (8.86), p=0.05
Razazian, 2016[70] Aerobic/Postural control RCT Poor	A. Aquatic Exercise, 24 sessions over 8 weeks (n=18) B. Yoga, 24 sessions over 8 weeks (n=18) C. Attention control (18)	A vs. B vs. C Age: 35.4 vs. 33.3 vs. 33.1 Female: 100% EDSS: 3.44 vs. 3.89 vs. 3.25 RRMS: 61% vs. 72% vs. 67% SPMS: 11% vs. 6% vs. 11% Progressive-relapsing MS: 28% vs. 22% vs. 22%	A vs. B vs. C, mean (SD), p=between groups: BDI: 19.17 (7.83) vs. 19.72 (7.04) vs. 20.78 (6.22) (baseline) 4.78 (3.42) vs. 5.06 (2.92) vs. 21.33 (6.88) (postintervention) Mean change in BDI between groups: A vs. C MD 14.94, 95% CI 10.57 to 19.31, p<0.001 B vs. C MD 15.21, 95% CI 11.06 to 19.36, p<0.001 A vs. B MD –0.27, 95% CI –4.50 to 3.96, p=0.90

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Roppolo, 2013[233] Multimodal Quasiexperimental Fair	A. Aerobic + Strength training, 24 sessions over 12 weeks (n=17) B. Control group (activity not specified) (n=18)	A vs. B Age: 40 vs. 40 Female: 100% EDSS: 1.5 vs. 2.0	A vs. B, mean (SD), p=between groups BDI: 8.8 (5.8) to 3.4 (2.9) vs. 9.2 (3.7) to 17.0 (7.0), MD 13.2, 95% CI 9.86 to 16.55, p<0.001
Russo, 2018[95] Aerobic exercise RCT Fair	A. RAGT, 18 sessions over 6 weeks then 36 sessions of rehab exercises over 12 weeks (n=30) B. Rehab exercises, 54 sessions over 18 weeks (n=15)	A vs. B Age: 42 vs. 41 Female: 53% vs. 67%	A vs. B, mean difference, p=between groups HRSD one month postintervention: 10.0 vs. 12.5 (baseline) 7.0 vs. 7.0 (postintervention) Mean difference between groups: –2.5, 95% CI –7.135 to 2.135, p=0.29
Sadeghi Bahmani, 2019[61] Aerobics/ Postural control RCT Fair	A. Endurance training (treadmill, cycling, walking, jogging), 24 sessions over 8 weeks (n=26) B. Balance and coordination exercises, 24 sessions over 8 weeks (n=24) C. Attention control, 24 sessions over 8 weeks (n=21)	A vs. B vs. C Age: 38 vs. 39 vs. 38 Female: 100% EDSS: 2.46 vs. 3.38 vs. 2.02	A vs. B vs. C, mean (SD), p=between groups: BDI-FS: 7.92 (5.11) to 5.12 (4.65) vs. 7.96 (6.67) to 5.29 (5.75) vs. 6.24 (4.47) to 6.52 (4.91) A vs. C: MD 3.08, 95% CI 0.33 to 5.84, p=0.028 B vs. C: MD 2.95, 95% CI –0.26 to 6.16, p=0.072 A vs. B: MD 0.13, 95% CI –3.00 to 3.26, p=0.935
Sadeghi Bahmani, 2020 Aerobic exercise RCT Fair	A. Aquatic exercise, 16 sessions over 8 weeks (n=20) B. Aquatic exercise, 24 sessions over 8 weeks (n=18) C. Active control, (social program) 16 to 24 sessions over 8 weeks (n=22)	A vs. B vs. C Age: 39.35 vs. 40.61 vs. 33.77 Female: 100% EDSS (median): 3.0 vs. 1.5 vs. 1.5	Mean (SE) of change scores, p=between all 3 groups BDI-Fast Screen: 4.80 (5.90) vs. 7.83 (4.91) vs. 6.05 (4.49), p<0.001
Straudi, 2016[97] Aerobic exercise RCT Good	A. RAGT, 12 sessions o)ver 6 weeks (n=27) B. Walking therapy without RAGT, 12 sessions over 6 weeks (n=25)	A vs. B Age: 52 vs. 54 Female: 63% vs. 68% EDSS: 6.43 vs. 6.46 PPMS: 33% vs. 28% SPMS: 67% vs. 72%	PHQ-9: T2-T0: –1.7 (3.24) vs. –3.04 (4.66), p=0.213

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Straudi, 2019[98] Aerobic exercise RCT Good	A. RAGT, 12 sessions over 4 weeks (n=36) B. Overground walking, 12 sessions over 4 weeks (n=36)	A vs. B Age: 56 vs. 55 Female: 67% vs. 69% EDSS: 6.5 vs. 6.5 PPMS: 50% vs. 45% SPMS: 50% vs. 55%	A vs. B, mean difference between groups: PHQ-9: –0.4, 95% CI –2.3 to 1.4, p=0.86

Abbreviations: BDI = Beck Depression Inventory; BDI-FS = Beck Depression Inventory-Fast Screen; BMI = body mass index; CES-D = Center for Epidemiologic Studies Depression Scale; CI = confidence interval; CIS = Clinically Isolated Syndrome; EDSS = Expanded Disability Status Scale; HADS = Hospital Anxiety and Depression Scale; HRSD = Hamilton Rating Scale for Depression; IDS16-SR = 16-item version of Inventory of Depressive Symptomatology Self-Rated; MD = mean difference; MDI = Major Depression Inventory; NR = not reported; PANAS = Positive and Negative Affect Schedule; PHQ-9=Patient Health Questionnaire-9; PPMS = primary progressive multiple sclerosis; RAGT = robot-assisted gait training; RCT = randomized controlled trial; RRMS = relapsing-remitting multiple sclerosis; SD = standard deviation; SE- standard error; SPMS = secondary progressive multiple sclerosis; VR = virtual reality

Results from head-to-head exercise interventions in MS RCTs not already discussed include cycling versus vestibular rehabilitation,[79,80] treadmill versus yoga,[120] and aquatic exercise versus yoga[70] or versus relaxation exercises on a mat.[70,71] In two trials all exercise arms demonstrated statistically significantly improved depression scores at end of treatment compared with baseline. One good-quality aquatics trial found improved depression scores at end of treatment versus the control group with the differences maintained at 10 weeks postintervention.[70,71] However, there were no differences between cycling and vestibular rehabilitation or between aquatic exercise and yoga in change in depression scores with exercise. In one RCT, yoga was associated with improved depression and anxiety scores compared with control, but treadmill training was associated with greater improvement than yoga on anxiety scores.[120]

Two poor-quality quasiexperimental studies compared calisthenics with neuro-rehabilitation exercises[63] and Pilates with multimodal exercises.[62] Scores on the HADS anxiety scale were improved with calisthenics and with neuro-rehabilitation exercises, but there were no differences between groups. There were also no differences in pre-post exercise changes on the BDI between Pilates and multimodal exercises (aerobic, strengthening, balance, and walking exercises).

Spinal Cord Injury

Three fair-quality RCTs (n=171) examined the effects of physical exercise on mental health in primarily male participants with SCI, most in their 30s and 40s[89,138,139,244,245] (Table 41). All three RCTs administered instruments to measure depression and two of the three trials administered instruments to assess anxiety.[89,244,245] Exercise interventions included precision track walking, treadmill walking with body weight support as needed, arm cycling, general exercises, whole body strength plus aerobics, and upper body strength plus aerobics. No RCT utilized a waitlist or no exercise control. Exercise did not improve anxiety or depression scores from baseline in any of the trials, and there were also no differences on mental health measures between exercise groups within trials (p>0.05).

Table 41. Effects of exercise on depression and anxiety in spinal cord injury

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Akkurt, 2017[89] Aerobic exercise RCT Fair	A. Arm ergometer, 36 sessions over 12 weeks plus 120 sessions general exercises over 12 weeks (n=17) B. General exercises, 120 sessions over 12 weeks (n=16)	A vs. B Age: 33 vs. 37 Female: 5% vs. 19% Ambulatory:41% vs. 50% Wheelchair user: 59% vs. 50% Paraplegia:100% vs. 94%	A vs. B, median: <u>HADS change scores</u>: 0 vs. 0.5, p>0.05 <u>CES-D change scores</u>: –3 vs. 3, p>0.05
Galea, 2018[245] Multimodal exercise RCT Fair	A. Whole body strength + aerobics, 36 sessions over 12 weeks (n=60) B. Upper body strength + aerobics, 36 sessions over 12 weeks (n=56)	A vs. B Age: 40.1 vs. 42.8 Female: 15% vs.16% ASIA A: 48% vs. 50% ASIA B: 15% vs. 14% ASIA C: 12% vs. 9% ASIA D: 25% vs. 27% C2-C8: 48% vs. 59% T1-T6: 30% vs. 23% T7-T12: 22% vs. 18%	A vs. B, mean (SD), p=between groups: <u>HADS-Anxiety</u> 10.3 (1.8) vs. 10.5 (1.8) (baseline) 10.4 (1.6) vs. 10.1 (1.6) (postintervention) MD 0.29, 95% CI –0.25 to 0.83, p=0.291 (postintervention) MD –0.14,95% CI –0.89 to 0.60, p=0.701 (24 weeks—12 weeks postintervention) <u>HADS-Depression</u> 10.5 (2) vs. 10.4 (2.1) (baseline) 10 (1.6) vs. 10.2 (1.3) (postintervention) MD –0.28, 95% CI –0.83 to 0.27, p=0.309 (postintervention) 10.1 (1.5) vs. 10.2 (1.4) MD –0.23 (95% CI –0.81 to 0.35), p=0.428 (24 weeks—12 weeks postintervention)
Yang, 2014[138] Aerobic Exercise RCT (Crossover) Fair	A. Precision track walking training, 40 sessions over 8 weeks (n=11) B. BWS (if needed) treadmill walking, 40 sessions over 8 weeks (n=11)	A vs. B Age: 44 vs. 48 Female: 30% vs. 30% Able to walk $\geq$ 5 meters with walking aid or braces	A vs. B Pre-post change scores (estimated from graph) CES-D: –2.7 vs. –2.4, p>0.05 Both groups achieved significant improvement from baseline, p<0.05

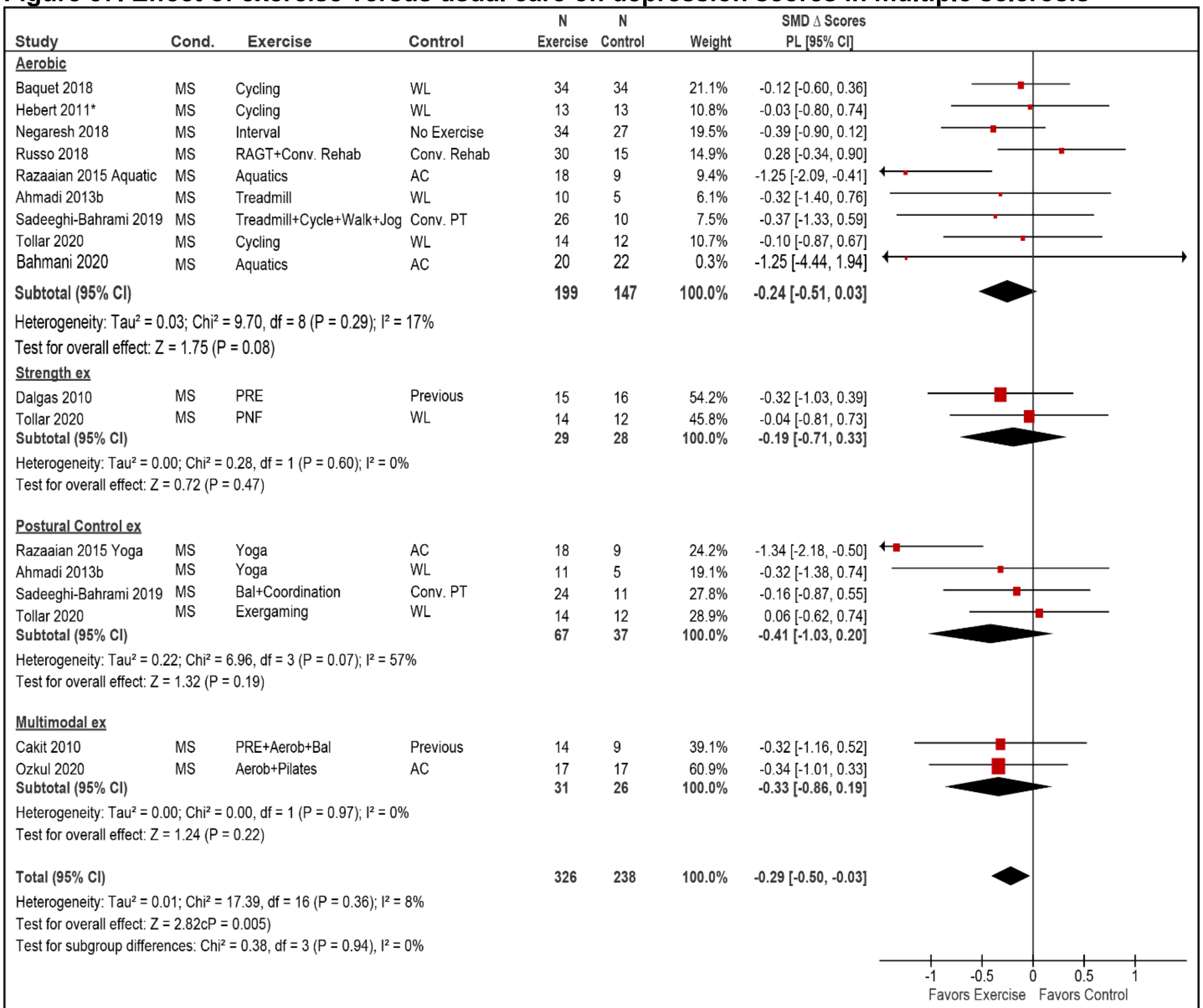
Abbreviations: ASIA = American Spinal Injury Association Impairment Scale; BWS = body weight supported; CI = confidence interval; CES-D = Center for Epidemiologic Studies Depression Scale; HADS = Hospital Anxiety and Depression Scale; MD = mean difference; RCT = randomized controlled trial; SD = standard deviation

Depression Across Interventions and Populations

In order to determine if general physical exercise (e.g., RAGT, cycling, and strength training) has an effect on depression scores, we looked for RCTs that included a low-intensity usual care, waitlist control, or no intervention comparison arm in any included population. Eleven RCTs (9 fair quality[53,61,72,77,80,83,95,120,203,232]and 2 poor quality[70,225]) in participants with MS reported data that could be combined in meta-analysis. Interventions included treadmill, cycling, motion gaming, interval exercises, RAGT, and progressive resistance exercises with and without aerobic plus balance exercises. Usual care consisted of waitlist controls, conventional rehabilitation, and continuation of previous activity level. One trial assessed postintervention depression at a 4-week posttreatment followup, rather than immediately postintervention.[95] Pooled analysis of these RCTs (n=522) found physical exercise associated with greater improvement in depression

scores compared with usual care (SMD –0.29, 95% CI –0.50 to –0.03, I^2=8%, p=0.005) (Figure 37). There were no differences between groups based on type of exercise intervention (p=0.94).

Figure 37. Effect of exercise versus usual care on depression scores in multiple sclerosis



Abbreviations: Δ = change; AC = attention control; Aerob = aerobic exercise; Bal = balance training; CI = confidence interval; Cond. = condition; Conv. = conventional; ex = exercise; MD = mean difference; MS = multiple sclerosis; PL = profile likelihood; PNF = proprioceptive neuromuscular facilitation; PRE = progressive resistance exercise; Previous = continuation of previous activities; PT = physical therapy; RAGT = robotic assisted gait training; SMD = standardized mean difference; WL = waitlist

These findings in trials comparing exercise with no exercise or usual care provided moderate-strength evidence of a benefit of exercise versus no exercise or versus low-intensity usual care on depression scores in adult participants with MS. There was much less evidence in SCI (3 trials, n=171)[89,138,245] where there was no difference in depression with exercise, although data could not be pooled (SOE: low). No studies with depression outcomes that met inclusion criteria were identified in participants with CP (SOE: insufficient).

Only two studies, one in MS[63] and one in SCI,[244,245] reported results from instruments measuring anxiety, resulting in insufficient evidence from which to draw conclusions regarding the benefit of exercise on anxiety.

Sexual Function

One fair-quality study randomized 62 women with MS to aquatic exercise two times weekly, three times weekly, or to an active control (social encounters at hospital) for 8 weeks.[72] The Female Sexual Function Index contains 19 questions covering sexual desire, sexual arousal, lubrication, orgasm, sexual satisfaction, and pain. Aquatic exercises included warm up, walking, stretching, gymnastics, relay races, strength training, team competitions, and crossing the pool alone. Higher scores indicated greater sexual function. After controlling for baseline values, the highest scores were achieved in the group that exercised two times weekly (52.14) followed by three times weekly (48.80), and active control (42.80) (p<0.001).

KQ2b: Intermediate Outcomes

Forty-two studies (36 RCTs, 5 quasiexperimental studies, and 1 cohort study) evaluated the effect of physical activity on intermediate outcomes.[53,63,75-78,82,88,89,91-93,117,125,132-137,140,147,186,198,204,206-209,211-213,216-222,224,227,228,230,231,234-237,242,243,246,247,249] Eighteen studies enrolled participants with MS (n=984),[53,63,76-78,117,147,186,198,204,206,220-222,224,227,228,230,231] (Table 42), 11 studies enrolled children with CP (n=401),[88,125,132,207-209,211-213,216,217,234-237,242,243] (Table 43), and 13 enrolled participants with SCI (n=519)[75,82,89,91-93,133-137,140,213,249] (Table 44).

Table 42. Intermediate outcomes of physical activity in participants with multiple sclerosis

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population (Multiple Sclerosis)	Results
Abbasi, 2019[186] Postural control RCT Fair	A. Whole body vibration, 18 sessions over 6 weeks (n=22) B. No treatment, no exercise (n=24)	A vs. B Age: 37 vs. 39 Female: 4.5% vs. 16.7% EDSS: 1.54 vs. 1.55	A vs. B, median difference (interquartile range), p-value is between groups Strength: Trunk Flexor: 25.83 (8.83 to 46.41) vs. –0.33 (–5.67 to 6.75), p<0.001 Trunk Extensor: 38.17 (20.75 to 70) vs. –1.49 (–11.83 to 3.49), p<0.001
Amiri, 2019[147] Postural control RCT Fair	A. Core stability training, 30 sessions over 10 weeks (n=35) B. Conventional care including stretching and range of motion exercises (n=34)	A vs. B Age: 32 vs. 31 Female: 100% EDSS: 3.56 vs. 3.74	Core strength tests (R/L hip abduction, R/L external rotation) demonstrate significant differences in strength based on baseline EDSS score (2.5-3.5; 3.5-4.5; 4.5-5.5), p<0.001 Plank test: significant differences between groups based on EDSS score, p<0.001 Overall static balance tests demonstrate significant differences in strength based on baseline EDSS score and significant differences compared with the control group, p<0.001 Greatest improvements seen in those with greatest disability (least strong)

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population (Multiple Sclerosis)	Results
Baquet, 2018[77] Aerobic exercise RCT Fair	A. Bicycle ergometry, 24-36 sessions over 12 weeks (n=34) B. Waitlist control group (n=34)	A vs. B Age: 38.2 vs. 39.6 Female: 62% vs. 74% EDSS: 1.7 vs. 1.8 RRMS: 100%	A vs. B, mean difference between groups: VO_2 peak (ml/min): –51.4, 95% CI –165.2 to 62.5, p=0.37 VO_2 peak (ml/min/kg): –0.9, 95% CI –2.5 to 0.6, p=0.24
Bulguroglu, 2017[206] Strength RCT Poor	A. Mat Pilates, 16 sessions over 8 weeks (n=12) B. Reformer Pilates, 16 sessions over 8 weeks (n=13) C. Attention control, 16 sessions over 8 weeks (n=13)	A vs. B vs. C Age: 45 vs. 37 vs. 40 Ambulatory: 100% EDSS: 1.8 vs. 2.0 vs. 1.0	A vs. B. vs. C, median: Modified pushup (repetitions/30 seconds): 6.5 to 10 vs. 3 to 10 vs. 7 to 7 Modified sit-up (repetitions/30 seconds): 6 to 7.5 vs. 10 to 15 vs. 4 to 8 Trunk flexor test (seconds): 2.32 to 6 vs. 4.91 to 13.3 vs. 6.46 to 6.4 Prone bridge (seconds): 18.29 to 25.23 vs. 22.31 to 37.53 vs. 20.68 to 21.21 Pilates groups improved significantly over baseline while the control group did not.
Collett, 2011[82] Aerobic exercise RCT Poor	A. Combined intermittent and continuous static cycling, 24 sessions over 12 weeks (n=20) B. Intermittent static cycling, 24 sessions over 12 weeks (n=21) C. Continuous static cycling, 24 sessions over 12 weeks (n=20)	A vs. B vs. C Age: 55 vs. 50 vs. 52 Female: 53% vs. 78% vs. 80% Ambulatory: 100%	Change postintervention: no data provided Leg Power: NS
Dodd, 2011[204] Strength RCT Good	A. Progressive resistance: 20 sessions over 10 weeks (n=39) B. Social program (attention control), 10 sessions x 10 weeks plus usual care (n=37)	A vs. B Age: 47.7 vs. 50.4 Female: 72% vs. 74% Ambulation index 2 (mild): 47% vs. 54% 3 (moderate): 39% vs. 26% 4 (severe): 14% vs. 20% Gait aid (yes): 33% vs. 37%	A vs. B, mean difference between groups: Max leg press (kg): MD 10.8, 95% CI 4.9 to 16.7, p<0.05 Reverse leg press (kg): MD 5.7, 95% CI 1.9 to 9.5, p<0.05
Duff, 2018[198] Strength RCT Fair	A. Pilates + massage, 24 sessions of Pilates and 12 massages over 12 weeks (n=15) B. Massage, 12 massages over 12 weeks (n=15)	A vs. B Age: 45.7 vs. 45.1 Female: 80% vs. 73% Ambulatory: 100% Wheelchair user: 0% RRMS: 93% vs. 73% SPMS: 0% vs. 13% PPMS: 7% vs. 13%	A vs. B, mean change: % body fat: –0.2, 95% CI –1.4 to 1.0 vs. –0.8, 95% CI –2.0 to 0.4, p=0.51

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population (Multiple Sclerosis)	Results
Ebrahimi, 2015[228] Multimodal exercise RCT Poor	A. Whole body vibration + low-intensity exercise, 30 sessions over 10 weeks (n=17) B. Usual care (n=17)	A vs. B Age: 37.06 vs. 40.75 Female: 69% vs. 86% Ambulatory: 100% EDSS: 3.12 vs. 3.10	A vs. B, mean (SD) Modified pushup: 5.31 (4.75) vs. 2.42 (3.99) (baseline) 12.12 (6.54) vs. 2.92 (3.83) (postintervention) Time X Group p=0.07
Faramarzi, 2020[230] Banitalebi, 2020[231] Multimodal exercise RCT Fair	A. Resistance + cycling or running + balance exercises + Pilates + stretching, 36 sessions over 12 weeks (n=46) B. Waitlist control (n=43)	A vs. B Age criteria: (18 to 50) Female: 100% EDSS 0 to 4: 48% to 48% EDSS 4.5 to 6: 27% vs. 27% EDSS 6.5 to 8: 23% vs. 23%	A vs. B, Positive effect of exercise on: Cholesterol: p=0.020, effect of disability*exercise p=0.549 HDL: p<0.001, effect of disability*exercise p=0.408 LDL: p<0.001, effect of disability*exercise p=0.826 TG: p=0.005, effect of disability*exercise p=0.982 VO_2 peak: p=0.004, effect of disability*exercise p=0.097 Body fat %: p=0.001, effect of disability*exercise p=0.76
Gervasoni, 2014[117] Aerobic Exercise RCT Fair	A. 30 minutes conventional therapy + 15 minutes treadmill training, 12 sessions over 2 weeks (n=15) B. 45 minutes conventional therapy, 12 sessions over 2 weeks (n=15)	A vs. B Age: 49.6 vs. 45.7 Female: 40% Able to walk 6 meters with or without assist device RRMS: 47.6% PPMS: 19.0% SPMS: 33.3%	A vs. B, mean difference between groups: Resting HR: 3.76, 95% CI –4.92 to 12.44, p=0.40
Heine, 2017[78] Aerobic exercise RCT Fair	A. Leg cycling, 48 sessions over 16 weeks (n=43) B. MS nurse consultation, 3 consultations over 16 weeks (n=46)	A vs. B Age: 43.1 vs. 48.2 Female: 74% vs. 72% Ambulatory: 100% EDSS: 2.5 vs. 3.0 RRMS: 72% vs. 74% SPMS: 7% vs. 11% PPMS: 21% vs. 15%	A vs. B, mean (SD), p=between groups VO_2 peak (L/min): MD 0.048 (0.082), p=0.561 VO_2 peak (mL/kg/min): MD 0.979 (1.075), p=0.364

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population (Multiple Sclerosis)	Results
Kerling, 2015[220] Multimodal exercise RCT Fair	A. Full body progressive resistance + aerobic training, 36 sessions over 12 weeks (n=30) B. Aerobic training, 36 sessions over 12 weeks (n=30)	A vs. B Age: 42.3 vs. 45.6 Female: 80% vs. 67% EDSS: 2.6 vs. 3.1	A vs. B, postintervention mean (SD) VO_2 peak (mL/min):1756 (599) vs. 1676 (494); Time X Group p=0.71 VO_2 peak (ml/min/kg): 24.6 (7.4) vs. 23.7 (7.1); Time X Group p=0.72 Resting HR: 90 (11) vs. 85 (13); Time X Group p=0.63 Right knee extensor: 107.7 (28.0) vs. 99.3 (42.3), p=NR; Time X Group p=0.50 Left knee extensor: 108.2 (33.1) vs. 95.6 (43.8); Time X Group p=0.95 Right knee flexor: 61.3 (18.7) vs. 55.9 (24.6); Time X Group p=0.72 Left knee flexor: 64.0 (23.7) vs. 51.7 (24.85); Time X Group p=0.31 Right extensor shoulder: 51.8 (14.9) vs. 49.9 (20.1); Time X Group p=0.85 Left extensor shoulder: 50.0 (18.9) vs. 46.9 (18.6);Time X Group p=0.98 Right flexor shoulder: 36.5 (10.0) vs. 36.9 (14.1);Time X Group p=0.67 Left flexor shoulder: 36.9 (12.4) vs. 35.9 (12.5);Time X Group p=0.60
Keser, 2011[63] Aerobic exercise Quasiexperimental Poor	A. Calisthenics, 18 sessions over 6 weeks (15) B. Neuro-rehabilitation 18 sessions over 6 weeks (15)	A vs. B Age: 36 vs. 35 Female: 53% vs. 47% EDSS: 2.9 vs. 2.8	A vs. B, mean change, p=between groups: UE Right Strength: 8.67 (10.17) vs. 15.19 (7.77), p<0.05 UE Left Strength: 7.86 (11.97) vs. 16.25 (10.95), p<0.05 LE Right Strength: 15.76 (11.17) vs. 20.66 (6.18), p>0.05 LE Left Strength: 18.54 (7.59) vs. 24.17 (16.69), p>0.05
Negaresh, 2019[53] Aerobic exercise RCT Fair	A. Normal BMI cycling UE/LE, 24 sessions over 8 weeks (n=18) B. Normal BMI control (n=15) C. Overweight cycling UE/LE, 24 sessions over 8 weeks (n=17) D. Overweight control (n=13)	A vs. B vs. C vs. D Age: 31.2 vs. 29.1 vs. 32.1 vs. 2.1 Female: 64% vs. 64% vs. 64% vs. 69% RRMS: 100%	A vs. B vs. C vs. D, mean difference between groups (scores are estimates from graph) VO_2 peak: 2.7 vs. 0 vs. 1.9 vs. 0.6, p=0.001 Interaction, p=0.17 BMI: –0.10 vs. –0.15 vs. –0.45 vs. –0.20, p=0.53 Interaction p=0.38
Sandroff, 2017[221] Multimodal exercise RCT Fair	A. Resistance + aerobics + balance: 72 sessions over 24 weeks. (n=43) B. Stretching and toning, 72 sessions over 24 weeks (n=40)	A vs. B Age: 49.8 vs. 51.2 Female: 83.7% vs. 87.5% EDSS 4-6: 100% Walking difficulties: 100%	A vs. B, mean (SD) VO_2 Peak (ml/kg/min): 16.5 (6.5) vs. 15.4 (6.2), p=NR (baseline) 17.1 (5.9) vs. 15.9 (5.5), p=NR (postintervention) Time X Group interaction p>0.20

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population (Multiple Sclerosis)	Results
Sangelaji, 2016[222] Multimodal exercise RCT Fair	A. 1 aerobic + 3 resistance training, 32 sessions over 8 weeks (n=10) B. 2 aerobic + 2 resistance training, 32 sessions over 8 weeks (n=10) C. 3 aerobic + 1 resistance training, 32 sessions over 8 weeks (n=10) D. No intervention control (n=10)	A vs. B vs. C vs. D Age: 36 vs. 31 vs. 34 vs. 34 Female: 60% vs. 60% vs. 60 vs. 60% Baseline EDSS: 1.33 vs. 2.06 vs. 1.95 vs. 1.81	Mean difference (SE) vs. control group (Kg): Left Knee flexion: A. –5.57 (2.09), p=0.01 B. –3.17 (2.14), p=0.15 C. –5.54 (2.04), p=0.01 Right Knee flexion: A. –4.61 (1.89), p=0.02 B. –5.08 (1.94), p=0.04 C. –4.05, 1.85, p=0.01 Left Knee Extension: A. –7.77 (2.73, p=0.01 B. –5.08 (2.80), p=0.08 C. –7.95 (2.68, p=0.01 Right Knee Extension: A. –4.88 (3.48), p=0.17 B. –1.62 (3.56), p=0.65 C. –6.30 (3.41), p=0.07
Wens, 2015b[224] (high intensity) Multimodal exercise RCT Fair	A. Resistance training + high-intensity interval training, 30 sessions over 12 weeks (n=12) B. Resistance training + high-intensity continuous cardiovascular training, 30 sessions over 12 weeks (n=11) C. No intervention – “sedentary control” (n=11)	A vs. B vs. C Age: 43 vs. 47 vs. 47 Female: 42% vs. 45% vs. 82% EDSS: 2.3 vs. 2.7 vs. 2.5 RRMS: 83% vs. 73% vs. 73% CPMS: 17% vs. 27% vs. 27%	Mean (SD) of % change, p=vs. control: **A vs. C** VO_2 max (ml/min): 17.8% (4.6%) vs. 2.5% (4.1%), p<0.01 VO_2 max (ml/min/kg):17.8% (4.6%) vs. 2.5% (4.1%), p<0.01 Resting HR: 12.5% (4.6%) vs. 14.3% (3.8%), p>0.05 % Body fat: −3.9% (2.0%) vs. −2.8% (1.6%), p>0.05 **B vs. C** VO_2 max (ml/min): 7.5% (5.8%) vs. 2.5% (4.1%), p>0.05 VO_2 max (ml/min/kg): 7.5% (5.8%) vs. 2.5% (4.1%), p>0.05 Resting HR: 7.0% (5.8%) vs. 14.3% (3.8%), p>0.05 % Body fat: −2.5% (1.2%) vs. −2.8% (1.6%), p>0.05
Wens, 2015a[227] (impact of 24) Multimodal exercise RCT Poor	A. Progressive resistance + aerobics, 60 sessions over 24 weeks (n=29) B. Nonexercise control (n=15)	A vs. B Age: 48 vs. 49 Female: 59% vs. 53% EDSS: 3.25 vs. 3.36	A vs. B, mean difference between groups: Resting HR: 9.0, 95% CI 6.57 to 11.43, p<0.001 Body weight (kg): 1.9, 95% CI –0.124 to 0.07 Body fat %: 2.0, 95% CI 0.67 to 3.33, p=0.003 No differences in glucose and insulin Knee extension and flexion improved with exercise. Group X Time interaction p<0.05

Abbreviations: BMI = body mass index; CI = confidence interval; CPMS = chronic progressive multiple sclerosis; EDSS = Expanded Disability Status Scale; HR = heart rate; LE = lower extremity; MD = mean difference; NR = not reported; NS = not significant; PPMS = primary progressive multiple sclerosis; RCT = randomized controlled trial; RRMS = relapsing-remitting multiple sclerosis; SD = standard deviation; SPMS = secondary progressive multiple sclerosis; UE = upper extremity; VO_2 max = maximal oxygen uptake

Table 43. Intermediate outcomes of physical activity in participants with cerebral palsy

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population (Cerebral Palsy)	Results
Cho, 2020[216] Strength RCT Poor	A. Progressive resistance, 18 sessions over 6 weeks (n=13) B. Conventional therapy, 18 sessions over 6 weeks (n=12)	A vs. B Age: 5.54 vs. 7.17 Female: 69% vs. 33% GMFCS: 2.08 vs. 2.33 GMFM: 69.98 vs. 68.15	A vs. B, mean (SD) of change, p=between groups Knee extensor strength: Nondominant: -2.196 (0.048) vs. -2.078 (0.062), p=0.436 Dominant: -3.065 (0.010) vs. -590 (0.567), p=0.029
Johnston, 2011[125] Aerobic exercise RCT Fair	A. Partial BWS treadmill training x 20 sessions over 2 weeks, then 50 sessions at home over 10 weeks (n=14) B. Individualized strength-based PT, 20 sessions over 2 weeks, then 50 session at home over 10 weeks (n=12)	A vs. B Age: 9.6 vs. 9.5 Female: 50% vs. 42% GMFCS II: 7% vs. 8% GMFCS III: 64% vs. 50% GMFCS IV: 29% vs. 42% Diplegic CP: 57% vs. 33% Triplegic CP: 0% vs. 17% Quadriplegic CP: 43% vs. 50%	A vs. B, mean scores (SD) Knee extension strength: 3.90 (3.09) to 3.58 (2.82) vs. 3.09 (3.15) to 3.80 (4.22), p>0.05 Knee flexion strength: 2.47 (1.45) to 2.43 (1.54) vs. 2.35 (2.04) to 2.98 (3.26), p>0.05 Dorsiflexion strength: 0.86 (1.21) to 0.69 (0.78) vs. 0.62 (0.75) to 0.77 (0.66), p>0.05 Plantarflexion strength: 3.44 (1.91) to 3.23 (1.45) vs. 3.06 (3.62) to 3.14 (3.32), p>0.05
Kaya Kara, 2019[242] Multimodal RCT Fair	A. Strength + balance training, 36 sessions over 12 weeks (n=15) B. Usual care (n=15)	A vs. B Age: 11.8 vs. 11.3 Female: 53% vs. 53% MAC I: 47% vs. 47% MAC II: 33% vs. 27% MAC III: 20% vs. 28%	A vs. B, mean difference, Effect size, p-value is between groups Affected lower leg 1 RM (kg): 54.33, ES 3.23, p<0.001 Unaffected lower leg 1 RM (kg): 44.33, ES 2.74, p<0.001
Kirk, 2016[217] Strength Quasiexperimental Poor	A. Progressive resistance, 36 sessions over 12 weeks (n=12) B. Usual care (n=23)	A vs. B Age: 36.5 Female: 43% Wheelchair user: 17%	A, mean (SD): Statistically significant Groups X Time interaction for all exercises below for the most affected leg (kg): Ankle dorsiflexion 1RM: 5.7 (0.6) to 10.4 (1.1) Ankle plantarflexion 1RM: 30.3 (4.9) to 71.8 (6.7) Knee flexion 1RM: 16.3 (2.0) to 29.5 (3.1) Knee extension 1RM: 72.3 (5.8) to 104.5 (6.7)

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population (Cerebral Palsy)	Results
Makhov, 2018[243] Multimodal RCT Poor	A. Therapeutic gymnastics + strength 94 sessions over 15 weeks (n=18) B. Therapeutic gymnastics (passive exercises only) (n=17)	A vs. B Age: 7-9 years Female: Spastic diplegia or spastic tetra paresis: 100%	A vs. B, mean (SD), p-value is between groups Strength quadriceps femoris: 1.29 (0.49) to 1.92 (0.38) vs. 1.36 (0.56) to 1.61 (0.61), p<0.05
Nsenga, 2013[88] Aerobic exercise Quasiexperimental Fair	A. Cycle ergometry, 24 sessions over 8 weeks (n=10) B. No training control (n=10)	A vs. B Age: 14.2 vs. 14.2 Female: 40% vs. 40% Ambulatory: 100% Hemiplegia: 80% vs. 80%	A vs. B, mean difference between groups: VO_2 peak (ml/kg/min): 7.00, 95% CI 1.93 to 12.07, p=0.007 VO_2 peak (ml/min): graph indicates increase in VO_2 peak after training in intervention group (p<0.05) but not in control group; between group differences not calculable
Nsenga Leunkeu, 2012[132] Aerobic exercise Quasiexperimental Fair	A. Treadmill walking, 24 sessions over 8 weeks, (n=12) B. No training, (n=12)	A vs. B Age: 14.2 vs. 14.2 Female: 50% vs. 50% Hemiplegic CP: 83% vs. 83% GMFCS I: 67% vs. 67% GMFCS II: 33% vs. 33%	A vs. B, mean (estimates from bar graph): VO_2 peak: 32.5 to 39.0 vs. 32.5 to 32.5, no difference in baseline values, significant difference in postintervention values favoring treatment, statistical significance between groups not clear
Scholtes, 2010[209] Scholtes, 2012[207] Scholtes, 2008[208] Strength RCT Fair	A. Progressive resistance, 36 sessions over 12 weeks (n=26) B. Usual care (n=25)	A vs. B Age: 10.33 vs. 10.25 Female: 33% vs. 50% Ambulatory: 100% Bilateral: 71% vs. 60% GMFM I: 54% vs. 48% GMFM II: 33% vs. 36% GMFM III: 13% vs. 16%	A vs. B, Regression effect size Knee extensors (N/kg): 0.56, 95% CI 0.13 to 0.99, p=0.01 Knee flexors (N/kg): 0.05, 95% CI –0.25 to 0.36, p=0.71 Hip flexor (N/kg): 0.16, 95% CI –0.22 to 0.55, p=0.41 Hip abductor (N/kg): 0.27, 95% CI 0.00 to 0.54, p=0.05
Slaman, 2014[235] Slaman, 2015a[237] Slaman, 2015b[234] Multimodal exercise RCT Fair	A. Strength training + aerobic fitness, 48 sessions over 3 months plus 8-10 counseling sessions on physical activity and sports participation over 3 months: (n=28) B. Usual care (n=29)	A vs. B Age: 20 vs. 20 Female: 48.3% vs. 57.1% Ambulatory: 97% vs. 89% Wheelchair user: 3.3% vs. 10.7% Unilateral CP: 52% vs. 50% GMFM I: 61% vs. 55% GMFM II: 32% vs. 31% GMFM III: 7% vs. 10% GMFM IV: 0% vs. 3%	A vs. B, mean difference between groups: VO_2 peak (mL/min): MD 195.2, 95% CI 57.3 to 333.1, p<0.01 Weight (kg): MD –0.6, 95% CI –2.2 to 0.9, p=0.46 Hip flexion: MD 1.4 (95% CI –63.0 to 66.0), p=0.97 Hip abduction: MD –38.6, 95% CI –93.1 to 15.9, p=0.17 Knee extension: MD 23.7, 95% CI –58.6 to 106.1, p=0.57 Total cholesterol: MD –0.50, 95%CI –3.22 to –0.01, p=0.07 HDL: MD 0.01 (95% CI –0.21 to 0.21), p=0.38 SBP (mmHg): MD 1.5, 95% CI –5.6 to 8.6, p=0.68 DBP (mmHg): MD –3.0, 95% CI –7.9 to 1.9, p=0.24

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population (Cerebral Palsy)	Results
Taylor, 2013[211] Strength RCT Good	A. Progressive resistance, 24 sessions over 12 weeks (n=23) B. Usual care (n=25)	A vs. B Age: 18.17 vs. 18.58 Female: 44% vs. 48% No gait aid 57% vs. 60% GMFM II: 57% vs. 64% GMFM III: 43% vs. 36%	A vs. B, mean difference between groups: Max leg press (1Rep Max; kg): 14.8, 95% CI 4.3 to 25.3, p<0.05 Reverse leg press (1RepMax; kg): –0.7, 95% CI –4.3 to 2.8), p>0.05
Tedla, 2014[213] Strength RCT Poor	A. Strength training 18 sessions over 6 weeks + conventional PT 1-2 days/week (n=31) B. Conventional PT 3-5 sessions/per for 6 weeks (n=31)	A vs. B (data are for completers only; n=30 vs. 30) Age: 9.1 vs. 8.9 years Female: 33% vs. 33% Gross motor function classification system: I: 7% vs. 3% II: 20% vs. 27% III: 37% vs. 27% IV: 37% vs. 43%	A vs. B, change in scores, p-value is between groups Change in Strength of Trunk, Hip, Knee, Ankle: significantly better in group A than B, p<0.05

Abbreviations: BWS = body weight supported; CI = confidence interval; CP = cerebral palsy; DBP = diastolic blood pressure; EDSS = Expanded Disability Status Scale; GMFCS = Gross Motor Function Classification System; GMFM = Gross Motor Function Measure; HDL = high-density lipoprotein cholesterol; HR = heart rate; MD = mean difference; NR = not reported; PT = physical therapy; RM = one-repetition maximum; SBP = systolic blood pressure; SD = standard deviation; VO_2 peak = highest value of VO_2 attained

Table 44. Intermediate outcomes of physical activity in participants with spinal cord injury

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population (Spinal Cord Injury)	Results
Akkurt, 2017[89] Aerobic exercise RCT Fair	A. Arm ergometer, 36 sessions over 12 weeks plus general exercises,120 sessions over 12 weeks (n=17) B. General exercises, 120 sessions over 12 weeks (n=16)	A vs. B Age: 33 vs. 37 Female: 5% vs. 19% Ambulatory:41% vs. 50% Wheelchair user: 59% vs. 50% Paraplegia:100% vs. 94%	A vs. B, median change, p=between groups: VO_2 peak (ml/kg/min): 4.30 vs. 1.35, p=0.02 FEV1 (ml): –0.14 vs. 0.17, p>0.05 FVC (ml): –0.31 vs. –0.20, p>0.05 FEV1/FVC, 3.51 vs. –0.50, p>0.05 SBP (mmHg): 0 vs. 0, p>0.05 DBP (mmHg): 0 vs. 0, p>0.05 T-chol: 10 vs. 2, p>0.05 TG: 5.5 vs. 26, p>0.05 LDL: 0 vs. –3.5, p>0.05 HDL: 0 vs. 5.5, p>0.05

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population (Spinal Cord Injury)	Results
Alexeeva, 2011[133] Aerobic exercise RCT Fair	A. BWS treadmill training, 39 sessions over 13 weeks (n=9) B. BWS track training, 39 sessions over 13 weeks (n=14) C. Structured PT, 39 sessions over 13 weeks (n=12)	A vs. B vs. C Age: 43 vs. 36 vs. 35 Female: 11% vs. 14% vs. 17% ASIA D: 100% Cervical: 89% vs. 57% vs. 58%	A vs. B vs. C, mean (SD) VO_2 peak (ml/km/min): 12% nonsignificant increase within groups, but no differences between groups, p>0.05 MMT (combined upper and lower limb strength): 71.5 (15.1) to 78.1 (15.3) vs. 69.5 (12.1) to 73.3 (11.5) vs. 76.3 (11.6) to 81.8 (11.0) (6-9% significant increase within groups; no difference among groups, p>0.05)
Chen, 2016[218] Strength RCT Fair	A. Pulmonary rehabilitation: 365 sessions over 52 weeks (n=49) B. Usual care (n=49)	A vs. B Age: 62.3 vs. 63.1 Female: 0% T1–2: 35% vs. 35% T3–4: 33% vs. 33% T5–6: 33% vs. 33%	A vs. B, mean (SD), p=postintervention: FEV1: 1.17 (0.25) to 2.20 (0.45) vs. 1.17 (0.45) to 1.14 (0.44), p<0.05 FVC: 2.16 (0.36) to 2.98 (0.54) vs. 2.16 (0.42) to 2.17 (0.42), p<0.05 FEV1/FVC: 0.53 (0.17 to 0.75 (0.08) vs. 0.53 (0.17) to 0.52 (0.15), p<0.05
Giangregorio, 2012[134] Craven, 2017[137] Aerobic exercise RCT Fair	A. BWS treadmill walking with FES, 48 sessions over 16 weeks (n=17) B. Aerobic and resistance training, 48 sessions over 16 weeks (n=17)	A vs. B Age: 56.6 vs. 54.1 Female: 18% vs. 29% Tetraplegia: 82% vs. 71% UEMS: 38.3 vs. 37.5 LEMS: 30.4 vs. 27.9	A vs. B, mean (SD), p=between groups BMD Total Hip: 0.89 (0.20) to 0.88 (0.20) vs. 0.86 (0.24) to 0.87 (0.23), p>0.05 BMD Distal Femur: 0.89 (0.16) to 0.87 to 0.15) vs. 0.81 (0.18) to 0.80 (0.18), p>0.05 BMD Proximal Tibia: 0.71 (0.18) to 0.71 (0.15) vs. 0.68 (0.19) to 0.66 (0.19), p>0.05 Fat mass (kg): 25.4 (9.5) to 24.3 (9.5) vs. 23.2 (10.8) to 23.0 (10.7), p>0.05
Gorman, 2019[75] Aerobic exercise RCT Fair	A. RAGT, 36 sessions over 3 months (n=17) B. Aquatic therapy, 36 sessions over 3 months (n=15)	A vs. B Age: 45.4 vs. 46.9 Community Ambulation: 83% vs. 67% Tetraplegic: 67% vs. 73%	A vs. B, mean (SD), p=between groups VO_2 peak (ml/kg/min): 16.48 (5.39) to 16.18 (5.11) vs.13.33 (3.06) to 14.31 (3.88), p=0.063
Jones, 2014a Jones, 2014b[246] Multimodal exercise RCT Poor	A. Activity-based therapy, 72 sessions over 24 weeks (n=20) B. Waitlist (n=21)	A vs. B Age: 42 vs. 34 Female: 5% vs. 48% Tetraplegia: 75% vs. 76% AIS C: 35% vs. 52% AIS D: 65% vs. 48%	A vs. B, mean change (SD), p=between groups: BMI: 0.005 (1.15) vs. 0.723 (2.22), p=0.288 Weight (lbs): –2.0 (8.29) vs. 5.03 (14.05), p=0.314
Jung, 2014[76] Aerobic exercise RCT Fair	A. Aquatic exercise, 24 sessions over 8 weeks (n=10) B. Land exercise, 24 sessions over 8 weeks (n=10)	A vs. B Age: 42.1 vs. 51.1 Female: 30% vs. 50%	A vs. B, mean change scores, p=between groups: FVC(L): 1.8 (1.3) vs. 0.31 (1.6), p=0.031 FEV1(L): 1.1 (1.2) vs. 0.21 (0.3); p=0.038 FER(L/sec): 10.0 (9.7) vs. 5.4 (7.0), p=0.238 FEV1/FVC: 3.7 (2.3) vs. 2.1 (3.4), p=0.243

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population (Spinal Cord Injury)	Results
Lavado, 2013[92] Aerobic exercise RCT Fair	A. Hand cycling + distance with wheelchair + general exercises, 32-48 sessions over 16 weeks (n=21) B. Usual care (n=21)	A vs. B Age: 34.1 vs. 38.5 Female: 14% vs. 19% Community ambulators: 0% C5-L2: 100%	A vs. B, median: VO_2 peak (mL/min): 939 to 1154 (p=0.009) vs. 896 to 834, p=0.906; Postintervention comparison (no control for baseline values) p<0.001
Lai, 2010[91] Aerobic Exercise Quasiexperimental Fair	A. Functional electrical stimulation cycling exercises, 36 sessions over 12 weeks (n=12) B. Control group (n=12)	A vs. B Age: 28.9 vs. 28.2 Female: 17% vs. 17% Ambulatory: 0% Paraplegia: 10 (67%) vs. 10 (67%)	A vs. B, mean difference between groups: BMD Femoral Neck: –0.003, 95% CI –0.12 to 0.11, p=0.96 BMD Distal Femur: –0.05, 95% CI –0.12 to 0.03, p=0.21
Mogharnasi, 2019[219] Strength RCT Poor	A. Upper body resistance training: 24 sessions over 8 weeks (n=10) B. Usual care (n=10)	A vs. B Age: 25.33 vs. 25.50 Female: 0% Ambulatory: 0% Wheelchair user: 100% T9: 10% vs. 20% T10: 20% vs. 20% T11: 20% vs. 0% T12: 50% vs. 60%	A vs. B, mean difference between groups: BMI: –0.83, 95% CI –1.85 to 0.19, p=0.11 % Body fat: –1.2, 95% CI –3.11 to 0.71,p=0.22 T-chol: –16.00, 95% CI –11.21 to –20.78, p<0.001 HDL: 4.2, 95% CI 0.84 to 7.56, p=0.01 LDL: –6.5, 95% CI –9.81 to –3.20, p<0.001 TG: –25.3, 95% CI –32.74 to –17.86, p<0.001
Totosy de Zepetnek, 2015[249] Multimodal RCT Fair	A. Progressive resistance + aerobic training, 32 sessions over 16 weeks (n=12) B. Maintain existing physical activity levels (n=11)	A vs. B Age: 39 vs. 42 Female: 0% vs. 18% AIS A-B: 25% vs. 45% AIS C-D: 75% vs. 55%	A vs. B, mean (SD), p-value between groups: SBP: 116 (18) to 116 (15) vs. 118 (18) to 116 (17), p>0.05 DBP: 68 (9) to 67 (9) vs. 74 (13) to 72 (11), p>0.05 HR: 75 (13) to 71 (13) vs. 75 (10) to 74 (10), p>0.05 HbA1c (mmol/mol): 35.7 (11.6) to 36.6 (11.2) vs. 34.9 (4.8) to 34.7 (3.9), p>0.05 TC (mmol/L): 1.5 (0.9) to 4.3 (1.0) vs. 4.1 (0.9) to 4.1 (0.9), p>0.05 LDL (mmol/L): 2.9 (0.9) to 2.7 (0.7) vs. 2.5 (0.7) to 2.4 (0.6), p>0.05 HDL (mmol/L): 1.01 (0.2) to 1.01 (0.3) vs. 1.13 (0.2) to 1.17 (0.3), p>0.05 TG: 1.3 (0.6) to 1.4 (0.6) vs. 1.1 (0.7) to 1.0 (0.7), p>0.05 BMI: 27.3 (5.2) to 27.0 (5.0) vs. 25.7 (4.9) to 26.6 (4.7), p<0.05
Valent, 2010[93] Aerobic exercise Cohort study Fair	A. Hand cycle ergometry, 15-72 sessions over 9-33 weeks (n=20) B. Unclear (matched control) (n=17)	A vs. B Age: 46 vs. 40 Female: 24% vs. 24% Paraplegia: 10 (59%) vs. 11 (65%)	A vs. B, mean change scores FVC%: –9.4 vs. –7.8, p=0.619 PEF%: –12.6 vs. –10.0, p=0.722 VO_2 peak (ml/min): 0.21 vs. 0.13, p=0.356 VO_2 peak (ml/kg/min): 2.9 vs. 1.5, p=0.274

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population (Spinal Cord Injury)	Results
Van der Scheer, 2016[140] Aerobic exercise RCT Fair	A. Low-intensity wheelchair treadmill training, 32 sessions over 16 weeks (n=14) B. Usual care (n=15)	A vs. B Age: 55 vs. 57 Female: 14% vs. 33% Paraplegia: 64% vs. 73%	A vs. B, median change, p=between groups: VO_2 peak (L/min): 0.05 to –0.07, p=0.01

Abbreviations: ASIA = American Spinal Injuries Association Impairment Scale; BMD = bone mineral density; BMI = body mass index; CI = confidence interval; DBP = diastolic blood pressure; FER = forced expiratory ratio; FEV1 = forced expiratory volume; FVC = forced vital capacity; HbA1c = hemoglobin A1c; HR = heart rate; LDL = low-density lipoprotein cholesterol; MMT = Maximal Muscle Testing combined upper and lower limb strength; NS = not significant; PEF = peak expiratory flow; PT = physical therapy; RAGT = robot-assisted gait training; SBP = systolic blood pressure; SD = standard deviation; TG = triglyceride; UEMS = Upper Extremity Motor Score

The range of mean ages enrolled in studies of participants with CP was 6.3 years to 38 years, in studies of participants with MS was 29 years to 52 years, and for participants with SCI was 28 years to 63 years. The proportion of females enrolled ranged from a low of none in an SCI study, to a high of 100 percent two studies of participants with MS. Race was not reported in any of these studies. Reporting of characteristics at baseline related to spasticity or overall mobility varied according to condition. In studies of participants with CP, most were in GMFCS level I or II. In the studies of participants with MS, baseline disability ranged from 1.7 to 3.7 on the EDSS (range of scale 0-10 with higher values representing more problems walking), except for one study that enrolled only participants with EDSS scores of 4-6,[221] and one with 23 percent of enrolled subjects in the range of 6.5 to 8 points on the EDSS/Wheelchair use was not reported in studies of participants with CP or MS. The studies of participants with SCI varied in the way disability was reported and the level of disability; 59 to 100 percent had paraplegia and wheelchair use ranged from 50 to 100 percent.

Interventions studied and comparisons made also varied widely. Eighteen studies evaluated aerobic interventions (10 vs. usual care), nine evaluated strength interventions (8 vs. usual care, 1 vs. attention control), and fourteen evaluated multimodal interventions (12 vs. usual care). In the 17 of 20 studies categorized as comparing interventions with usual care, the control groups consisted of standard PT regimens, waitlist, “attention control” (nonphysical activity social interactions), and unspecified “usual care” interventions. The two prioritized intermediate outcomes were VO_2 peak, reported in 15 studies, and pulmonary function tests, reported in 4 studies (see Table 42 for more details). Other intermediate outcomes reported included weight-based outcomes, lipids, heart rate, glucose, strength changes, percent body fat, and bone mineral density.

Evidence on the impact of physical activity interventions on intermediate outcomes is mostly insufficient to draw conclusions. There was low-strength evidence that aerobic interventions improve VO_2 peak in participants with CP and SCI, but evidence was inconsistent in patients with MS. For other comparisons and outcomes there were several instances where a single study found a significant benefit of an intervention on one or more outcomes or that there was no difference between groups, but interpretation is limited due to small sample size, methodological limitations, and lack of corroborating evidence.

Comparisons With Usual Care

Aerobic Exercises Versus Usual Care

VO_2 peak was the most commonly reported intermediate outcome in studies of aerobic exercise. Evidence in participants with CP and SCI indicated improved VO_2 peak with exercise (SOE: low), while evidence in participants with MS was inconsistent (SOE: insufficient). In three fair-quality RCTs of participants with MS (Table 42), only one found a significant improvement in VO_2 peak, a study of weight-based upper and lower body cycling training,[53] while regular cycling programs versus usual care did not impact VO_2 peak (Table 42).[77,78] Two fair-quality quasiexperimental studies compared an aerobic exercise with usual care in adolescents with CP over 8 weeks (n=44 total).[88,132] VO_2 peak measured in ml/kg/min was increased significantly more with cycle-ergometry in one study, and in both studies VO_2 peak measured in ml/min was increased significantly with aerobic exercise (Table 43) (SOE: low). In participants with SCI, three studies reported VO_2 peak, with two fair-quality RCTs (n=71) finding a significant increase with aerobic exercise training,[92,140] and a small (n=17), fair-quality cohort study not finding a difference, although the endpoint values were higher in the aerobic exercise group (Table 44) (SOE: low).[93]

Pulmonary function was not improved with aerobic training in a cohort study of participants with SCI (Table 44).[93] This is insufficient-strength evidence to draw conclusions due to study limitations, lack of corroborating evidence, and imprecision. Other intermediate outcomes reported in these studies were not found to have significant improvement with aerobic exercise (e.g., pulmonary function tests, bone density, weight, BMI).[53,91,93,117]

Strength Exercises Versus Usual Care

Nine studies evaluated strength exercise programs and reported intermediate outcomes. Three studies were in participants with MS,[198,204,206] four in participants with CP,[207,211,213,217] and two in participants with SCI.[213,218,219] One of these was a poor-quality quasiexperimental study (Table 43).[217] None of these RCTs reported on VO_2 peak/max. A fair-quality RCT (n=98) of a pulmonary rehabilitation program in participants with SCI over 52 weeks found all pulmonary function tests measured to be significantly improved with the intervention (Table 44).[218] For example, forced expiratory volume (FEV1) increased from 1.17 to 2.20 with pulmonary rehabilitation compared with a small decrease (1.17 to 1.14) in the control group ($p<0.05$).

In participants with MS, three RCTs measured improvement in strength in various ways, comparing strength training compared with usual care or social programs (attention control) (Table 42).[147,204,206] Each study found one or more measures of strength were significantly improved with strength training over 8 to 12 weeks (Table 42). A single fair-quality RCT compared Pilates plus massage to massage alone and found no impact on percent body fat over 12 weeks.[198]

In studies that enrolled participants with CP, results were mixed with improved strength demonstrated on one or more measures in each study[207,211,213,217] but not on all measures.[207,211,216] Strength training lasted for 12 weeks in three of these studies[207,211,217] and 6 weeks in two studies.[213,216]

Multimodal Exercises Versus Usual Care

Ten RCTs (in 11 publications) evaluated multimodal exercise programs with usual care and reported an intermediate outcome.[221,224,227,228,230,231,234-237,242,243,246,247,249] Four were poor

quality,[227,228,243,246,247] and the rest were fair. In participants with MS, three fair-quality RCTs evaluated multimodal exercise programs and reported VO_2 peak[221] or VO_2 max.[224,231] In a study of mostly women with baseline EDSS scores all 4-6 (some walking impairment), resistance training, aerobics, and balance training over 24 weeks did not improve VO_2 peak compared with stretching and toning.[221] The second study enrolled participants with mean baseline EDSS of 2.5 (little or no walking impairment), and the intervention groups had less than half women, while the control group had 82 percent women.[224] This study compared resistance training plus either high-intensity interval training (n=12) or plus high-intensity continuous cardio training (n=11) with usual care (n=11) over 12 weeks. The addition of interval training resulted in greater improvement in VO_2 peak than usual care, while the addition of continuous cardio training did not improve VO_2 max or VO_2 peak significantly compared with usual care (Table 42).[224] The disparity in the proportion of women in the intervention versus control arms added to the study limitations. The third study enrolled women only, with 50 percent having EDSS scores of 4 or higher (23% with 6.5 to 8, more significant impairment). A multimodal intervention of resistance training, aerobic training, balance, Pilates, and stretching for 12 weeks resulted significantly improved VO_2 peak in the overall analysis, however when differences between groups in disability at baseline were taken into account the difference was no longer significant.[231] In participants with CP, a single fair-quality RCT (n=57) found strength training plus aerobic training and counseling over 12 weeks improved VO_2 peak significantly in young adults (mean age 20 years), most of whom were in GMFM categories I and II at enrollment.[234-237]

Changes in strength were measured in four RCTs of multimodal interventions. In three studies of multimodal exercise programs in participants with MS (2 with progressive resistance training and aerobics, 2 with WBV, and 1 with low-intensity exercise), results varied in terms of significance depending on the specific measure reported, but overall there was some benefit seen across the studies (Table 42).[222,224,227,228] In participants with MS, effect on percent body fat was positive in two studies of progressive resistance training plus aerobic exercise,[224,227] but weight or BMI was not significantly different between groups in three RCTs.[224,227,234-237] In young adults with CP, no improvement was seen (Table 43).[234-237] Resting heart rate, lipids, and glucose were reported in few studies and were not different compared with control groups. In one study of participants with SCI, multimodal exercise maintained BMI, while the control group BMI increased.[249] Other intermediate outcomes (blood pressure, heart rate, A1c, and lipids) were not significantly different between groups.

Head-to-Head Comparisons

Aerobic Exercises

Seven fair-quality RCTs[75,76,82,89,125,133-137] evaluated comparisons of different multimodal interventions. In participants with MS (n=20), 8 weeks of aquatic exercise improved FEV1 and forced vital capacity (FVC) significantly more than land exercises (Table 42); other pulmonary function test measures were not significantly different.[76] VO_2 peak was reported in three RCTs in participants with SCI, with two studies (n=67) not finding a significant difference between groups (RAGT vs. aquatic therapy and body-weight supported treadmill vs. track training).[75,133] A third study (n=33) found significantly greater improvement with an arm ergometry training over general exercises over 12 weeks.[89] Pulmonary function tests were reported in two RCTs (Table 44). In participants with SCI (n=33) pulmonary function tests showed small changes with

no significant differences between an arm ergometer program compared with a general exercise program over 12 weeks.[89]

Change in strength was measured in three RCTs of participants with SCI,[89,133-137] and one each of participants with CP[125] and with MS,[82] with none finding differences between interventions. Other intermediate outcomes reported in head-to-head comparisons of aerobic exercise programs included resting heart rate, waist circumference, fat mass, blood pressure, and lipids. These were reported in very few studies and no differences were found between interventions.

Multimodal Exercises

Three fair-quality RCTs of participants with MS compared a multimodal exercise program with either another multimodal program (2 studies),[222,224] or an aerobic exercise program (1 study).[220] One study reported VO_2 peak,[220,224] and one study reported VO_2 max.[224] In a study comparing resistance training plus high-intensity interval training or plus high-intensity continuous cardio training over 12 weeks, the interval training group had a greater improvement in VO_2 peak (17.8% increase vs. 7.5% increase), but a formal statistical analysis was not undertaken.[224] Resting heart rate increased more with interval training (12.5% vs. 7.0%), and percent body fat (–3.9% vs. –2.5%) was reduced in both groups, slightly more in the interval training group. In the other study resistance training plus aerobic training did not improve VO_2 peak more than aerobic training alone over 12 weeks.[220] This study also reported that resting heart rate and strength changes did not differ between groups. The third study compared three multimodal groups, with varying levels of aerobic and resistance training with control, but did not make statistical comparisons across the interventions groups directly. Strength outcomes were greater in the groups with more resistance or more aerobic training, compared with equal amounts of each, although the differences were small.[222]

A single study of children with CP compared multimodal training with gymnastics and strength training with passive gymnastics only, finding that quadriceps strength was improved more with multimodal training after 15 weeks (Table 43).[243]

KQ2c: Harms of Immobility

Reduction of harms due to immobility was rarely studied in trials of physical activity in MS, CP, and SCI. Two RCTs in participants with SCI provided evidence for this subquestion.

Decubitus Ulcer

There were no trials identified that assessed the prevention, formation, or improvement of decubitus ulcer as a function of physical activity.

Urinary Tract Infection

One fair-quality RCT (n=42) in participants with SCI examined the effectiveness of aerobic exercise as treatment for chronic asymptomatic bacteriuria.[92] All spinal cord lesions were between C8 and T12 segments. The mean age of participants was 36 years and 17 percent were female with a mean time since injury of 4.8 years. The intervention group received 16 weeks of arm cycling, performed distance with a wheelchair, strength exercises, and muscle stretching two to three times a week in addition to usual PT sessions. The control group received only the PT sessions. Urine was collected by catheter or urine jet. The outcome was eradication of bacteriuria or continued negative urine culture versus the need for antibiotics regardless of bacteriuria.

Chronic asymptomatic bacteriuria was identified in 24 patients (57%) before treatment (52% intervention vs. 62% control) and in 18 patients (43%) after treatment (14% intervention vs. 71% control), which was a statistically significant difference between groups (relative risk 0.20, 95% CI 0.07 to 0.54, p<0.001). The authors pointed out that there was no adjustment made for individual fluid intake, which may have impacted the findings. In patients who required antibiotics, the locus of infection was not specified and urinary culture not conducted prior to the initiation of antibiotics. No other trials of urinary tract infection were identified.

Bowel Dysfunction

Twenty-four participants with incomplete T8 to L2 SCI were randomized to RAGT or body weight-supported treadmill training in one fair-quality RCT.[113] Participant mean age was 40 years, 33 percent were female, and all participants had a duration of injury of less than 6 months. Both groups underwent defecation management training before beginning walking training four times weekly for 1 month. Outcomes were enema dose needed and defecation time. After 16 training sessions, the RAGT group required a lower enema dose after training than the treadmill group when compared with baseline dose requirements (–29 mL vs. –11 mL, p<0.05). The RAGT group also had a reduced defecation time compared with defecation times before training (–29 min vs. –15 min, p<0.05), indicating improved bowl function with RAGT. No other trials of bowel dysfunction were identified.

Autonomic Dysreflexia

No study meeting inclusion criteria for this review reported incidence of autonomic dysreflexia as a function of harm reduction with physical activity. Autonomic dysreflexia as potential harm of physical activity is discussed in KQ2e.

KQ2d: Risk of Adverse Outcomes Due to MS, CP, SCI

Nineteen studies (18 RCTs and 1 cohort study) representing 945 participants evaluated the effect of physical activity on spasticity in participants using or at risk for requiring wheelchairs (Tables 45, 46, 47).[71,73,74,94,96,99,100,111,121,125,134,136,158,159,163,174,204,207-210,223,244,245,267] We did not find eligible studies that reported other relevant outcomes.

Table 45. Impact of physical activity interventions on spasticity in participants with multiple sclerosis

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population (Multiple Sclerosis)	Results
Calabro, 2017[96] Aerobic exercise RCT Good	A. Lokomat-Pros (RAGT + VR), 40 sessions over 8 weeks (n=20) B. Lokomat-Nanos (RAGT), 40 sessions over 8 weeks (n=20)	A vs. B Age: 44 vs. 41 Female: 65% vs. 60% EDSS: 4.40 vs. 4.75	Effect size, p-value is between groups: MAS: –0.01, 95% CI –0.539 to 0.539, p=0.40

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population (Multiple Sclerosis)	Results
Castro-Sanchez, 2012[71] Aerobic exercise RCT Good	A. Ai-Chi aqua therapy with Tai-Chi music, 60 sessions over 20 weeks (n=36) B. Relaxation exercises on exercise mat without music, 60 sessions over 20 weeks (n=37)	A vs. B Age: 46 vs. 50 Female: 72% vs. 65% EDSS: 6.3 vs. 5.9 PPMS: 17% vs. 24% SPMS: 25% vs. 32%	Mean (SD) baseline to postintervention, p-value between groups: Spasm VAS: 5 (2.8) to 2 (4.3) vs. 6 (3.1) to 4 (4.5), 91% improvement vs. 10% improvement, p<0.05 The difference on the spasm VAS was maintained at 24 weeks (4 weeks postintervention) but there was no difference between groups at 30 weeks.
Dodd, 2011[204] Strength RCT Good	A. Progressive resistance, 20 sessions over 10 weeks (n=36) B. Social program (attention control), 10 sessions over 10 weeks (n=35)	A vs. B Age: 47.7 vs. 50.4 Female: 72% vs. 74% Ambulation index 2 (mild): 47% vs. 54% 3 (moderate): 39% vs. 26% 4 (severe): 14% vs. 20%	Mean difference between groups: MSIS-88 stiffness: –2.4, 95% CI –0.52 to 0.5 MSIS-88 muscle spasms: –2.8, 95% CI –5.6 to 0.03)
Pompa, 2017[94] Aerobic exercise RCT Fair	A. RAGT, 12 sessions over 4 weeks (n=21) B. Conventional walking training, 12 sessions over 4 weeks (n=22)	A vs. B Age: 47 vs. 50 Female: 48% vs. 55% PPMS: 0% vs. 13.6% EDSS 6.62 vs. 6.50	A vs. B, mean SD, p=between groups: Spasticity VAS 100mm ranged from "no problem" to "very bad": 5.05 to 3.40 vs. 5.31 to 5.23, p=0.048.
Tarakci, 2013[223] Multimodal exercise RCT Fair	A. Exercise (e.g., range of motion, strength, flexibility, balance, core stability), 36 sessions over 12 weeks (n=51) B. Waitlist control (n=48)	A vs. B Age: 41.5 vs. 39.7 Female: 67% vs. 63% EDSS: 9.0 vs. 8.4 RRMS: 63% vs. 69%	A vs. B, mean, p-values are between groups, MAS: RHipFlexors: 1.35 to 0.68 vs.1.52 to 1.65, p<0.001 LHipFlexors: 1.29 to 1.00 vs. 1.52 to 1.65, p=0.015 RHamstring: 1.35 to 0.70 vs. 1.28 to 1.47, p<0.001 LHamstring: 1.01 to 0.54 vs. 1.02 to 1.26, p<0.001 RAchilles: 0.86 to 0.68 vs. 0.94 to 1.10, p=0.014 LAchilles: 0.58 to .27 vs. 0.81 to 0.89, p<0.001
Vermohlen, 2018[158] Postural control RCT Fair	A. Hippotherapy, 12 sessions over 12 weeks plus standard care (n=32) B. Standard care (n=38)	A vs. B Age (median years): 50 vs. 51 Female: 90% vs. 73% EDSS: 5.4 vs. 5.3	A vs. B, mean difference between groups: Spasticity NRS: −0.9 (95% CI: −1.9 to −0.1), p=0.031

Abbreviations: CI = confidence interval; EDSS = Expanded Disability Status Scale; MAS = Modified Ashworth Scale; MSIS-88 = Multiple Sclerosis Impact Scale; NRS = numeric rating scale; PPMS = primary progressive multiple sclerosis; RAGT = robot-assisted gait training; RCT = randomized controlled trial; RRMS = relapsing-remitting multiple sclerosis; SD = standard deviation; VAS = Visual Analog Scale; VR = virtual reality

Table 46. Impact of physical activity interventions on spasticity in children with cerebral palsy

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population (Cerebral Palsy)	Results
Adar, 2017[73] Aerobic exercise RCT Fair	A. Aquatic exercise, 30 sessions over 6 weeks (n=17) B. Land-based exercise, 30 sessions over 6 weeks (n=15)	A vs. B Age:10.1 vs. 9.3 Female: 53% vs. 40% GMFCS median (range): 2 (1-4) vs. 2 (1-4)	Median pre-post p-values on MAS for each treatment arm Median pre-post p-values on MAS for each treatment arm <u>RKneeFlexors</u> Location: Aquatics 0.039, Land 0.008 <u>LKneeFlexors</u> Location: Aquatics 0.003, Land 0.003 <u>RAnkleFlexors</u> Location: Aquatics 0.005, Land 0.001 <u>LAnkleFlexors</u> Location: Aquatics 0.046, Land 0.046 <u>RHipAdductors</u> Location: Aquatics 0.025, Land 0.083 <u>LHipAdductors</u> Location: Aquatics 0.003, Land 0.013
Chrysagis, 2012[121] Aerobic exercise RCT Fair	A. Treadmill training, 36 sessions over 12 weeks (n=11) B. Conventional PT, 36 sessions over 12 weeks (n=11)	A vs. B Age: 15.90 vs. 16.09 Female: 45% vs. 36% Ambulatory: 100%	A vs. B (mean change, p=value) <u>MAS</u>: <u>Knee extensors</u>: 0.32 vs. 0.18, p=0.827 <u>Knee flexors</u>: 0.31 vs. 0.22, p=0.632 <u>Foot plantar flexors</u>: 0.32 vs. 0.17, p=0.460
El-Shamy, 2018[181] Postural control RCT Fair	A. Robotic upper-limb therapy, 36 sessions over 12 weeks (n=15) B. Conventional therapy of stretching and strength exercises, 36 sessions over 12 weeks (n=15)	A vs. B Age: 6.9 vs. 6.8 Female: 40% vs. 27% MACS I: 33% vs. 40% MACS II: 53% vs. 40% MACS III: 13% vs. 20%	Mean difference between groups: Spasticity MAS: –0.4, 95% CI –0.8 to –0.1, p<0.05
Johnston, 2011[125] Aerobic exercise RCT Fair	A. Partial BWS treadmill training with 20 sessions over 2 weeks, then 50 sessions at home over 10 weeks (n=14) B. Individualized strength-based PT, 20 sessions over 2 weeks, then 50 session at home over 10 weeks (n=12)	A vs. B Age: 9.6 vs. 9.5 Female: 50% vs. 42% GMFCS II: 7% vs. 8% GMFCS III: 64% vs. 50% GMFCS IV: 29% vs. 42%	Mean difference between groups, p=between groups <u>KinCom computerized dynamometer</u>: <u>Plantar Flexor Spasticity (J/^{O}/s):</u> –0.0003, p=0.75 <u>Knee flexor spasticity (J/^{O}/s):</u> –0.0026, p=0.59
Lai, 2015[74] Aerobic exercise Cohort study Fair	A. Aquatic therapy, 24 sessions over 12 weeks, rehab exercises, 24-36 sessions over 12 weeks (n=11) B. Rehab exercises, 24-36 sessions over 12 weeks (n=13)	A vs. B Age: 7.6 vs. 6.6 Female: 64% vs.31% GMFCS I: 9% vs. 8% GMFCS II:36 % vs. 46% GMFCS III: 27% vs. 23% GMFCS IV: 27% vs. 23%	A vs. B (ANCOVA p-values) <u>MAS:</u> Ankle: 0.614 Knee: 1.000 Wrist: 1.000 Elbow: 1.000

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population (Cerebral Palsy)	Results
Lucena-Anton, 2018[163] Postural control RCT Fair	A. Hippotherapy, 12 sessions over 12 weeks plus physiotherapy, 24 sessions over 12 weeks (n=22) B. PT, 24 sessions over 12 weeks (n=22)	A vs. B Age: 9.5 vs. 8.2 Female: 41% vs. 32% Nonambulatory: 100%	A vs. B, mean (baseline to posttreatment), p=between groups MAS: Left Abductors: 2.77 to 2.50 vs. 2.59 to 2.54, p=0.040 Right Abductors: 2.22 to 1.77 vs. 2.40 to 2.31, p=0.047
Qi, 2018a[210] Strength RCT Fair	A. Strength exercises + neuromuscular electrical stimulation, 30 sessions over 6 weeks (n=50) B. Neuromuscular electrical stimulation, 30 sessions over 6 weeks (n=50)	A vs. B Age: 5.8 vs. 6.0 Female: 48% vs. 46% Comprehensive Spasticity Scale: 12.0 vs. 12.3	Mean difference between groups: CSS: 1.6, 95% CI 0.33 to 2.87, p=0.01
Scholtes, 2010[209] Scholtes, 2012[207] Scholtes, 2008[208] Strength RCT Fair	A. Progressive resistance, 36 sessions over 12 weeks (n=24): B. Usual care (n=25)	A vs. B Age: 10.33 vs. 10.25 Female: 33% vs. 50% Ambulatory: 100 GMFCS I: 54% vs. 48% GMFCS II: 33% vs. 36% GMFCS III: 13% vs. 16%	A vs. B, mean (SD), p=between groups Spasticity (0-5, higher=greater spasticity): 1.00 (1.32) vs. 2.00 (1.32) (baseline) 2.00 (1.11) vs. 1.50 (1.10) (postintervention) Effect Size: 0.46, 95% CI −0.34 to 1.26, p=0.26
Wu, 2017b[99] Aerobic exercise RCT Fair	A. RAGT (resistive force), 18 sessions over 6 weeks (n=11) B. Treadmill only training, 18 sessions over 6 weeks (n=10)	A vs. B Age: 11.3 vs. 10.5 Female: 45% vs. 40% Nonwhite: 54.5% vs. 50% GMFCS I: 9% vs. 17% GMFCS II: 55% vs. 25% GMFCS III: 27.vs. 42% GMFCS IV: 9% vs. 17%	A vs. B, mean (SD) MAS (Baseline vs. 6 weeks vs. 8 weeks followup) 0.62 (0.46) to 0.67 (0.60) to 0.41 (0.38), p=0.18, vs. 0.65 (0.36) to 0.48 (0.47) to 0.58 (0.44), p=0.19
Wu, 2017a[100] Aerobic exercise RCT Fair	A. RAGT with resistance, 18 sessions over 6 weeks (n=10) B. RAGT with assistance,18 sessions over 6 weeks (n=10)	A vs. B Age: 10.6 vs. 10.8 Female: 50% vs. 45% GMFCS I: 8% vs. 0% GMFCS II: 42% vs. 45% GMFCS III: 42% vs. 36% GMFCS IV: 8% vs. 18%	Mean (SD), p=between groups postintervention: MAS 0.65 (0.57) to 0.83 (0.66) to 0.63 (0.39) followup vs. 0.85 (0.67) to 0.68 (0.56) to 0.87 (0.55) followup MD 0.35, 95% CI –0.19 to 0.89, p=0.21

Abbreviations: ANCOVA = analysis of covariance; BWS = body weight supported; CSS = Comprehensive Spasticity Scale; CI = confidence interval; GMFCS = Gross Motor Function Classification System; IQR = interquartile range; MAS=Modified Ashworth Scale; MACS = manual ability classification system; MD = mean difference; PT = physical therapy; RAGT = robot-assisted gait training; RCT = randomized controlled trial; SD = standard deviation; VR = virtual reality

Table 47. Impact of physical activity interventions on spasticity in participants with spinal cord injury

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population (Spinal Cord Injury)	Results
Galea, 2018[245] Multimodal exercise RCT Fair	A. Whole body strength + aerobics, 36 sessions over 12 weeks (n=60) B. Upper body strength + aerobics, 36 sessions over 12 weeks (n=56)	A vs. B Age: 40.1 vs. 42.8 Female: 15% vs.16% ASIA A: 48% vs. 50% ASIA B: 15% vs. 14% ASIA C: 12% vs. 9% ASIA D: 25% vs. 27% C2-C8: 48% vs. 59% T1-T6: 30% vs. 23% T7-T12: 22% vs. 18%	A vs. B 1.8 (1.1) vs. 1.5 (1) (baseline) 1.6 (1.1) vs. 1.8 (1.1), MD –0.25 (95% CI –0.61 to 0.1), p=0.163
Kapadia, 2014[136] Aerobic exercise RCT Fair	A. BWS treadmill walking with FES, 48 sessions over 16 weeks (n=17) B. Aerobic and resistance training, 48 sessions over 16 weeks (n=17)	A vs. B Age: 56.6 vs. 54.1 Female: 18% vs. 29% Tetraplegia: 82% vs. 71% UEMS: 38.3 vs. 37.5 LEMS: 30.4 vs. 27.9	MAS: No between group differences in MAS involving the hip, knee, and ankle joints.
Kumru, 2016[111] Aerobic exercise RCT Fair	A. RAGT with rTMS, 20 sessions over 4 weeks (n=15) B. RAGT with Sham rTMS, 20 sessions over 4 weeks (n=16)	A vs. B Age: 51 vs. 49 Female: 33% vs. 13% ASIA A; 0% ASIA B: 0% ASIA C: 80% vs. 88% ASIA D: 20% vs. 22% Cervical or Thoracic: 100% Cervical: 53% vs. 38%	A vs. B Mean difference between groups: MAS: –0.20, 95% CI –0.94 to 0.54, p=0.59

Abbreviations: ASIA = American Spinal Injury Association Impairment Scale; BWS = bodyweight supported; CI = confidence interval; FES = functional electrical stimulation; LEMS = Lower Extremity Motor Score; MAS = Modified Ashworth Scale; RAGT = robot-assisted gait training; rTMS = transcranial magnetic stimulation; UEMS = Upper Extremety Motor Score

Six studies enrolled participants with MS (n=396) (Table 45), ten enrolled children or adolescents with CP (n=457) (Table 46), and three enrolled participants with SCI (n=181) (Table 47). The range of mean ages enrolled in studies of participants with CP was 4.7 to 16 years, in studies of participants with MS was 39.7 to 51 years, and in participants with SCI was 40.1 years to 56.6 years. The proportion of females enrolled ranged from a low of 15 percent in a SCI study, to a high of 90 percent in a study of participants with MS. Race was reported in only two studies, both of children with CP (nonwhite race 52% and 48%).[99,100] Reporting of characteristics at baseline related to spasticity or overall mobility varied according to condition. In studies of participants with CP, most were in GMFCS level II or III, with fewer participants in levels I and IV, except for the study of the youngest participants (mean age 4.8 years) where over 73 percent were in GMFCS level V. In the studies of participants with MS, baseline disability ranged from 4.4 to 9 on the EDSS (range of scale 0 to 10 with higher values representing more problems walking). The studies of participants with spinal cord injuries varied in the way disability was reported and the level of disability. Two of the RCTs enrolled mostly participants (100% and 77%) at the ASIA scale C and D level (motor incomplete, motor function preserved at some level),[111,134-136] while the third enrolled participants at each ASIA score level with more than 60 percent at level A (complete impairment, no sensory or motor function) or B (sensory

incomplete, but motor function complete).[244,245] The proportion of participants using wheelchairs, full or part-time, was not explicitly reported.

Interventions studied and comparisons made varied widely. Eleven studies evaluated aerobic interventions[71,73,74,94,96,99,100,111,121,125,136] (2 vs. usual care, including standard PT), four evaluated strength interventions[181,204,207-210] (1 vs. usual care, 1 vs. attention control), two evaluated balance interventions[158,163,267] (all vs. usual care), and two evaluated multimodal interventions (1 vs. usual care). In the 8 of 18 studies categorized as comparing interventions with usual care, the control groups consisted of standard PT regimens, waitlist, "attention control" (nonphysical activity social interactions) and unspecified "usual care" interventions. The most commonly reported outcome of spasticity was the Modified Ashworth Scale (MAS) (range 0-4, measure of resistance on passive soft tissue stretching), used in 10 studies.[73,74,96,99,100,111,121,136,163,181]

Seven of 19 studies found a significant difference between groups. In comparisons to usual care control groups, balance interventions in four RCTs (1 of hippotherapy in participants with CP,[158] 1 of hippotherapy in participants in MS,[163] 1 of robotic upper-limb therapy in children with CP,[181] and 1 of a multimodal therapy in participants with MS[223]) significantly improved spasticity. In head-to-head comparisons, robot-assisted treadmill training improved spasticity more than nonassisted treadmill training,[99] aquatic Tai Chi with music improved spasticity more than relaxation exercises on land without music,[71] and neuromuscular electrical stimulation with strength training improved spasticity more than neuromuscular electrical stimulation alone.[210] All other comparisons did not find differences in the effect on spasticity. The details of these studies are summarized below.

Because the studies were small (n=11 to 116), most were fair quality, and for each population-intervention-comparison there was only a single study, the majority of this evidence is insufficient to draw conclusions. The two exceptions were a good-quality RCT of progressive resistance training compared with a social program (attention control) that found no difference in spasticity between groups in participants with MS, providing low-strength evidence of no clear benefit of strength training on spasticity,[204] and a good-quality RCT, also in participants with MS, of aquatic-based Ai-Chi versus relaxation exercises on land that provided low-strength evidence of benefit with aquatics on a spasm visual analogue scale.[71,73,74,94,96,99,100,111,121,125,134,136,158,159,163,174,204,207-210,223,244,245,267]

Comparisons With Usual Care

Aerobic Exercises Versus Usual Care

Two fair-quality studies compared an aerobic exercise with usual care in participants with CP over 12 weeks, with neither finding a significant benefit on measures of spasticity.[74,121] Both were small studies (n=22 total), with one being an RCT of treadmill training in adolescents with CP.[121] Evaluation of knee extensors and flexors and foot flexors showed small differences (<0.5 difference on a 5-point scale) favoring the intervention numerically, which did not reach statistical significance. The other study was a cohort study that evaluated aquatic therapy compared with standard rehabilitation exercises, with adjusted analysis not finding differences at the ankle, knee, wrist, or elbow.[74]

Strength Exercises Versus Usual Care

Two RCTs evaluated the effect of progressive resistance training on spasticity, with neither finding a significant benefit.[204,207-209] In a small good-quality RCT of participants with MS

(n=71), an attention control social program was used as the comparison group intervention. Using the Multiple Sclerosis Spasticity Scale-88, muscle stiffness and muscle spasms were not significantly improved with strength training (Table 45).[204] A small fair-quality trial (n=49) in children with CP reported small improvement in the intervention group compared with the control group, but the difference between groups was not significant (Table 46). Spasticity was measured using goniometry to identify the joint angle at which a sudden increase in muscle tone occurred during a fast passive stretch (0-5-point scale, 5 being the worst). Another small (n=30) fair-quality RCT in children with CP assessed robotic upper limb therapy over 12 weeks, compared with conventional therapy and found that spasticity was improved with the nintervention,[181] based on the MAS (Table 46).

Balance Exercises Versus Usual Care

Two fair-quality RCTs evaluated hippotherapy over 12 weeks. One was of participants with CP (n=44),[163] and the other in participants with MS (n=70).[158] In the study of children with CP, none of whom were ambulatory, there was a significant difference in spasticity between groups on the MAS on both the left and right adductors.[163] The magnitude of difference was small (0.22 and 0.36 on a 5-point scale), but the effect size was considered medium to large (Cohen's d = 0.638 and 0.646, respectively). In the other RCT of mostly women (82%) with MS with mean baseline EDSS of 5.4, 12 weeks of hippotherapy also had significantly lower spasticity based on a 0-10 numeric rating scale (numeric rating scale −0.9, 95% CI −1.9 to −0.1, p=0.031).[158] The magnitude of effect is small, but larger than seen in other studies.

Multimodal Exercises Versus Usual Care

A single small fair-quality RCT of participants with MS, whose mean baseline EDSS score was 8.7, evaluated an exercise program that included range of motion, strength, flexibility, balance, and core stability exercises over 12 weeks compared with a waitlist control group.[223] Based on the MAS, significant improvement was seen at all testing points compared with control (Table 45). The magnitude of difference varied based on the location of testing (e.g. difference of 0.7 at right hip flexor vs. 0.39 at left Achilles-tendon on a 5-point scale), but the control group value deteriorated slightly over the 12-week period.

Head-to-Head Comparisons

Aerobic Exercises

In participants with MS (Table 45), one RCT compared RAGT with a conventional walking program.[94] In this RCT of participants with baseline EDSS scores of 6.6, using a Visual Analog Scale (VAS) (0-100), RAGT improved spasticity more than conventional walking exercises (–1.65 vs. 0.08, p=0.048), but the difference is small and the spasticity level was low in both groups at baseline (5.05 and 5.31). In another RCT (good quality), the Lokomat® RAGT was compared with and without a virtual reality program (n=40).[96] At baseline, participants' disability was less than the previous study (EDSS 4.6). At 8 weeks, there was not a significant improvement from baseline in either group, nor was the difference between groups significant based on the MAS. In a third study (good quality, n=73), participants with mean EDSS at baseline of 6.1 were assigned to aquatic Ai Chi with music or to land-based relaxation exercises without music. Based on a 0 to 100 VAS scale, spasticity was improved more in the aquatic

group after 20 weeks (Table 46).[71] The difference between groups remained significant at week 24 (4 weeks postintervention) but not at week 30.

In children with CP (Table 46), four fair-quality RCTs compared one form of aerobic exercise with another and reported on spasticity.[73,99,100,125] Three studies found no benefit of either intervention on measures of spasticity, one comparing partial body weight support-treadmill training with individualized strength training for 12 weeks (n=26),[125] one comparing RAGT with nonassisted treadmill training over 6 weeks with an 8-week followup (n=21),[99] and one comparing RAGT with resistance or assistance (Table 46).[100] These studies were very small, such that differences may not have been found due to inadequate statistical power. The fourth RCT compared an aquatic exercise program with a land-based program for 6 weeks (n=32), finding statistically significant improvement in both groups.[73] Statistical comparisons were not made between groups, and data were not provided to conduct such calculations.

In participants with incomplete SCI, two fair-quality RCTs compared aerobic interventions with each other, but neither found a difference in the effect on spasticity (Table 47).[111,134-136] The first compared functional electric stimulation in body weight supported treadmill training with an aerobic and resistance training program over 16 weeks (n=34).[136] At baseline 78 percent were ambulatory. There was no difference in spasticity at the end of the study in either group, or between groups. In the second RCT (n=31), RAGT with and without rTMS was evaluated over 4 weeks, using a sham rTMS for the control group.[111] At baseline, 84 percent were ASIA level C for impairment (motor incomplete). Neither group had significant improvements in spasticity at 4 weeks, nor was there a significant difference between groups.

Strength Exercises

A fair-quality RCT in children with CP compared neuromuscular electrical stimulation with and without strength training exercises over 6 weeks (n=100).[210] Mean age was 6 years, and the Comprehensive Spasticity Scale score was 12.1 (mean) at baseline (scores of 10-12 defined as moderate spasm). After 6 weeks, while the score was reduced to the level of "mild spasm" in both groups, the combined neuromuscular electrical stimulation and strength training group had a significantly greater reduction, resulting in a mean score of 7.6 compared with a mean score of 9.5 in the control group ($p<0.05$).

Multimodal Exercises

A fair-quality RCT of participants with incomplete SCI (n=116) compared whole body strength and aerobic training (locomotor training, functional electrical stimulation-assisted leg cycling, and trunk and lower extremity exercises) with upper body strength and aerobic training only.[244,245] In this study, 49 percent of participants had ASIA scale level A impairment at baseline (complete SCI). Spasticity was measured using the self-reported Penn Spasm Frequency Score, rated 0 (no spasms) to 4 (4 being spontaneous spasms occurring >10/hour) over the past week. The baseline mean score for whole body strength and aerobic training was 1.8, and for upper body strength and aerobic training was 1.5. There was no improvement and no difference between groups after 12 weeks ($p=0.163$).

KQ2e: Physical Activity Harms

Most included studies of physical activity in participants with MS, CP, and SCI did not assess or did not report adverse events or harms experienced by study participants. This included greater than 60 percent of studies in participants with SCI and CP and greater than 40 percent of studies in participants with MS. A small proportion of trials (11%) reported that there were no harms, adverse events, serious adverse events, and/or study withdrawals due to adverse events.

In studies that reported adverse events, sometimes the events were not broken down into intervention versus control groups. That is, some studies reported that many or most study participants experienced "sore muscles" or "aches and pains," contributing to the challenge of determining which interventions are associated with which harms. Overuse injuries were rarely described as an "overuse" injury but musculoskeletal issues (i.e., joint pain, muscle soreness, sprains, muscle cramps) were frequently cited without being associated with a particular intervention.

Other potential harms that may be associated with physical exercise and that are especially concerning include autonomic dysreflexia (that could be fatal), fractures, and falls.

One fair-quality RCT (n=116) in participants with C2 to T12 SCI (49% ASIA Impairment Scale [AIS]-A, 26% AIS-D) randomized participants to intensive whole-body exercises versus intensive upper-body exercise for 12 weeks (36 sessions).[244,245] Whole-body exercises included locomotor training, FES-assisted leg cycling, and assisted and resisted exercises to strengthen the trunk, upper limbs, and lower limbs. Upper-body exercises involved arm cycling and upper-body strength exercises, such as chest press and biceps/triceps curls.

This trial[245] systematically monitored participants for adverse events and recorded 719 total such events (404 with full-body exercise and 309 with upper-body exercise). In the full-body exercise group (n=60), there were 26 instances of autonomic dysreflexia (3 were considered serious) and 5 episodes of dizziness/nausea (possibly related to autonomic dysreflexia). In the upper-body exercise group (n=56), there were 7 episodes of autonomic dysreflexia and 15 episodes of headache (possibly related to autonomic dysreflexia). Data on the number of participants who experienced each adverse event were not provided. Although only three episodes of autonomic dysreflexia were rated as serious by study personnel, this trial demonstrates the need for cardiovascular monitoring of exercise participants, especially participants with SCI and those experiencing intense interventions to minimize cardiovascular risk. This trial provides low-strength evidence of increased episodes of dysreflexia with more intense exercise versus less intense exercise, in this case whole body exercise versus upper body exercises.

In addition to episodes of autonomic dysreflexia, one participant in the full-body intervention group above experienced bilateral insufficiency fractures of the medial femoral condyle and tibial plateau.[245] Across all included studies reporting adverse events, fracture was one of the most commonly cited specific harms and occurred in at least eight trials. However, not all fractures were study related; fractures also occurred in participants assigned to various exercise groups (e.g., aerobics, aquatics, cycling, hippotherapy) in addition to control groups. There was no indication of increased fracture risk with any particular exercise intervention versus another intervention or versus a control intervention, but evidence was limited.

Six trials reported the occurrence of one or more falls. Falls were reported in hippotherapy,[158,164,165] Pilates,[200,201] balance training,[141,143] and usual physiotherapy.[200,201] Although one fall from a horse resulted in a fractured humerus,[165] data were too sparse to determine if falls were more strongly associated or if the consequences of falls were more severe

with one intervention versus a no exercise or usual care control (RR 3.74, 95% CI 0.80 to 17.45, p=0.093) (SOE: Insufficient).

KQ2f: Physical Activity Characteristics

Three RCTs provided evidence for this KQ and all studies enrolled participants with MS (n=397).[59,192,193,197] Details for each RCT are provided below.

Hospital-Based Versus Home-Based Calisthenics

Two fair-quality RCTs (n=83) enrolled participants with MS and compared hospital or center-based exercise with home-based exercise.[59,229] In one trial, participants were, on average, 33 years old (range 18 to 50 years), were 56 percent female, and had a mean EDSS score of 3.5.[59] All participants received a 12-week, 36-session exercise program that consisted of calisthenics 3 days per week and relaxation 2 days per week. Sessions included 15 minutes of warmup, 20 minutes of intensive calisthenics, and 15 minutes of cool down and relaxation. In the hospital group, exercises were conducted by a physiatrist. Participants in the control group were to conduct the same exercises at home with daily telephone followup. Both groups significantly improved on the 10MWT from baseline with no differences between groups (p=0.442). Quality of life was also significantly improved in both groups but was not different between groups (p=0.146). Both the hospital-based and the home-based group improved significantly on the BBS compared with baseline, but the hospital-based group saw a greater improvement (p=0.031). At baseline, 62.5 percent of participants had depressive symptoms and 52.7 percent had symptoms of anxiety. At the conclusion of the 12-week exercise program, both groups saw statistically significant improvement on both the HADS-D (depression) and the HADS-A (anxiety) scales, but the hospital-based exercise group improved to a greater degree than the home-based exercise group (p<0.001).

In the second trial, participants were 51 years of age on average, 76 percent were female, and most required unilateral (36%) or bilateral (22%) ambulation aids.[229] The intervention group received sixteen 60-minute group exercise sessions aimed at improving gait and balance. Sessions were led by physiotherapists and exercises were performed at moderate to high intensity. The control group performed similar exercises at home. Gait speed, walking endurance, and balance did not improve over time and there were no statistically significant differences between the groups on the 10MWT, 6MWT, or the BBS (p>0.05 for all comparisons).

Findings from these trials are mixed and suggest that for some outcomes, home exercise with close followup may yield similar improvements as hospital-based interventions. In one trial,[59] depression scores improved to a greater degree with hospital-based exercises, but confirmation of these findings are needed to determine when home-based, unobserved activity provides similar benefits to clinic or hospital-based physical activity interventions.

Physiotherapist-Led Versus Fitness-Instructor-Led Exercise

One poor-quality RCT in participants with MS randomized individuals with minimal gait impairment (Guy's Neurological Disability Scale [GNDS] mobility section score of 0 to 2) to group exercise led by a physiotherapist (n=63) or by a fitness instructor (n=67).[192,193] The mean age of participants was 51 years, 73 percent were female, and 52 percent had RRMS. Only the physiotherapist-led exercise program was predefined and consisted of aerobic and strength exercises weekly for 10 weeks. Participants were also advised to continue walking, cycling,

swimming, or running at home for 30 minutes twice a week, and from week 6 on, an additional self-directed strength and aerobic session was added.

The fitness instructor-led program was not predefined and was conducted at 11 different sites across Ireland to reflect typical community programs available to MS patients. Most weekly sessions consisted of a combination of aerobic and strength training with no additional, self-directed training at home specified.

Both groups saw statistically significant improvement on the MSIS-29 physical and psychological components and on the 6MWT from baseline measurements. However, the groups were not compared with each other but were each compared with a control group (n=49) that was instructed not to change exercise habits. Both the physiotherapist-led and the fitness instructor-led groups saw greater improvement over the control group on all measures. Due to high attrition, this trial provides limited support for the effectiveness of aerobic and strength focused community-based programs in MS patients with no or low levels of gait impairment.

Group Versus Individual Physiotherapy

One poor-quality RCT randomized participants with MS who needed bilateral support for gait and possibility a wheelchair for longer distances (GNDS mobility section 3 or 4) to group versus individual physiotherapy.[197] The mean age of participants was 55 years, 60 percent were female, and 43 percent were diagnosed with secondary-progressive MS. Both groups received 10 weekly sessions of group or individual physiotherapy.

The group physiotherapy program was self-paced and consisted of strength and balance exercises to reduce falls and improve balance and mobility. Progression was based on individual ability. Participants in the individual physiotherapy group received treatment based on the individual's problem list and goals.

Both group physiotherapy and individual physiotherapy were associated with improved scores from baseline on the MSIS-29 physical component and on the BBS. Group physiotherapy was also associated with improved scores from baseline on the MSIS-29 psychological component, while individual physiotherapy was associated with improved walking distance on the 6MWT. Due to breaking of randomization and attrition greater than 20 percent, this study provided limited evidence for similar benefits of group versus individual physiotherapy in MS patients with reduced mobility.

Other Comparisons

No included studies utilized telehealth or varied the level of training provided to study participants. Physical activity in trials of home-based exercise were typically not observed and therefore did not meet inclusion criteria for this review. Analysis across trials to further examine the effects of intervention location, amount of instruction, or level of supervision was not feasible due to significant heterogeneity in study populations, interventions, and comparators.

KQ3: Patient Factors and Physical Activity

This KQ evaluates the benefits and harms of the interventions according to patient characteristics, subgroups, demographics, condition, and intervention variations reported in the included studies.

Key Points

- In participants with incomplete SCI, having better function and more recent injury at baseline was associated with better response to aerobic interventions than those with worse function and longer time since injury (2 RCTs). A study of women with MS found more improvement in strength and balance with core stability training in those whose baseline disability was worse. Other subgroup analyses (3 RCTs) did not find evidence of variation in effects based on baseline function or spasticity in children with CP (total body vibration), or based on weight category in participants with MS (cycling).
- Comparisons of findings across studies of participants with CP did not suggest differences in results on walking outcomes by age group (children, adolescents, adults). This finding required confirmation from direct evidence based on subgroup analyses of age within studies. Data were too homogeneous to compare outcomes by age in MS or SCI. Evaluations of differences by sex or race/ethnicity were not possible.
- Comparisons of findings according to condition (CP, MS, SCI) across studies was limited by small numbers of studies in each comparison. With aerobic interventions, VO_2 peak was significantly improved in participants with SCI (2 RCTs) and CP (2 RCTs), but not in participants with MS (2 RCTs). No other differences were identified. These findings required confirmation from direct evidence based on subgroup analyses of participant diagnosis within studies.

Detailed Synthesis

Few studies evaluated the effect of the interventions according to patient characteristics or other subgroups. Only one study[168] undertook analysis of the effects of the exercise intervention according to demographic characteristics (KQs 3a), and no study evaluated harms according to baseline patient characteristics. Six studies (2 in SCI,[138,247] 3 in MS[53,147,231] and 1 in CP[168]) evaluated the effects of interventions according to patient characteristics or factors such as baseline functional ability, recency of onset of condition, and weight (Table 48).

In participants with incomplete SCI, two small studies found that those with better function or more recent injury had better response to physical activity interventions. In a small (n=22) crossover RCT in participants with incomplete SCI (>7 months since injury), two methods of walking retraining were compared (endurance and precision training) over 2 months[138]

Improvement on the 6MWT was significant with endurance training among participants with better walking speed at enrollment (>0.5 meters per second; p=0.03), while for those with lower walking function at baseline, no test was significantly improved with either training method. A secondary analysis of data from a small RCT (n=38) of participants with chronic (>12 months) incomplete SCI who were assigned to activity-based therapy evaluated predictors of response to intervention according to baseline characteristics.[246,247] Response was defined as improvement of at least 45.1 meters on the 6MWT, 0.13 m/s on the 10MWT, and reduction of at least 25.7 seconds for the TUG test, representing what the authors considered conservative estimates of minimally important differences. Participants having a response on the 6MWT were greatest (statistically significant) among those with AIS grade D (vs. grade C), and in those whose injury occurred less than 3 years before treatment (vs. >3 years). Changes on the 10MWT and the TUG test were not significantly different based on these patient factors. Other patient factors evaluated, including injury level, lower-extremity motor score, and use of a walker prior to study, were not found to impact the likelihood of improvement on any measure. A trial of

women with MS (n=69) compared core stability training with conventional care (including stretching) over 10 weeks and found that improvement in strength and balance outcomes was greater in participants with greater disability at baseline.[147] Specifically, women with worse baseline EDSS (scores ranging from 3.5 to 4.5 and 4.5 to 5.5) improved significantly more than those with better baseline scores (range 2.5 to 3.5). One study of children with CP found hippotherapy associated with improved sitting assessment scores compared with no hippotherapy in children with less disability (GMFCS I), whereas those with GMFCS II did not show improvement.[168]

In contrast, analyses in three other studies of physical activity interventions did not find evidence of variation in effects based on baseline function or spasticity in children with CP, baseline function in women with MS, or based on weight category in participants with MS.

A study of participants with RRMS evaluated interval cycling training (upper and lower extremity) for 2 months, stratifying analysis by weight categories (normal BMI <25, overweight >25).[53] Although fatigue and depression scores improved in the exercise groups, no interactions were found between weight subgroups on weight status (BMI category), fatigue, or depression. A trial of a multimodal exercise program over 12 weeks adjusted analyses based on disability at baseline (grouped by low, moderate and severe based on EDSS).[230,231] While improvements were seen on the 6MWT and the TUG and in serum lipids, VO_2, and percent body fat prior to adjustment, none were found to show significant differences between the intervention and control after adjustment.

Table 48. Within-study subgroup analyses of effects of exercise in participants with MS, SCI, or CP

Author, Year Intervention Study Design Study Quality	Intervention	Population	Results
Amiri, 2019[147] Postural control RCT Fair	A. Core stability training, 30 sessions over 10 weeks (n=35) B. Conventional care including stretching and range of motion exercises (n=34)	A vs. B Age: 32 vs. 31 Female: 100% EDSS: 3.56 vs. 3.74 MS	Core strength tests (R/L hip abduction, R/L external rotation) demonstrated significant differences in strength based on baseline EDSS score (2.5-3.5; 3.5-4.5; 4.5-5.5), p<0.001 Plank test: significant differences between groups based on EDSS score, p<0.001 Overall static balance tests demonstrated significant differences in strength based on baseline EDSS score and significant differences compared with the control group, p<0.001 Greatest improvements seen in those with greatest disability (least strong)

Author, Year Intervention Study Design Study Quality	Intervention	Population	Results
Faramarzi, 2020[230] Banitalebi, 2020[231] Multimodal exercise RCT Fair	A. Resistance + cycling or running + balance exercises + Pilates + stretching, 36 sessions over 12 weeks (n=46) B. Waitlist control (n=43)	A vs. B Age criteria: (18 to 50) Female: 100% EDSS 0 to 4: 48% to 48% EDSS 4.5 to 6: 27% vs. 27% EDSS 6.5 to 8: 23% vs. 23%	A vs. B, Positive effect of exercise on: Cholesterol: p=0.020, effect of disability*exercise p=0.549 HDL: p<0.001, effect of disability*exercise p=0.408 LDL: p<0.001, effect of disability*exercise p=0.826 TG: p=0.005, effect of disability*exercise p=0.982 VO_2 peak: p=0.004, effect of disability*exercise p=0.097 Body fat %: p=0.001, effect of disability*exercise p=0.76 TUG: p<0.001, effect of disability*exercise p=0.396 6MWT: p<0.001, effect of disability*exercise p=0.587
Jones, 2014[246] Multimodal exercise Secondary analysis of responders in an RCT Poor	A. Activity-based therapy (developmental sequence activities, resistance training, and locomotor training) (n=38) No control for this analysis	Age: 38 years Female: 29% Motor Incomplete SCI ASIA C or D SCI	6MWT response (>45.1 meters improvement): AIS Grade C vs. D: OR 11.00 (95% CI 1.24 to 7.97) </>3 years since injury: OR 4.80 (95% CI 1.04 to 22.10) Other outcomes (10MWT and TUG): not significantly different based on AIS grade or time since injury No outcome found significantly different in other subgroups (injury level, lower extremity function, use of a walker)
Matusiak-Wieczorek, 2020Matusiak-Wieczorek, 2020 #19901 Postural control RCT Fair	A. Hippotherapy, 24 sessions over 12 weeks (n=15) B. Hippotherapy, 12 sessions over 12 weeks (n=15) C. No hippotherapy (n=15)	A vs. B vs. C Age: 7.93 vs. 7.60 vs. 8.13 Female: 40% vs. 47% vs. 47% GMFCS I: 67% vs. 80% vs. 47% GMFCS II: 33% vs. 20% vs. 53%	A vs. B vs. C, mean (SD), p=between groups SAS improvement vs. no improvement: A vs. C (6-7 year olds): p<0.001 B vs. C (6-7 year olds): p=0.022 A vs. B (6-7 year olds): p=0.105 A vs. C (8-12 year olds): p=0.379 B vs. C (8-12 year olds): p=0.442 A vs. C (8-12 year olds): p=0.397 A vs. C (GMFCS I): p=0.001 B vs. C (GMFCS I): p=0.073 A vs. B (GMFCS I): p=0.030 A vs. C (GMFCS II): p=0.326 B vs. C (GMFCS II): p=0.509 A vs. B (GMFCS II): p=0.429
Negaresh, 2019[53] Aerobic Exercise RCT Fair	A. Interval cycling training of upper and lower extremity 24 sessions over 8 weeks Normal BMI (n=18) Overweight (n=17) B. Control Normal BMI (n=15) Overweight: (n=13)	A vs. B Age: 31 vs. 31 Female: 65% vs. 67% EDSS: 1.65 vs. 1.54 MS	No significant interactions between weight status and fatigue or depression outcomes (p>0.05) Training groups improved significantly more than control groups, regardless of weight on fatigue, depression, aerobic capacity, and TUG

Author, Year Intervention Study Design Study Quality	Intervention	Population	Results
Yang, 2014[138] Aerobic Exercise RCT (Crossover) Fair	A. BWS (if needed) treadmill walking, 40 sessions over 8 weeks (n=10) B. Precision track walking training, 40 sessions over 8 weeks (n=10)	A vs. B Age: 48 vs. 44 Female: 30% vs. 30% Able to walk ≥5 meters with walking aid or braces: 100% SCI	A. Precision training: No significant improvements across groups B. Endurance training: 6MWT improved significantly only in those with baseline walking speed >0.5 m/s No changes in 10MWT (patient selected speed or fast speed) or Spinal Cord Injury–Functional Ambulation Profile

Abbreviations: 6MWT = 6-Minute Walk Test; 10MWT = 10-Meter Walk Test; AIS = ASIA Impairment Scale; ASIA = American Spinal Injury Association Impairment Scale; BMI = body mass index; BWS = body weight supported; CI = confidence interval; CP = cerebral palsy; EDSS = Expanded Disability Status Scale; GMFCS = Gross Motor Function Classification System; GMFM-88 = Gross Motor Function Measure 88; MMAS = Modified Modified Ashworth Scale; MS = multiple sclerosis; OR = odds ratio; RCT = randomized controlled trial; RRMS = relapsing-remitting multiple sclerosis; SCI = spinal cord injury; TUG = Timed Up and Go Test; VO2 max = maximal oxygen uptake

KQ3a: Patient Demographics

One included study conducted subgroup analyses on patient demographics (i.e., age).[168] Qualitative comparison of effects seen in these subgroups (age, sex, or race/ethnicity) may provide some insight into potential variation.

Age

One CP study[168] (n=45) compared the results of 12 weeks of hippotherapy on the Sitting Assessment Scale based on participant age and found that compared to a no hippotherapy control group, younger children aged 6 and 7 years had improved sitting scores, whereas there was no significant improvement on the Sitting Assessment Scale with hippotherapy among children age 8 through 12 years versus no hippotherapy.

Within populations, comparing similar interventions, there was either inadequate variation in age or heterogeneity in outcomes assessed to evaluate impact of age. For example, across seven studies of cycling exercises in participants with MS, mean age varied from 31 to 59 years (with two studies not clearly reporting age of participants), with the study of the youngest cohort evaluating TUG, fatigue, depression, and aerobic capacity,[53] and the study of the oldest cohort evaluating disability (using EDSS) and quality of life. Across 15 studies of mainly cycling or treadmill interventions in participants with SCI (that reported age and a prioritized outcome), there was not a wide variation in the age of enrolled participants, with a median of 43 years (range 33 to 56 years).[75,76,89,90,92,93,107-113,133-136,138-140] Studies of participants in their 30s predominately evaluated oxygen consumption outcomes, where studies of participants in their 50s more commonly evaluated walking tests. The 10MWT was the most commonly reported across these studies, with no apparent differences in findings for younger and older participants, in that improvements were not found.[111,133-136] Other intervention types had fewer studies, with no ability to evaluate the effect of age.

Across 22 studies of aerobic-type exercise in participants with CP, 13 included children (median age 9 years), 8 included adolescents (median age 16 years), and 1 included adults (median age 27 years).[73,74,85-88,99-102,105,121-128,131,132,218] Looking at studies of children versus teens, in very global terms, the findings are similar; three of six and four of nine studies reported

positive findings on walking tests, while one of three and one of four reported positive findings in gross motor function in children and adolescents (respectively). The measures reported are too varied to be compared with evaluate any potential differences in magnitude of effects. The single study of adults found improved walking speed on the 6MWT.[126] Other intervention types had fewer studies, with no ability to evaluate the effect of age.

Sex

As noted above, there were no studies that evaluated males and females as subgroups. In order to evaluate this factor across studies, it would be necessary to compare studies that enrolled largely males (e.g. >75%) with those that enrolled largely females where the other patient characteristics were similar and that studied similar interventions. While there is some variation across conditions in the proportions of females enrolled, we found no instance of studies that would be comparable based on sex alone.

Race/Ethnicity

Race and ethnicity were poorly reported in the included studies. For example, in the 22 studies of aerobic interventions in participants with CP, half did not report race or ethnicity, while in 17 studies of cycling or treadmill exercise interventions in participants with SCI, only one reported on the race of participants. While several studies were conducted in countries outside of the United States (e.g., Iran or China), they were also mostly unclear on the race or ethnicity of the participants enrolled. Because of this poor reporting, and lack of heterogeneous groups to compare, we were unable to evaluate any impact of race/ethnicity on the outcomes of the interventions.

KQ3b: Variations by Condition and Intervention

In evaluating the potential variation of effects of physical activity interventions across the three populations, we compared results where we had adequate data to conduct meta-analysis, where the comparison was some form of usual care, where there was more than one condition with the same outcome measure reported, and measures of balance (e.g., BBS) according to intervention category (aerobic, balance, strength).

Aerobic Interventions

One RCT in adults with CP[126] and four RCTs in participants with MS reported on the 6MWT for aerobic interventions.[54,66,77,79,80] None found a significant benefit and there was no clear difference according to population. Two studies each in participants with MS, SCI, and CP reported VO_2 peak. The results appeared to vary by population in these studies. Studies in patients with SCI (2 RCTs, MD –206 mL/min, 95% CI –359 to –53, I^2 51%),[92,140] and with CP (2 studies, MD of 6.5 to 7.0 ml/kg/min, both statistically significant but not combinable)[88,132] found a benefit with aerobic exercise. In contrast, participants with MS did not show a benefit (2 RCTs, MD 0.20 mL/min, 95% CI –127 to 127, I^2 0%).[77,78] No other outcomes were reported across the different populations.

Strength Interventions

The 6MWT was reported in one RCT of children with CP,[211,212] and in three RCTs of participants with MS.[52,198,202,203] None found a significant benefit and there were no clear

difference according to population. No other outcomes were reported across the different populations.

Balance Interventions

One RCT of participants with MS[143] and one in participants with SCI[189] reported no effect of the intervention on the 10MWT, and no clear difference according to population. The BBS score was reported in one RCT of participants with CP[50] and five RCTs in participants with MS.[141,143,144,158,159] All studies showed improved balance, with variation in the magnitude of benefit, and no clear difference according to population. Results for the TUG test varied by population; one RCT in participants with CP found no benefit,[50] four RCTs of participants with MS found no benefit but variation in the direction of the nonsignificant effects across studies,[143,144,175,185] and one RCT in participants with SCI found a small benefit (–1.30 seconds, 95% CI –2.16 to –0.44).[189] No other outcomes were reported across the different populations.

Multimodal Interventions

On the 6MWT, six of seven RCTs of participants with MS[192,193,197,221,222,226,228] and one of participants with SCI[247] showed improvements and no clear difference according to population. The seventh study of patients with MS did not find a significant improvement, after adjusting for baseline disability scores.[231] In contrast, on the 10MWT, four RCTs of participants with MS[222,223,225,228] did not find a benefit, while one RCT in participants with SCI found a benefit (–11.20 seconds, 95% CI –22.44 to –0.04).[247] The TUG test was not improved in either MS patients (3 RCTs)[225,228,231] or in SCI patients (1 RCT),[247] and there were no clear difference according to population. No other outcomes were reported across the different populations.

KQ4: Methodological Gaps

Key Points

- Conclusions that can be drawn from research on physical activity in patients with MS, CP, and SCI were limited by small sample sizes, inadequate descriptions of population characteristics and control group activities, incomplete data analysis, inadequate reporting of adverse events, and few RCTs rated good quality (low risk of bias). There were few studies in MS and CP that enrolled a more disabled population.
- A few large, well-conducted RCTs of longer duration would greatly strengthen the evidence base. Large, cohort studies could provided data on long-term health outcomes, as well as potential harms from the intervention

Detailed Synthesis

Methodological weakness not discussed in subquestions below included inadequate description of control groups, inadequate reporting of baseline data, inadequate reporting of harms or adverse events, and inadequate between group analysis. Gaps in the evidence included fewer studies in CP and SCI than in MS with less evidence available for MS in males, SCI in females, and CP in adults. The lack of harms data is also a research gap, as is the relative lack of studies in MS and CP that enrolled a more disabled population.

Although interventions received in the intervention groups were generally well described, in many cases participants in the control groups were described as maintaining their usual level of activity without comment on what that usual level of activity was (e.g., no physical activity at all, daily walk to the mailbox, balance exercises). The control group was also described as continuing their usual physiotherapy without comment on what that physiotherapy entailed (e.g., 2 hourly sessions of free weights, 3 sets of 12 reps biceps curls and triceps extensions plus walking on a treadmill at 1.5 miles per hour for 15 minutes plus leg lifts and abdominal crunches on mat). In order to minimize across-study heterogeneity, it is important to pool trials with not just similar interventions, but also similar control groups, which was challenging at times when control group participation was not well described.

Participant baseline data were also not always well presented. Most studies provided mean age and the proportion of males and females per study arms, but often data were lacking in characteristics that may predict a better or worse outcome. For example, studies often gave no indication of the level of impairment of participants per treatment arms. The EDSS was the characteristic most often provided to indicate degree of impairment. But many studies did not provide that information or the type of MS with which MS participants were diagnosed (e.g., RRMS, PPMS), the specific level of injury in patients with SCI, or the GMFCS and degree of spasticity in patients with CP. Baseline participant data was also often provided for only the participants who were analyzed rather than all patients randomized. Many studies also did not provide disease severity or use of assistive technology (including use of wheelchairs) and did not control for these factors, although some trials did limit eligibility to patients with a range of disease severity.

Another methodological weakness was how data were analyzed in trials. Many studies did not fully take baseline data into account when comparing the performance between intervention and control groups. In some cases, the intervention group improved significantly from baseline whereas the control group had not. This was given as evidence of the superiority of the intervention. Another data analysis method that can yield misleading results occurred when studies compared baseline data and found no difference between groups and then measured postintervention data and found a statistically significant difference between groups favoring the intervention. Neither of these methods considered the difference between the *changes* in outcome measure before and after the intervention which can lead to faulty conclusions.

Another weakness, which is also a gap, is the lack of information on harms of the intervention. Many trials did not report any harms or adverse events and did not report that there were no harms or adverse events. In this case, it is impossible to determine whether adverse events occurred but were not reported in the publication, whether adverse events occurred but were not captured by the researchers, or whether no adverse events occurred. In trials designed to demonstrate that a treatment is effective, harms are often not adequately addressed but all trials should have an adequate means to document harms and adverse events experienced by study participants and report all of them in publications.

Another research gap is the limited information in certain populations based on the lower prevalence of disease (i.e., MS in males, SCI in females). Evidence in CP is largely limited to trials of children. Expanding the sample size would assist in capturing a broader range of individuals and provide information to fill in research gaps.

KQ4a: Types of Studies

Out of the 168 included studies in this review, 44 percent enrolled participants with MS, 38 percent were conducted in participants with CP, and 18 percent were in participants with SCI. Most of these studies were RCTs (n=146, 87%), a few were quasiexperimental trials where participants were not randomized into groups (n=15, 9%), and the remainder were cohort studies with at least two groups of participants (n=7, 4%). Most studies were rated fair quality, however most of the nonrandomized studies (quasiexperimental and cohort studies) were rated poor quality (n=12, 55%) and were primarily conducted in participants with CP (n=11, 50%).

KQ4b: Weaknesses in Study Design

Within the included studies, multiple weakness in study design were identified. These involved sample size, study duration, and inclusion/exclusion criteria.

One weakness in study design concerned small sample sizes. Sample size cutoffs for eligibility in this review were at least n=20 in CP and SCI and n=30 in MS. These sample sizes are actually rather small and reflect the difficulty in recruiting large numbers of participants. This could be due to the prevalence of the diseases included (i.e., MS, CP, and SCI), potentially reduced mobility of the patient sample, other patient comorbidities, and/or logistical difficulties that may make participation in research less likely. Small sample sizes (vs. larger sample sizes) increase the difficulty in demonstrating a treatment effect as it is harder to achieve statistical significance with fewer numbers. Small sample sizes also increase the likelihood that even a RCT will have differences in prognostic factors between treatment and control groups that may render findings unreliable. In this review, only a few studies enrolled more than 100 participants.

An additional study design weakness regarded study duration. Most studies were terminated immediately postintervention, which ran typically 12 or 16 weeks. Without longitudinal followup, it is impossible to determine if the intervention is associated with prevention of detrimental clinical health outcomes (e.g., stroke or development of diabetes). To determine a treatment effect, some studies included intermediate health outcomes such as heart rate, blood pressure, and blood glucose. Extrapolation from these intermediate outcomes to long-term health benefit is not ideal. Also, since most studies excluded individuals with known cardiovascular or metabolic disease, it is impossible to comment on the benefit of the intervention regarding secondary prevention (e.g., preventing a second heart attack) or tertiary prevention (e.g., reducing angina or heart failure symptoms).

KQ4c: Future Research

An ideal study would be a RCT that includes a no treatment arm, such as waitlist control or attention control group. This would provide the information needed to determine if the intervention worked or not in the included patient population. Including a usual care arm as a comparator would provide additional information but only if what usual care entails is adequately described. The intervention(s) should use standard methods, when possible, that also need to be well described, either in the publication or in a cited or included protocol. In order to

maintain the statistical power needed to demonstrate a difference between groups, the number of intervention groups would be limited to that supported by the sample size.

An ideal study would also be large enough to permit subgroup analyses. For example, a study that enrolled sufficient males and females would be able to demonstrate if there is a difference in treatment effect that could be attributed to gender. A trial that enrolled individuals with varying degrees of disability could suggest whether the intervention has a greater effect in those with greater versus lesser impairment. A trial that enrolled participants across a spectrum of ages could comment on the impact of age on the treatment effect. A large study (RCT or cohort study) would also be more likely to retain sufficient numbers of participants to facilitate a longitudinal analysis. This would enable the investigation of clinical outcomes that take time to develop (e.g., coronary artery disease) as well as potential harms of the intervention.

An ideal study would have a prespecified and consistent method for identifying harms and adverse events experienced during the study. Any data collection forms should be available for review. Assessors should be blinded. The number of study participants who experienced a specific adverse event should be provided for each study group, not just the number of total adverse events, as any participant may have multiple or repeated adverse events. All adverse events should be specified, not just those experienced by more than 5 or 10 percent—the death of only one participant could be due to the intervention and is important to report, even if fewer than 5 percent died.

An ideal study would also receive a good-quality rating or demonstrate low risk of bias. Studies with low risk of bias tend to generate conservative estimates of effect compared with studies rated medium or high risk of bias (fair or poor quality). Requirements for low risk of bias include appropriate methods of randomization (e.g., computer generated random numbers) and concealment of the allocation (e.g., centrally managed), and successful randomization, that is, baseline characteristics of participants, especially those known to be prognostic factors (e.g., participant BMI on the development of diabetes). Other criteria for low risk of bias (high quality) include blinding of all involved when possible, especially blinding of outcome assessors, analyzing all participants in the groups to which they were randomized with minimum attrition, and no or minimal difference in attrition between groups. Two or more larger, well-conducted RCTs typically generate more reliable and stable estimates of effect than would a greater number of smaller studies rated fair or poor quality.

Discussion

Key Findings and Strength of Evidence

We included 168 studies (n=7,511), of which 146 were randomized controlled trials (RCTs). Key findings and strength of evidence are summarized in Table 49. Overall strength of evidence grades and detailed domain assessments appear in Appendix H.

The average sample size was 45 (range 20 to 242), with only 3 studies with samples sizes of 100 or more. Most studies were rated moderate risk of bias. The bulk of the evidence was in participants with multiple sclerosis (MS). In participants with MS, walking ability may be improved with treadmill training and multimodal exercise regimens that include strength training; function may be improved with treadmill training, balance exercises, and motion gaming; balance is likely improved with postural control exercises (that may also reduce risk of falls) and may be improved with aquatic exercises, robot-assisted gait training (RAGT), treadmill training, motion gaming, and multimodal exercises; activities of daily living (ADL) may be improved with aquatic therapy; sleep may be improved with aerobic exercises; female sexual function may be improved with aquatic exercise; and cardiovascular fitness (VO_2 peak) may be improved with multimodal exercises. In participants with cerebral palsy (CP), balance may be improved with hippotherapy and motion gaming and function may be improved with cycling, hippotherapy, and treadmill training. In participants with spinal cord injury (SCI), evidence suggests that ADL may be improved with RAGT. When RCTs were pooled across types of exercise, physical activity interventions were found to improve walking in MS, to likely improve balance and depression in MS, and may improve aerobic fitness and function in participants with CP or with SCI. When populations were combined, dance may improve function in participants with MS and CP. The majority of this evidence is low strength. Evidence on long-term health outcomes was not found. For intermediate outcomes such as blood pressure, lipid profile, and blood glucose, there was insufficient evidence from which to draw conclusions. There was inadequate reporting of adverse events in many trials. However, physical activity was associated with low-strength evidence of increased autonomic dysreflexia episodes in SCI.

Table 49. Effects of physical activity interventions compared with usual care[a]

Intervention Category Intervention	Multiple Sclerosis Studies Strength of Evidence[b] (Direction of Finding)	Cerebral Palsy Studies Strength of Evidence[b] (Direction of Finding)	Spinal Cord Injury Studies Strength of Evidence[b] (Direction of Finding)
Aerobic Exercise **Dance (1 RCT in MS and 1 RCT in CP)[a]**	Low (function improvement)	Low (function improvement)	Insufficient
Aerobic Exercise **Aerobics**	Low (sleep improvement)	Insufficient	Insufficient
Aerobic Exercise **Aquatics**	Low (balance, ADL improvement, female sexual function)	Insufficient	Insufficient
Aerobic Exercise **Cycling**	Low (no clear benefit on walking)	Low (function improvement)	Insufficient

Intervention Category Intervention	Multiple Sclerosis Studies Strength of Evidence[b] (Direction of Finding)	Cerebral Palsy Studies Strength of Evidence[b] (Direction of Finding)	Spinal Cord Injury Studies Strength of Evidence[b] (Direction of Finding)
Aerobic Exercise Robot-Assisted Gait Training	Low (balance improvement) Low (no clear benefit in function)	Insufficient	Low (ADL improvement) Low (no clear benefit on walking, function)
Aerobic Exercise Treadmill	Low (walking, function, and balance improvement)	Low (function improvement)	Insufficient
Postural Control Balance Exercises	Moderate (balance improvement)	Insufficient	Insufficient
Postural Control Balance Exercises	Low (fall risk improvement)	Insufficient	Insufficient
Postural Control Balance Exercises	Low (function improvement)	Insufficient	Insufficient
Postural Control Hippotherapy	Insufficient	Low (balance and function improvement)	Insufficient
Postural Control Tai Chi	Insufficient	Insufficient	Insufficient
Postural Control Motion Gaming	Low (function, balance improvement)	Low (balance improvement)	Insufficient
Postural Control Whole Body Vibration	Insufficient	Insufficient	Insufficient
Postural Control Yoga	Low (no clear benefit on function)	Insufficient	Insufficient
Strength Interventions Muscle Strength Exercise	Low (no clear benefit in walking, function, balance, quality of life, spasticity)	Low (no clear benefit in walking and function)	Insufficient
Multimodal Exercise Progressive Resistance or Strength Exercise Plus Aerobic or Balance	Low (walking, balance, VO_2 improvement)	Low (no clear benefit in function, quality of life)	Insufficient

Intervention Category Intervention	Multiple Sclerosis Studies Strength of Evidence[b] (Direction of Finding)	Cerebral Palsy Studies Strength of Evidence[b] (Direction of Finding)	Spinal Cord Injury Studies Strength of Evidence[b] (Direction of Finding)
All Types of Exercise	High (walking improvement)	Low (function)	Low (function)
	Moderate (balance, depression improvement, no clear benefit on function)	Low (VO_2 improvement)	Low (VO_2 improvement, increased episodes of autonomic dysreflexia[c], no clear benefit on depression)

Abbreviations: ADL = activities of daily living; CP = cerebral palsy; MS = multiple sclerosis; RCT = randomized controlled trial
[a] Strength of evidence color shading: blue=high strength of evidence, green=moderate, yellow=low, white=insufficient
[b] Strength of evidence based on combining the two populations, multiple sclerosis and cerebral palsy

[c] Whole-body exercise versus exercise limited to upper body

Findings in Relationship to What Is Already Known

The 2018 Physical Activity Guideline Advisory Committee Scientific Report[268] found strong evidence that within the general population, sedentariness is linked to increased risk of all-cause mortality and cardiovascular mortality, in a dose-response fashion. Additionally, there was strong evidence of an association between sedentary behavior and increased risk of developing type 2 diabetes and cardiovascular disease. The committee also found moderate evidence that moderate to vigorous exercise of any duration was associated with health benefits, such as improved blood pressure and lipid profile.

Unfortunately, we identified no evidence in people with MS, CP, and SCI concerning risk of mortality, the development of diabetes, or the development of cardiovascular disease in relation to physical exercise as defined in this review. The evidence for improvement in intermediate outcomes was limited to low-strength evidence for improvement in VO_2 peak with exercise in participants with CP and SCI. Evidence for other intermediate health outcomes such as blood pressure and lipid profile was too sparse to draw conclusions.

We were also not able to draw general conclusions regarding potential harms of physical exercise; all trials were designed to assess benefits and only one trial in participants with SCI appeared to systematically monitor participants for adverse events, recording over 700 adverse events.[245] This trial demonstrated the need for cardiovascular monitoring during aerobic exercise, especially in people with SCI, as out of 33 episodes of autonomic dysreflexia, three were considered serious. While a 2014 systematic review[269] of adverse events in cardiovascular-related training programs in SCI (n=38 studies) reported no serious episodes of autonomic dysreflexia, this review found functional electrical stimulation ambulation associated with a 4 percent fracture rate, although there were few adverse events reported in studies of volitional exercise in SCI.

A 2014 systematic review[270] examined the safety of exercise training in MS (n=26 studies) and found no increased risk for relapse between exercise and control groups (4.6% vs. 6.3%) or the risk of experiencing any adverse event (2.0% vs. 1.2%).

We identified no systematic reviews of safety in people with CP.

Multiple Sclerosis

A 2013 systematic review was conducted to inform guideline development on the effects of exercise on fitness, mobility, fatigue, and health-related quality of life in adults with MS.[271] This review included 54 studies published before December 2011 and found that in people with mild to moderate MS, physical exercise improved aerobic capacity and muscle strength. The authors also concluded that exercise may improve mobility and health-related quality of life. These findings are largely consistent with our review, which determined that physical exercise improved walking ability, balance, and depression in participants with MS, although support for improvement in health-related quality of life and aerobic fitness was limited. The evidence for strength was mixed but the sole good-quality trial found a strength benefit in participants with MS.

A 2017 systematic review of 18 studies (n=290) that enrolled participants with MS and severe mobility disability (e.g., Expanded Disability Status EDSS score ≥6) concluded that limited evidence suggests conventional resistance exercise and adapted exercise training may improve physical fitness and function in this population.[272] The authors also note that adapted exercise may not be feasible due to cost and accessibility.

Cerebral Palsy

2016 guidelines from The Netherlands were based on a systematic review that included five RCTs to determine physical activity recommendations for people with CP.[46] The included interventions consisted of cardiorespiratory endurance training, which was compared with no intervention. Some of the included trials indicated improved aerobic capacity after training and some showed improved strength. These results are similar to this review, which found evidence for improved aerobic fitness with exercise, although the evidence for strength outcomes was mixed. The current review also found evidence for improved balance and function with physical activity that was not identified in the Dutch review.

Spinal Cord Injury

A 2017 systematic review[273] conducted as the foundation for exercise guidelines for people with SCI included 211 studies, 189 studies in chronic SCI. Search dates were between 1980 and 2016 and included RCTs, non-RCTs, pre-post series, case series, and cross-sectional cohort studies (in chronic SCI most were pre-post studies, 16 RCTs). The review concluded that upper body aerobic exercise at moderate to vigorous intensity plus upper body strength exercises can improve cardiorespiratory fitness, power, strength, and body composition in participants with SCI. The current review has similar conclusions for improved aerobic fitness with physical exercise and improved walking and function with RAGT, but there was insufficient evidence from trials meeting inclusion criteria for improved body composition with physical exercises in participants with SCI.

This current systematic review has stricter criteria for study inclusion than other systematic reviews. For example, case series and single-arm pre-post studies were not included. Additionally, the physical exercise intervention had to include at least 10 sessions on 10 different days and the activity had to be observed by a researcher or healthcare provider. Sample sizes also had to be met (n=20 in CP and SCI, n=30 in MS). These stricter criteria alone may explain any differences between previous systematic reviews and this review. The current review was also limited to studies published in 2008 and beyond; the other reviews included studies published in

the 1980s and 1990s, which may not have the methodological rigor as trials conducted more recently.

Applicability and Generalizability

Due to the strict criteria for trial inclusion in this review and because participants in trials received extra attention, training, and supervision and may have been healthier and more mobile than individuals not participating in trials, applicability to individual patients with MS, CP, and SCI and generalizability to other populations may be reduced.

Factors that could impact the applicability of our findings include the trial setting. Some trials were conducted in a rehabilitation facility, a special school, university, hospital or other location, but often the setting was not specified. Additionally, the cost of equipment may limit the ability of patients to participate in some types of exercise evaluated in clinical trials. For example, a treadmill with body weight support or the robotic equipment needed to engage in RAGT may be cost prohibitive for many patients, making these interventions less applicable to patients seen in primary care.

Another factor concerns the selection of participants. Patients were often excluded from trials if they had known cardiovascular disease, metabolic disease, or mental illness. Children with CP were typically excluded for recent surgery, an uncontrolled seizure disorder, contractures or significant spasticity in addition to a lack of other major medical or cognitive problems. This could reduce applicability to primary care patients who may have a medical, psychological, or cognitive issue not represented in clinical trials. Most studies enrolled participants with less disability, rather than the full spectrum of ability, although across studies the distribution of ability was wide. Additionally, this review included patients with MS, CP, or SCI and the findings may not be as applicable to primary care patients with a different disease or condition, although disabilities may be similar across conditions (e.g., Parkinson's disease with MS, severe arthritis with SCI) that would increase applicability.

Exercise dose may also influence applicability. We required a minimum of 10 exercise sessions on 10 different days of any intensity, for any duration, and over any period of time for a trial to be eligible for inclusion. No trials included identical training arms where only the duration of the exercise session or the period of time over which the exercise occurred varied. Four trials in this review varied intensity of exercise (two in MS, two in CP). In MS, downhill treadmill training was associated with significantly better results on mobility and function than uphill treadmill training,[119] but there was no difference on mobility or balance with whole body vibration (WBV) versus whole body light vibration.[185] In CP, there was no difference on function between RAGT with resistance compared with RAGT with assistance[100] but improved sitting scores with 24 hippotherapy sessions over 12 weeks compared with 12 sessions.[168] A 2019 systematic review[274] of trials that enrolled participants with CP found that improvement in Gross Motor Function Measure scores was positively related to the number of hours trained daily. Additionally, this report focused on supervised exercise training and excluded all leisure-time and lifestyle physical activity interventions, which may have greater and more sustained short- as well as long-term health effects.

Limitations of the Evidence Base

Interventions tended to vary by population. For example, most hippotherapy trials were conducted in participants with CP, whereas most trials with a strength component were in participants with MS, while RAGT trials were well dispersed across the three included

populations. However, there were few trials or no trials of several interventions conducted in participants with SCI, limiting the ability to draw firm conclusions on benefits of these particular training modalities. Even when trials of various interventions were pooled in meta-analyses, few trials were conducted in an SCI population, resulting in insufficient evidence for several outcomes. For some of the interventions, there was also little evidence in participants with CP.

Another limitation is the rather large proportion of included studies that were rated poor quality (25%). This rating was given because of serious methodological limitations in trials such as high attrition or lack of similarity of patient characteristics between groups at baseline, which could jeopardize the reliability of the findings. Additionally, it is often impossible to blind participants to exercise category, particularly if they are in the no exercise, attention control, or a waitlist control group. We conducted sensitivity analyses excluding poor-quality trials to determine if pooled results depended on the inclusion of poor-quality studies and reported both results. Additionally, studies were usually less than 6 months in duration, which did not permit assessment of clinical health outcomes that take time to develop, such as coronary artery disease. Few studies conducted subgroup analysis, which was often not possible because sample sizes of trials were so small, often less than 40 participants. Although some studies reported the physical activity to be low, moderate, or high intensity, most studies did not include a description of involved effort and studies often did not include a measure of intensity of the intervention (e.g., perceived effort or degree of energy expenditure) making it impossible to compare studies based on intensity, or describe the activities the control group experienced, making it difficult to determine which studies could be pooled in a meta-analysis. Many studies did not report harms or did not report that there were no harms or adverse events. Without adequate assessment and reporting of adverse events, the potential harms of a particular physical exercise regime are unknown. See Key Question 4 results for additional information on weakness and gaps in the evidence base. Additionally, many studies did not include a usual care or no treatment arm. Without a usual care comparator, it is difficult to be certain if a particular intervention is effective, even if postintervention assessment values are statistically improved from baseline values. It could be that just being in a study results in improvement unrelated to the intervention. Most of the RAGT studies in CP and SCI included in this review did not have a usual care arm, limiting the ability to draw conclusions regarding RAGT effectiveness in these populations. Below is a discussion of the limitations stratified by the effort needed to overcome major limitations of the evidence base.

Addressing Limitations: Minimal Effort

Studies often did not describe the activities the control group experienced, making it difficult to determine which studies could be pooled in a meta-analysis. In studies that did not use a waitlist control or a no-treatment control (including no usual care physical activities), it is important to specify the nature of the control intervention. This includes number of sessions, length of sessions, and specifics of physical activities involved, rather than just stating "usual care," "routine physiotherapy," or "conventional rehabilitation," since what is usual care in one medical center, geographic area, or country may be very different from another.

Studies often did not report harms or did not report that there were no harms or adverse events. Without adequate assessment and reporting of adverse events, the potential harms of a particular physical exercise regime are unknown. Studies should report that "adverse events were not assessed" or indicate how adverse events and harms were systematically identified (e.g., by

questionnaire, by standardized interview) and provide documentation of any questionnaire or list of interview questions used.

Another limitation is the rather large proportion of included studies that were rated poor quality. Straightforward ways to improve study quality ratings are to report the specifics of randomization (e.g., random numbers table, cite randomization website used) and to report how the allocation was concealed (e.g., opaque, sealed, sequentially-numbered envelopes; central, Web-based reporting of allocation). Reporting who was blinded in the study is also an important aspect of trial design that should be mentioned (and blinding those who can be blinded, especially the outcome assessor, improves the reliability of the results).

These are simple additions to reporting how a given trial was actually conducted and require little or no additional work.

Addressing Limitations: Moderate to Large Effort

Not all the elements assessed in quality rating a trial are as easy to improve upon. Studies rated poor quality usually have other flaws in addition to inadequate reporting of study methodology. Serious methodological limitations in trials such as high attrition and/or lack of similarity of patient characteristics between groups at baseline could also jeopardize the reliability of the findings.

To reduce baseline differences in patient characteristics between treatment groups in trials with small sample sizes, the technique of minimization can decrease the risk of bias that happens when the two groups being compared are dissimilar on prognostic participant characteristics such as age, gender, or comorbidities. Low quality ratings due to large or unequal attrition between groups is more difficult to remedy without anticipating why participants are likely to leave the study.

Addressing Limitations: Large Effort

Small sample size is perhaps the most difficult limitation to overcome and this has no easy remedy given the populations we have included in this review. The cost of conducting studies with larger sample sizes are generally higher and larger studies may be more time-consuming to complete, especially if study enrollment is slow. Crossover studies reduce the required sample size needed to demonstrate a treatment effect, but are associated with their own potential bias due to potentially inadequate washout from the previous treatment(s). Several smaller studies can be pooled to demonstrate a treatment effect, but require standardized methodology across trials.

Another technique to increase sample size would be to broaden the definition of the study population. For example, the population could be wheelchair users without mobility due to lower limb dysfunction. This could include participants with limb paralysis, weakness, or absence, broadening the population to individuals with MS, CP, SCI, as well as stroke, amputation, amyotrophic lateral sclerosis, and others. In addition to reporting overall findings, results could be stratified by condition or by category of condition (e.g., MS or neurological disease) or some other method of grouping populations that would be meaningful.

Implications for Clinical and Policy Decision Making

This review has implications for clinical and policy decision making for patients using a wheelchair or patients who may potentially benefit from using a wheelchair in the future. This review provides evidence for the necessity of implementing physical activity programs for

people with disability and/or chronic conditions. Not only is physical activity in general associated with improved physical function, but it is also associated with improved mental health as well. This review also provides limited evidence that physical activity may help prevent negative consequences of sustained sedentariness, such as increased spasticity. Physical activity should be a prescribed element in overall healthcare for those with disabilities and not just an afterthought. Findings of this review are consistent with previous reviews and support current guidelines that advise regular exercise in people with MS, CP, and SCI. Exercise interventions that are strength focused should include aerobic elements (and balance exercises as needed). Exercise interventions that consist primarily of cycling should include strength and/or balance exercises as well for optimum improvement in function. In general, evidence supports physical exercise to improve walking ability, function, balance, depression, strength, and aerobic fitness.

Implications for All Providers

It is important for providers to understand the barriers to physical exercise for their patients. This may include lack of accessibility,[275,276] lack of time,[275,277-279] lack of enjoyment with prescribed exercise,[275,279] and lack of adequate social support.[275,278,280,281] Other potential barriers to exercise include lack of transportation,[276,279,281] lack of awareness of the relationship between exercise and health,[277,279] and high cost.[276,277,281] All providers should address these and any other potential barriers that may exist with their patients when prescribing physical activity. Motivational interviewing may be helpful.[282-284] Providers need to take the individual patient into account. The exercise modality with the greatest evidence for benefit in MS may not be the best choice for their particular patient with MS.

Implications for Primary Care Providers with MS, CP, and SCI Patients

Broadly speaking, in patients with MS, CP, and SCI, moving the body in an effort to improve cardiovascular fitness is desired. In patients with SCI, consideration should be given to monitoring the patient's cardiovascular and thermodynamic response to ensure a particular cardiovascular activity at a specific intensity is safe for the patient, so as to avoid serious episodes of autonomic dysreflexia, which may be life threatening. We found benefits in all three included populations with aerobic exercise.

Strength exercises should also be an included part of any exercise routine for patients with MS, CP, and SCI. Although this review found support for improved walking with combined strength and aerobic exercises in study participants with MS but insufficient evidence for benefit in CP and SCI, a 2019 systematic review[285] found improved function (Gross Motor Function Measure [GMFM] scores) in children with CP. Cardiovascular fitness and muscle strength may be improved with aerobic and resistance training, based on a 2019 systematic review of systematic reviews in people with SCI.

Balance exercises may also prove beneficial additions to a physical exercise program for people with MS, CP, and SCI. This review found that balance training may improve balance, function, and/or quality of life in MS and CP. While the evidence was too sparse to draw a conclusion regarding balance training in SCI, a 2019 RCT[248] that enrolled people with chronic SCI reported improved balance with a combination of aerobic, strength, and core stability training.

Implications for Primary Care Providers With Patients With Disabilities Other than MS, CP, or SCI

Although we limited this review to evidence in MS, CP, and SCI, other medical illnesses and injuries may respond similarly to physical activity as our included populations. For instance, patients with Parkinson's disease or Lyme disease may have similar issues and challenges as patients with MS. Patients with intellectual disability and motor impairment due to other neurological disease or inborn errors of metabolism may face similar challenges as patients with CP. And patients with stroke, arthritis, or the wheelchair-using elderly may have issues and challenges similar to those with SCI. As long as physical exercise can be performed safely, aerobic, strength, and balance training may benefit these populations as well.

Several systematic reviews of the effects of physical exercise on the health of people with other conditions have found benefits to exercise. For example, a 2016 review[286] found gait performance improved with gait and strength training in people with lower limb amputation using a prosthesis. A 2019 systematic review[287] found that home-based exercise improved balance and gait speed in people with Parkinson's disease and that the improvement was similar to that seen in center-based exercise. A 2019 systematic review[288] in stroke patients reported improved walking speed and endurance with a combination of aerobic and strength exercises. A 2015 systematic[289] review of elderly patients reported a large effect of Pilates in improving muscle strength, walking, ADL, and quality of life. A 2015 systematic review[290] found improved depression scores with exercise in adult patients with arthritis.

Similar to able-bodied people, physical exercise has the potential to benefit those with various disabilities.

Implications for Physical Activity During a Pandemic

Life during a pandemic may present unique challenges to those with mobility constraints. Quarantined individuals may be less likely to exercise and frailty may increase without regular physical activity. A rapid review concerning those who are now housebound due to COVID-19 concluded that people should continue to engage in strength, resistance, and balance training, that adding a social element may help with motivation and decrease mental distress, and that technology that supports physical activity such as use of the internet or video games may be helpful.[291] The Multiple Sclerosis Association of America has a Webinar on dealing with the COVID-19 pandemic and recommends continuing to keep physically active.[292] An article in Frontiers in Neurology recommends accelerating the use of telemedicine to care for patients with CP during a pandemic indicating that telemedicine can enable healthcare personnel to manage medication and provide exercises for the patient in a home environment.[293] A Department of Veterans Affairs tip sheet for veterans with SCI recommends continuing to care for oneself and move the body during the pandemic.[294] There are several online resources that patients with MS, CP, SCI, and other conditions may find useful to modify or jumpstart an exercise routine. One such website provides a chair-based 10-minute workout for those whose exercise routines have been upended by COVID-19.[295] Results from this report can also inform efforts to maintain physical activity during the COVID-19 pandemic. Exercise activities that can be done at home and were found to have benefits include dance, stationary cycling, treadmill, motion gaming and multimodal progressive training activities for children with CP and adults with MS. Balance exercises can be done at home, and were found beneficial for patients with MS. Combining the evidence on all aerobic activities, many of which can be done at home, showed beneficial results

for patients with CP, MS, or SCI. Even though keeping physically active may be more of a challenge during a pandemic, it is important to continue to do so.

Limitations of the Systematic Review Process

We excluded non-English language articles and studies published only as abstracts. Additionally we did not check for publication bias due to insufficient number of trials available for most meta-analyses and the heterogeneity in physical exercise interventions, comparisons groups, and patient populations evaluated in trials. Statistical heterogeneity was present in a number of meta-analyses. We used a random effects model and conducted stratified analysis based on the intervention. Due to scope limitations, we did not include leisure-time physical activity or physical activity conducted outside of the research study, which is the bulk of physical activity in all populations; it is also difficult to compare the results between different leisure-time physical activities without well-defined physical activity parameters that exists in trials.

Research Recommendations

Larger, well-conducted RCTs are needed in patients with MS, CP, and SCI to address evidence gaps and to confirm current findings. Large, controlled cohort studies could also provide data on long-term outcomes and harms of the intervention. Larger sample sizes would enable subgroup analyses based on patient characteristics and comorbidities. Longer duration studies would enable identification of interventions that demonstrate reduced cardiovascular and metabolic adverse events and improved mortality, fitness, function, and quality of life over the long term. Studies providing data on the intensity of physical activity are needed. Studies that enroll participants with high degrees of disability are also needed. Studies, if possible, should have a control arm that receives no treatment, such as a waitlist control, to demonstrate that a particular intervention is effective when compared with no treatment.

Conclusion

Physical activity was associated with improvements in walking ability, general function, balance (including fall risk), depression, sleep, activities of daily living, female sexual function, and aerobic capacity, depending on population enrolled and type of exercise utilized. No studies reported long-term cardiovascular or metabolic disease health outcomes. Future trials could alter these findings, and further research is needed to examine health outcomes and to understand the magnitude and clinical importance of benefits seen in intermediate outcomes.

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Abbreviations and Acronyms

Abbreviation	Definition
1MWT	1-Minute Walk Test
2MWT	2-Minute Walk Test
6MWT	6-Minute Walk Test
10MWT	10-Meter Walk Test
25FWT	25-Foot Walk Test
ABCS	Activities-specific Balance Confidence Scale
AC	attention control
ADL	Activities of Daily Living
AE	adverse event
AHRQ	Agency for Healthcare Research and Quality
AIS	Asia Impairment Scale
ANCOVA	analysis of covariance
ARAT	Action Research Arm tests
ASIA	American Spinal Injury Association Impairment Scale
ASIA-LEMS	American Spinal Injuries Association Impairment Scale - Lower Extremity Motor Score
ASIA-UEMS	American Spinal Injuries Association Impairment Scale - Upper Extremity Motor Score
BBS	Berg Balance Scale
BDI	Beck Depression Inventory
BDI-FS	Beck Depression Inventory-Fast Screen
BMD	bone mineral density
BMI	body mass index
BWS	body weight supported
CES-D	Center for Epidemiologic Studies Depression Scale
CHART	Craig Handicap and Assessment Reporting Technique
CI	confidence interval
CIS	Clinically Isolated Syndrome
CoDuSe	core stability, dual tasking, sensory strategies
CP	cerebral palsy
CPMS	chronic progressive multiple sclerosis
CPQoL	Cerebral Palsy Quality of Life scale
CV	Cardiovascular
CVD	cardiovascular disease
DBP	diastolic blood pressure
DGI	Dynamic Gait Index
EDSS	Expanded Disability Status Scale
EPC	Evidence-based Practice Center
EQ-5D	EuroQOL-5 Dimension Questionnaire
FABS	Fullerton Advanced Balance Scale
FAC	functional ambulation category

Abbreviation	Definition
FAP	Functional Ambulation Profile
FER	forced expiratory ratio
FES	functional electrical stimulation
FEV1	forced expiratory volume
FIM	Functional Independence Measure
FPRE	functional progressive resistance exercise
FVC	forced vital capacity
GMFCS	Gross Motor Function Classification System
GMFM	Gross Motor Function Measure
GMFM-66	Gross Motor Function Measure 66
GMFM-66-D	Gross Motor Function Measure 66 (standing)
GMFM-66-E	Gross Motor Function Measure 66 (walking, running, jumping)
GMFM-88	Gross Motor Function Measure 88
GMFM-88-D	Gross Motor Function Measure 88 (standing)
GMFM-88-E	Gross Motor Function Measure 88 (walking, running, jumping)
GNDS	Guy's Neurological Disability Scale
HADS	Hospital Anxiety and Depression Scale
HAQUAMS	Hamburg Quality of Life Questionnaire in Multiple Sclerosis questionnaire
HbA1c	Hemoglobin A1c
HiMAT	High-level Mobility Assessment Tool
HOMA	homeostatic model assessment
HR	heart rate
HRSD	Hamilton Rating Scale for Depression
ICF	International Classification of Functioning
IDS16-SR	16-item version of Inventory of Depressive Symptomatology Self-Rated
IPA	Impact on Participation and Autonomy
IQR	interquartile range
KQ	Key Question
LEMS	Lower Extremity Motor Score
LMN	lower motor neuron
MACS	manual ability classification system
MAS	Modified Ashworth Scale
MD	mean difference
MDI	Major Depression Inventory
MiniBEST	Mini Balance Evaluation System Test
MMAS	Modified Modified Ashworth Scale
MMT	Maximal Muscle Testing combined upper and lower limb strength
MQLIM	Multicultural Quality of Life Index
MS	multiple sclerosis
MSFC	multiple sclerosis functional composite
MSIS-29	Multiple Sclerosis Impact Scale-29
MSIS-88	Multiple Sclerosis Impact Scale-88

Abbreviation	Definition
MSQOL	Multiple Sclerosis Quality of Life
MSWS-12	Multiple Sclerosis Walking Scale-12
MusiQoL	Multiple Sclerosis International Quality of Life questionnaire
NIH	National Institutes of Health
NR	not reported
NRS	numeric rating scale
NS	not significant
PA	previous activity
PANAS	Positive and Negative Affect Schedule
PBS	Pediatric Balance Scale
PDDS	Patient Determined Disease Steps
PEDI	Pediatric Evaluation Disability Inventory
PEF	peak expiratory flow
PHQ-9	Patient Health Questionnaire-9
PICOTS	Population, Intervention, Comparator, Outcome, Timing, Setting
PL	profile likelihood
PODCI	Pediatric Outcomes Data Collection Instrument
PPMS	primary progressive multiple sclerosis
PRE	progressive resistance exercise
PT	physical therapy
QLS	Questionnaire of Life Satisfaction
QOL	quality of life
RAGT	robot-assisted gait training
RCT	randomized controlled trial
RRMS	relapsing-remitting multiple sclerosis
rTMS	transcranial magnetic stimulation
SAWS	Satisfaction with Abilities and Well-Being Scale
SBP	systolic blood pressure
SCI	spinal cord injury
SCIM	Spinal Cord Independence Measure
SCiM3-M	Spinal Cord Independence Measurement III mobility section
SD	standard deviation
SE	standard error
SF-12	Short Form (12) Health Survey
SF-36 MCS	Short-Form 36 Mental Component Score
SF-36 PCS	Short-Form 36 Physical Component Score
SIQR	semi-interquartile range
SOE	strength of evidence
SPMS	secondary progressive multiple sclerosis
SSST	Six Spot Step Test
STATA	Software for Statistics and Data Science

Abbreviation	Definition
TBS	Tinetti Balance Scale
tDCS	transcranial direct current stimulation
TEP	Technical Expert Panel
TG	triglyceride
TOP	task-oriented physical therapy
TOO	Task Order Officer
TUG	Timed Up and Go Test
UEMS	Upper Extremity Motor Score
UMN	upper motor neuron
VAS	visual analog scale
VO_2 max	maximal oxygen uptake
VO_2 peak	highest value of VO_2 attained upon an incremental or other high-intensity exercise test
VR	virtual reality
WBV	whole body vibration
WeeFIM	Wee-Functional Independence Measure for children
WHOQOL	World Health Organization Quality of Life
WISCI	Walking Index for Spinal Cord Injury

Appendixes

Appendix A. Literature Search Strategies

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to November 3, 2020

Search: RCTs and controlled observational studies

1. Spinal Cord Injuries/
2. ("spinal cord injury" or "SCI" or (spin* adj2 injur*)).ti,ab.
3. exp Multiple Sclerosis/
4. "multiple sclerosis".ti,ab.
5. Cerebral Palsy/
6. "cerebral palsy".ti,ab.
7. Disabled Persons/
8. Paraplegia/ or Quadriplegia/
9. (wheelchair or quadripleg* or parapleg* or tetrapleg*).ti,ab.
10. or/1-9
11. exp Exercise/
12. exp Exercise Therapy/
13. exp Physical Fitness/
14. Weight Lifting/
15. Yoga/
16. exp Martial Arts/
17. Equine-Assisted Therapy/
18. Bicycling/
19. Hydrotherapy/
20. exp Balneology/
21. Swimming/
22. Vibration/
23. sports/ or sports for persons with disabilities/
24. (exercise or "standing frame" or vibration or stretch* or flexibility or yoga or "martial art*" or "tai chi" or "tai ji" or hippotherapy or (equine adj2 therapy) or resistance or "weight lift*" or "weight train*" or ergometry or bicycl* or "strength train*" or treadmill or "gait train*" or swim* or aquatherapy or hydrotherapy or sport*).ti,ab.
25. ("physical fitness" or "physical activity").ti,ab.
26. or/11-25
27. 10 and 26
28. limit 27 to randomized controlled trial
29. 27 and (random* or control* or trial or cohort or group* or arm*).ti,ab.
30. 28 or 29
31. limit 30 to yr="2008 -Current"
32. limit 31 to english language

Search: Systematic reviews

1. Spinal Cord Injuries/
2. ("spinal cord injury" or "SCI" or (spin* adj2 injur*)).ti,ab.
3. exp Multiple Sclerosis/
4. "multiple sclerosis".ti,ab.
5. Cerebral Palsy/
6. "cerebral palsy".ti,ab.
7. Disabled Persons/
8. Paraplegia/ or Quadriplegia/
9. (wheelchair or quadripleg* or parapleg* or tetrapleg*).ti,ab.
10. or/1-9
11. exp Exercise/
12. exp Exercise Therapy/
13. exp Physical Fitness/
14. Weight Lifting/
15. Yoga/
16. exp Martial Arts/
17. Equine-Assisted Therapy/
18. Bicycling/
19. Hydrotherapy/
20. exp Balneology/
21. Swimming/
22. Vibration/
23. sports/ or sports for persons with disabilities/
24. (exercise or "standing frame" or vibration or stretch* or flexibility or yoga or "martial art*" or "tai chi" or "tai ji" or hippotherapy or (equine adj2 therapy) or resistance or "weight lift*" or "weight train*" or ergometry or bicycl* or "strength train*" or treadmill or "gait train*" or swim* or aquatherapy or hydrotherapy or sport*).ti,ab.
25. ("physical fitness" or "physical activity").ti,ab.
26. or/11-25
27. 10 and 26
28. 27 and (systematic or meta*).ti,ab.
29. limit 27 to (meta analysis or systematic reviews)
30. 28 or 29
31. limit 30 to yr="2008 -Current"

Search: Evaluation studies

1. Spinal Cord Injuries/
2. ("spinal cord injury" or "SCI" or (spin* adj2 injur*)).ti,ab.
3. exp Multiple Sclerosis/
4. "multiple sclerosis".ti,ab.
5. Cerebral Palsy/
6. "cerebral palsy".ti,ab.
7. Disabled Persons/
8. Paraplegia/ or Quadriplegia/
9. (wheelchair or quadripleg* or parapleg* or tetrapleg*).ti,ab.
10. or/1-9
11. exp Exercise/
12. exp Exercise Therapy/
13. exp Physical Fitness/
14. Weight Lifting/
15. Yoga/
16. exp Martial Arts/
17. Equine-Assisted Therapy/
18. Bicycling/
19. Hydrotherapy/
20. exp Balneology/
21. Swimming/
22. Vibration/
23. sports/ or sports for persons with disabilities/
24. (exercise or "standing frame" or vibration or stretch* or flexibility or yoga or "martial art*" or "tai chi" or "tai ji" or hippotherapy or (equine adj2 therapy) or resistance or "weight lift*" or "weight train*" or ergometry or bicycl* or "strength train*" or treadmill or "gait train*" or swim* or aquatherapy or hydrotherapy or sport*).ti,ab.
25. ("physical fitness" or "physical activity").ti,ab.
26. or/11-25
27. 10 and 26
28. (pre or before).ti,ab.
29. (post or after).ti,ab.
30. limit 27 to (comparative study or evaluation studies)
31. 27 and (28 or 29)
32. Pilot Projects/
33. pilot.ti,ab.
34. 27 and (32 or 33)
35. 30 or 31 or 34
36. limit 35 to yr="2008 -Current"
37. limit 36 to english language
38. limit 37 to randomized controlled trial
39. 37 and (random* or control* or trial or cohort or group* or arm*).ti,ab.
40. 37 not (38 or 39)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials November 3, 2020

1. Spinal Cord Injuries/
2. ("spinal cord injury" or "SCI" or (spin* adj2 injur*)).ti,ab.
3. exp Multiple Sclerosis/
4. "multiple sclerosis".ti,ab.
5. Cerebral Palsy/
6. "cerebral palsy".ti,ab.
7. Disabled Persons/
8. Paraplegia/ or Quadriplegia/
9. (wheelchair or quadripleg* or parapleg* or tetrapleg*).ti,ab.
10. or/1-9
11. exp Exercise/
12. exp Exercise Therapy/
13. exp Physical Fitness/
14. Weight Lifting/
15. Yoga/
16. exp Martial Arts/
17. Equine-Assisted Therapy/
18. Bicycling/
19. Hydrotherapy/
20. exp Balneology/
21. Swimming/
22. Vibration/
23. sports/ or sports for persons with disabilities/
24. (exercise or "standing frame" or vibration or stretch* or flexibility or yoga or "martial art*" or "tai chi" or "tai ji" or hippotherapy or (equine adj2 therapy) or resistance or "weight lift*" or "weight train*" or ergometry or bicycl* or "strength train*" or treadmill or "gait train*" or swim* or aquatherapy or hydrotherapy or sport*).ti,ab.
25. ("physical fitness" or "physical activity").ti,ab.
26. or/11-25
27. 10 and 26
28. limit 27 to randomized controlled trial
29. 27 and (random* or control* or trial or cohort or group* or arm*).ti,ab.
30. 28 or 29
31. limit 30 to yr="2008 -Current"
32. limit 31 to english language
33. limit 32 to medline records
34. 32 not 33

Database: EBM Reviews - Cochrane Database of Systematic Reviews 2005 to November 3, 2020

1. ("spinal cord injury" or "SCI" or (spin* adj2 injur*)).ti,ab.
2. "multiple sclerosis".ti,ab.
3. "cerebral palsy".ti,ab.
4. (wheelchair or quadripleg* or parapleg* or tetrapleg*).ti,ab.
5. (exercise or "standing frame" or vibration or stretch* or flexibility or yoga or "martial art*" or "tai chi" or "tai ji" or hippotherapy or (equine adj2 therapy) or resistance or "weight lift*" or "weight train*" or ergometry or bicycl* or "strength train*" or treadmill or "gait train*" or swim* or aquatherapy or hydrotherapy or sport*).ti,ab.
6. ("physical fitness" or "physical activity").ti,ab.
7. (1 or 2 or 3 or 4) and (5 or 6)
8. limit 7 to full systematic reviews

Database: PsycINFO 1806 to November Week 1 2020

1. spinal cord injuries/
2. ("spinal cord injury" or "SCI" or (spin* adj2 injur*)).ti,ab.
3. multiple sclerosis/
4. "multiple sclerosis".ti,ab.
5. exp paralysis/
6. ("cerebral palsy" or wheelchair or quadripleg* or parapleg* or tetrapleg*).ti,ab.
7. or/1-6
8. physical activity/ or exp exercise/
9. physical fitness/
10. yoga/
11. recreation/ or athletic participation/ or martial arts/ or weightlifting/ or sports/
12. vibration/
13. (exercise or "standing frame" or vibration or stretch* or flexibility or yoga or "martial art*" or "tai chi" or "tai ji" or hippotherapy or (equine adj2 therapy) or resistance or "weight lift*" or "weight train*" or ergometry or bicycl* or "strength train*" or treadmill or "gait train*" or swim* or aquatherapy or hydrotherapy or sport*).ti,ab.
14. ("physical fitness" or "physical activity").ti,ab.
15. or/8-14
16. 7 and 15
17. limit 16 to yr="2008 -Current"
18. limit 17 to english language
19. 18 and (random* or control* or trial or cohort or group* or arm*).ti,ab.
20. limit 18 to ("0300 clinical trial" or 2100 treatment outcome)
21. 19 or 20

Database: EBSCO CINAHL Plus with Full Text to November 3, 2020

1. (MH "spinal cord injuries")
2. TI "spinal cord injur*" OR TI sci
3. (MH "Multiple Sclerosis")
4. TI multiple sclerosis
5. (MH "Cerebral Palsy")
6. TI cerebral palsy
7. (MH "Paraplegia") OR (MH "Quadriplegia")
8. TI wheelchair OR TI parapleg* OR TI quadripleg* OR TI tetrapleg*
9. S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8
10. (MH "Exercise+") OR (MH "Leisure Activities+") OR (MH "Physical Fitness+") OR (MH "Physical Activity") OR (MH "Sports+")
11. (MH "Weight Lifting") OR (MH "Resistance Training")
12. (MH "Yoga")
13. (MH "Vibration")
14. TI exercise OR TI "standing frame" OR TI vibration OR TI stretch* OR TI flexibility OR TI yoga OR TI "martial art*" OR TI "tai chi" OR TI "tai ji" OR TI hippotherapy OR TI "equine therapy" OR TI "resistance train*"
15. TI "weight train*" OR TI ergometry OR TI bicycl* OR TI "strength train*" OR TI treadmill OR TI "gait train*" OR TI swim* OR TI aquatherapy OR TI hydrotherapy OR TI sport*
16. TI "physical fitness" OR TI "physical activity"
17. S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16
18. S9 AND S17
19. TI random* or TI control* or TI trial or TI cohort or TI group* or TI arm*
20. AB random* or AB control* or AB trial or AB cohort or AB group* or AB arm*
21. S19 OR S20
22. S18 AND S21
23. S18 AND S21 Limiters - Published Date: 20080101-20191231; Exclude MEDLINE records

Database: Elsevier Embase Web to February 6, 2019

('spinal cord injury'/exp OR 'spinal cord injury' OR 'multiple sclerosis'/exp OR 'multiple sclerosis' OR 'cerebral palsy' OR 'disabled person' OR 'paraplegia' OR 'quadriplegia' OR 'tetraplegia') AND ('exercise' OR 'kinesiotherapy' OR 'fitness' OR 'physical activity' OR 'sport' OR 'weight lifting' OR 'yoga' OR 'martial art' OR 'hippotherapy' OR 'cycling' OR 'swimming' OR 'hydrotherapy' OR 'vibration' OR 'resistance training') AND 'article'/it AND (2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py OR 2019:py) AND [english]/lim AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)

Database: EBSCO Rehabilitation & Sports Medicine Source to November 3, 2020

1. (MH "spinal cord injuries")
2. TI "spinal cord injur*" OR TI sci
3. (MH "Multiple Sclerosis")
4. TI multiple sclerosis
5. (MH "Cerebral Palsy")
6. TI cerebral palsy
7. (MH "Paraplegia") OR (MH "Quadriplegia")
8. TI wheelchair OR TI parapleg* OR TI quadripleg* OR TI tetrapleg*
9. S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8
10. (MH "Exercise+") OR (MH "Leisure Activities+") OR (MH "Physical Fitness+") OR (MH "Physical Activity") OR (MH "Sports+")
11. (MH "Weight Lifting") OR (MH "Resistance Training")
12. (MH "Yoga")
13. (MH "Vibration")
14. TI exercise OR TI "standing frame" OR TI vibration OR TI stretch* OR TI flexibility OR TI yoga OR TI "martial art*" OR TI "tai chi" OR TI "tai ji" OR TI hippotherapy OR TI "equine therapy" OR TI "resistance train*"
15. TI "weight train*" OR TI ergometry OR TI bicycl* OR TI "strength train*" OR TI treadmill OR TI "gait train*" OR TI swim* OR TI aquatherapy OR TI hydrotherapy OR TI sport*
16. TI "physical fitness" OR TI "physical activity"
17. S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16
18. S9 AND S17
19. TI random* or TI control* or TI trial or TI cohort or TI group* or TI arm*
20. AB random* or AB control* or AB trial or AB cohort or AB group* or AB arm*
21. S19 OR S20
22. S18 AND S21
23. S18 AND S21 Limiters - Published Date: 20080101-2019123

Appendix B. Included Studies List

1. Abbasi M, Kordi Yoosefinejad A, Poursadeghfard M, et al. Whole body vibration improves core muscle strength and endurance in ambulant individuals with multiple sclerosis: a randomized clinical trial. Mult Scler Relat Disord. 2019 Jul;32:88-93. doi: 10.1016/j.msard.2019.04.028. PMID: 31071658.
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3. Adar S, Dundar U, Demirdal ÜS, et al. The effect of aquatic exercise on spasticity, quality of life, and motor function in cerebral palsy. Turk J Phys Med Rehab. 2017 Aug 14;63(3):239-48. doi: 10.5606/tftrd.2017.280. PMID: 31453460.
4. Afrasiabifar A, Karami F, Najafi Doulatabad S. Comparing the effect of Cawthorne-Cooksey and Frenkel exercises on balance in patients with multiple sclerosis: a randomized controlled trial. Clin Rehabil. 2018 Jan;32(1):57-65. doi: 10.1177/0269215517714592. PMID: 28629268.
5. Ahmadi A, Arastoo AA, Nikbakht M, et al. Comparison of the effect of 8 weeks aerobic and yoga training on ambulatory function, fatigue and mood status in MS patients. Iran Red Crescent Med J. 2013 Jun;15(6):449-54. doi: 10.5812/ircmj.3597. PMID: 24349740.
6. Ahmadizadeh Z, Khalili MA, Ghalam MS, et al. Effect of whole body vibration with stretching exercise on active and passive range of motion in lower extremities in children with cerebral palsy: A randomized clinical trial. Iranian Journal of Pediatrics. 2019;29(5) doi: 10.5812/ijp.84436.
7. Akkurt H, Karapolat HU, Kirazli Y, et al. The effects of upper extremity aerobic exercise in patients with spinal cord injury: a randomized controlled study. Eur J Phys Rehabil Med. 2017 Apr;53(2):219-27. doi: 10.23736/S1973-9087.16.03804-1. PMID: 27824234.
8. Al-Sharman A, Khalil H, El-Salem K, et al. The effects of aerobic exercise on sleep quality measures and sleep-related biomarkers in individuals with Multiple Sclerosis: a pilot randomised controlled trial. NeuroRehabilitation. 2019;45(1):107-15. doi: 10.3233/NRE-192748. PMID: 31403958.
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11. Aras B, Yasar E, Kesikburun S, et al. Comparison of the effectiveness of partial body weight-supported treadmill exercises, robotic-assisted treadmill exercises, and anti-gravity treadmill exercises in spastic cerebral palsy. Turk J Phys Med Rehabil. 2019 Jun;65(4):361-70. doi: 10.5606/tftrd.2019.3078. PMID: 31893273.
12. Arntzen EC, Straume B, Odeh F, et al. Group-based, individualized, comprehensive core stability and balance intervention provides immediate and long-term improvements in walking in individuals with multiple sclerosis: A randomized controlled trial. Physiother Res Int. 2020 Jan;25(1):e1798. doi: 10.1002/pri.1798. PMID: 31268223.

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Appendix C. Excluded Studies List

Table C-1. Study exclusion reasons

Full Text Exclusion Reason	Exclusion Code
Ineligible population (not multiple sclerosis, cerebral palsy or spinal cord injury)	3
Ineligible intervention (e.g., < than 10 sessions and or < than 10 days, only family/caregiver observed)	4
Ineligible comparator	5
Ineligible outcomes	6
Ineligible design (i.e., case reports, case series)	7
Pre-post studies	8
Studies outside of search dates (before January 2008 or for systematic reviews 2014 or older)	9
Not a study (letter, editorial, nonsystematic review)	10
Inadequate samples size (MS and SCI n<30 and CP n<20)	11
Systematic review, not used, but checked for includable studies	12
Not English language	13
Non-U.S. applicable study setting	14
Nonhuman population (animal study)	15

Note: Codes 1-2 used for included studies and background

1. Abasiyanik Z, Ertekin O, Kahraman T, et al. The effects of clinical pilates training on walking, balance, fall risk, respiratory and cognitive functions in persons with multiple sclerosis: a randomized controlled trial. Mult Scler. 2018;Conference: 23rd annual RIMS conference. 2018. Netherlands 24(6):862. Exclusion: 10.
2. Abasiyanik Z, Ertekin O, Kahraman T, et al. The effects of Clinical Pilates training on walking, balance, fall risk, respiratory, and cognitive functions in persons with multiple sclerosis: A randomized controlled trial. Explore (NY). 2019 Jul 17;17:17. doi: 10.1016/j.explore.2019.07.010. PMID: 31377306. Exclusion: 4.
3. Abbaspoor E, Zolfaghari M, Ahmadi B, et al. The effect of combined functional training on BDNF, IGF-1, and their association with health-related fitness in the multiple sclerosis women. Growth Horm IGF Res. 2020 Jun;52:101320. doi: 10.1016/j.ghir.2020.101320. PMID: 32305012. Exclusion: 11.
4. Abd-Elmonem AM, Elhady HSA. Effect of rebound exercises on balance in children with spastic diplegia. Int J Ther Rehabil. 2018 Sep;25(9):467-74. doi: 10.12968/ijtr.2018.25.9.467. Exclusion: 14.
5. Abdel Gawad HA, Abdel Karim AE, Mohammed AH. Shock wave therapy for spastic plantar flexor muscles in hemiplegic cerebral palsy children. Egypt J Med Hum Genet. 2015;16(3):269-75. doi: 10.1016/j.ejmhg.2014.12.007. Exclusion: 14.
6. Abdel-Aziem AA, El-Basatiny HM. Effectiveness of backward walking training on walking ability in children with hemiparetic cerebral palsy: a randomized controlled trial. Clin Rehabil. 2017 Jun;31(6):790-7. doi: 10.1177/0269215516656468. PMID: 27356944. Exclusion: 14.

7. Abouelkheir RAA, Khalil ME, Abd-Elfattah HM. Hippotherapy versus traditional physiotherapy on gait in spastic diaplegic children. Indian J Public Health Res Dev. 2019;10(12):1472-5. doi: 10.37506/v10/i12/2019/ijphrd/192416. Exclusion: 6.

8. Aburub A, Khalil H, Al-Sharman A, et al. The association between physical activity and sleep characteristics in people with multiple sclerosis. Mult Scler Relat Disord. 2017 Feb;12:29-33. doi: 10.1016/j.msard.2016.12.010. PMID: 28283102. Exclusion: 4.

9. 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 Jul;96(7):1329-38. doi: 10.1016/j.apmr.2015.01.005. PMID: 25596001. Exclusion: 12.

10. Adepoju F, Hamzat T, Akinyinka O. Comparative efficacy of progressive resistance exercise and biomechanical ankle platform system on functional indices of children with cerebral palsy. Ethiop. 2017 Jan;27(1):11-6. doi: 10.4314/ejhs.v27i1.3. PMID: 28458486. Exclusion: 14.

11. Afkar A, Ashouri A, Rahmani M, et al. Effect of exercise therapy on quality of life of patients with multiple sclerosis in Iran: a systematic review and meta-analysis. Neurol Sci. 2017 Nov;38(11):1901-11. doi: 10.1007/s10072-017-3047-x. PMID: 28687973. Exclusion: 12.

12. Aguirre-Guemez AV, Perez-Sanpablo AI, Quinzanos-Fresnedo J, et al. Walking speed is not the best outcome to evaluate the effect of robotic assisted gait training in people with motor incomplete spinal cord injury: a systematic review with meta-analysis. J Spinal Cord Med. 2017 Oct 25;42(2):142-54. doi: 10.1080/10790268.2017.1390644. PMID: 29065788. Exclusion: 12.

13. Aidar FJ, Carneiro AL, Costa Moreira O, et al. Effects of resistance training on the physical condition of people with multiple sclerosis. J Sports Med Phys Fitness. 2018 Jul-Aug;58(7-8):1127-34. doi: 10.23736/S0022-4707.17.07621-6. PMID: 28944644. Exclusion: 11.

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22. Ali MSM, Elazem FHA, Anwar GM. Effect of core stabilizing program on balance in spastic diplegic cerebral palsy children. Int J Pharmtech Res. 2016;9(5):129-36. Exclusion: 14.

23. Alphonsus KB, Su Y, D'Arcy C. The effect of exercise, yoga and physiotherapy on the quality of life of people with multiple sclerosis: systematic review and meta-analysis. Complement Ther Med. 2019 Apr;43:188-95. doi: 10.1016/j.ctim.2019.02.010. PMID: 30935529. Exclusion: 12.

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49. Bansi J, Bloch W, Gamper U, et al. Training in MS: influence of two different endurance training protocols (aquatic versus overland) on cytokine and neurotrophin concentrations during three week randomized controlled trial. Mult Scler. 2013 Apr;19(5):613-21. doi: 10.1177/1352458512458605. PMID: 22936334. Exclusion: 4.

50. Bansi J, Bloch W, Gamper U, et al. Cycling under immersion affects growth factor BDNF, cardiorespiratory fitness, fatigue and health-related quality of life in persons with multiple sclerosis. A randomized controlled study. Mult Scler J Exp Transl Clin. 2014 START: 2014 Jun 6 CONFERENCE END: 2014 Jun 7, 19th Annual Rehabilitation in Multiple Sclerosis Conference, RIMS 2014 Brighton United Kingdom;20(7):979-80. doi: 10.1177/1352458514533628. Exclusion: 4.

51. Bansi J, Bloch W, Gamper U, et al. Endurance training in MS: short-term immune responses and their relation to cardiorespiratory fitness, health-related quality of life, and fatigue. J Neurol. 2013 Dec;260(12):2993-3001. doi: 10.1007/s00415-013-7091-z. PMID: 24036849. Exclusion: 4.

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53. Barbarulo AM, Lus G, Signoriello E, et al. Integrated cognitive and neuromotor rehabilitation in multiple sclerosis: a pragmatic study. Front Behav Neurosci. 2018 Sep 5;12(196) doi: 10.3389/fnbeh.2018.00196. PMID: 30271331. Exclusion: 5.

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55. Barfield JP, Malone LA. Perceived exercise benefits and barriers among power wheelchair soccer players. J Rehabil Res Dev. 2013;50(2):231-8. PMID: 23761004. Exclusion: 7.

56. Barfield JP, Newsome L, Malone LA. Exercise intensity during power wheelchair soccer. Arch Phys Med Rehabil. 2016 Nov;97(11):1938-44. doi: 10.1016/j.apmr.2016.05.012. PMID: 27288710. Exclusion: 3.

57. Barry A, Cronin O, Ryan AM, et al. Impact of short-term cycle ergometer training on quality of life, cognition and depressive symptomatology in multiple sclerosis patients: a pilot study. Neurol Sci. 2018 Mar;39(3):461-9. doi: 10.1007/s10072-017-3230-0. PMID: 29280019. Exclusion: 5.

58. Barthelemy A, Gagnon DH, Duclos C. Gait-like vibration training improves gait abilities: a case report of a 62-year-old person with a chronic incomplete spinal cord injury. Spinal Cord Ser Cases. 2016 Jul 21;2:16012. doi: 10.1038/scsandc.2016.12. PMID: 28053756. Exclusion: 7.

59. Bauerfeind J, Koper M, Wieczorek J, et al. Sports injuries in wheelchair rugby - A pilot study. J Hum Kinet. 2015 Nov 22;48:123-32. doi: 10.1515/hukin-2015-0098. PMID: 26834880. Exclusion: 11.

60. Baunsgaard CB, Nissen UV, Brust AK, et al. Exoskeleton gait training after spinal cord injury: an exploratory study on secondary health conditions. J Rehabil Med. 2018 Sep 28;50(9):806-13. doi: 10.2340/16501977-2372. PMID: 30183055. Exclusion: 8.

61. Baxter K. The effect of core strengthening versus extremity strengthening on mobility measures in patients with multiple sclerosis. Dissertation Abstracts International: Section B: The Sciences and Engineering. 2018;78(10-B(E)):No Pagination Specified. Exclusion: 12.

62. Bayon C, Martin-Lorenzo T, Moral-Saiz B, et al. A robot-based gait training therapy for pediatric population with cerebral palsy: goal setting, proposal and preliminary clinical implementation. J Neuroengineering Rehabil. 2018 Jul 27;15(1):69. doi: 10.1186/s12984-018-0412-9. PMID: 30053857. Exclusion: 11.

63. Beani E, Menici V, Ferrari A, et al. Feasibility of a home-based action observation training for children with unilateral cerebral palsy: An explorative study. Front Neurol. 2020;11 doi: 10.3389/fneur.2020.00016. Exclusion: 4.

64. Bedair R, Al-Talawy H, Shoukry K, et al. Impact of virtual reality games as an adjunct treatment tool on upper extremity function of spastic hemiplegic children. Int J Pharmtech Res. 2016;9(6):1-8. Exclusion: 14.

65. Bernhardt L, Marziniak M. Specific resistance training for patients with multiple sclerosis. Mult Scler J Exp Transl Clin. START: 2011 Oct 19 CONFERENCE END: 2011 Oct 22, 5th Joint Triennial Congress of the European and Americas Committees for Treatment and Research in Multiple Sclerosis Amsterdam Netherlands;17(10 SUPPL. 1):S465. Exclusion: 10.

66. Biasotto-Gonzalez DA, Grecco LC, Neto HP, et al. Effect of treadmill gait training on static and functional balance in children with cerebral palsy: randomized controlled clinical trial. Gait Posture. 2013;38:S69-S70. doi: 10.1016/j.gaitpost.2013.07.150. Exclusion: 10.

67. Bickel CS, Yarar-Fisher C, Mahoney ET, et al. Neuromuscular electrical stimulation-induced resistance training after SCI: A review of the dudley protocol. Top Spinal Cord Inj Rehabil. 2015;21(4):294-302. doi: 10.1310/sci2104-294. PMID: 26689694. Exclusion: 8.

68. Birgani PM, Ashtiyani M, Rasooli A, et al. Can an anti-gravity treadmill improve stability of children with cerebral palsy? Conf Proc IEEE Eng Med Biol Soc. 2016 08;2016:5465-8. doi: 10.1109/EMBC.2016.7591963. PMID: 28269494. Exclusion: 11.

69. Bisson EJ, Fakolade A, Petrin J, et al. Exercise interventions in multiple sclerosis rehabilitation need better reporting on comorbidities: a systematic scoping review. Clin Rehabil. 2017 Oct;31(10):1305-12. doi: 10.1177/0269215517698734. PMID: 28933610. Exclusion: 12.

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1194. Zwinkels M, Takken T, Ruyten T, et al. Body mass index and fitness in high-functioning children and adolescents with cerebral palsy: what happened over a decade? Res Dev Disabil. 2017 Dec;71:70-6. doi: 10.1016/j.ridd.2017.09.021. PMID: 29024824. Exclusion: 4.

1195. Zwinkels M, Verschuren O, Lankhorst K, et al. Sport-2-stay-fit study: health effects of after-school sport participation in children and adolescents with a chronic disease or physical disability. BMC Sports Sci Med Rehabil. 2015;7:22. doi: 10.1186/s13102-015-0016-7. PMID: 26445674. Exclusion: 3.

Appendix D. Included and Excluded Study Details and Systematic Reviews Evaluated

Table D-1. Included and excluded study definitions and characteristics

Study Design	Definition/Characteristics	Include/Exclude
Systematic Reviews	A literature review that uses systematic methods to synthesize, summarize, and grade evidence, on outcomes to address specific research questions.	Include systematic reviews published since 2014 for examination of reference lists for relevant studies
Randomized Controlled Trial	Participants randomized to two or more groups where each group receives a different intervention.	Include
Comparative Cohort Study	An observational study of 2 groups of participants where one group received an intervention and second group received a control or other intervention and participants are followed forward; participants were not randomized to different groups.	Include
Pre-Post Study	An observational study of one group of participants where baseline values are compared with values after an intervention and all participants received the same intervention; the study reports results from the group of participants (reporting is not selective).	Exclude unless need to include due to limited or no evidence from RCTs and cohort studies
Case Series	A publication that reports findings from more than one individual; if individuals were involved in a study, the publication does not report results from all participants but from those who demonstrate some finding (reporting is selective).	Exclude
Case Report	A publication that reports findings from one individual (reporting is selective).	Exclude

Systematic Reviews: Reference Lists Evaluated for Eligibility for Inclusion in the Review

1. 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 Jul;96(7):1329-38. doi: 10.1016/j.apmr.2015.01.005. PMID: 25596001.

2. Afkar A, Ashouri A, Rahmani M, et al. Effect of exercise therapy on quality of life of patients with multiple sclerosis in Iran: a systematic review and meta-analysis. Neurol Sci. 2017 Nov;38(11):1901-11. doi: 10.1007/s10072-017-3047-x. PMID: 28687973.

3. Aguirre-Guemez AV, Perez-Sanpablo AI, Quinzanos-Fresnedo J, et al. Walking speed is not the best outcome to evaluate the effect of robotic assisted gait training in people with motor incomplete spinal cord injury: a systematic review with meta-analysis. J Spinal Cord Med. 2017 Oct 25;42(2):142-54. doi: 10.1080/10790268.2017.1390644. PMID: 29065788.

4. Alashram AR, Padua E, Annino G. Effects of whole body vibration on motor impairments in patients with neurological disorders: a systematic review. Am J Phys Med Rehabil. 2019 Jun 21;21:21. doi: 10.1097/PHM.0000000000001252. PMID: 31246611.

5. Alphonsus KB, Su Y, D'Arcy C. The effect of exercise, yoga and physiotherapy on the quality of life of people with multiple sclerosis: systematic review and meta-analysis. Complement Ther Med. 2019 Apr;43:188-95. doi: 10.1016/j.ctim.2019.02.010. PMID: 30935529.
6. Aravind N, Harvey LA, Glinsky JV. Physiotherapy interventions for increasing muscle strength in people with spinal cord injuries: a systematic review. Spinal Cord. 2019 Jun;57(6):449-60. doi: 10.1038/s41393-019-0242-z. PMID: 30723256.
7. Armstrong EL, Spencer S, Kentish MJ, et al. Efficacy of cycling interventions to improve function in children and adolescents with cerebral palsy: a systematic review and meta-analysis. Clin Rehabil. 2019 Jul;33(7):1113-29. doi: 10.1177/0269215519837582. PMID: 30935240.
8. Baxter K. The effect of core strengthening versus extremity strengthening on mobility measures in patients with multiple sclerosis. Dissertation Abstracts International: Section B: The Sciences and Engineering. 2018;78(10-B(E)):No Pagination Specified.
9. Bisson EJ, Fakolade A, Petrin J, et al. Exercise interventions in multiple sclerosis rehabilitation need better reporting on comorbidities: a systematic scoping review. Clin Rehabil. 2017 Oct;31(10):1305-12. doi: 10.1177/0269215517698734. PMID: 28933610.
10. Bloemen M, Van Wely L, Mollema J, et al. Evidence for increasing physical activity in children with physical disabilities: a systematic review. Dev Med Child Neurol. 2017 10;59(10):1004-10. doi: 10.1111/dmcn.13422. PMID: 28374442.
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Appendix E. Criteria for Assessing Quality and Internal Validity of Individual Studies

Quality Assessment Criteria: Randomized Controlled Trials

Table E-1. Methods to assess quality of trials: assessment of internal validity

Assessment Question	Yes/ No/ Unclear	Description
1. Was the assignment to the treatment groups really random?	Yes	Use of the term "randomized" alone is not sufficient for a judgment of "Yes". Explicit description of method for sequence generation must be provided. Adequate approaches include: Computer-generated random numbers, random numbers tables
	No	Randomization was either not attempted or was based on an inferior approach (e.g., alternation, case record number, birth date, or day of week)
	Unclear	Insufficient detail provided to make a judgment of yes or no.
2. Was the treatment allocation concealed?	Yes	Adequate approaches to concealment of randomization: Centralized or pharmacy-controlled randomization, serially-numbered identical containers, on-site computer based system with a randomization sequence that is not readable until allocation *Note: If a trial did not use adequate allocation concealment methods, the highest rating it can receive is "Fair".*
	No	Inferior approaches to concealment of randomization: Use of alternation, case record number, birth date, or day of week, open random numbers lists, serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)
	Unclear	No details about allocation methods. A statement that "allocation was concealed" is not sufficient; details must be provided.
3. Were groups similar at baseline in terms of prognostic factors?	Yes	Parallel design: No clinically important differences Crossover design: Comparison of baseline characteristics must be made based on order of randomization. *Note: Determine beforehand which prognostic factors are important to consider. A statistically significant difference does not automatically constitute a clinically important difference.*
	No	Clinically important differences
	Unclear	Statement of "no differences at baseline", but data not reported; or data not reported by group, or no mention at all of baseline characteristics. For crossover design, only reported baseline characteristics of the overall group.
4. Were outcome assessors blinded to treatment allocation? **5. Was the care provider blinded?** **6. Was the patient blinded?**	Yes	Explicit statement(s) that outcome assessors/care provider/patient were blinded. Double-dummy studies and use of identically-appearing treatments are also considered sufficient blinding methods for patients and care providers.
	No	No blinding used, open-label
	Unclear, described as double-blind	Study described as double-blind but no details provided.
	Not reported	No information about blinding

Assessment Question	Yes/ No/ Unclear	Description
7. Did the article include an intention-to-treat analysis or provide the data needed to calculate it (i.e., number assigned to each group, number of subjects who finished in each group, and their results)?	Yes	All patients that were randomized were included in the analysis. Specify if imputation methods (e.g., last-observation carried forward) were used. OR Exclusion of 5% of patients or less is acceptable, given that the reasons for exclusion are not related to outcome (e.g., did not take study medication) and that the exclusions would not be expected to have an important impact on the effect size
	No	Exclusion of greater than 5% of patients from analysis OR less than 5%, with reasons that may affect the outcome (e.g., adverse events, lack of efficacy) or reasons that may be due to bias (e.g., investigator decision)
	Unclear	Numbers analyzed are not reported
8. Was the rate of overall attrition and the difference between groups in attrition within acceptable levels?	Yes	**Overall attrition[a]:** The overall attrition rate was below the level that was established by the review team. **Differential attrition:** The absolute difference between groups in rate of attrition was below 10%.
	No	**Overall attrition:** The overall attrition rate was above the level that was established by the review team. **Differential attrition:** The difference between groups in the overall attrition rate or in the rate of attrition for a specific reason (e.g., adverse events, protocol violations, etc.) was 10% or more.
	Unclear	**Overall attrition:** Insufficient information provided to determine the level of attrition **Differential attrition:** Insufficient information provided to determine the level of attrition

[a] **Overall attrition:** There is no empirical evidence to support establishment of a specific level of attrition that is universally considered “important”. The level of attrition considered important will vary by review and should be determined a priori by the review teams. Attrition refers to discontinuation for ANY reason, including lost to followup, lack of efficacy, adverse events, investigator decision, protocol violation, consent withdrawal, etc.

Quality Assessment Criteria: Nonrandomized Studies

Table E-2. Nonrandomized studies: guidance for quality assessment

Assessment Question	Yes/ No/ Unclear	Description
1. Was the selection of patients for inclusion unbiased?	Yes	• Same pre-specified eligibility criteria for all groups • Same strategy for obtaining groups • Enroll random or consecutive sample of all patients meeting eligibility criteria • Samples drawn from same source and same timeperiod
	No	• One or more of the above were not met
	Unclear	Insufficient detail provided to make a judgment of yes or no.
2. Differences in predetermined prognostic factors at baseline?	Yes	• ~10% difference in dichotomous outcomes • Clinically meaningful differences in continuous outcomes
	No	• Differences above limits set a priori
	Unclear	Insufficient detail provided to make a judgment of yes or no.

Assessment Question	Yes/ No/ Unclear	Description
3. Was the rate of overall attrition and the difference between groups in attrition within acceptable levels?	Yes	**Overall attrition[a]:** The overall attrition rate was below the level that was established by the review team **Differential attrition:** The absolute difference between groups in rate of attrition was below 10%
	No	**Overall attrition:** The overall attrition rate was above the level that was established by the review team. **Differential attrition:** The difference between groups in the overall attrition rate was 10% or more
	Unclear	**Overall attrition:** Insufficient information provided to determine the level of attrition **Differential attrition:** Insufficient information provided to determine the level of attrition
4. Were the events investigated prespecified and defined?	Yes	Events were explicitly defined, including methods for categorizing continuous variables.
	No	
5. Was there a clear description of the techniques used to identify the events?	Yes	Techniques used to identify the events were clearly described, including who ascertained, timing and methods used
	No	
6. Was there unbiased and accurate ascertainment of events?	Yes	Ascertainment was conducted by an independent individual or endpoint committee using appropriate data sources and validated techniques with limited reliance on patient recall. Ascertainment should be blinded where possible and appropriate.
	No	
	Unclear	Insufficient detail provided to make a judgment of yes or no
7. Were potential confounding variables and risk factors identified and examined using acceptable statistical techniques? Such techniques include: stratification, multivariable regression, propensity score matching.	Yes	Use one of the acceptable techniques to address multiple variables considered important. Not all variables must be considered to achieve "yes", but multiple should be addressed.
	No	
	Unclear	Insufficient detail provided to make a judgment of yes or no, or too few variables considered, or variables considered not deemed important.

Assessment Question	Yes/ No/ Unclear	Description
8. Was the duration of followup reasonable for investigated events? Should be determined a priori, by outcome – may differ for adverse events, for example.	Yes	
	No	
	Unclear	Insufficient detail provided to make a judgment of yes or no.

[a] **Overall attrition:** The level of attrition considered important will vary by review and should be determined a priori by the review teams. Attrition refers to discontinuation for ANY reason, including lost to followup, lack of efficacy, adverse events, investigator decision, consent withdrawal, etc. Generally ≤20% is considered a reasonable cutoff for acceptable attrition, but greater levels may be acceptable depending on the duration of study and population characteristics.

Appendix E References

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Appendix F. Evidence Tables

Table F-1. Study description and results (continued in Table F-2)

Author, Year **Intervention Type** **Duration of Postintervention Followup** **Quality** **(See Appendix B for Full Citation)**	**Intervention and Comparison**	**Population** **Age (Mean)** **Gender (% Female)** **Race (%)** **Ambulatory (%)** **Wheelchair User (%)** **Condition Specific (%)** **Other (%)**	**Prioritized Outcomes**	**Other Outcomes**
Acar, 2016 **Postural Control** Motion gaming Postintervention, 6 weeks Poor	A. Nintendo Wii gaming plus neuro-developmental treatment, 12 sessions over 6 weeks (n=15) B. Neurodevelopmental treatment, 12 sessions over 6 weeks (n=15)	A vs. B Age (mean years): 9.53 vs. 9.73 Female: 7 (47%) vs. 9 (60%) Race: NR Ambulatory: NR Wheelchair user: NR GMFCS I: 40% vs. 40% GMFCS II: 60% vs. 60% Spastic hemiparesis: 100% Manual Ability Classification System median score, (range): 2 (range 1–3) vs. 2 (range 1–3) GMFCS, levels I-V: Level 1: 6 cases vs. 6 cases Level 2: 9 cases vs. 9 cases	A vs. B, mean (SD) Baseline QUEST (Minimum score=0, Maximum score=100) QUEST Dissociated movements (score): 80.1 (7.73) vs. 81.4 (10.70) QUEST Grasps (score): 42.2 (18.76) vs. 53 (16.45) QUEST Weight bearing (score): 69.2 (19.46) vs. 75.4 (17.07) QUEST Protective extension (score): 72.9 (14.78) vs. 71 (23.52) Postintervention QUEST (Minimum score=0, Maximum score=100) QUEST Dissociated movements: 85.6 (8.54) vs. 86.4 (8.78) QUEST Grasps (score): 47.1 (16.64) vs. 55.7 (15.30) QUEST Weight bearing (score): 72.7 (19.60) vs. 77.3 (15.43) QUEST Protective extension (score): 77 (12.66) vs. 74 (23.36) *Mean Change Data - not included? WeeFIM, (18 items, 7-point scale, 1=total assistance required to 7=complete independence, 7 to 126-point total range) WeeFIM: 46 (8.23) vs. 48.3 (7.27) (baseline) WeeFIM: 46.7 (7.51) vs. 48.9 (7.14) (postintervention)	NA

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Abbasi, 2019 **Postural Control** Whole body vibration Immediately postintervention, 6 weeks Fair	A. Whole body vibration, 18 sessions over 6 weeks (n=22) B. No treatment, no exercise (n=24)	A vs. B Age: 37 vs. 39 Female: 5% vs. 17% EDSS: 1.54 vs. 1.55	A vs. B, Median (Interquartile range), p-value is between groups MSQOL-54 (PCS): 4.20 (1.73, 8.40) vs. –1.26 (–3.28, 0), p<0.001 MSQOL-54 (MCS): 5.96 (2.71, 11.89) vs. –0.17 (–2.20, 0.07), p<0.001	A vs. B, Median (Interquartile range) followup-baseline scores, p=between groups: Trunk Flexor: Med Diff 25.83 (8.83 to 46.41) vs. –0.33 (–5.67 to 6.75), p<0.001 Trunk Extensor: Med Diff 38.17 (20.75 to 70) vs. –1.49 (–11.83 to 3.49), p<0.001
Adar, 2017 **Aerobic Exercise** Aquatics Postintervention, 0 weeks Fair	A. Aquatic exercise, 30 sessions over 6 weeks (n=17) B. Land-based exercise, 30 sessions over 6 weeks (n=15)	A vs. B Age (mean years): 10.1 vs. 9.3 Female: 9 (53%) vs. 6 (40%) Race: NR Ambulatory: NR Wheelchair user: NR Other: A: Spastic Diplegia (65%) vs. Hemiplegia (35%) B: Spastic Diplegia (67%) vs. Hemiplegia (33%)	A vs. B, Mean change scores: TUG: -0.13 (0.14) vs. -0.16 (0.13), p=0.664 GMFM-88: 0.05 (0.05) vs. 0.05 (0.03), p=0.451 WeeFIM motor: 0.04 (0.04) vs. 0.06 (0.06),p=0.860 WeeFIM total: -0.13 (0.14) vs. -0.16 (0.13), p=0.287	NA

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Afrasiabifar, 2018 **Postural Control** Balance Postintervention, 12 weeks Good	A. Cawthorne-Cooksey exercise: 36 sessions, 3 times a week, over 12 weeks, (n=24) B. Frankel exercises: number of sessions NR, over 12 weeks, (n=23) C. Usual care control (n=25)	A vs. B vs. C Age (mean years): 32.4 vs. 32 vs. 33.6 Female: 20 (83%) vs. 17 (74%) vs. 19 (76%) Race: NR Ambulatory: NR Wheelchair user: NR Body mass index (kg/m^2, mean): 23.4 vs. 23.6 vs. 23.3 MS subtype Relapsing-remitting: 23 (95.8%) vs. 22 (95.7%) vs. 23 (92%) Primary and secondary progressive: 1 (4.2%) vs. 1 (4.3%) vs. 2 (8%)	NA	A vs. B vs. C, mean (SD) Balance score (BBS 0-56, higher scores=better balance) A vs. B BBS: 30.9 (5.6) vs. 31.6 (5.1), (baseline) 33.9 (6.1) vs. 32.5 (5.1), (6 weeks) 39.8 (4.5) vs. 33.9 (5.6), (postintervention) A vs. C BBS: 30.9 (5.6) vs. 30.3 (6), (baseline) BBS: 33.9 (6.1) vs. 29.8 (6.2), (6 weeks) BBS: 39.8 (4.5) vs. 29.1 (6.5), (postintervention) B vs. C BBS: 31.6 (5.1) vs. 30.3 (6), (baseline) BBS: 32.5 (5.1) vs. 29.8 (6.2), (6 weeks) BBS: 33.9 (5.6) vs. 29.1 (6.5), (postintervention) Mean differences, paired comparisons A + B BBS: −0.7 (95% CI −4.8 to 3.4), p=0.9, (baseline) BBS: 1.4 (95% CI −2.8 to 5.5), p=0.7, (6 weeks) BBS: 5.9 (95% CI 1.9 to 9.9), p=0.001, (postintervention)

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Afrasiabifar, 2018 **(Continued)**				A + C BBS: 0.6 (95% CI −3.3 to 4.6), p=0.9, (baseline) BBS: 4.1 (95% CI −0.02 to 8.2), p=0.05, (6 weeks) BBS: (95% CI 10.7 to 6.8 14.6), p=0.001, (postintervention) B + C BBS: 1.3 (95% CI −2.7 5.2), p=0.7, (baseline) BBS: 2.7 (95% CI −1.4 to 6.9), p=0.2, (6 weeks) BBS: 4.8 (95% CI 0.9 to 8.8), p=0.01, (postintervention)
Ahmadi, 2013 **Aerobic Exercise** Treadmill **Postural Control** Yoga Immediately postintervention, 8 weeks Fair	A. Treadmill, 24 sessions over 8 weeks (n=10) C. Yoga, 24 sessions over 8 weeks (n=11) B. Waitlist control (n=10)	A vs. B vs. C Age: 37 vs. 32 vs. 37 Female: 100% EDSS: 2.40 vs. 2.00 vs. 2.25	A vs. B vs. C, Mean (SD), p=between groups: BDI: 8.50 (3.06 to 5.60 (3.40) vs. 17.36 (12.42) to 11.09 (12.46) vs. 11.90 (9.39) to 12.50 (8.1) A vs. B, p=0.11 A vs. C, p=0.11 B. vs. C, p=0.001 BAI: 7.90 (5.91) to 6.10 (4.95) vs. 12.45 (4.54) to 6.45 (3.61) vs. 7.50 (6.77) to 8.20 (7.39) A vs. B, p=0.01 A vs. C, p=0.22 B vs. C, p=0.001 A vs. B, Mean (SD), p-value between groups: 10MWT: 12.45 (4.54) to 6.45 (3.61) vs. 7.50 (6.77) to 8.20 (7.39), p=0.01 2MWT: 109 (17.44) to 120.36 (20.62) vs. 121.50 (27.73) to 119.05 (27.12), p=0.11 B vs. C, Mean (SD), p-value between groups: 10MWT: 12.45 (4.54) to 6.45 (3.61) vs. 9.16 (1.88) to 9.47 (1.92), p=0.11 2MWT: 109 (17.44) to 120.36 (20.62) vs. 121.50 (27.73) to 119.05 (27.12), p=0.11	A vs. B, Mean (SD), p-value between groups: BBS: 47.72 (6.78) to 53.81 (3.40) vs. 44.50 (8.48) to 41.70 (8.48), p=0.07 B vs. C, Mean (SD), p-value between groups: BBS: 47.72 (6.78) to 53.81 (3.40) vs. 44.50 (8.48) to 41.70 (8.48), p=0.07

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Ahmadizadeh, 2020 **Postural Control** Whole Body Vibration Postintervention, 6 weeks Fair	A. Whole body vibration + stretching, 18 sessions over 6 weeks (n=10) B. Stretching only, 16 sessions over 6 weeks (n=10)	A vs. B Age: 6.9 vs. 8.1 Gender: NR Race: NR Hemiplegic: 30% vs. 60% Diplegic: 60% vs. 40% Quadrapletic: 10% vs. 0%	A vs. B, mean (SD): <u>6MWT:</u> 158.8 (100.24) to 189.45 (115.47) vs. 194 (78.82) to 271.5 (60.81), p=0.04	NA
Akkurt, 2017 **Aerobic Exercise** Hand cycling Postintervention, 0 weeks Fair	A. Arm ergometer exercises + general exercises (120 sessions over 12 weeks), 36 sessions over 12 weeks (n=17) B. General exercises, 120 sessions over 12 weeks (n=16)	A vs. B Age (mean years): 33 vs. 37 Female: 1 (5%) vs. 3 (19%) Race: NR Ambulatory: 7 (41%) vs. 8(50%) Wheelchair user: 10 (59%) vs. 8 (50%) Other: Quadriplegia 0 (0%) vs. 1 (6%) Paraplegia 17 (100%) vs. 15 (94%)	A vs. B (SD) VO_2 Peak 19.1(NR) vs. 15.45(NR) (baseline) 23.4(NR) vs. 16.8 (NR); p=0.020 (postintervention at 12 weeks) HAD-S, CES-D, PFTs, FIM, WHOQoL: All NS Calculated A vs. B, Mean change scores: <u>FIM</u>: 0.5 vs. -0.5, p=1.00 <u>CHART-sf</u>, p>0.05 <u>WHOQOL-Bref</u>, p>0.05	Waist circumference, BP, Lipids: All NS

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Alexeeva 2011 **Aerobic Exercise** Treadmill Pre to post Fair	A. Body weight supported treadmill training maximum 60 minutes for 3 days a week for 13 weeks (39 sessions) B. Body weight supported track training maximum 60 minutes for 3 days a week for 13 weeks (39 sessions) C. Structured physical therapy maximum 60 minutes for 3 days a week for 13 weeks (39 sessions)	International Standards for Neurological Classification of Spinal Cord Injury C or D Mean age 36.0 years 30 males and 5 females (86% male)	Pre, post 10 minute walk test (meters/second) A. 0.30 (0.26) to 0.46 (0.40) B. 0.22 (0.20) to 0.44 (0.33) C. 0.41 ((0.34) to 0.51(0.36) Combined there was an increase in walking speed (p=0.001) but no group by time effect (no difference among groups) Tinetti Balance A. 9.8 (5.4) to 19.4 (5.0) B. 10.5 (3.4) to 11.9 (2.5) C. 10.1(3.6) to 12.9 (2.7) Significant time by group interaction (p<0.05), with post-hoc group C improving (p<0.001) and B improving (p<0.01) but not A (p=0.23) Peak oxygen uptake Baseline ranged from 10 to 26 ml/kg/minute and overall modest 12% increase in each group but no differences among groups	MMT (Maximal Muscle Testing combined upper and lower limb strength) A. 71.5 (15.1) to 78.1 (15.3) B. 69.5 (12.1) to 73.3 (11.5) C. 76.3 (11.6) to 81.8 (11.0) Overall 6%-9% increase across groups; each group achieved a significant increase (p<0.05 for each), no difference among groups SAWS (13 components) (lower score is improvement) Completed pre, immediately post and 1 month later (28 of 35 participants completed surveys) A. 39.3 (8.3) to 35.2 (8.7) to 31.2 (7.8) B. 35.9 (6.9) to 32.4 (7.6) to 32.4 (6.4) C. 36.6 (9.9) to 29.0 (7.9) to 31.4 (5.5) Across groups significant improvement (p=0.03)
Al-Sharman, 2019 **Aerobic Exercise** Aerobics Postintervention, 6 weeks Poor	A. Moderate intensity exercise with stair stepper, 18 sessions over 6 weeks (n=17) B. Home exercises (n=13)	A vs. B Age: 39 vs. 32 Female: 76% vs. 77% EDSS: 2.1 vs. 1.9	A vs. B, Mean (SD), p-value is between groups: PSQI: 8.0 (3.8) to 4.6 (2.3) vs. 8.9 (4.3) to 7.1 (3.2), p<0.001 ISI: 12.8 (5.3) to 6.6 (4.08) vs. 10.3 (3.3) to 8.7 (5.1), p=0.04	Total Sleep Time: 333.38 (84.6) to 372.4 (59.4) vs. 325.9 (84.5) to 320 (54), p=0.05

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Amiri, 2019 **Postural Control** Balance exercises Postintervention, 10 weeks Fair	A. Core Stability Training, 30 sessions over 10 weeks (n=35) B. Conventional care including stretching and range of motion exercises (n=34)	A vs. B Age: 32 vs. 31 Female: 100% EDSS: 3.58 vs. 3.74 RRMS: 100%	Significant interaction between time and group according to baseline EDSS score for core muscle function (i.e., core endurance and core strength tests) and static and dynamic stability (p<0.05) Core strength tests (R/L hip abduction, R/L external rotation) demonstrate significant differences in strength based on baseline EDSS score (2.5-3.5; 3.5-4.5; 4.5-5.5), p<0.001	Plank test: significant differences between groups based on EDSS score, p<0.001 Overall static balance tests demonstrate significant differences in strength based on baseline EDSS score and significant differences compared with the control group, p<0.001 Greatest improvements seen in those with greatest disability (least strong)
Aras, 2019 **Aerobic Exercise** Robot-Assisted Gait Training Postintervention, 4 weeks, and 6 month followup Fair	A. RAGT, 20 sessions over 4 weeks (n=10) B. Partial body-weight supported treadmill training, 20 sessions over 4 weeks (n=10) C. Anti-gravity treadmill training, 20 sessions over 4 weeks (n=9)	A vs. B Age: NR Female: 40% vs. 40% vs. 33.3% Race: NR GMFCS II: 90% vs. 70% vs. 88.9% Hemiplegic: 30% vs. 30% vs. 33.3%	A vs. B vs. C, mean change (SD): <u>6MWT</u>: 39.6 (40.4) vs. 37.6 (20.2) vs. 48.3 (25.1), p>0.05 for all pairwise comparisons <u>6MWT (3 mo followup)</u>: 45.2 (44.4) vs. 48.6 (37.8) vs. 58.2 (22.9), p>0.05 for all pairwise comparisons <u>GMFM-D:</u> 3.6 (2.5) vs. 4.6 (4.6) vs. 3.5 (2.5), p>0.05 for all pairwise comparisons <u>GMFM-D (3 month followup)</u>: 3.6 (2.5) vs. 4.6 (4.6) vs. 3.5 (2.5), p>0.05 for all pairwise comparisons <u>GMFM-E</u>: 2.4 (2.0) vs. 2.6 (1.7) vs. 3.7 (1.9), p>0.05 for all pairwise comparisons <u>GMFM-E (3 month followup):</u> 2.6 (1.8) vs. 2.6 (1.7) vs. 3.7 (1.9), p>0.05 for all pairwise comparisons	NA
Arntzen, 2019 Arntzen, 2020 **Postural Control** Balance exercises 7 weeks, plus 18, and 30 weeks Good	A. GroupCoreDIST, 18 sessions over 6 weeks + home exercises (n=39) B. Usual care (n=40)	A vs. B Age: 52 vs. 48 Female: 69% vs. 73% EDSS: 2.45 vs. 2.28 RRMS: 82% vs. 90% PPMS: 13% vs. 5% SPMS: 5% vs. 5%	A vs. B, Mean Difference between groups: Mini-BEST: MD 1.91, 95% CI 1.07 to 2.76, p<0.001 MWT at 7 weeks: MD 16.7, 95% CI 8.15 to 25.25 2MWT at 30 weeks: MD 16.38, 95% CI 7.65 to 25.12 10MWT at 7 weeks: MD 0.48, 95% CI 0.11 to 0.85 10MWT at 30 weeks: MD 0.33, 95% CI -0.04 to 0.71 MSWS-12 at 7 weeks: MD 9.77, 95% CI 3.19 to 16.35 MSWS-12 at 30 weeks: MD 3.87, 95% CI -2.80 to 10.54	NA

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Aviram 2017 **Aerobic Exercise** Treadmill Postintervention, 6 months Fair	A. Treadmill walking 60-minute session twice a week over 3 months (total 30 sessions) B. 8 stations circuit resistance training, including stair climbing and balance sessions similar duration and number of sessions	GMFCS II or III (II/III 70/25) N=95 Mean age 16.6 years 61 males and 34 females (64% males)	Pre, post and 6 months after the intervention 6 minute walk test (meters) A. 342 (79) to 370 (65) to 365 (69) B. 292 (80) to 325 (79) to 320 (84) Change score pre to post, pre to followup A. 29.1 (6.9), 20.9 (4.0) B. 33.7 (6.0), 29.9 (6.7) Between group difference NS p=0.31 10 meter walk test (velocity in m/sec) A. 0.73 (0.20) to 0.80 (0.26) to 1.0 (0.25) B. 0.80 (0.25) to 0.94 (0.32) to 2.0 (0.28) Change score pre to post, pre to followup A. 0.072 (0.21), 0.272 (0.45) B. 0.124 (0.27), 0.278 (0.49) Between group difference NS p=0.41 Timed Up and Go A. 13.9 (4.4) to 11.3 (3.7) to 10.3 (4.8) B. 1401 (5.3) to 12.8 (3.3) to 11.0 (2.9) Change score pre to post, pre to followup A. -1.21 (0.40), -2.82 (0.51) B. -2.72 (0.38), 3.52 (0.61) Between group difference p=0.014 favoring B GMFM-66 A. 64.7 (5.4) to 66.5 (5.8) to 66.5 (5.8) B. 68.2 (10.3) to 71.5 (9.9) to 71.0 (10.6) Change score pre to post, pre to followup A. 1.96 (0.41), 1.98 (0.40) B. 3.27 (0.38), 3.10 (0.44) Between group difference p=0.001 favoring B Overall measures improved from pre to post measures and pre to followup measure showed a significant improvement. No significant group by time differences between groups at followup (ANOVA).	NA

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Aydin, 2014 **Aerobic Exercise** Aerobic Exercise Postintervention, 12 weeks Fair	A. Callisthenic exercises (in clinic): 60 sessions, over 12 weeks, (n=16) B. Callisthenic exercises (home-based): 60 sessions, over 12 weeks, (n=20)	A vs. B Age (mean years): 32.6 vs. 33 Female: 9 (56%) vs. 11 (55%) Race: NR Ambulatory: NR Wheelchair user: NR MS duration (years): 6.4 vs. 7.4 BMI (cm/Kg2): 26.12 vs. 25.25 EDSS: 3.6 vs. 3.4	A vs. B, mean (SD) 10MWT 10.81 (2.15) vs. 9.95 (1.92), p=0.211 (baseline) 9.47 (1.56) vs. 9.02 (1.78), p=0.386 (postintervention) Pre-post exercise intra-group comparison: Difference1.34 (1.26) vs. 0.93 (1.12), p<0.001 vs. p=0.001 HADS-A 10.63 (7.33) vs. 11.05 (5.73), p=0.762 (baseline) 8.69 (6.11) vs. 10.00 (5.36), p=0.482 (postintervention) Pre-post exercise intra-group comparison: Difference-1.94 (2.35) -1.05 (1.32), p=0.002 vs. p=0.004 HADS-D 8.50 (3.74) vs. 6.75 (3.23), p=0.212 (baseline) 6.13 (3.26) vs. 8.60 (2.41), p=0.011 (postintervention) Pre-post exercise intra-group comparison: Difference -1.94 (2.35) vs. 1.85 (1.60), p=0.003 vs. p<0.001 MusiQoL 63.69 (17.00) vs. 59.75 (14.06), p=0.293 (baseline) 76.00 (18.81) vs. 69.00 (15.11), p= 0.119 (postintervention) Pre-post exercise intra-group comparison: Difference12.31 (7.45) vs. 9.25 (6.99), p=0.001 vs. p<0.001	2.68 A vs. B, mean (SD) BBS 47.56 (6.57) vs. 48.95 (5.38), p=0.369 (baseline) 50.94 (4.97) vs. 50.40 (5.27), p=0.700 (postintervention) Pre-post exercise intra-group comparison: Difference 3.38 (2.78) vs. 1.45 (1.85), p=0.001 vs. p=0.003

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Azimzadeh, 2015 **Postural Control** Tai Chi Postintervention, 12 weeks Poor	A. Tai Chi + psychological classes and physical therapy: 24 sessions, 2 sessions per week over 12 weeks (n=16) B. Psychological classes and physical therapy. (control): 2 sessions per week over 12 weeks (n=18)	A vs. B Age (mean years*): 37.5 vs. 33 Female: 16 (100%) vs. 18 (100%) Race: NR Ambulatory: NR Wheelchair user: NR Duration of MS less than 6 years: 5 vs. 4 Duration of MS 6 to 10 years: 3 vs. 6 Duration of MS more than 10 years: 8 vs. 7 EDSS: 0-1: 7 vs. 3 1.5-2.5: 4 vs. 6 3-4: 3 vs. 2 4.5-5.5: 2 vs. 1 A vs. B Age range*: (n=16) vs. (n=18) 20 to 30 years: 6 (37%) vs.6 (33.3%) 31 to 40 years: 2 (12.5%) vs. 10 (55.6%) 41 to 50 years: 7 (43.8%) vs. 2 (11/1%) 51 to 60 years: 1 (6.2%) vs. 0 (0%) *calculated	NA	A vs. B BBS, mean (SD) 52.25 (3.39) vs. 53.22 (2.23), p=0.496 (baseline) 53.94 (2.23) vs. 53.61 (2.14), p=0.546 (postintervention)

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Bahrami, 2019a **Aerobic Exercise** Treadmill Immediately postintervention, 8 weeks Fair	A. Treadmill, 16 sessions over 8 weeks (n=15) B. Physiotherapy, 16 sessions over 8 weeks (n=15)	A vs. B Age: 30 vs. 25 Female: 47% vs. 40% GMFCS I; 47% vs. 53% GMFCS II: 13% vs. 13% GMFCS III: 40% vs. 33%	A vs. B, Mean (SD); percentage change score, p=between groups 10MWT: 1.080 (0.47) to 1.22 (0.50) [22.46% change] vs. 0.99 (0.56) to 1.02 (0.61) [1.28% change], % change p<0.05 6MWT: 291.13 (160.28) to 342.63 (174.62) [23.68% change] vs. 276.10 (167.19) to 308.57 (181.22)[16.54% change], % change p>0.05 WHOQOL-Brief: 3.55 (.55) to 3.66 (0.59) [3.83% change] vs. 3.33 (0.69) 3.57 (0.67) [8.94% change], % change p>0.05	NA
Baquet, 2018 **Aerobic Exercise** Cycling Postintervention, 12 weeks Fair	A. Bicycle ergometry, 24-36 sessions over 12 weeks (n=34) B. Waitlist control group (n=34)	A vs. B Age (mean years): 38.2 vs. 39.6 Female: 21 (62%) vs. 25 (74%) Race: NR Ambulatory: NR Wheelchair user: NR Other: RRMS 34 (100%) vs. 34 (100%)	A vs. B Mean Difference between groups: 6MWT: 4.0, 95% CI -36.5 to 44.5, p=0.85 25 foot walk: -0.1, 95% CI -0.4 to 0.2, p=0.49 MSWS: -0.3, 95% CI -2.1 to 1.6, p=0.78 HAQUAMS: -0.4, 95% CI -4.5 to 3.7, p=0.84	NA

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Bleyenheuft, 2017 **Postural Control** Balance Postintervention, 12 weeks Poor	A. Virtual reality (HABIT-ILE): 13 6.4 hour sessions over 13 days (n=10) B. Usual care control (physical therapy): 2 weeks (n=10)	A vs. B Age (mean years): 10.5 vs. 11.4 Female: 4 (40%) vs. 5 (50%) Race: NR Ambulatory: NR Wheelchair user: NR GMFCS level II: 2 vs. 2 GMFCS level III: 7 vs. 7 GMFCS level IV: 1 vs. 1	A vs. B, mean (SD) GMFM-66 55 (5.9) vs. 55 (8.7), p=0.894, (baseline) 62 (6.4) vs.57 (6.6), p<0.001, (postintervention) 6MWT 190 (108.5) vs. 194 (101.1), p=0.940 (baseline) 236 (105.1) vs. 182 (101.1), p=0.026, p-value NS (postintervention)	A vs. B, mean (SD) Pediatric Evaluation of Disability Inventory (PEDI) 52 (12.4) vs. 51 (14.6), p=0.987, (baseline) 60 (10.7) vs. 51 (15.8), p=0.001, (postintervention) Pediatric Balance Scale (PBS) 33 (17.5) vs. 30 (23.9), p=0.749, (baseline) 42 (21.3) vs. 26 (23.2), p=0.002 NS, (postintervention) ABILOCO-Kids (Disability Inventory), logit (SD) -2.5 (2.1) vs.-1.4 (2.2), p=0.291, (baseline) (0.4 (1.7; 0.1), p=0.072 vs. 1.4 (2.6; 0.4), p=0.236 (postintervention)
Brichetto, 2015 **Postural Control** Balance Postintervention, 4 weeks Good	A. Personalized rehab (tailored to sensory impairment): 12 sessions over 4 weeks (n=16) B. Traditional rehab (visual rehab for balance disorders): 12 sessions over 4 weeks (n=16)	A vs. B Age (mean years): 50.1 vs. 51.0 Female: 11 (69%) vs. 12 (75%) Race: NR Ambulatory: NR Wheelchair user: NR Relapsing–remitting: 9 (56%) vs.10 (63%) Secondary progressive: 5 (31%) vs. 4 (25%) Primary progressive: 2 (13%) vs. 2 (13%) Disease duration (years): 9.5 vs. 12 EDSS: 3.7 vs. 3.7	NA	BBS, mean (SD) 46.5 (3.6) vs. 45.8 (6.6) (baseline) 52.8 (2.8) vs. 47.8 (6.1) (postintervention), p<0.001

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Bryant, 2013 **Aerobic Exercise** Cycling Postintervention, 12 weeks Fair	A: Static bike group, 18 sessions over 6 weeks (n=11) B: Treadmill group, 18 sessions over 6 weeks (n=12) C: Control group no intervention (n=12)	A vs. C Age (mean years): 14.3 vs. 13.8 Female: 5 (45%) vs. 7 (58%) Race: NR Ambulatory: 0 (0%) vs. 0 (0%) Wheelchair user: 11 (100%) vs. 12 (100%) Other: CP: 100% had bilateral CP B vs. C Age (mean years): 13.5 vs. 13.8 Female: 3 (25%) vs. 7 (58%) Race: NR Ambulatory: 12 (100%) vs. 12 (1000%) Wheelchair user: 12 (100%) vs. 12 (100%) Other: CP: 100% had bilateral CP	A vs. C, mean (SD) GMFM-66: NS B vs. C, mean (SD) GMFM-66: NS	NA

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Bulguroglu, 2017 **Muscle Strength** Postintervention, 0 weeks Poor	A. Mat Pilates: 16 sessions over 8 weeks (n=12) B. Reformer Pilates: 16 sessions over 8 weeks (n=13) C. Usual care: relaxation and respiration exercises at home for 16 sessions over 8 weeks (n=13)	A vs. B vs. C Age (mean years): 45 vs. 37 vs. 40 Female: NR Race: NR Ambulatory: 12 (100%) vs. 13 (100%) vs. 13 (100%) Wheelchair user: NR Duration of illness (mean years): 4.5 vs. 5 vs. 3	Data reported as median (IQR) A vs. C TUG (seconds): 6.5 (5.2 to 7.0) vs. 5.2 (4.6 to 6.1) (baseline) 5.7 (5.0 to 6.5) vs. 4.9 (4.5 to 5.3) (postintervention) MSQoL-54-MCS (0-100, higher=increased QOL): 74.54 (65.43 to 83.41) vs. 75.65 (68.08 to 86.38) (baseline) 77.23 (70.72 to 84.54) vs. 78.52 (64.77 to 89.21) (postintervention) MSQoL-54-PCS (0-100, higher=increased QOL): 74.54 (65.43 to 83.41) vs. 77.35 (68.17 to 88.31) (baseline) 75.8 (70.83 to 86.42) vs. 82.64 (66.77 to 91.27) (postintervention) B vs. C TUG (seconds): 6.4 (5.0 to 8.9) vs. 5.2 (4.6 to 6.1) (baseline) 5.4 (4.9 to 7.1) vs. 4.9 (4.5 to 5.3) (postintervention) MSQoL-54-MCS (0-100, higher=increased QOL): 74.58 (70.39 to 80.58) vs. 75.65 (68.08 to 86.38) (baseline) 69.2 (65.86 to 71.41) vs. 78.52 (64.77 to 89.21) (postintervention) MSQoL-54-PCS (0-100, higher=increased QOL): 71.14 (67.26 to 74.35) vs. 77.35 (68.17 to 88.31) (baseline) 76.3 (74.39 to 83.37) vs. 82.64 (66.77 to 91.27) (postintervention)	Data reported as median (IQR) A vs. C ABC (0-100, higher=better balance): 76.6 (62.7 to 92.7) vs. 90.6 (74.4 to 97.4) (baseline) 80.5 (71.7 to 97.3) vs. 91.9 (75.6 to 99.1) (postintervention) Modified pushup (repetitions/30 seconds): 6.5 (1.25 to 14.25) vs. 7 (5 to 9) (baseline) 10 (6 to 20) vs. 7 (2.5 to 9.5) (postintervention) Modified sit-up (repetitions/30 seconds): 6 (0 to 15.5) vs. 4 (0 to 14) (baseline) 7.5 (0 to 18.5) vs. 8 (0 to 14) (postintervention) Trunk flexor test (seconds): 2.32 (0 to 10.25) vs. 6.46 (0 to 12.18) (baseline) 6 (2.17 to 17) vs. 6.4 (0.49 to 16.06) (postintervention) Prone bridge (seconds): 18.29 (8.08 to 26.65) vs. 20.68 (9.62 to 29.94) (baseline) 25.23 (8.31 to 53.85) vs. 21.21 (10.70 to 24.98) (postintervention) B vs. C ABC (0-100, higher=better balance): 69.4 (52.8 to 87.8) vs. 90.6 (74.4 to 97.4) (baseline) 69.4 (52.8 to 87.8) vs. 91.9 (75.6 to 99.1) (postintervention) Modified pushup (repetitions/30 seconds): 3 (1 to 11.5) vs. 4 (0 to 14) (baseline) 10 (4 to 16) vs. 8 (0 to 14) (postintervention)

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Bulguroglu, 2017 **(Continued)**			A vs. B TUG (seconds): 6.5 (5.2 to 7.0) vs. 6.4 (5.0 to 8.9) (baseline) 5.7 (5.0 to 6.5) vs. 5.4 (4.9 to 7.1) (postintervention) –0.5 (–0.7 to –0.1) vs. –0.6 (–1.0 to 0.01), p=0.849 (post-pre change) MSQoL-54-MCS (0-100, higher=increased QOL): 74.54 (65.43 to 83.41) vs. 74.58 (70.39 to 80.58) (baseline) 77.23 (70.72 to 84.54) vs. 74.58 (70.39 to 80.58) (postintervention) 4.5 (1.7 to 5.9) vs. 5.1 (2.9 to 7.2), p=0.414 (post-pre change) MSQoL-54-PCS (0-100, higher=increased QOL): 74.54 (65.43 to 83.41) vs. 71.14 (67.26 to 74.35) (baseline) 75.8 (70.83 to 86.42) vs. 76.3 (74.39 to 83.37) (postintervention) 4.4 (2.1 to 7.1) vs. 6.3 (4.5 to 8.8), p=0.231 (post-pre change)	Modified sit-up (repetitions/30 seconds): 10 (0 to 21) vs. 4 (0 to 14) (baseline) 15 (2 to 22) vs. 8 (0 to 14) (postintervention) Trunk flexor test (seconds): 4.91 (0 to 11.80) vs. 6.46 (0 to 12.18) (baseline) 13.3 (1.35 to 23.73) vs. 6.4 (0.49 to 16.06) (postintervention) Prone bridge (seconds): 22.31 (4.72 to 44.71) vs. 20.68 (9.62 to 29.94) (baseline) 37.53 (14.63 to 60.73) vs. 21.21 (10.70 to 24.98) (postintervention) A vs. B ABCS (0-100, higher=better balance): 76.6 (62.7 to 92.7) vs. 69.4 (52.8 to 87.8) (baseline) 80.5 (71.7 to 97.3) vs. 69.4 (52.8 to 87.8) (postintervention) 5 (0.7 to 11.1) vs. 2.5 (0.2 to 16.9), p=0.913 (post-pre change) Modified pushup (repetitions/30 seconds): 6.5 (1.25 to 14.25) vs. 3 (1 to 11.5) (baseline) 10 (6 to 20) vs. 10 (4 to 16) (postintervention) 2 (1 to 4) vs. 2 (1.5 to 7), p=0.507 (post-pre change) Modified sit-up (repetitions/30 seconds): 6 (0 to 15.5) vs. 10 (0 to 21) (baseline) 7.5 (0 to 18.5) vs. 15 (2 to 22) (postintervention) 0 (0 to 1) vs. 1 (0 to 5.5), p=0.199 (post-pre change)

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Bulguroglu, 2017 **(Continued)**				Trunk flexor test (seconds): 2.32 (0 to 10.25) vs. 4.91 (0 to 11.80) (baseline) 6 (2.17 to 17) vs. 13.3 (1.35 to 23.73) (postintervention) 0.6 (IQR, 0 to 5.4) vs. 7.6 (0.5 to 10.8), p=0.044 (median, post-pre change) Prone bridge (seconds): 18.29 (8.08 to 26.65) vs. 22.31 (4.72 to 44.71) (baseline) 25.23 (8.31 to 53.85) vs. 37.53 (14.63 to 60.73) (postintervention) 6.2 (IQR, 0.4 to 30.1) vs. 9.1 (2.3 to 16.2), p=0.957 (post-pre change)
Burschka, 2014 **Postural Control** Tai Chi Postintervention, 24 weeks Poor	A. Tai Chi: 48 sessions (2 sessions per week) over 24 weeks, 6 months (n=15) B. Usual care control: (n=17)	A vs. B Age (mean years): 42 vs. 43 Female: 10 (66%) vs. 12 (71%) Race: NR Ambulatory: 100% Wheelchair user: NR BMI: 24.2 vs. 25.5 MS duration (mean years): 6 vs. 7.8 MS Course Relapsing-remitting: 14 vs. 13 Secondary progressive: 0 vs. 4 Clinically isolated syndrome: 1 vs. 0 EDSS score <5: 100% vs. 100% EDSS (range, median): 1–4, median=2 vs. 1–4.5, median=4	A vs. B, mean (SD) Depression (15-item questionnaire Center for Epidemiological Studies Depression Scale CES-D) (ADS score) 12.21 (6.66) vs. 13.87 (10.82) (baseline) 7.67 (5.12) vs. 16.13 (11.99) (postintervention) Depression, main effect of time [F (1,27)=6.61, p<0.05, partial η2=0.19] Time by Group interaction [F (1,27)=6.55, p<0.05, partial η2=0.20] Quality of Life Questionnaire of Life Satisfaction (QLS - 7 item, 1–7 rating scale, max score 420 points) 215.77 (25.55) vs. 204.46 (27.77) (baseline) 232.57 (25.62) vs. 193.81 (36.2) (postintervention) QSL significant main effect Group [F (1,24)=8.64, p< 0.01, partial η2 = 0.19]	A vs. B, mean (SD) Balance (14 tasks, measured 1=achieved task, 0=failed task) Balance, 8.00 (2.83) vs. 6.88 (4.09) (baseline) 9.33 (2.26) vs. 6.53 (4.49) (postintervention) Coordination, main effect of time [F (1,30) = 4.89, p<0.05, partial η2=0.14] Time by group interaction [F (1,30) =6.57, p<0.05, partial η2=0.18]

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Cakit, 2010 **Multimodal Exercise** Postintervention, 0 weeks Poor	A. Progressive resistance cycling + balance exercises (lower extremity strengthening): 16 sessions over 8 weeks (n=14) B. Usual care (n=9)	A vs. B (data only for those that completed the study: n=14 vs. 9) Age (mean years): 36.4 vs. 35.5 Female: 9 (64%) vs. 6 (67%) Race: NR Ambulatory: NR Assistive device: 4 (28.5%) vs. 3 (37.5%) Duration of MS (mean years): 9.2 vs. 6.6 Fall frequency last year (mean): 2.0 vs. 2.4	Data reported as mean (SD) A vs. B BDI (0-63, higher=worse depression): 22.8 (12.7) vs. 27.0 (17.6), p=NR (baseline) 17.2 (12.3) vs. 25.4 (22.8), p=NR (postintervention) -5.5 (5.3) vs. -1.6 (6.0), p=<0.05 (pre-post change) TUG (seconds): 10.7 (1.4) vs. 14.6 (9.1), p=NR (baseline) 9.3 (0.8) vs. 14.4 (9.5), p=NR (postintervention) -1.3 (1.2) vs. -0.2 (0.8), p<0.05 (pre-post change) 10MWT (seconds): 12.0 (2.4) vs. vs. 12.2 (3.1), p=NR (baseline) 10.0 (1.6) vs. 12.3 (3.2), p=NR (postintervention) -1.9 (1.2) vs. 0.1 (0.8), p<0.05 (pre-post change) DGI (0-24; ≥16 high risk for falls, <19 decreased risk for falls): 17.4 (4.4) vs. 16.4 (4.9), p=NR (baseline) 20.1 (3.8) vs. 16.8 (5.7), p=NR (postintervention) 2.7 (0.5) vs. 0.4 (0.4), p<0.01 (pre-post change) SF-36 subscale - Physical Functioning 43.3 (16.6) vs. 43.2 (17.7) (baseline) 64.6 (18.6) vs. 51.0 (20.5) (postintervention) 21.2 (14.4) vs. 7.7 (7.4) (pre-post change) SF-36 subscale - Role-physical Function 15.9 (23.1) vs. 30.0 (20.9) (baseline) 50.0 (43.3) vs. 35.0 (37.1) (postintervention) 34.0 (30.1) vs. 5.0 (44.7) (pre-post change)	Data reported as mean (SD) A vs. B FES (0 to 100; higher scores=increased confidence in performing ADL): 19.7 (11.7) vs. 32.4 (24.1), p=NR (baseline) 8.3 (5.6) vs. 29.8 (24.1), p=NR (postintervention) -11.3 (7.8) vs. -2.6 (3.1), p<0.01 (pre-post change)

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Cakit, 2010 **(Continued)**			SF-36 subscale - Bodily pain 60.6 (25.5) vs. 72.0 (28.9) (baseline) 69.5 (28.7) vs. 76.0 (29.9) (postintervention) 8.8 (5.8) vs. 4.0 (4.0) (pre-post change) SF-36 subscale - General Health 50.1 (17.6) vs. 64.8 (13.9) (baseline) 54.5 (21.5) vs. 68.0 (23.4) (postintervention) 4.3 (8.4) vs. 3.2 (11.7) (pre-post change) SF-36 subscale - Vitality 40.9 (16.2) vs. 53.0 (14.8) (baseline) 50.0 (27.2) vs. 64.0 (21.6) (postintervention) 9.0 (19.3) vs. 11.0 (20.4) (pre-post change) SF-36 subscale - Social Functioning 62.5 (25.6) vs. 65.0 (1.1) (baseline) 65.9 (28.0) vs. 70.0 (27.3) (postintervention) 3.4 (23.1) vs. 5.0 (16.7) (pre-post change) SF-36 subscale - Role-emotional functioning 33.3 (36.4) vs. 66.6 (47.1) (baseline) 57.5 (44.9) vs. 86.6 (18.2) (postintervention) 24.2 (49.6) vs. 19.9 (50.5) (pre-post change) SF-36 subscale - Mental health 35.0 (19.6) vs. 38.0 (15.6) (baseline) 42.2 (22.7) vs. 45.0 (21.5) (postintervention) 7.2 (13.4) vs. 7.0 (6.7) (pre-post change)	

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Calabro, 2017 Intervention type: **Aerobic Exercise** Robot-Assisted Gait Training Postintervention, 8 weeks Good	A. Lokomat-Nanos (RAGT), 40 sessions over 8 weeks (n=20) B. Lokomat-Pros (RAGT + VR, 40 sessions over 8 weeks (n=20)	A vs. B Age (mean years): 41 vs. 44 Female: 60 (%) vs. 65 (%) Race: NR Ambulatory: NR Wheelchair user: NR Other: disease duration mean: 11.5 years vs. 11.5 years EDSS 4.75 vs. 4.4 years of education 10 vs. 11	A. TUG T0: 9.8, T1: 8, p=0.002 Initial 10, T1 7.9, p=0.001 BBS T0: 36, T1:44, p=0.003 T0:35, T1:50, p<0.001 MAS T0:1.5, T1:0.5, p=0.2 T0:2, T1:1, p=0.1 FIM T0:89, T1:92, p=0.3 T0:87, T2:89, p=0.4	A. HRSD T0: 12, T1: 7, p=0.003 T0: 10, T1: 6, p<0.001

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Callesen, 2019 **Postural Control** Balance exercises **Strength interventions** Muscle Strength Exercises Postintervention, 10 weeks Fair	A. Progressive resistance training (n=23): 20 sessions over 10 weeks -Median number of sessions completed (range): 17 (8 to 19) B. Balance training (n=28): 20 sessions over 10 weeks -Median number of sessions completed (range): 16 (6 to 20) C. Waitlist control (n=20)	A vs. B vs. C Median age: 52 vs. 51 vs. 56 years Female: 70% vs. 82% vs. 80% Race: NR Ambulatory: 100% vs. 100% vs. 100% Gait assistive devices: 17% vs. 11% vs. 10% Median duration of illness: 15 vs. 10 vs. 11 years MS type - Relapsing remitting: 70% vs. 75% vs. 65% - Secondary progressive: 22% vs. 14% vs. 15% - Primary progressive: 70% vs. 9% vs. 20% Median EDSS: 4 vs. 4 vs. 3.5	Mean change scores (95% CI); mean difference (MD) between groups (95% CI) A vs. C 6MWT (meters) 22.8 (4.6 to 41.0) vs. 11.3 (−6.0 to 28.5), MD 12.6 (−11.3 to 36.5), p=0.30 MSWS −6.5 (3.0 to 10.1) vs. −1.3 (−2.2 to 4.7), MD −4.2 (−10.0 to 1.6), p=0.16 25FWT (meters/second) 0.06 (−0.01 to 0.13) vs. 0.04 (−0.03 to 0.11), MD 0.02 (−0.08 to 0.13), p=0.66 SSST (seconds) −0.9 (−2.0 to 0.2) vs. −0.4 (−1.5 to 0.7), MD −0.5 (−2.1 to 1.0), p=0.52 B vs. A 6MWT (meters) 28.5 (13.6 to 43.4) vs. 2.8 (4.6 to 41.0), MD 4.9 (−17.5 to 27.3), p=0.67 MSWS −9.3 (6.3 to 12.3) vs. −6.5 (3.0 to 10.1), MD −3.1 (−8.2 to 2.0), p=0.23 25FWT (meters/second) 0.14 (0.08 to 0.20) vs. 0.06 (−0.01 to 0.13), MD 0.08 (−0.02 to 0.18), p=0.11 SSST (seconds) −2.6 (−3.6 to –1.7) vs. −0.9 (−2.0 to 0.2), MD −1.7 (−3.1 to –0.2), p=0.02	MiniBEST 2.1 (0.8 to 3.4) vs. 0.9 (−0.4 to 2.2), MD 1.1 (−0.7 to 2.9), p=0.24 MiniBEST 4.1 (3.0 to 5.2) vs. 2.1 (0.8 to 3.4), MD 2.2 (0.5 to 3.9), p=0.01

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Carling, 2017 **Postural Control** Balance Postintervention, 7 weeks Fair	A. Group CoDuSe balance exercises: 14 sessions over 7 weeks (n=23) B. Waitlist (Late start) controls: (n=25)	A vs. B Age (mean years): 62 vs. 55 Female: 19 (76%) vs. 16 (62%) Race: NR Ambulatory: 100% RRMS: 0% vs. 23% SPMS: 68% vs. 58% PPMS: 32% vs. 19% Baseline EDSS: 6.16 vs. 6.06 Baseline No Falls: 48% vs. 46% Baseline Multiple Falls: 20% vs. 35%	A vs. B TUG: MD 4.41 SE 3.17, p=0.17 2MWT: -3.24 SE 3.37, p=0.34 Sit to Stand: 0.24 SE 2.12, p=0.91 10MWT: 1.49 SE 3.84, p=0.70 Falls Efficacy Scale International: -1.66 SE 2.39, p=0.49 MS Walking Scale: -7.21 SE 3.60, p=0.051 Trend for falls before treatment, during treatment, after treatment in control group only: -1.24 (1.66), p<0.001	BBS: MD 3.65 SE 1.44, p=0.015
Castro-Sanchez, 2012 **Aerobic Exercise** Aquatics Postintervention, 20 weeks, and 30 weeks Good	A. Ai-Chi aqua therapy with Tai-Chi music, 40 sessions over 20 weeks (n=36) B. Same exercises as group A on exercise mat without music, 40 sessions over 20 weeks (n=37)	A vs. B Age: 46 vs. 50 Female: 72% vs. 65% EDSS: 6.3 vs. 5.9 PPMS: 17% vs. 24% SPMS: 25% vs. 32%	A vs. B, Median (SD), p-value=between groups: MSIS-29 Physical: 48 (15.91) to 41 (12.37) vs. 46 (18.34) to 45 (17.14), p=0.014 MSIS-29 Psychological: 34 (29.47) to 21 (15.73) vs. 30 (23.53) to 25 (19.36), p=0.023 Differences in MSIS-29 maintained at 30 weeks BDI: 14 (7.72) to 5 (3.2) vs. 15 (8.68) to 13 (5.91), p<0.05 Mean (SD) baseline to post-intervention, p-value between groups: Spasm VAS: 5 (2.8) to 2 (4.3) vs. 6 (3.1) to 4 (4.5), 91% improvement vs. 10% improvement, p<0.05	Barthel Index: 91 (7.12) to 86 (9.23) vs. 87 (10.34) to 88 (8.92), p>0.05

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Chen, 2016 **Muscle Strength** 8 weeks – mid intervention 16 weeks – mid intervention Post–52–week intervention 4 weeks Fair	A. Pulmonary rehabilitation: 365 sessions over 52 weeks (n=49) B. Usual care (n=49)	A vs. B Age (mean years): 62.3 vs. 63.1 Female: 0 (0%) vs. 0 (0%) Race: NR Ambulatory: NR Wheelchair user: NR Injury Level -T1–2: 17 (35%) vs. 17 (35%) -T3–4: 16 (33%) vs. 16 (33%) -T5–6: 16 (33%) vs. 16 (33%)	Data reported as mean (SD) A vs. B FEV1 1.17 (0.25) vs. 1.17 (0.47), p>0.05 (baseline) 1.69 (0.39) vs. 1.16 (0.46), p<0.05 (8 weeks, mid intervention) 2.20 (0.44) vs. 1.17 (0.46), p<0.05 (16 weeks, mid intervention) 2.20 (0.45) vs. 1.14 (0.44), p<0.05 (postintervention) 1.18 (0.27) vs. 1.16 (0.46), p>0.05 (4-week followup) FVC 2.16 (0.36) vs. 2.16 (0.42), p>0.05 (baseline) 2.66 (0.57) vs. 2.17 (0.42), p<0.05 (8 weeks, mid intervention) 2.95 (0.56) vs. 2.17 (0.42), p<0.05 (16 weeks, mid intervention) 2.95 (0.54) vs. 2.17 (0.42), p<0.05 (postintervention) 2.15 (0.35) vs. 2.16 (0.42), p>0.05 (4-week followup) MVV 50.5 (11.8) vs. 50.5 (11.8), p>0.05 (baseline) 64.4 (12.4) vs. 50.5 (11.1), p<0.05 (8 weeks, mid intervention) 75.1 (6.8) vs. 53.8 (11), p<0.05 (16 weeks, mid intervention) 75.2 (6.8) vs. 51.5 (10.6), p<0.05 (postintervention) 53.8 (11.0) vs. 52.9 (11.7), p>0.05 (4-week followup)	NR

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Chen, 2016 **(Continued)**			EV1/FVC: 0.53 (0.17) vs. 0.53 (0.17), p>0.05 (baseline) 0.65 (0.15) vs. 0.53 (0.16), p<0.05 (8 weeks, mid intervention) 0.75 (0.07) vs. 0.53 (0.15), p<0.05 (16 weeks, mid intervention) 0.75 (0.08) vs. 0.52 (0.15), p<0.05 (postintervention) 0.56 (0.12) vs. 0.53 (0.16), p>0.05 (4-week followup) SF-36 Subscale - Physical function 54.2 (7.8) vs. 54.2 (7.8), p>0.05 (baseline) 73.8 (7.1) vs. 54.5 (7.57), p<0.05 (8-weeks, mid-intervention) 79.8 (12.0) vs. 54.4 (8.0), p<0.0 (16 weeks, mid-intervention) 81.1 (3.1) vs. 54.4 (7.7), p<0.05 (postintervention) 54.4 (8.0) vs. 54.6 (7.9), p>0.05 (4-week followup) SF-36 Subscale - Social function 50.6 (11.8) vs. 50.6 (11.8), p>0.05 (baseline) 3.7 (6.2) vs. 51.9 (10.9), p<0.05 (8-weeks, mid-intervention) 79.6 (5.4) vs. 50.5 (11.8), p<0.05 (16 weeks, mid-intervention) 80.1 (9.4) vs. 51.2 (11.0), p<0.05 (postintervention) 51.2 (11.0) vs. 50.6 (11.8), p>0.05 (4-week followup) SF-36 Subscale - Role emotional 54.3 (7.85 vs. 5.3 (6.9), p>0.05 (baseline) 64.4 (12.0) vs. 54.4 (7.7), p<0.05 (8-weeks, mid-intervention) 75.1 (6.8) vs. 54.5 (7.5), p<0.05 (16 weeks, mid-intervention) 76.3 (7.3) vs. 54.3 (7.8), p<0.05 (postintervention) 54.2 (7.8) vs. 54.4 (7.7), p>0.05 (4-week followup)	

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Chen, 2016 **(Continued)**			SF-36 Subscale - Mental health 54.1 (7.7) vs. 54.2±7.8, p>0.05 (baseline) 64.3 (12.0) vs. 54.6±7.9, p<0.05 (8-weeks, mid-intervention) 75.3 (6.7) vs. 54.1±7.7, p<0.05 (16 weeks, mid-intervention) 75.1 (6.8) vs. 54.2±7.8, p<0.05 (postintervention) 54.2 (7.8) vs. 54.2±7.8, p>0.05 (4-week followup) SF-36 Subscale - Body pain 51.6 (11.3) vs. 51.2 (11.0), p>0.05 (baseline) 52.7 (11.9) vs. 50.6 (11.8), p>0.05 (8-weeks, mid-intervention) 52.2 (10.5) vs. 51.6 (11.3), p>0.05 (16 weeks, mid-intervention) 51.9 (10.8) vs. 51.5 (10.6), p>0.05 (postintervention) 51.5 (10.6) vs. 51.9 (10.8), p>0.05 (4-week followup)	

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Cho, 2020 **Muscle Strength** Immediately Postintervention, 6 weeks Poor	A. Functional progressive resistance exercise (FPRE), 12 sessions over 6 weeks (n=13) B. Control group, Conventional therapy, 18 sessions; 3 times a week, over 6 weeks, (n=12)	A vs. B Age (mean years): 5.54 vs. 7.17 Female: 9 (69%) vs. 4 (33%) Race: NR Ambulatory: 100% Wheelchair user: NR GMFM Classification Level (1-4 higher scores=physical impairments): 2.08 vs. 2.33 GMFM score: 69.98 vs. 68.15 BMI (Z-score, mean): 0.14 vs. 0.60	A vs. B, mean (SD) GMFM-88 score 69.98 (21.55) vs. 68.15 (27.15) (baseline) 71.78 (21.05) vs. 63.48 (27.48) (postintervention), p=0.019 for group A and 0.375 for group B for change from baseline Increase pre-post for FPRE group p=0.019; control group showed no significant difference, p=0.375.	A vs. B, mean (SD) Dynamic Balance, Forward functional reach test (F-FRT): 21.62 (6.87) vs. 28.17 (14.49) (baseline) 26.65 (7.92), p=0.000 vs. 25.37 (10.20), p=0.261 (postintervention) Dynamic Balance, Side functional reach test (S-FRT): 11.57 (5.72) vs. 15.52 (10.43) (baseline) 16.21 (5.37), p=0.003 vs. 15.95 (8.26), p=0.793 (postintervention) Knee extensor muscle strength, non-dominant side: 40.62 (30.61) vs. 34.54 (28.55) (baseline) 51.24 (33.58), p=0.048 vs. 40.59 (29.50), p=0.062 (postintervention) Knee extensor muscle strength, dominant side 30.45 (27.57) vs. 41.61 (34.00) (baseline) 52.39 (33.13), p=0.010) vs. 43.12 (32.17), p=0.567 (postintervention)

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Chrysagis 2012 **Aerobic Exercise** Treadmill Postintervention, 0 weeks Fair	A. Treadmill training 30 minutes at comfortable speed 3 times a week for 12 weeks B. Conventional physical therapy 3 times a week for 12 weeks	GMFCS I-III n=22 mean age 16.9 years 13 males and 9 females (59% male)	GMFM (Gross Motor Function Measure) (average D [standing] and E [walking] subscales) A. 67.81 (18.22) to 71.67 (18.22) B. 64.45 (18.61) to 65.1(16.53) Difference between groups F=9.088, p=0.007 Medium effect size d=0.38 95% CI -0.50 to 1.26 MAS (spasticity) Knee extensors A. 2.59(0.62) to 2.27 (0.60) B. 2.00(0.54) to 1.51(0.56) No difference between groups F=0.237, p=0.827 Knee flexors A. 2.45 (0.68) to 2.12(0.67) B. 2.40(0.66) to 2.18 (0.71) No difference between groups F=0.237, p=0.632 Foot plantar flexors A. 2.50(0.50) to 2.18(0.56) B. 2.40 (0.62) to 2.22 (0.56) No difference between groups F=0.570, p=0.046	NA

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Claerbout, 2012 **Postural Control** Whole Body Vibration Postintervention, 0 weeks Fair	A. Whole body vibration + conventional therapy: 10 sessions over 3 weeks (n=20) B. Whole body light vibration + conventional therapy: 10 sessions over 3 weeks (n=18) C. Conventional therapy (n=17) [All patients participated in a minimum 3–week multi–disciplinary rehabilitation program which included daily PT/OT sessions (+ other therapies)]	A vs. B vs. C Age (mean years): 39.1 vs. 43.8 vs. 47.6 Female: 6 (28.6%) vs. 4 (22.2%) vs. 11 (64.7%) Race: NR Ambulatory: NR Wheelchair user: NR Disease duration (mean years): 12.1 vs. 12.5 vs. 10.3 EDSS: 5.3 vs. 5.1 vs. 5.2	A vs. C TUG (seconds): 13.4 (9.8) vs. 15.6 (9.3), p>0.05 (baseline) 12.6 (11.3) vs. 14.8 (10.2) (postintervention) −0.8 (2.3) vs. 0.8 (5.5) (pre-post change) −9.1% (19.5%) vs. −4.9% (23.6%) (pre-post % change) Time X Group p>0.05 3 minute walk test (meters): 150.9 (89.4) vs. 143.3 (58.7), p>0.05 (baseline) 195.9 (103.3) vs. 162.3 (62.0) (postintervention) 45.0 (42.6) vs. 20.4 (27.95) (pre-post change) 38.7% (40.3%) vs. 15.8% (20.3%) (pre-post % change) Time X Group p>0.05 B vs. C TUG (seconds): 14.5 (8.8) vs. 15.6 (9.3), p>0.05 (baseline) 11.4 (5.3) vs. 14.8 (10.2) (postintervention) −3.2 (4.7) vs. 0.8 (5.5) (pre-post change) −16.2% (16.4%) vs.−4.9% (23.6%) (pre-post % change) Time X Group p>0.05 3 min walk test (meters): 172.2 (82.7) vs. 143.3 (58.7), p>0.05 (baseline) 209.6 (74.2) vs. 162.3 (62.0) (postintervention) 37.4 (34.3) vs. 20.4 (27.95) (pre-post change) 31.8% (37.2%) vs. 15.8% (20.3%) (pre-post % change) Time X Group p>0.05 A vs. B TUG (seconds): 13.4 (9.8) vs. 14.5 (8.8), p>0.05 (baseline) 12.6 (11.3) vs. 11.4 (5.3) (postintervention) −0.8 (2.3) vs. −3.2 (4.7) (pre-post change) −9.1% (19.5%) vs. −16.2 (16.4%) (pre-post % change) Time X Group p>0.05	A vs. C BBS: 45.1 (12.2) vs. 46.7 (7.0), p>0.05 (baseline) 49.0 (11.5) vs. 48.5 (7.7) (postintervention) 3.9 (4.4) vs. 0.2 (7.5) (pre-post change) 10.0% (11.8%) vs. 3.9% (5.8%) (pre-post % change) Time X Group p>0.05 B vs. C BBS: 43.0 (13.3) vs. 46.7 (7.0), p>0.05 (baseline) 47.2 (12.7) vs. 48.5 (7.7) (postintervention) 4.2 (6.1) vs. 0.2 (7.5) (pre-post change) 12.0 (19.4) vs. 3.9% (5.8%) (pre-post % change) Time X Group p>0.05 A vs. B BBS: 45.1 (12.2) vs. 43.0 (13.3), p>0.05 (baseline) 49.0 (11.5) vs. 47.2 (12.7) (postintervention) 3.9 (4.4) vs. 4.2 (6.1) (pre-post change) 10.0% (11.8%) vs. 12.0 (19.4) (pre-post % change) Time X Group p>0.05

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Claerbout, 2012 **(Continued)**			3 min walk test (meters): 150.9 (89.4) vs. 143.3 (58.7), p>0.05 (baseline) 195.9 (103.3) vs. 209.6 (74.2) (postintervention) 45.0 (42.6) vs. 37.4 (34.3) (pre-post change) 38.7% (40.3%) vs. 31.8% (37.2%) (pre-post % change) Time X Group p>0.05	
Collett, 2010 **Aerobic Exercise** Cycling Postintervention, 12 weeks Poor	A. Combined intermittent and continuous static cycling, 24 sessions over 12 weeks (n=20) B. Intermittent static cycling, 24 sessions over 12 weeks (n=21) C. Continuous static cycling, 24 sessions over 12 weeks (n=20)	A vs. B vs. C Age (mean years): 55 vs. 50 vs. 52 Female: 9 (53%) vs. 14 (78%) vs. 16 (80%) Race: NR Ambulatory: 20 (100%) vs. 21 (100%) vs. 20 (100%) Wheelchair user: NR Other: MS subtypes NR	A vs. B vs. C (SD) Change post-intervention: no data provided 2MWT, SF-36 total, TUG: All NS	Barthel Index Total, Leg Power: All NS

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Curtis, 2018 **Postural Control** Balance Postintervention, 24 weeks Fair	A. Trunk control training: 120 sessions over 24 weeks (n=14) B. Usual care (n=14)	A vs. B Age (mean years): 8 vs. 8 Female: 3 (21%) vs. 7 (50%) Race: NR Ambulatory: NR Wheelchair user: NR Primary motor disability -Spactic: 7 (50%) vs. 9 (64%) -Dyskinetic: 7 (50%) vs. 5 (36%) -Ataxic: 0 vs. 0 GMFCS -III: 2 (14%) vs. 3 (21%) -IV: 4 (29%) vs. 2 (14%) -V :8 (57%) vs.9 (64%)	A vs. B GMFM–66 36.6 (10.6) vs. 35.3 (9.7) (baseline) 38.4 (10.6) vs. 35.9 (8.8), p=NR (postintervention) 36.9 (10.3) vs. 35.7 (10.9), p=NR (24-week followup) 1.8 (4.0) vs. 0.7 (3.3); MD 1.1 (95% CI –2.2 to 4.4, p>0.05) (pre-post change) 0.3 (2.9) vs. 0.5 (4.7); MD 0.1 (95% CI –3.6 to 3.3, p>0.05) (prefollowup change) SATCO Static, median (quartiles) 2 (1:4) vs. 1 (1:4.5) (baseline) 2.5 (1:4.25) vs.1 (1:4.25), p=NR (postintervention) 2.5 (1:4) vs. 2.5 (1:4), p=NR (24-week followup) 0 (−0.25:0.25) vs. 0 (0:0), p>0.05 (pre-post change) 0 (−1:1) vs. 0 (0:0), p>0.05 (prefollowup change) SATCO Active, median (quartiles) 1 (1:3) vs. 1 (1:3) (baseline) 2.5 (1:5) vs. 1 (1:2.5), p=NR (postintervention) 2.5 (1:4) vs. 1 (1:2.5), p=NR (24-week followup) 0 (0:0.25) vs. 0 (0:0), p>0.05 (pre-post change) 0 (0:1) vs. 0 (0:0), p>0.05 (prefollowup change) SATCO Reactive, median (quartiles) 3 (1:4.5) vs. 4 (0.75:5) (baseline) 3 (2:4) vs. 5 (1:6), p=NR (postintervention) 3 (2:4) vs. 3 (3:5), p=NR (24-week followup) 0 (0:1) vs. 0 (−0.5:1), p>0.05 (pre-post change) 0 (−1:0) vs. 0 (−2:0), p>0.05 (prefollowup change)	A vs. B PEDI Self Care: 40.0 (10.7) vs. 38.3 (14.5) (baseline) 41.5 (10.5) vs. 36.5 (17.4), p=NR (postintervention) 42.9 (11.7) vs. 41.7 (18.0), p=NR (24-week followup) 1.5 (4.2) vs. −1.8 (10.2), p>0.05 (pre-post change) 3.0 (4.7) vs. 3.4 (6.3), p>0.05 (prefollowup change) PEDI Self Care – Caregiver Assistance: 29.6 (20.2) vs. 28.6 (22.0) (baseline) 30.2 (20.0) vs. 27.1 (23.3), p=NR (postintervention) 31.1 (20.6) vs. 28.2 (24.2), p=NR (24-week followup) 0.7 (7.2) vs. −1.5 (8.4), p>0.05 (pre-post change) 1.5 (13.5) vs. −0.4 (8.9), p>0.05 (prefollowup change) PEDI Mobility 26.0 (15.1) vs. 24.3 (17.3) (baseline) 26.8 (14.4) vs. 25.3 (20.0), p=NR (postintervention) 28.8 (15.9) vs. 25.4 (20.0), p=NR (24-week followup) 0.9 (8.4) vs. 1.0 (7.6), p>0.05 (pre-post change) 2.8 (9.0) vs. 1.1 (6.4), p>0.05 (prefollowup change)

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Curtis, 2018 **(Continued)**				PEDI Mobility – Caregiver Assistance 29.2 (18.3) vs. 23.7 (22.8) (baseline) 30.3 (20.0) vs. 22.8 (26.5), p=NR (postintervention) 25.0 (19.5) vs. 23.0 (25.3), p=NR (24-week followup) 1.1 (12.6) vs. −0.9 (6.6), p>0.05 (pre-post change) −4.2 (17.2) vs. −0.6 (5.8), p>0.05 (prefollowup change)

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Dalgas, 2009 Dalgas, 2010 **Muscle Strength** Postintervention, 0 weeks Dalgas, 2009: Fair to Good Dalgas, 2010: Poor	A. Progressive resistance: 24 sessions over 12 weeks (n=15) B. Usual care (continue previous activity level) (n=16)	A vs. B (according per-protocol analysis) Age (mean years): 45 vs. 48 Female: 10 (63%) vs. 10 (67%) Race: NR Ambulatory: 15 (100%) vs. 16 (100%) Wheelchair user: NR	Data reported as mean (95% CI) A vs. B (according per-protocol analysis) MDI (20 to 24, mild depression; 25 to 29, moderate depression; >29, major depression): 10.3 (95% CI 7.0 to 13.5) vs. 8.8 (95% CI 6.4 to 11.3) (baseline) 7.9 (95% CI 5.2 to 10.6) vs. 9.9 (95% CI 7.4 to 12.5) (postintervention) NR vs. NR; MD NR, p=0.01 (post-pre change) SF-36 MCS (0-100, higher=better QOL): 54.3 (95% CI 50.4 to 58.2) vs. 55.0 (95% CI 50.5 to 59.5) (baseline) 56.8 (95% CI 52.4 to 61.2) vs. 53.1 (95% CI 49.3 to 56.8) (postintervention) NR vs. NR; MD NR, p=0.09 (post-pre change) SF-36 PCS (0-100, higher=better QOL): 41.4 (95% CI 37.5 to 45.3) vs. 42.6 (95% CI 38.5 to 46.6) (baseline) 44.9 (95% CI 40.9 to 48.9) vs. 41.6 (95% CI 37.8 to 45.4) (postintervention) NR vs. NR; MD NR, p=0.01 (post-pre change) 6MWT (meters): 440.9 (95% CI 346.0 to 535.7) vs. 437.8 (95% CI 367.8 to 507.9) (baseline) 495.4 (95% CI 401.2 to 589.6) vs. 436.2 (95% CI 355.6 to 516.7) (postintervention) 15.3% (95% CI 9.8 to 20.9) vs. 3.9% (95% CI -1.2 to 8.9); MD NR, p<0.05 (post-pre % change) 10MWT (seconds): 7.7 (95% CI 5.6 to 9.7) vs. 7.3 (95% CI 5.9 to 8.6) (baseline) 6.6 (95% CI 4.9 to 8.4) vs. 7.9 (95% CI 6.0 to 9.9) (postintervention) -12.3% (95% CI -16.8 to -7.9) vs. 6.7% (95% CI -0.7 to 14.1); MD NR, p<0.05 (post-pre % change)	Data reported as mean (95% CI) A vs. B (according per-protocol analysis) Max leg press (pounds): 102.4 (95% CI 76.7 to 128.1) vs. NR (baseline) 140.1 (95% CI 112.1 to 168.1) vs. 86.4 (72.4 to 100.4) (postintervention) 37.1% (95% CI 26.6 to 47.6) vs. NR; MD NR, p=NR (post-pre % change) EDSS (0-10, higher=greater disability): 3.7 (95% CI 3.2 to 4.2) vs. 3.9 (95% CI 3.5 to 4.4), p>0.05 (baseline) 3.9 (95% CI 3.3 to 4.6) vs. 4.0 (95% CI 3.4 to 4.6) (postintervention) 3.9% (95% CI -3.4% to 11.2%) vs. -0.7% (95% CI -9.3 to 7.9); MD NR, p=NR (post-pre % change)

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Demuth, 2012 Companion to: Fowler, 2010 **Aerobic Exercise** Cycling Postintervention, 0 weeks Fair	A. Stationary cycling, 30 sessions over 12 weeks (n=33) B. Control No Intervention (n=31)	A vs. B Age (mean years): 10.7 vs. 11.2 Female: 13 (42%) vs. 20 (65%) Race: African-American 5 (16%) vs. 3 (10%) White 18 (58%) vs. 15 (48%) Asian 1 (3%) vs. 5 16(%) Other 7 (23%) vs. 8(26%) Ambulatory: 33 (100%) vs. 31 (100%) Wheelchair user: NR Other: CP type NR	A vs. B (SD) GMFM-66: Change from baseline: 1.2, 95% CI 0.5 to 1.8) vs. 0.5, 95% CI -0.2 to 1.3, between groups p=0.23 600-Yard Walk-Run Test: Change from baseline: 5.6, 95% CI 1.6 to 9.5 vs. 2.5, 95% CI -1.1 to 6.0, p=0.24 Peds Quality of Life Total Score: Mean difference between groups: 3.5, 95% CI -2.0 to 8.8, p=0.21 PedsQL Emotional Functioning 55.6 (NR) vs. 68.1 (NR) (baseline) 64.7 (NR) vs. 68.3 (NR); p=0.046 (postintervention) PedsQL Physical Functioning, Psychosocial Health Summary, Social Functioning, School Functioning, Total Score: All NS	NA

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Deutz, 2017 **Postural Control** Hippotherapy Middle of treatment (after 8-week observational phase and 16- to 20-week intervention) and end of treatment (after 16-week washout period, 16- to 20-week intervention, and 8-week observational phase) Poor	A. Early treatment group (ETG), 16 to 32 units of hippotherapy over 16 to 20 weeks in addition to usual conventional physiotherapy (n=35) B. Late treatment group (LTG), usual conventional physiotherapy over 16 to 20 weeks (n=38) Crossover trial with a washout period of 16 weeks between two intervention periods	A vs. B Age (mean years): 9.29 vs. 8.87 Female: 12 (34%) vs. 17 (45%) Race: NR Ambulatory: NR Wheelchair user: NR GMFCS level: GMFCS level II: 10 (29%) vs. 17 (45%) GMFCS level III: 7 (20%) vs. 10 (26%) GMFCS level IV: 18 (51%) vs. 11 (29%) Preterm children: 26 (74%) vs. 28 (74%) Nonpreterm children: 9 (26%) vs. 10 (26%)	A vs. B 16 to 20 weeks GMFM-66: Direct treatment effect resulting from the mixed model approach: p=0.3193, F=1.01, DF=(1, 47) Difference in means between the two treatments: 0.52 (95% CI –0.52 to 1.55) CHQ-28: Psychosocial: Difference in means: -0.21 (95% CI -3.89 to 3.47) Direct treatment effect: p=0.9089 Physical: Difference in means: 4.77 (95% CI -1.12 to 10.66) Direct treatment effect: p=0.1092 KIDSCREEN-27: Difference in means: 1.07 (95% CI -2.53 to 4.68) Direct treatment effect: p=0.5483	NR

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Dodd, 2011 **Muscle Strength** Immediately postintervention, 12 weeks Good	A. Progressive resistance: 20 sessions over 10 weeks (n=39) B. Usual care + social program: leisure and social activities not expected to have a fitness or training effect (i.e. massage, luncheons and educational sessions, including some that enabled participants to experience a single session of different physical therapies such as Bobath therapy and yoga): 10 sessions over 10 weeks (n=37)	A vs. B [for patients with postintervention assessment (n=36 vs. 35)] Age (mean years): 47.7 vs. 50.4 Female: 26 (72%) vs. 26 (74%) Race: NR Ambulation index -2 (mild): 17 (47%) vs. 19 (54%) -3 (moderate): 14 (39%) vs. 9 (26%) -4 (severe): 5 (14%) vs. 7 (20%) Gait aid use (yes): 12 (33%) vs. 13 (37%) Fatigued (MFIS>38): 22 (61%) vs. 19 (54%)	Data reported as mean (SD) A vs. B (n=36 vs. 35, ITT analysis) 2 min walk test (meters): 120.2 (35.8) vs. 112.1 (37.2) (baseline) 122.9 (35.1) vs. 112.9 (38.5) (postintervention) 118.6 (39.0) vs. 113.7 (40.3) (12 weeks) 2.8 (14.4) vs. 0.7 (13.4); MD 2.6 (95% CI -4.0 to 9.1), p>0.05; effect size=0.27 (95% CI -0.20 to 0.74) (post-pre change) -1.6 (15.6) vs. 1.6 (9.0); MD -3.4 (95% CI -9.5 to 2.7), p>0.05; effect size=0.12 (95% CI -0.34 to 0.59) (12 week-pre change) MSIS-88 muscle stiffness (12 to 48, higher=increased muscle stiffness): 27.0 (8.8) vs. 25.1 (9.0) (baseline) 22.4 (7.8) vs. 24.7 (7.9) (postintervention) 26.5 (8.7) vs. 24.2 (8.2) (12 weeks) -3.6 (7.6) vs. -0.5 (6.0); MD -2.4 (95% CI -5.2 to 0.5), p>0.05; effect size=-0.29 (95% CI -0.76 to 0.18) (post-pre change) -0.5 (7.0) vs. -0.7 (7.7); MD 0.8 (95% CI -2.3 to 4.0), p>0.05; effect size=0.27 (95% CI -0.20 to 0.74) (12 week-pre change) MSIS-88 muscle spasms (14 to 56, higher=increased muscle spasms): 22.3 (7.7) vs. 22.8 (9.2) (baseline) 20.3 (6.1) vs. 23.3 (7.6) (postintervention) 23.4 (8.5) vs. 21.7 (6.3) (12 weeks) -2.0 (6.2) vs. 0.5 (8.9); MD -2.8 (95% CI -5.6 to 0.03), p>0.05; effect size=0.43 (-0.90 to 0.04) (post-pre change) 1.1 (8.2) vs. -1.1 (7.5); MD 1.9 (95% CI -1.1 to 5.0), p>0.05; effect size 0.22 (95% CI -0.24 to 0.69) (12 week-pre change)	Data reported as mean (SD) A vs. B (n=36 vs. 35, ITT analysis) WHO-QOL Overall QOL (1-5, higher=decreased QOL): 3.0 (1.0) vs. 2.9 (1.0) (baseline) 3.3 (0.9) vs. 2.9 (1.2) (postintervention) 3.1 (1.0) vs. 3.0 (1.0) (12 weeks) 0.3 (1.2) vs. -0.1 (1.0); MD 0.4 (95% CI -0.04 to 0.9), p>0.05; effect size=0.37 (95% CI -0.10 to 0.84) (post-pre change) 0.1 (1.1) vs. 0.1 (1.0); MD -0.001 (95% CI -0.4 to 0.4), p<0.05; effect size=0.10 (95% CI -0.37 to 0.56) (12 week-pre change) Max leg press (kg): 70.0 (36.0) vs. 62.2 (37.6) (baseline) 85.8 (46.5) vs. 66.0 (41.6) (postintervention) 80.2 (40.5) vs. 68.3 (42.5) (12 weeks) 15.9 (15.5) vs. 3.9 (11.1); MD 10.8 (95% CI 4.9 to 16.7), p<0.05; effect size=0.44 (95% CI -0.03 to 0.91) (post-pre change) 10.2 (13.7) vs. 6.2 (11.6); MD 3.5 (95% CI -2.5 to 9.4), p>0.05; effect size 0.28 (95% CI -0.18 to 0.75) (12 week-pre change) Reverse leg press (kg): 30.8 (22.3) vs. 27.4 (18.0) (baseline) 37.3 (21.2) vs. 28.5 (18.1) (postintervention) 35.8 (20.1) vs. 32.1 (19.5) (12 weeks) 6.5 (8.7) vs. 1.1 (7.9); MD 5.7 (95% CI 1.9 to 9.5), p<0.05; effect size=0.44 (95% CI -0.03 to 0.91) (post-pre change) 5.0 (10.1) vs. 4.7 (7.9); MD 0.7 (95% CI -3.5 to 4.9), p>0.05; effect size=0.18 (95% CI -0.28 to 0.65) (12 week-pre change)

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Doulatabad, 2013 **Postural Control** Yoga Postintervention, 12 weeks Poor	A. Yoga: 24 sessions over 12 weeks (n=30) B. Usual care control: no intervention, over 12 weeks (n=30)	A vs. B Age (average): 31.6 (range: 18 to 45) Female: 30 (100%) vs. 30 (100%) Race: NR Ambulatory: NR Wheelchair user: NR	A. vs. B., mean (SD) MSQoL-54 (10 indicates best quality of life): 4.9±1.9 vs.6.9±1.5 (baseline) 7.4±2.16 vs. 6.8±1.9 (postintervention), p=0.001	NA
Duarte Nde, 2014 **Aerobic Exercise** Treadmill Postintervention, 3 weeks and 5 weeks Fair Note: May share participants with Grecco, 2014	A. Treadmill + tDCS, 10 sessions over 2 weeks (n=12) B. Treadmill + sham tDCS, 10 sessions over 2 weeks, (n=12)	A vs. B Age: 8 vs. 8 Female: NR GMFCS I: 25% vs. 17% GMFCS II: 50% vs. 57% GMFCS III: 25% vs. 25%	A vs. B, Mean (SD), p-value=between groups: PEDI self-care: 46.1 (10) to 48.0 (9.5) vs. 45.0 (9.2) to 45.5 (9.3); MD 1.4, 95% CI -6.21 to 9.01, p=0.718 PEDI mobility: 38.0 (8.5) to 41.7 (7.4) vs. 38.3 (7.4) to 39.5 (7.6); MD 2.5, 95% CI -3.71 to 8.71, p=0.430	A vs. B, Mean (SD), p-value=between groups: PBS: 40.5 (9.4) to 45.3 (7.9) vs.39.1 (9.8) to 39.7 (8.4); MD 4.2, 95% CI -2.88 to 11.28, p=0.245

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Duff, 2018 **Muscle Strength** Postintervention, 0 weeks Fair	A. Pilates + massage: 24 sessions of Pilates and 12 massages over 12 weeks (n=15) B. Massage: 12 massages over 12 weeks (n=15)	A vs. B Age (mean years): 45.7 vs. 45.1 Female: 12 (80%) vs. 11 (73%) Race: NR Ambulatory: (100%) vs. 100 (100%) Wheelchair user: 0 (0%) vs. 0 (0%) MS type -relapsing-remitting: 14 (93%) vs. 11 (73%) -secondary progressive: 0 (0%) vs. 2 (13%) -primary progressive: 1 (7%) vs. 2 (13%) Relapse in 30 days before baseline: 2 (13%) vs. 3 (20%)	Data reported as mean (SD) A vs. B TUG with left turn (seconds): 10.1 (4.6) vs. 8.6 (4.9), p>0.05 (baseline) 8.6 (2.8) vs. 8.9 (5.0) (postintervention) -1.5 (SD 2.8; 95% CI –2.7 to –0.4) vs. 0.3 (SD 0.9; 95% CI –0.9 to 1.4), p=0.03 (pre-post change) TUG with right turn (seconds): 9.9 (4.0) vs. 9.2 (4.9), p>0.05 (baseline) 8.8 (3.3) vs. 9.5 (5.5) (postintervention) –1.1 (95% CI –2.1 to –0.1) vs. 0.3 (95% CI –0.7 to 1.4), p=0.6 (pre-post change) 6MWT (meters): 419.9 (138.2) vs. 455.1 (165.7), p>0.05 (baseline) 472.3 (149.5) vs. 470.1 (168.1) (postintervention) 52.4 (95% CI 32.7 to 72.1) vs. 15.0 (95% CI –4.7 to 34.7), p=0.01 (pre-post change) MSQoL-54-PCS (0 to 100, higher=increased QOL): 53.7 (19.6) vs. 59.3 (18.5), p>0.05 (baseline) 58.3 (17.6) vs. 61.7 (19.5) (postintervention) 4.6 (95% CI –1.3 to 10.5) vs. 2.4 (95% CI –3.5 to 8.3), p=0.60 (pre-post change) MSQoL-54-MCS (0 to 100, higher=increased QOL): 62.7 (19.3) vs. 71.3 (15.4), p>0.05 (baseline) 68.6 (18.8) vs. 75.5 (13.8) (postintervention) 5.9 (95% CI –0.5 to 12.2) vs. 4.2 (95% CI –2.1 to 10.6), p=0.71 (pre-post change)	Data reported as mean (SD) A vs. B FABS (0-4, higher=increased balance): 28.7 (11.7) vs. 28.0 (13.2), p>0.05 (baseline) 31.0 (9.2) vs. 30.2 (13.3) (postintervention) 2.3 (95% CI 0.3 to 4.3) vs. 2.2 (95% CI 0.2 to 4.2), p=0.96 (pre-post change) % body fat: 32.7 (8.3) vs. 32.2 (10.5), p>0.05 (baseline) 32.5 (7.6) vs. 31.4 (11.1) (postintervention) –0.2 (95% CI –1.4 to 1.0) vs. –0.8 (95% CI –2.0 to 0.4), p=0.51 (pre-post change)

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Duffell, 2014 **Aerobic Exercise** Robot-Assisted Gait Training Postintervention, 4 weeks Poor	A. Robot-assisted gait training (RAGT), 12 sessions over 4 weeks (n=23) B. No intervention (n=29)	A vs. B Age: NR Female: NR Incomplete: 100%	A vs. B, p=between groups 10MWT achieved MID (0.13m/s): 13% vs. 8%, p>0.05 6MWT and TUG: p>0.05	NA
Ebrahimi, 2015 **Multimodal** Postintervention, 0 weeks Poor	A. Whole body vibration + low intensity exercise: 30 sessions over 10 weeks (n=16) B. Usual care (n=14)	A vs. B (Data are for those with complete followup data) Age (mean years): 37.06 vs. 40.75 Female: 11 (69%) vs. 12 (86%) Race: NR Ambulatory: 16 (100%) vs. 14 (100%) Wheelchair user: NR Baseline EDSS: 3.12 vs. 3.10 Use of disease–modifying drugs: 10 (62.5%) vs. 8 (57.1%) Duration of disease (mean years): 6.5 vs. 10.5	Data reported as mean (SD) A vs. B TUG (seconds) 11.32 (5.21) vs. 14.43 (3.20) (baseline) 11.16 (8.82) vs. 14.57 (4.02) (postintervention) Group p=0.05 10MWT (seconds) 17.67 (8.92) vs. 21.16 (6.36) (baseline) 13.37 (4.59) vs. 19.39 (6.52) (postintervention) Group p=0.56 6MWT (meters) 184.01 (101.04) vs. 150.37 (65.18) (baseline) 272.32 (105.60) vs. 162.80 (60.57) (postintervention) 47.99% vs. NR (pre-post % change) Group p=0.01 MSQ0L-54-PCS (0-100, higher=increased QOL) 45.80 ± 9.70 vs. 43.38 ± 15.43 (baseline) 53.36 ± 11.9 vs. 45.53 ± 7.30 (postintervention) Group p=0.40 MSQOL-54-MCS (0-100, higher=increased QOL) 50.87 ± 15.46 vs. 41.66 ± 17.07 (baseline) 58.34 ± 14.89 vs. 50.10 ± 14.72 (postintervention) Group p=0.42	Data reported as mean (SD) A vs. B Modified pushup 5.31 (4.75) vs. 2.42 (3.99) (baseline) 12.12 (6.54) vs. 2.92 (3.83) (postintervention) Group p=0.07 EDSS (1-10, higher scores=greater disability) 3.12 (1.19) vs. 3.10 (0.76) (baseline) 2.65 (1.20) vs. 3.03 (0.69) (postintervention) –15.06% vs. NR (pre-post % change) Group p=0.01 BBS (0-56, higher scores=better balance) 40.37 (9.97) vs. 34.00 (9.13) (baseline) 46.43 (8.34) vs. 35.85 (7.22) (postintervention) 15.00% vs. NR (pre-post % change) Group p=0.01

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Elnaggar 2019 **Strength** Plyometric training Postintervention, 8 weeks Fair	A. Plyometric training, 16 sessions over 8 weeks (n=19) B. Usual care (n=20)	Age: 9.47 vs. 10.3 Female: 32% vs. 45% Race: NR Abulatory: 100% vs. 100% Wheelchair user: NR All patients were considered to have mildly spastic CP	A vs. B, Mean (SD) [pre-post change score and MD calculated by EPC] 10MWT (m/s): 1.18 (0.08) vs. 1.21 (0.09) (baseline) 1.29 (0.06) vs. 1.25 (0.05) (post-intervention) 0.11 (0.05) vs. 0.04 (0.06), MD 0.07 (95% CI 0.04 to 0.10) (pre-post change score)	NA
El-Shamy, 2018 **Postural Control** Motion gaming Postintervention, 12 weeks Fair	A. Robotic upper-limb therapy, 36 sessions over 12 weeks (n=15) B. Conventional therapy of stretching and strength exercises, 36 sessions over 12 weeks (n=15)	A vs. B Age: 6.9 vs. 6.8 Female: 40% vs. 27% MACS I: 33% vs. 40% MACS II: 53% vs. 40% MACS III: 13% vs. 20%	A vs. B, Mean (SD), p=between groups Spasticity MAS: –0.4, 95% CI –0.8 to –0.1, p<0.05 QUEST total: 61.9 (2) to 84.6 (2.7) vs. 62.3 (1.8) to 79.1 (2); MD 5.9, 95% CI 3.7 to 7.3, p<0.05	NA

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Emara, 2016 **Aerobic Exercise** Treadmill Postintervention, 12 weeks Fair	A. Treadmill training, 36 sessions over 12 weeks (n=11) B. Suspension training, (dynamic spider cage) 36 sessions over 12 weeks (n=11)	A vs. B Age (mean years): 6.6 vs. 6.9 Female: 7 (64%) vs. 6 (55%) Race: NR Ambulatory: NR Wheelchair user: NR Baseline GMFM-d: gross motor functional measure dimension D (standing): GMFM-d: 12 (1.6) vs. 12.0 (0.7) Baseline GMFM-e: gross motor function measure dimension E (walking): GMFM-e: 10.9 (1.3) vs. 10.4 (0.8) Baseline 10-m Walking Test: 0.4 (0.04) vs. 0.4 (0.03) Baseline Five times sit to stand: 21.5 (1.3) vs. 21.7 (1.5)	A vs. B, mean (SD) **6 weeks (18-sessions)** GMFM-d: 13.7 (1.2) vs. 15.3(1.9), p=0.04 GMFM-e: 13.2 (1.9 vs. 14.3 (1.9), p=0.21 10-m Walking Test: 0.4 (0.05) vs. 0.5 (0.04), p=0.12 Five times sit to stand: 20.1 (1.0 vs. 19.5 (0.9), p=0.26 **12 weeks (36-sessions)** GMFM-d: 15.8 (1.5) vs. 19.2 (2.1), p=0.001 GMFM-e: 14.8 (1.5) vs. 17.2 (2.1), p=0.008 10-m Walking Test: 0.5 (0.04) vs. 0.6 (0.04) Five times sit to stand: 18.9 (1.0) vs. 17.7(0.8)	NR

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Esclarin-Ruz, 2014 **Aerobic Exercise** Robot-Assisted Gait Training Postintervention, 8 weeks Fair	A. Robotic locomotor training plus overground therapy 40 sessions over 8 weeks (n=44) B. Overground therapy, 40 sessions over 8 weeks (n=44)	A vs. B Age (mean years): UMN injury: 43.6 vs. 44.9 LMN injury: 36.4 vs. 42.7 Female: UMN 29% vs. 29% LMN 30% vs. 29% Race: NR Ambulatory: NR Wheelchair user: NR Other: N (%) vs. N (%)	A vs. B, mean (SD) 10MWT UMN: 0.48 (0.25) to 0.54 (0.31) vs. 0.36 (0.25) to 0.39 (0.31) LMN: 0.24 (0.11) to 0.46 (0.25), vs. 0.28 (0.27) to 0.45 (0.25) p=0.09 6MWT UMN: 122.3 (49.2) to 187.48 (103.78) vs. 93.3 (53.1) to 119.41 (89.25) LMN: 82.7 (45.5) to 157.54 (89.51) vs. 94.3 (75.1) to 145.62 (125.15) PGIC Scale UMN: LMN: LEMS UMN: 30 (10.4) to 38.33 (10.6) vs. 27 (10.9) to 32.28 (11.04) LMN: 21 (10.3) to 27.15 (11.10) vs. 20 (9.9) to 22.57 (10.8) WISCI-II UMN: 5.9 (4.5) to 13.47 (5.65) vs. 4.9 (4.1) to 11.04 (5.09) LMN: 6 (3.2) to 12.45 (4.17) vs. 5 (3.7) to 10.8 (4.54) FIM/Motor UMN: 5 (2.7) to 8.95 (2.96) vs. 4.9 (4.1) to 7.05 (2.62) LMN: 6 (2.9) to 8.9 (2.61) vs. 5 (2.8) to 8.67 (2.65)	A vs. B, mean (SD)

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Faramarzi, 2020 Has companion: Banitalebi, 2020 **Multimodal Exercise** Immediately Postintervention, 12 weeks Fair	A. Combined exercise (resistance + endurance + Pilates + balance + stretch) - Low disability group (EDSS < 4.5) 36 sessions (3 per week) over 12 weeks (n=23) B. Combined exercise - Moderate disability group (4.5 ≤ EDSS ≤ 6) 36 sessions (3 per week) over 12 weeks (n=13) C. Combined exercise - High disability group (EDSS ≥ 6.5) 36 sessions (3 per week) over 12 weeks (n=11) Controls (Low-disability, Moderate-disability, High-disability) D. Waitlist control Low (n=23) E. Waitlist control Moderate (n=13) F. Waitlist control High (n=11)	A vs. B vs. C vs. D Age: NR (between 18 and 50 years) Female: 100% Race: NR Ambulatory: 100% Wheelchair user: NR EDSS score: EDSS < 4.5: A. 23 (24%) vs. D. (low) 23 (24%) EDSS ≤ 4.5 to ≤ 6: B.13 (14%) vs. D. (moderate) 13 (14%) EDSS ≥ 6.5: C.11 (12%) vs. D. (high) 11 (12%) Baseline VO_2-peak (ml/kg/min), mean (SD): A. 23.1 (5.6) B. 17.9 ± 7.5 C.15.2 ± 8 vs. D. (low) 21.4 ± 4.8 (moderate) 17.4 ± 5.8 (high) 17.8 ± 6.7	A vs. B vs. C vs. D vs. E vs. F Mean change from baseline (95% CI) p=between groups (postintervention) [change value calculated by EPC from figures] 6MWT A vs. D 63.1 (95% CI -15.6 to 139.5) vs. -11.1 (95% CI -44.6 to 21.7) B vs. E 49.7 (95% CI 1.5 to 97.83) vs. -1.9 (95% CI -35.0 to 32.4) C vs. F 64.1 (95% CI 39.2 to 88.6) vs. -13.1 (95% CI -42.8 to 17.4) Exercise group effect on 6MWT, p<0.001 Test for interaction (presumably between disability strata) were NS TUG (lipids) A vs. D -1.5 (95% CI -4.1 to 1.2) vs. 0.72 (95% CI -0.34 to 1.8) B vs. E -1.6 (95% CI -3.6 to 0.37) vs. -0.3 (95% CI -4.9 to 4.5) C vs. F -1.9 (95% CI -3.9 to 0.03) vs. 1.4 (95% CI 0.05 to 2.6) Exercise group effect on TUG, p<0.001 Test for interaction (presumably between disability strata) were NS VO_2-peak change (mL/kg/min): Significant positive correlation between changes Vo2 peak) with exercise, p=0.041 There was a significant condition main effect on change in Vo2 peak, p=0.004	Faramarzi, 2020 Has companion: Banitalebi, 2020 **Multimodal Exercise** Immediately Postintervention, 12 weeks Fair

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Field-Fote, 2011 Has companions: Kressler, 2013 Sandler, 2017 **Aerobic Exercise** Robot-Assisted Gait Training Postintervention, 12 weeks Fair	A. Treadmill BWS Training with Manual Assistance, 60 sessions over 12 weeks (n=17) (TM) B. Treadmill BWS Training with Electrical Stimulation, 60 sessions over 12 weeks (n=18) (TS) C. Overground BWS Training with Electrical Stimulation, 60 sessions over 12 weeks (n=15) (OG) D. Treadmill BWS Training with Robotic Assistance, 60 sessions over 12 weeks (n=14) (LR)	A vs. B Age (mean years): 39.3 vs. 38.5 vs. 42.2 vs. 45 Female: 17.7% vs. 22.2% vs. 13.9% vs. 18% Race: White or non-Hispanic 58.8% vs. 44.4% vs. 40.0% vs. 42.9% Hispanic 29.4% vs. 38.9% vs. 40% vs. 35.7% African American 11.8% vs. 16.7% vs. 20% vs. 21.4% Ambulatory: NR Wheelchair user: NR Other: 2 min walk, in meters TM: 22.1 (21.4) TS: 20.6 (23.1) OG: 24.0 (35.3) LR:16.8 (11.3) Short distance overground walking speed, m/s 0.17 (0.14) vs. 0.18 (0.18) vs. 0.19 (0.20) vs. 0.17 (0.10)	A vs. B, mean (SD) Short distance over ground speed, change in m/s TM: 0.04 (0.07) TS: 0.05 (0.09) OG: 0.09 (0.11) LR: 0.01 (0.05) Distance walked (2 min), change in meters TM:0.8 (7.7) TS: 3.8 (6.3) OG: 14.2 (15.2) LR: 1.2 (5.1) LEMS, left leg, change in score TM: 1.7 (1.8) TS: 1.5 (2.7) OG: 1.1 (1.5) LR: 1.2 (3.2) LEMS, right leg, change in score TM: 1.5 (2.1) TS: 1.6 (2.0) OG: 1.7 (2.3) LR: 1.3 (1.5)	A vs. B, mean (SD)

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Forsberg, 2016 **Postural Control** Balance Postintervention, 8 weeks Fair	A. CoDuSe balance exercises: 14 sessions over 7 weeks (n=35) B. Usual care control: (n=38)	A vs. B Age (mean years): 52 vs. 56 Female: 28 (80%) vs. 31 (82%) Race: NR Ambulatory: NR Wheelchair use/assistive walking device: 18 (51%) vs. 26 (68%) Wheelchair use/assistive walking device indoors: 5 (14%) vs. 7 (18%) MSIS physical subscale (0–100):54 (18%) vs. 56 (14%) MSIS psychosocial subscale (0–100): 22 (10%) vs. 22 (8%) Type of MS - Relapsing-remitting: 20 (57%) 13 (34%) Type of MS -Primary progressive: 4 (11%) vs. 5 (13%) Type of MS -Secondary progressive: 11 (31%) vs. 20 (53%)	A. vs. B., mean (SD) TUG: 13.7 (5.5) vs.17.0 (9.1), (baseline) 0.5 (8.5) vs. −1.0 (3.8), (postintervention) Difference between groups, least square means adjusted for baseline value: 1.4 (95% CI −1.7 to 4.5), p=0.37 MS walking scale (12–60): 40.0 (9.9) vs.41.6 (9.7), (baseline) −3.4 (5.0) vs. 0.1 (5.2), (postintervention) Difference between groups, least square means adjusted for baseline value: −3.7 (95% CI −6.0 to −1.3), p=0.0026 Sit-to-Stand: 35.2 (12.1) vs.42.0 (16.6), (baseline) −3.6 (8.2) vs. −4.1 (9.8), (postintervention) Difference between groups, least square means adjusted for baseline value: −2.2 (95% CI −5.6 to 1.2); p=0.21	A. vs. B., mean (SD) BBS: 48.9 (5.8) vs.45.1 (9.0), (baseline) 2.6 (4.1) vs. 1.6 (4.1), (postintervention) Difference between groups, least square means adjusted for baseline value: 2.1 (95% CI 0.5 to 3.8); p=0.011
Fosdahl, 2019b **Multimodal Exercise** Postintervention, 16 weeks and 32 weeks Fair	A. Strength training (progressive resistance exercise) + stretching, 48 sessions over 16 weeks (n=17) B. Usual care (n=20)	A vs. B Age: 10.4 vs. 10.0 Female: 59% vs. 30% Ambulatory: 100% GMFM: I: 59% vs. 60% II: 41% vs. 35% III: 0% vs. 5%	A vs. B, Mean change score (SD) 6MWT (meters) −45.7 (55.4) vs. −55.4 (55.5), adj. MD10.6 (95% CI −29.3 to 50.6), p=0.590 (pre-post change) −51.1 (72.8) vs. −56.6 (59.6), adj. MD 7.2 (95% CI −43.3 to 57.7), p=0.772 (16-week change) GDI (Gait Deviation Index) −0.4 (4.4) vs. −0.8 (7.14), adj. MD −1.0 (95% CI −5.3 to 3.3), p=0.650 (pre-post change) −0.7 (6.0) vs. 1.01 (5.9), adj. MD −1.4 (95% CI −5.6 to 2.8), p=0.504 (16-week change)	NA

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Fowler, 2010 Has companion: Demuth, 2012 **Aerobic Exercise** Cycling Postintervention, 0 weeks Fair	A. Stationary cycling 30 sessions over 12 weeks (n=29) B. Control No Intervention (n=29)	A vs. B Age (mean years): 11.1 vs. 11.6 Female: 13 (42%) vs. 20 (64%) Ambulatory: 31 (100%) vs. 31 (100%) Wheelchair user: NR Race: African American 5 (16%) vs. 3 (10%) White 18 (58%) vs. 15 (48%) Asian 1 (3%) vs. 5 (16%) Other 7 (23%) vs. 8 (26%) CP subtype NR	A vs. B (SD) GMFM-66 69.6 (NR) vs. 68.8 (NR) (baseline) 70.8 (NR) vs. 69.3 (NR); p=0.002 in A (postintervention) 600 yard walk-run test speed (m/min) 85.0 (NR) vs. 81.6 (NR) (baseline) 90.6 (NR) vs. 84.1 (NR); p=0.008 in A (postintervention) 30 sec walk test speed (m/min): NS	NA

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Fox, 2016 **Muscle Strength** Postintervention, 4 weeks Fair	A. Pilates: 12 sessions over 12 weeks (n=33) B. Standardized exercises (PT): 12 sessions over 12 weeks (n=32) C. Relaxation: 3 sessions over 12 weeks (n=29)	A vs. B vs. C Age (mean years): 53.97 vs. 54.60 vs. 53.78 Female: 28 (84.9%) vs. 25 (71.4%) vs. 21 (65.6%) Race: NR Ambulatory: NR (at minimum, required the ability to walk about 20 m without resting with the use of 2 walking aids) Wheelchair user: NR MS type: Relapsing-remitting: 13 (39.4%) vs. 13 (37.1%) vs. 12 (37.5%) Secondary progressive: 8 (24.2%) vs. 11 (31.4%) vs. 11 (34.4%) Primary progressive: 12 (36.4%) vs. 11 (31.4%) Benign: 0 (0%) vs. 0 (0%") vs. 1 (3.1%)	Data reported as mean (SD) A vs. C 10MWT (seconds): 16.16 (7.72) vs. 15.52 (6.22) (baseline) 14.43 (7.56) vs. 14.94 (5.66), adj. MD -0.50 (95% CI -4.68 to 3.69), p>0.05 (postintervention) 14.90 (8.22) vs. 15.39 (5.95), adj. MD -0.50 (95% CI -4.68 to 3.69), p>0.05 (4-week followup) MSWS-12 (0-100, higher scores=decreased walking ability): 72.15 (19.47) vs. 70.61 (21.31) (baseline) 63.49 (23.78) vs. 68.39 (23.69), adj. MD -4.90 (95% CI -19.11 to 9.32), p>0.05 (postintervention) 67.39 (24.65) vs. 71.10 (21.71), adj. MD -3.71 (95% CI -17.93 to 10.50), p>0.05 (4-week followup) B vs. C 10MWT (seconds): 12.85 (5.05) vs. 15.52 (6.22) (baseline) 10.73 (4.46) vs. 14.94 (5.66), adj. MD -4.20 (95% CI -8.42 to 0.01), p>0.05 (postintervention) 12.94 (9.18) vs. 15.39 (5.95), adj. MD -2.45 (95% CI -6.67 to 1.77), p>0.05 (4-week followup) MSWS-12 (0-100, higher scores=decreased walking ability): 59.38 (22.90) vs. 70.61 (21.31) (baseline) 47.84 (24.61) vs. 68.39 (23.69), adj. MD -20.55 (95% CI -34.87 to -6.23), p<0.05 (postintervention) 51.41 (26.79) vs. 71.10 (21.71), adj. MD -19.69 (95% CI -34.01 to -5.37), p<0.05 (4-week followup)	Data reported as mean (SD) ABCS (0-100, higher scores=better balance): A vs. C 3.94 (1.53) vs. 4.20 (1.67) (baseline) 4.76 (2.14) vs. 4.27 (1.95), adj. MD 0.49 (95% CI -0.76 to 1.74), p>0.05 (postintervention) 4.52 (2.15) vs. 4.21 (1.74), adj. MD 0.31 (95% CI -0.94 to 1.56), p>0.05 (4-week followup) B vs. C 4.74 (2.19) vs. 4.20 (1.67) (baseline) 5.74 (2.36) vs. 4.27 (1.95), adj. MD 1.48 (95% CI 0.21 to 2.74), p<0.05) (postintervention) 5.46 (2.52) vs. 4.21 (1.74), adj. MD 1.26 (95% CI -0.01 to 2.52), p>0.05 (4-week followup) A vs. B 3.94 (1.53) vs. 4.74 (2.19) (baseline) 4.76 (2.14) vs. 5.74 (2.36), adj. MD 0.98 (95% CI -0.24 to 2.21) (postintervention) 4.52 (2.15) vs. 5.46 (2.52), adj. MD 0.95 (95% CI -0.28 to 2.17) (4-week followup)

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Fox, 2016 **(Continued)**			A vs. B 10MWT (seconds): 16.16 (7.72) vs. 12.85 (5.05) (baseline) 14.43 (7.56) vs. 10.73 (4.46), adj. MD -3.71 (95% CI -7.79 to 0.37), p>0.05 (postintervention) 14.90 (8.22) vs. 12.94 (9.18), adj. MD -1.96 (95% CI -6.04 to 2.13), p>0.05 (4-week followup) MSWS-12 (0-100, higher scores=decreased walking ability): 72.15 (19.47) vs. 59.38 (22.90) (baseline) 63.49 (23.78) vs. 47.84 (24.61), adj. MD -15.65 (-29.50 to -1.79), p<0.05 (postintervention) 14.90 (8.22) vs. 51.41 (26.79), adj. MD -15.97 (95% CI -29.83 to -2.12), p<0.05 (4-week followup)	

Author, Year **Intervention Type** **Duration of Postintervention Followup** **Quality** **(See Appendix B for Full Citation)**	**Intervention and Comparison**	**Population** **Age (Mean)** **Gender (% Female)** **Race (%)** **Ambulatory (%)** **Wheelchair User (%)** **Condition Specific (%)** **Other (%)**	**Prioritized Outcomes**	**Other Outcomes**
Galea, 2018 **Multimodal Exercise** Postintervention, 12 weeks Fair	A. Strength + aerobics (n=60) B. Upper body strength + aerobics (n=56) (36 sessions over 12 weeks for both groups)	A vs. B Age (mean years): 40.1 vs. 42.8 Female: 9 (15%) 9 (16%) Race: NR Ambulatory: NR Wheelchair user: NR ASIA Impairment Scale classification -A: 29 (48%) vs. 28 (50%) -B: 9 (15%) vs. 8 (14%) -C: 7 (12%) vs. 5 (9%) -D: 15 (25%) vs. 15 (27%) Single neurological level -C2-C8: 29 (48%) vs. 33 (59%) -T1-T6: 18 (30%) vs. 13 (23%) -T7-T12: 13 (22%) vs. 10 (18%)	Data reported as mean (SD) A vs. B 6MWT (unit NR) 142.3 (103.5) vs. 176.4 (105.1) (baseline) 149 (103.7) vs. 170.8 (92.7), MD -18.36 (95% CI -68.57 to 31.84), p=0.451 (postintervention) 187.1 (93.3) vs. 133.2 (91), MD 27.12 (95% CI -12.69 to 66.94), p=0.168 (12 weeks) 10MWT (m/sec-1) 0.5 (0.4) vs. 0.5 (0.4) (baseline) 0.5 (0.3) vs. 0.6 (0.4), MD -0.01 (95% CI -0.1 to 0.08) (postintervention) 0.6 (0.3) vs. 1.4 (2.6), MD -0.72 (95% CI -2.41 to 0.98) (12 weeks) Penn Spasm Frequency Scale 1.8 (1.1) vs. 1.5 (1) (baseline) 1.6 (1.1) vs. 1.8 (1.1), MD -0.25 (95% CI -0.61 to 0.1), p=0.163 (postintervention) 1.6 (0.9) vs. 1.8 (1), MD 0 -0.12 (95% CI -0.44 to 0.19), p=0.446 (12 weeks) Perceived Stress Scale 11.7 (6.5) vs. 13.4 (6.1) (baseline) 11.7 (6.6) vs. 12 (5.8), MD 0.61 (95% CI -1.23 to 2.45) (postintervention) 11 (7.1) vs. 12.4 (6.7), MD -0.1 (95% CI -2.27 to 2.065) (12 weeks) HADS-Anxiety 10.3 (1.8) vs. 10.5 (1.8) 10.4 (1.6) vs. 10.1 (1.6), MD 0.29 (95% CI -0.25 to 0.83) (postintervention) 10 (2.2) vs. 10.2 (1.4), MD -0.14 (95% CI -0.89 to 0.6) (12 weeks) HADS-Depression 10.5 (2) vs. 10.4 (2.1) 10 (1.6) vs. 10.2 (1.3), MD -0.28 (95% CI -0.83 to 0.27), p=0.309 (postintervention) 10.1 (1.5) vs. 10.2 (1.4), MD -0.23 (95% CI -0.81 to 0.35), p=0.428 (12 weeks)	Data reported as mean (SD) A vs. B ASIA-UEMS (0-100, higher=increased strength): 41.8 (12.0) vs. 39.45 (11.7), p=NR (baseline) 41.5 (12.1) vs. 39.4 (11.9); MD -0.04 (95% CI -1.12 to 1.04), p=0.94 (postintervention) 43.0 (26.5) vs. 37. 5 (14.4); MD 1.65 (95% CI -1.3 to 4.6), p=0.27 (12 weeks) ASIA-LEMS (0-100, higher=increased strength): 10.4 (14.9) vs. 11.4 (17.9), p=NR (baseline) 12.51 (17.0) vs. 10.2 (17.2); MD 0.90 (95% CI -0.48 to 2.27), p=0.20 (postintervention) 13.2 (17.5) vs. 11.2 (17.8); MD 1.19 (95% CI -0.09 to 2.47), p=0.07 (12 weeks)

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Gandolfi, 2015 **Postural Control** Balance RCT Fair	A. Balance training (sensory integration), 15 sessions over 5 weeks (n=39) B. Conventional rehabilitation, 15 sessions over 5 weeks (n=41)	A vs. B Age (mean years): 47.21 vs. 49.56 Female: 28 (72%) vs. 31 (76%) Race: NR Ambulatory: NR Wheelchair user: NR EDSS score (median) 3.00 vs. 3.66 Q1–Q3: 2–4 vs. 2.50–4.25 MS duration (mean years): 12.25 vs. 15.24	A. vs. B., mean (SD) MSQOL-54 (0–100; higher=better performance) 63.09 (11.09) vs. 58.77 (11.05) (baseline) 65.56 (10.31) vs. 59.64 (9.80) (postintervention) 63.56 (10.27) 58.54 vs. (11.64) (1-month followup) Between-group difference (95% CI) mean: Before: 4.32 (95% CI −0.61 to 9.25) After: 5.92 (95% CI 1.44 to 10.40) Followup: 5.02 (95% CI −1.12 to 9.92), p<0.001 Number of falls 0.59 (.99) vs. 0.37 (0.54) (baseline) 0.03 (0.16) vs. 0.29 (0.34) (postintervention) 0.08 (0.27) vs. 0.27 (0.55) (1-month followup) Between-group difference (95% CI) mean: Before: 0.22 (95% CI −0.129 to 0.577) After:. −0.30 (95% CI −0.452 to −0.08) Followup: −0.191 (95% CI −0.385 to 0.003)	A. vs. B., mean (SD) BBS (0-56, higher=better performance) 47.97(4.89) vs. 46.49 (5.21) (baseline) 52.77 (3.15) vs. 47.79 (6.05) (postintervention) 52.92 (2.97) vs. 48.33 (5.88) (1-month followup) Between-group difference (95% CI) mean before: 1.49 (95% CI −0.76 to 3.74), after: 4.99 (95% CI 2.83 to 7.15) followup: 4.60 (95% CI 2.50 to 6.69), p<0.001

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Garrett, 2013a Garrett, 2013b (same author group a as Hogan 2014) **Postural Control** Yoga Postintervention, 12 weeks	A. Physiotherapist–led exercise: 10 sessions over 10 weeks (n=80) B. Yoga: 10 sessions over 10 weeks (n=77) C. Fitness Instructor–led exercise: 10 sessions over 10 weeks (n=86) D. Usual care (n=71)	A vs. B vs. C vs. D [baseline data abstracted from Garrett 2013a] Age (mean years): 51.7 vs. 49.6 vs. 50.3 vs. 48.8 Female: 50 (79%) vs.44 (70%) vs. 45 (68%) vs. 43 (87%) Race: NR Guys Neurological Disability Scale (Mobility Section) –0 (Gait unaffected): 19 (30%) vs. 26 (41%) vs. 15 (22%) vs. 21 (43%) –1 (Unsteady, but no aid use): 21 (33%) vs. 14 (22%) vs. 28 (42%) vs. 12 (28%) –2 (Uses unilateral aid outdoors): 1(33%) vs. 22 (34%) vs. 23 (34%) vs. 16 (33%) Wheelchair user: 0% vs. 0% vs. 0% vs. 0% Type of MS –Relapsing–remitting: 35 (55%) vs. 38 (60%) vs. 33 (49%) vs. 27 (55%) –Secondary progressive: 9 (14%) vs. 7 (11%) vs. 13 (19%) vs. 10 (20%) –Primary progressive: 5 (7%) vs. 8 (13%) vs. 9 (13%) vs. 3 (6%) –Benign: 0 (0%) vs. 1 (2%) vs. 3 (5%) vs. 1 (2%)	6MWT (meters) A vs. D 288 (94) vs. 350 (103) (baseline) 327 (185) vs. 315 (232) (postintervention) 10 (52) vs. –10 (91), p=0.02 (pre-post change) B vs. D 260 (80) vs. 350 (103) (baseline) 285 (152) vs. 315 (232) (postintervention) 0 (82) vs. –10 (91), p=0.73 (pre-post change) C vs. D 260 (80) vs. 350 (103) (baseline) 305 (186) vs. 315 (232) (postintervention) 20 (61) vs. –10 (91), p<0.01 (pre-post change) A vs. B 288 (94) vs. 260 (80) (baseline) 327 (185) vs. 285 (152) (postintervention) 313.9 (104.9) vs. 281.7 (112.5) (12 weeks; no ITT) 10 (52) vs. 0 (82) (pre-post change) C vs. B 260 (80) vs. 260 (80) (baseline) 305 (186) vs. 285 (152) (postintervention) 340.7 (88.9) vs. 281.7 (112.5) (12 weeks; no ITT) 20 (61) vs. 0 (82) (pre-post change) A vs. C 288 (94) vs. 260 (80) (baseline) 327 (185) vs. 305 (186) (postintervention) 313.9 (104.9) vs. 340.7 (88.9) (12 weeks; no ITT) 10 (52) vs. 20 (61) (pre-post change) ANOVA results for 6MWT: Group X Time p=0.129 Time p<0.001 Group p=0.124	MSIS–physical component (0–100) A vs. D 33.0 (18.0) vs. 29.6 (23.0) (baseline) 26.2 (17.2) vs. 29.9 (20.7) (postintervention) –6.9 (95% CI –10.8 to –2.9) vs. 0.3 (95% CI –4.0 to 4.6), p=0.02 (pre-post change) B vs. D 33.1 (20.0) vs. 29.6 (23.0) (baseline) 29.4 (19.4) vs. 29.9 (20.7) (postintervention) –4.0 (95% CI –7.5 to –0.5) vs. 0.3 (95% CI –4.0 to 4.6), p=0.12 (pre-post change) C vs. D 35.20 (20.0) vs. 29.6 (23.0) (baseline) 29.5 (19.9) vs. 29.9 (20.7) (postintervention) –5.7 (95% CI –9.1 to –2.4) vs. 0.3 (95% CI –4.0 to 4.6), p=0.03 (pre-post change) A vs. B 33.0 (18.0) vs. 33.1 (20.0) (baseline) 26.2 (17.2) vs. 29.4 (19.4) (postintervention) 27.7 (16.2) vs. 34.0 (21.8) (12 weeks; no ITT) –6.9 (95% CI –10.8 to –2.9) vs. –4.0 (95% CI –7.5 to –0.5) (pre-post change) C vs. B 35.20 (20.0) vs. 33.1 (20.0) (baseline) 29.5 (19.9) vs. 29.4 (19.4) (postintervention) 37.0 (24.1) vs. 27.7 (16.2) (12 weeks; no ITT) –5.7 (95% CI –9.1 to –2.4) vs. –4.0 (95% CI –7.5 to –0.5) (pre-post change) A vs. C 33.0 (18.0) vs. 35.20 (20.0) (baseline) 26.2 (17.2) vs. 29.5 (19.9) (postintervention) 27.7 (16.2) vs. 37.0 (24.1) (12 weeks; no ITT) –6.9 (95% CI –10.8 to –2.9) vs. –5.7 (95% CI –9.1 to –2.4) (pre-post change)

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Garrett, 2013a Garrett, 2013b (same author group a as Hogan 2014) **(Continued)**				ANOVA results for MSIS–physical Group X Time p=0.470 Time p<0.001 Group p=0.124 MSIS–psychological component (0–100), median (Semi–IQR) A vs. D 33.3 (15.0) vs. 22.2 (12.0) (baseline) 18.5 (18.5) vs. 18.5 (38.9) (postintervention) –11.1 (25.9) vs. 0 (16.7), p<0.01 (pre-post change) B vs. D 33.3 (17.0) vs. 22.2 (12.0) (baseline) 25.9 (33.3) vs. 18.5 (38.9) (postintervention) –3.7 (22.2) vs. 0 (16.7), p=0.04 (pre-post change) C vs. D 29.6 (13.0) vs. 22.2 (12.0) (baseline) 22.2 (29.6) vs. 18.5 (38.9) (postintervention) –3.7 (22.2) vs. 0 (16.7), p=0.02 (pre-post change) A vs. B 33.3 (15.0) vs. 33.3 (17.0) (baseline) 18.5 (18.5) vs. 25.9 (33.3) (postintervention) 23.4 (14.8) vs. 30.1 (20.9) (12 weeks; no ITT) –11.1 (25.9) vs. –3.7 (22.2) (pre-post change) C vs. B 29.6 (13.0) vs. 33.3 (17.0) (baseline) 22.2 (29.6) vs. 25.9 (33.3) (postintervention) 28.5 (22.7) vs. 30.1 (20.9) (12 weeks; no ITT) –3.7 (22.2) vs. –3.7 (22.2) (pre-post change)

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Garrett, 2013a Garrett, 2013b (same author group a as Hogan 2014) **(Continued)**				A vs. C 33.3 (15.0) vs. 29.6 (13.0) (baseline) 18.5 (18.5) vs. 22.2 (29.6) (postintervention) 23.4 (14.8) vs. 28.5 (22.7) (12 weeks; no ITT) –11.1 (25.9) vs. –3.7 (22.2) (pre-post change) ANOVA results for MSIS–psychological Time X Group p=0.446 Time p<0.0001 Group p=0.246
Gervasoni 2014 **Aerobic Exercise** Treadmill Postintervention, 0 weeks Fair	A. Treadmill 30 minutes + 15 minutes conventional physical therapy, 12 sessions over 2 weeks B. 45 minutes conventional physical therapy	n=30 18 male/12 female (60% male) Mean age=48.75 years (range NR) EDSS Mean 5.25 (3-6.5)	pre, post Dynamic Gait Index (walking + balance) A. 15.38 to 12.54 B. 16.00 to 18.07 p=0.51 Positive and Negative Affect Schedule Positive A. 29.0 to 30.0 B. 28.0 to 33.0 p=0.89 Negative A. 26.0 to 21.0 B. 23.0 to 21.0 p=0.48	NA

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Giangregorio 2012 (Body composition) Hitzig 2013 (quality of life) Kapadia 2014 (walking capacity) Craven 2017 (bone markers) **Aerobic Exercise** Treadmill Postintervention, 6 months Fair	A. Functional electrical stimulation walking while on body weight assisted treadmill 45 minutes, 3 times a week for 16 weeks B. Aerobic and resistance training for 40 to 50 minutes 3 times a week for 16 weeks	American Spinal Injury Association Impairment Scale C or D n=34 randomized and analyzed 27 Mean age 55.3 years 26 males and 8 females (76% males)	Pre, post and 8 months after intervention 10 meter walk test (seconds) A. 42.8 (46.2) to 35.2 (40.8) to 42.2 (67.7) B. 49.1 (41.7) to 28.7 (8.3) to 35.1 (18.8) No significant change over time p=0.084 and no difference between groups p=0.829 6 minute walk test (meters) A. 187.9 (123.4) to 217.1 (134.4) to 232.5 (138.9) B. 79.4 (83.9) to 130 (46.0) .to 126.4 (63.8) Overall increase in distance walked p=0.002 No significant difference between groups p=0.096 Timed up and go (seconds) A. 43.6 (25.5) to 33.0 (15.7) to 32.2 (19.1) B. 61.6 (36.2) to 49.5 (21.9) to 51.3 (19.6) Overall change over time p=0.016 and no difference between the groups p=0.138	SCIM (baseline to 12 months) A. 57.7 (17.8) to 64.1 (19.2) B. 63.9 (18.9) to 64.8 (13.4) SCIM mobility subscale A. 17.27 (7.25) to 21.33 (7.62) B. 19.09 (7.08) to 19.36 (17.36) Group by time interaction p=0.003 with A having improvement over time CHART CHART Mobility subscale A. 79.81 (21.00) to 85.28 (13.81) to 86.36(14.44) B. 82.09 (19.31) to 84.27 (11.89) to 88.45 (15.25) No differences between groups (group by time interaction p=0.840) CHART Social subscale A. 89.94 (13.12) to 90.31 (18.02) to 88.69 (17.10) B. 72.73 (24.00) to 89.64 (12.63) to 73.73 (31.15) Group by time interaction p=0.065 CHART Physical subscale A. 92.35 (11.75) to 93.72 (8.02) to 93.81 (6.16) B. 97.94 (2.49) to 94.99 (7.30) to 93.85 (5.01) Group by time interaction p=0.214 MAS No change overall scores and no significant group by time interaction p=0.942

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Giangregorio 2012 (Body composition) Hitzig 2013 (quality of life) Kapadia 2014 (walking capacity) Craven 2017 (bone markers) **(Continued)**				BMD mean change left total hip {g/cm2]) A. 0.90 (0.20) to 0.88 (0.20) to 0.89 (0.20) (p=0.41 B. 0.86 (0.21) to 0.87 (0.23) to 0.90 (0.21) p=0.06 No significant differences between groups in BMD or in any bone architecture indices (pQCT) at any time point Fat mass (kilogram) A. 25.4 (9.5) to 24.3 (9.5) to 25.2 (9.0) B. 23.4 (10.8) to 23.0 (10.7) to 23.3 (11.1) No differences over time or between groups
Gibson, 2018 **Aerobic Exercise** Aerobics Postintervention, 12 weeks Good	A. Running and running exercises, 48 sessions over 12 weeks (n=21) B. Usual care (n=21)	A vs. B Age: 12.4 vs. 12.5 Female: 33% vs. 38% GMFCS I: 57% vs. 60% GMFCS II: 38% vs. 40% GMFCS III: 5% vs. 0%	A vs. B, Mean Difference between groups: Shuttle Run Test (min): 0.9, 95% CI -0.3 to 2.2, p=0.142 HiMat: 0.8, 95% CI -2.7 to 4.3, p=0.651 10X5 sprint (sec): -1.3, 95% CI -5.4 to 2.8, p=0.535	NA

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Gorman, 2019 **Aerobic Exercise** Aquatics Postintervention, 12 weeks Fair	A. RAGT, 36 sessions over 3 months (n=18) B. Aquatic therapy, 36 sessions over 3 months (n=15)	A vs. B Age (mean years): 45.4 vs. 46.9 Female: NR Race: NR Ambulatory: Community Ambulation 16 (83%) vs. 10 (67%) Wheelchair user: NR Other: Time since injury (years): 6.6 vs. 12.2 Tetraplegic: 12 (67%) vs. 11 (73%) Paraplegic: 6 (33%) vs. 4 (27%) WISCI:9.5 ± 7.6 11.7 ± 6.5	A vs. B, mean (SD) Robotic Peak VO_2 change: 2.07 (p=0.03) vs. Arm ergometer peak VO_2 change Robotic: -0.30 (p=033) Aquatic: 0.98 (p=0.14)	NA

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Grecco 2013 **Aerobic Exercise** Treadmill RCT Postintervention, 3 weeks Fair	A. Transcranial motor cortex stimulation while treadmill training 5 times a week for 2 weeks (no body weight support) B. Treadmill training with placebo stimulation	GMFCS II or III (II/III 16/8) N=24 randomized and all completed Mean age 7.9 years 7 males and 17 females (29% males)	Pre, post and 3 weeks later 6 minute walk (meters) A. 223 (58) to 448.2(100.5) to 409.6 (81.6) (within group increase F=9.966, p<0.001) B. 255.4 (62.8) to 367.2 (97.6) to 345.4 (97.7) NS within group difference Change distance baseline to post, baseline to followup A. 199.6, 186.4 B. 111.8, 90.0 Between group comparison effect size pre to post 87.8 (p<0.05) and pre to followup 96.4 (p<0.05) GMFM-88 D scale A. 63.7 (7.0) to 75.3 (11.6) to 72.6 (12.4) (no significant change) B. 66.2 (6.2) to 70.0 (9.2) to 68.4 (9.8) (no significant change) Change score baseline to post, baseline to followup A. 11.5, 8.8 B. 3.7, 2.1 NS between group comparison effect sizes GMFM-88 E A. 54.1 (7.7) to 59.9 (11.1) to 60.7 (10.5) (no significant change) B. 60.7 (10.5) to 61.7 (10.7) to 60.1 (10.7) (no significant change) Change baseline to post, baseline to followup A. 0.8, 0.4 B. 1.0, 0.7 NS between group comparison effect sizes	NA

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Grecco 2014 **Aerobic Exercise** Treadmill RCT Postintervention, 4 weeks Fair	A. Treadmill walking 30 minute sessions 2 times a week for 7 weeks at 80% maximal speed B. Overground walking using assist devices if needed	GMFCD I-III (I/II/III of 13/15/5) n=33 Mean age 6.4 years 15 males and 18 females (45% male)	Pre, post and 1 month later 6 minute walk test (meters) A. 227.4(49.4) to 377.2 (93.0) to 360.2 (86.1) Post treatment and followup different from baseline p<0.05, post treatment different from baseline p<0.05 B. 222.6 (42.6), 268.0 (45.0), 257.6 (45.8) Post treatment and followup different from baseline p<0.05, post treatment different from baseline p<0.05 A. had greater improvement at post (p=0.001) and followup (p=0.001) Baseline to post treatment A. 149.7 B. 44.8 Effect size 10.4.2, p<0.000 Baseline to followup A. 137.6 B. 33.6 Effect size 104.2 p<0.000 Timed Up and Go (seconds) A. 14.3 (2.9) to 7.8 (2.2) to 8.6 (2.2) Post treatment and followup different from baseline p<0.05, post treatment different from baseline p<0.05 B. 12.8 (2.2), 10.5 (2.5), 11.2 (2.5) Post treatment and followup different from baseline p<0.05 Baseline to post treatment A. -6.4 B. -2 Effect size -4.3, p<0.004 Baseline to followup A. -5.7 B. -1.3 Effect size -4.4 p<0.005	Berg Balance Scale A. 34.9 (8.5), 46.7(7.6), 46.2 (7.4) Post treatment and followup different from baseline p<0.05, post treatment different from baseline p<0.05 B. 31.9 (7.0), 35.7(6.8), 35.6(5.2) Post treatment and followup different from baseline p<0.05 Baseline to post treatment A. 11.8 B. 3.3 Effect size 8.4, p<0.000 Baseline to followup A. 11.2 B. 3.2 Effect size 8.0 p<0.000 Pediatric Evaluation Disability Index A. 128.0(19.9), 139.0 (18.4), 140.8 (16.9) Post treatment and followup different from baseline p<0.05 B. 120.8(19.0), 125.8(16.2), 123.8(17.4) Post treatment and followup different from baseline p<0.05 Baseline to post treatment A. 11.0 B. 4.0 Effect size 7.0, p<0.035 Baseline to followup A. 12.2 B. 3.1 Effect size 9.7 p<0.010

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Grecco 2014 **(Continued)**			GMFM-88 (%) A. 81.6 (8.7) to 93.0 (5.7), to 91.7 (5.0); post treatment and followup different from baseline p<0.05, post treatment different from baseline p<0.05 B. 77.3(7.0) to 80.8 (7.2) to 80.7 (7.5); post treatment and followup different from baseline p<0.05 Baseline to post treatment A. 11.3 B 3.6 Effect size 7.7, p<0.000 Baseline to followup A. 10.0 B. 3.5 Effect size 6.5; p<0.000	NA
Harness, 2008 **Multimodal Exercise** Postintervention, 0 weeks Fair	A. Strength + cycling + vibration: averaging 7.3 hours per week of exercise over 6 months (n=22) B. Self-regulated exercise: averaging 5.2 hours per week of exercise over 6 months (n=9)	A vs. B Age (mean years): 37.8 vs. 34.5 Female: (13.6%) vs. 0 (0%) Race: NR Ambulatory: NR Wheelchair user: NR Time postinjury (mean months): 40.0 vs. 97.0, p=0.0057 Baseline ASIA-UEMS: 31.0 vs. 38.0, p=0.37	Data reported as mean (SEM) A vs. B EQ-5D (0-100, higher=increased QOL): 65.0 (4.0) vs. 67.0 (6.0), p=0.93 (baseline) 14.0 (5.0) vs. 3.0 (5.0), p=0.14 (post-pre change)	Data reported as mean (SEM) A vs. B ASIA-LEMS: 8.0 (2.0) vs. 4.0 (4.0), p=0.37 (baseline) 3.3 (0.9) vs. 0.0 (0.2), p=0.035 (post-pre change) ASIA-Total Motor 39.0 (3.0) vs. 42.0 (5.0), p=0.54 (baseline) 4.8 (1.0) vs. -0.1 (0.5), p=0.0001 (post-pre change) CHART (0-100, higher=increased handicap): 444.0 (19.0) vs. 521.0 (23.0), p=0.017 (baseline) 12.0 (15.0) vs. 0.1 (18.0), p=0.60 (post-pre change)

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Hasanpour-Dehkordi, 2014 "Comparison of regular aerobic and yoga on the quality of life in patients" Has companions: Hasanpour-Dehkordi, 2016; Hasanpour-Dehkordi, 2016 (2) **Postural Control** Yoga Postintervention, 12 weeks Poor	A. Yoga: 36 sessions over 12 weeks (n=20) B. Aerobics: X sessions over 12 weeks (n=20) C. Usual care control: (n=21)	A vs. B Age (mean years): 31.9 (A vs. B vs. C, NR) Female: 60 (98%) (A vs. B vs. C, NR) Race: NR Ambulatory: NR Wheelchair user: NR	A. vs. B. vs. C mean (SD) SF-36 QOL A. 1533 (759.10) (baseline) 2446 (540.76) (postintervention), p=0.05 B. 1240.24 (527.32) (baseline) 2050 (527.32) (postintervention), p=0.05 C. 1385.75 (600.04) (baseline) 1255.75(600.22) (postintervention), p=0.05 SF-36 QOL mean difference between groups A vs. B 229.32, p=0.07 A vs. C 1106.41, p=0.000 B vs. C 877.10, p-0.000	NA

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Hasanpour-Dehkordi, 2016 (2) "Influence of yoga and aerobics exercise on fatigue, pain and psychosocial status…" **Postural Control** Yoga Companion to: Hasanpour-Dehkordi, 2014 Postintervention, 12 weeks Poor	A. Yoga: 36 sessions over 12 weeks (n=20) B. Group exercise: X sessions over 12 weeks (n=20) C. Usual care control: (n=21)	A vs. B vs. C Age (mean years): 31.9 (A vs. B vs. C, NR) Female: 60 (98%) (A vs. B vs. C, NR) Race: NR Ambulatory: NR Wheelchair user: NR	A vs. B vs. C SF-36 QOL Mental health (baseline) (postintervention) Limited activities following emotional problems 41.9±9.16 vs. vs. (baseline) 35.65±12.3 (postintervention)	NA
Hasanpour-Dehkordi, 2016 "Effects of Yoga on Physiological Indices, Anxiety and Social Functioning" Companion to: Hasanpour-Dehkordi, 2014 **Postural Control** Yoga Postintervention, 12 weeks Poor	A. Yoga: 36 sessions over 12 weeks (n=30) B. Usual care control: (n=30) Yoga vs. usual care	A vs. B Age (mean years): 30 vs. 30 Female: NR Race: NR Ambulatory: NR Wheelchair user: NR	SF-36 QOL, mean1533 (759.10) vs. 1385.75 (600.04) (baseline), p=0.5 2446 (540.76) vs. 1255 (600.22) (postintervention), p=0.5 3.3 (5.63 SD) vs. 3.9 (4.4) (before and after score) (postintervention), p=0.05	NA

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Hebert, 2011 **Aerobic Exercise** Cycling Postintervention, 4 weeks Fair	A. Bicycle ergometry plus stretching, 12 sessions for 6 weeks (n=12) B. Vestibular rehabilitation (n=13) C. Waitlist control (n=13)	A vs. B vs. C Age: 46.8 vs. 42.6 vs. 50.2 Female: 75% vs. 85% vs. 85% Race: NR Ambulatory: 100% Wheelchair user: NR BDI-II total score, mean (SD): 16.5 (9.1) vs. 17.3 (8.6) vs. 18.5 (6.4)	From start to end of intervention Mean difference between groups 6MWT: A vs. B: effect size 39.1, 95% CI -105 to 183, p=1.00 A vs. C: effect size 62.7, 95% CI -81 to 2.7, p=1.00 B vs. C: effect size 23.6, 95% CI -117 to 165, p=1.00 BDI-II At 14 weeks-end of intervention phase to end of followup phase (14 weeks) (change from end of intervention) A vs. B BDI-II: 0.7 vs. 2.6 (p=1.000) 6MWT: -58.2 vs. 38. 9 (p=0.731) A vs. C BDI-II: 4.6 vs. 0.7 (p=0.385) 6MWT: -58.2 vs. -24.6 (p=1.000)	NA
Hebert, 2009 Companion to: Hebert, 2011 End of treatment: 14 weeks Fair	A. Balance + Eye movement exercises: 20 sessions over 14 weeks (n=44) B. No treatment (n=44)	A vs. B Age (mean years): 47 vs. 43 Female: 37 (84%) vs. 38 (86%) Race: NR Ambulatory: 100 % Baseline: 3.50 vs. 3.34 Baseline PHQ-9: 37.8 vs. 37.6 Baseline T25W: 6.19 vs. 5.53 Baseline SF-36 PCS: 35.8 vs. 35.4 Baseline SF-36 MCS: 42.6 vs. 42.9	A vs. B 6 weeks SF-36 PCS: MD 2.39 (95% CI -0.99 to 5.78, p=0.16) SF-36 MCS: MD 2.11 (95% CI -2.24 to 6.46, p=0.34) T25W: MD -0.02 (95% CI -0.27 to 0.23, p=0.86) 14 weeks SF-36 PCS: MD 1.92 (95% CI -1.51 to 5.34, p=0.27) SF-36 MCS: MD 1.82 (95% CI -2.58 to 6.23, p=0.41) T25W: MD -0.05 (95% CI -0.63 to 0.53, p=0.86)	NA

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Heine, 2017 **Aerobic Exercise** Cycling 16 weeks Postintervention, 36 weeks Fair	A. Leg cycling, 48 sessions over 16 weeks (43) B. MS nurse consultation, 3 consultations over 16 weeks (46)	A vs. B Age: 43.1 vs. 48.2 Female: 74% vs. 72% EDSS: 2.5 vs. 3.0 RRMS: 72% vs. 74% SPMS: 7% vs. 11% PPMS: 21% vs. 15% VO_2 peak (L/min): 1.75 vs. 1.53 Ambulatory: 100%	A vs. B VO_2 peak end of treatment: MD 0.048 (0.082), p=0.561 VO_2 peak end of followup: MD -0.046 (0.082), 0.579 Calculated A vs. B, Mean Difference (SE) between groups: IPA autonomy indoors: -0.11 (0.088), p=0.203 IPA family role: -0.082 (0.1222), p=0.502 IPA autonomy outdoors: -0.097 (0.125), p=0.438 IPA Social Relations: -0.138 (0.092), p=0.135 IPA Work/education: 0.225 (0.167), p=0.181	Impact on participation and autonomy: no significant difference on any subscale at end of treatment or at end of followup

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Herrero, 2012 **Postural Control** Hippotherapy Followup in weeks Postintervention, 12 weeks Fair	A. Hippotherapy simulator, (turned on and in workout mode) 10 sessions over 10 weeks (n=19) B. Hippotherapy simulator (turned off, sitty position only), 10 sessions over 10 week (n=19)	A vs. B Age (mean years): 9.95 (8.80–11.10) vs. 9.05 (7.58–10.53) Female: 5 (26%) vs. 6 (32%) Race: NR Ambulatory: NR Wheelchair user: NR Gross Motor Function Classification System levels I–V: Baseline GMFCS level I: 2 (11%) vs. 2 (11%) Baseline GMFCS level II: 2 (11%) vs. 1 (5%) Baseline GMFCS level III: 3 (16%) vs. 2 (11%) Baseline GMFCS level IV: 3 (16%) vs. 4 (21%) Baseline GMFCS level V: 9 (47%) vs. 10 (53%) Baseline Total Gross Motor Function Measure 42.75 (19.02) vs. 40.91 (17.50), p=0.758a Baseline Gross Motor Function Measure dimension B 29.84 (15.04) vs. 25.68 (15.40), p=0.405	A vs. B, mean (SD), Effect size for entire study period (95% CI) GMFCS: 10 weeks (end of treatment) 42.23 (15.63) vs. 43.02 (18.40) 22 weeks (followup) 43.54 (17.16) vs. 44.24 (19.76) difference 0.25 (95% CI –0.10 to 0.60)	A vs. B, mean (SD), Effect size for entire study period (95% CI) Gross Motor Function Measure (dimension B): 10 weeks (end of treatment) 26.95 (14.65) vs. 29.95 (14.87) 22 weeks (followup) 27.05 (15.26) vs. 30.11 (14.94), difference 0.25 (95% CI –0.10 to 0.60)

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Hochsprung, 2017 **Aerobic Exercise** Cycling Postintervention, 0 weeks Poor	A. Visual biofeedback cycling training, 12 sessions over 12 weeks (n=30) B. Home exercise program, sessions not stated (n=31)	A vs. B Age (mean years): NR Female: 20 (66%) vs. 16 (50%) Race: NR Ambulatory: 30 (100%) vs. 31 (100%) Wheelchair user: NR	A vs. B (SD) FAP (0.820) vs. (0.929) (baseline) (0.792) vs. (0.942); p=0.002 (postintervention) Calculated A vs. B Mean change scores: FFAP: 3.036 (p=0.002) vs. -1.06 (p=0.289) No comparison between groups provided	NA

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Hogan, 2014 (same author group and protocol as Garrett 2013a and 2013b - see notes) **Postural Control** Yoga Postintervention, 0 weeks	A. Group PT: 10 sessions over 10 weeks (n=48) B. 1–on1 PT: 10 sessions over 10 weeks (n=35) C. Yoga (n=13) D. Usual care (n=15)	A vs. B [for completers only] Age (mean years): 57 vs. 52 vs. 58 vs. 49 Female: 30 (%) vs. 15 (%) vs. 5 (%) vs. 2 (%) Race: NR Ambulation and Wheelchair use: patients use bilateral assistance for gait and may use a wheelchair for longer distance	6MWT (meters), median (semi–IQR) [The Kruskal Wallis test showed that there was no statistically significant difference between groups] A vs. D 101 (39.5) vs. 83.5 (44) (baseline) 121.2 (47.4) vs. 90 (35) (postintervention) 20.2 vs. 6.5 (pre-post change) B vs. D 83.8 (39.8) vs. 83.5 (44) (baseline) 100 (55) vs. 90 (35) (postintervention) 16.2 vs. 6.5 (pre-post change) C vs. D 70 (30) vs. 83.5 (44) (baseline) 45 (54.5) vs. 90 (35) (postintervention) −25 vs. 6.5 (pre-post change) A vs. B 101 (39.5) vs. 83.8 (39.8) (baseline) 121.2 (47.4) vs. 100 (55) (postintervention) 20.2 vs. 16.2 (pre-post change) C vs. B 70 (30) vs. 83.8 (39.8) (baseline) 45 (54.5) vs. 100 (55) (postintervention) −25 vs. 16.2 (pre-post change) A vs. C 101 (39.5) vs. 70 (30) (baseline) 121.2 (47.4) vs. 45 (54.5) (postintervention) 20.2 vs. −25 (pre-post change)	MSIS–physical component, mean (SD) A vs. D 50.5 (9.5) vs. 55.3 (9.5) (baseline) 45.9 (10.5) vs. 50.5 (11.3) (postintervention) −4.54 (95% CI −7.5 to −1.5) vs. −4.8 (95% CI −10.4 to −0.6) (pre-post change) B vs. D 54 (11.5) vs. 55.3 (9.5) (baseline) 49.4 (12) vs. 50.5 (11.3) (postintervention) −4.52 (95% CI −7.9 to −1.1) vs. −4.8 (95% CI −10.4 to −0.6) (pre-post change) C vs. D 48.3 (10.5) vs. 55.3 (9.5) (baseline) 49.6 (11.6) vs. 50.5 (11.3) (postintervention) 1.3 (95% CI –4.7 to 7.3) vs. −4.8 (95% CI −10.4 to −0.6) (pre-post change) A vs. B 50.5 (9.5) vs. 54 (11.5) (baseline) 45.9 (10.5) vs. 49.4 (12) (postintervention) −4.54 (95% CI −7.5 to −1.5) vs. −4.52 (95% CI −7.9 to −1.1) (pre-post change) C vs. B 48.3 (10.5) vs. 54 (11.5) (baseline) 49.6 (11.6) vs. 49.4 (12) (postintervention) 1.3 (95% CI –4.7 to 7.3) vs. −4.52 (95% CI −7.9 to −1.1) (pre-post change) A vs. C 50.5 (9.5) vs. 48.3 (10.5) (baseline) 45.9 (10.5) vs. 49.6 (11.6) (postintervention) −4.54 (95% CI −7.5 to −1.5) vs. 1.3 (95% CI –4.7 to 7.3) (pre-post change)

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Hogan, 2014 (same author group and protocol as Garrett 2013a and 2013b - see notes) **Postural Control** Yoga **(Continued)**				MSIS–psychological, median (semi–IQR) (The Kruskal Wallis test showed that there was no statistically significant difference between groups) A vs. D 18 (5.5) vs. 17 (4) (baseline) 15 (5.7) vs. 15 (4.5) (postintervention) −3 vs. 2 (pre-post change) B vs. D 18 (5.38) vs. 17 (4) (baseline) 17 (4.8) vs. 15 (4.5) (postintervention) −1 vs. 2 (pre-post change) C vs. D 14 (2.2) vs. 17 (4) (baseline) 15 (4) vs. 15 (4.5) (postintervention) 1 vs. 2 (pre-post change) A vs. B 18 (5.5) vs. 18 (5.38) (baseline) 15 (5.7) vs. 17 (4.8) (postintervention) −3 vs. −1 (pre-post change) C vs. B 14 (2.2) vs. 18 (5.38) (baseline) 15 (4) vs. 17 (4.8) (postintervention) 1 vs. −1 (pre-post change) A vs. C 18 (5.5) vs. 14 (2.2) (baseline) 15 (5.7) vs. 15 (4) (postintervention) −3 vs. 1 (pre-post change)

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Hota, 2020 **Postural Control** Balance Exercises Postintervention, 4 weeks Fair	A. Dual task exercises for upper and lower limbs, 24 sessions over 4 weeks (n=20) B. Control group – details NR, (n=20)	A vs. B Age 11-25: 40% vs. 30% Age 26-40: 25% vs. 45% Age 41-55: 25% vs. 25% Age 56-70: 10% vs. 0% Female: 10% vs. 10% Race: NR	A vs. B, mean (SD): <u>BBS</u>: MD 4.55, 95% CI 2.16 to 6.94 <u>Motor Assessment Scale</u>: MD 3.82, 95% CI 1.09 to 6.55, p=0.006	NA
Hsieh, 2018 **Postural Control** Motion gaming Postintervention, 12 weeks Fair	A. PC gaming using arm and trunk, 60 sessions over 12 (n=20) B PC gaming using mouse, 60 sessions over 12 weeks (n=20)	A vs. B Age (mean years): 7.33 vs. 7.41 Female: 6 (30%) vs. 5 (25%) Race: NR Ambulatory: NR Wheelchair user: NR CP subtype Spastic quadriplegia 11 (55%) vs. 12 (60%) Spastic diplegic 4 (20%) vs. 3 (15%) Athetoid 2 (10%) vs. 2 (10%) Ataxic 3 (15%) vs. 3 (15%) GMFCS level Level II 10 (50%) vs. 10 (50%) Level III 6 (30%) vs. 5 (25%) Level IV 4 (20%) vs. 5 (25%)	A vs. B TUG (score) 16.43 (2.12) vs. 15.60 (1.10) (baseline) 17.51 (1.70) vs. 15.91 (1.87) (postintervention)	A vs. B, mean (SD) BBS (score) 44.74 (2.75) vs. 44.39 (2.33) (baseline) 48.81 (4.74) vs. 45.37 (2.68) (postintervention)
Hsieh, 2020 **Postural Control** Motion Gaming Postintervention, 0 weeks Fair	A. PC gaming using balance board, 36 sessions over 12 weeks (n=28) B. PC gaming using mouse, 36 sessions over 12 weeks (n=28)	A vs. B Age: 7.9 vs. 8.1 Female: 32% vs. 31.5% Race: NR GMFCS I: 53.5% vs. 50% GMFCS II: 28.6% vs. 32.1% GMFCS III: 17.9% vs. 17.9% Deplegic: 57.1% vs. 42.9%	A vs. B, mean (SD) <u>2MWT:</u> 103.4 (16.6) to 120.1 (20.2) vs. 101.4 (23.1) to 106.1 (22.8), p=0.002 <u>PBS-total:</u> 29.9 (5.3) to 35.8 (5.5) vs. 32.3 (7.5) to 34.4 (5.9), p=0.002	NA

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Huang, 2015 **Aerobic Exercise** Robot-Assisted Gait Training Postintervention, 4 weeks Fair	A. RAGT, 16 sessions over 4 weeks (n=12) B. Body Weight Support Treadmill Training, 16 sessions over 4 weeks (n=12)	A vs. B Age (mean years): 41.7 vs. 38.4 Female: 5 (42%) vs. 3 (25%) Race: NR Ambulatory: NR Wheelchair user: NR Other: height 168.8 cm vs. 169.8 cm weight (kg) 66.1 vs. 65.3	A vs. B, mean (SD) A. Defecation time Before 93.0 +/-14.7 After 64.5 +/-11.6 B. Before 84.0 +/-15.2 After 69.5 +/-15.6	NA

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In, 2018 **Postural Control** Whole body vibration Postintervention, 0 weeks Fair	A. Whole body vibration + conventional physical therapy: 80 sessions over 8 weeks (n=14) B. Placebo whole body vibration + conventional physical training (n=14)	A vs. B (Data for completers only) Age (mean years): 46.1 vs. 49.9 Female: 5 (36%) vs. 4 (29%) Race: NR Ambulatory: 14 (100%) vs. 14 (100%) Wheelchair user: NR Duration (mean months): 13.7 vs. 14.3	A vs. B TUG (seconds) 13.7 (3.1) vs. 14.7 (4.5), p=0.608 (baseline) 11.4 (2.8) vs. 13.7 (4.1), p=NR (postintervention) –2.3 (1.3) vs. –1.0 (1.0), p=0.016 (post-pre change) Time X Group p=0.016 10MWT (seconds) 29.3 (9.0) vs. 28.8 (7.2), p=0.868 (baseline) 25.8 (8.1) vs. 27.5 (6.3), p=NR (postintervention) –3.5 (2.3) vs. –1.3 (1.4), p=0.005 (post-pre change) Time X Group p=0.005 Spasticity measured by manual muscle tester (kg) -Right ankle 11.9 (3.5) vs. 12.2 (3.2), p=0.785 (baseline) 8.8 (2.9) vs. 11.1 (2.9), p=NR (postintervention) –3.1 (1.9) vs. –1.1 (0.6), p=0.001 (post-pre change) Time X Group p=0.001 -Left ankle 13.2 (2.3) vs. 12.5 (3.1), p=0.526 (baseline) 10.1 (2.2) vs. 11.6 (2.3), p=NR (postintervention) –3.0 (1.7) vs. –0.9 (1.2), p=0.001 (post-pre change) Time X Group p=0.001	NA

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Johnston 2011 **Aerobic Exercise** Treadmill Postintervention, 4 weeks Fair	A. Partial body weight supported treadmill training with two 30 minute sessions 5 days a week for 2 weeks, followed by 30 minutes 5 days a week of home training for 10 weeks B. Individualized physical therapy sessions strength and weigh-bearing activities comparable session duration and number	Marginal ambulatory function and GMFCD III or IV n=34 randomized and 26 completed the study Mean age 9.5 years 14 males and 12 females (39% male)	Pre, post and 1 month later Gait speed (meters/second) A. 0.50(0.26) to 0.62 (0.31) to 0.63 (0.28) B. 0.44 (0.35) to 0.32 (0.50) to 0.44 (0.34) within group differences pre to post for both groups [body weight supported treadmill p=0.008, physical therapy p=0.007]; but gains only maintained in treadmill group GMFM A. 62.7 (17.5) to 63.3 (16.2) to 65.3 (16.5) B. 58.4 (26.9) to 60.1(25.1) to 60.6 (26.7) no significant change in either group and no difference between groups Pediatric Outcomes Data Collection Instrument (global) A. 50.4 (11.2) to 59.3 (11.4) to 60.0 (10.0) B. 50.9 (14.9) to, 52.0 (22.6) to 55.4 (21.7) score improved for all participants (p=0.003) but no difference between groups (p=0.73); only the treadmill group maintained the improvement	Plantar flexor spasticity A. 0.0013 (0.0012) to 0.0016 (0.0024) to 0.0012 (0.0018) B. 0.0030 (0.0024) to 0.003. (0.0021) to 0.0026 (0.0013) Knee flexor spasticity A. 0.0088 (0.0114), 0.0074 (0.0133), 0.0083 (0.0139) B. 0.0032 (0.0044), 0.0072 (0.0137), 0.0053 (0.0044) Knee extension strength A. 3.90 (3.09) to 3.58 (2.82) to 3.06 (3.25) B. 3.09 (3.15) to 3.80 (4.22) to 3.69 (3.66) Knee flexion strength A. 2.47 (1.45) to 2.43 (1.54) to 2.57 (1.65) B. 2.35 (2.04) to 2.98 (3.26) to 2.54 (2.09) No significant within or between group differences in spasticity or strength

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Jones, 2014a Jones, 2014b **Multimodal Exercise** Postintervention, 12 weeks (for ALL patients completing the Activity Based Therapy intervention) Poor (for both)	A. Activity–based therapy: 72 sessions over 24–weeks; actual frequency average 49.9 sessions (n=20) B. Waitlist (n=21)	A vs. B (for completers only) Age (mean years): 42.20 vs. 34.14, p=0.046 Female: 1 (5%) vs. 10 (48%), p=0.002 Race: NR Spinal Cord Injury Functional Ambulation Index: 13.44 vs. 18.6 Wheelchair user: NR Tetraplegia (C2 to T1) -LEMS ≥ 25: 8 (40%) vs. 7 (33%) -LEMS>25: 7 (35%) vs.9 (43%) Paraplegia (T2 to T10) -LEMS ≥ 25: 1 (5%) vs. 1 (5%) -LEMS > 25: 4 (20%) vs. 4 (19%) Time postinjury (mean months): 77.87 vs. 75.3	Data reported as mean (SD) A vs. B TUG (seconds) 190.9 (134.6) vs. 111.19 (112.9), p=0.048 (baseline) –37.2 (81.3) vs. –6.2 (18.1), p=0.267(pre-post change) 10MWT (meters/second) 0.227 (0.304) vs. 0.363 (0.411), p=0.240 (baseline) 0.096 (0.140) vs. 0.027 (0.104), p=0.036 (pre-post change) 6MWT (meters) 73.11 (92.57) vs. 117.6 (132.8), p=0.219 (baseline) 35.97 (48.15) vs. 3.0 (25.51), p=0.002 (pre-post change) BMI (kg/m^2) 27.14 (6.36) vs. 24.81 (6.64), p=0.260 (baseline) 0.005 (1.15) vs. 0.723 (2.22), p=0.288 (pre-post change) Weight (pounds) 197 (44.79) vs. 167 (46.35), p=0.040 (baseline) –0.20 (8.29) vs. 5.03 (14.05), p=0.314 (pre-post change) Data for ALL participants completing the Activity Based Therapy intervention (n=38) [Baseline vs. postintervention, MD (95% CI)] TUG (seconds): 149.50 (130.39) vs. 124.99 (126.21), MD –24.52 (95% CI –44.88 to –4.14), p=0.020 10MWT (meters/second): 0.304 (0.404) vs. 0.364 (0.389), MD 0.061 (95% CI 0.01 to 0.11), p=0.021 6MWT (meters): 96.30 (115.15) vs. 129.35 (127.08), MD 33.05 (95% CI 15.82 to 50.27), p=0.000	Data reported as mean (SD) A vs. B QUICKI (calculated using Lipid profiles) 0.35 (0.04) vs. 0.38 (0.06), p=0.071 (baseline) –0.002 (0.023) vs. –0.012 (0.045), p=0.921 (pre-post change) Reintegration to normal living index 78.3 (18.0) vs. 80.0 (17.1), p=0.760 (baseline) 4.6 (13.87) vs. –2.0 (10.01), p=0.087 (pre-post change) SCI-FAI 13.44 (13.4) vs. 18.6 vs. 11.5, p=0.294 (baseline) 5.0 (8.03) vs. -0.21 (2.83), p=0.031 (pre-post change) SCIM-III 62.7 (18.8) vs. 63.6 (25.5), p=0.891 (baseline) 1.35 (5.2) vs. 0.0 (4.53), p=0.393 (pre-post change)

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Jones, 2014a Jones, 2014b **(Continued)**			Odds of responding to Activity Based Therapy at postintervention (n=38) [% responding (n/N) vs. % responding (n/N), OR (95% CI)] TUG (positive response ≥25.7 second decrease) Tetraplegia vs. Paraplegia: 17.9% (5/28) vs. 20% (2/10), OR 1.15 (95% CI 0.18 to 7.14), p=0.881 AIS grade C vs. grade D: 14.3% (2/14) vs. 20.8% (5/24), OR 1.58 (95% CI 0.26 to 9.48), p=0.617 Lower extremity motor score <26 vs. >25: 25% (4/16) vs. 13.6% (3/22), OR 2.11 (95% CI 0.40 to 11.13), p=0.378 >3 years vs. <3 years since injury: 15.8% (3/19) vs. 21% (4/19), OR 1.42 (95% CI 0.27 to 7.44), p=0.617 Functional walker at home (>0.4m/s) vs. Non–functional walker at home (<0.4 m/s): 25.9% (7/27) vs. 0% (0/11), OR 8.42 (95% CI 0.44 to 161.16), p=0.157 10MWT (positive response ≥0.13 meter/second increase) Tetraplegia vs. Paraplegia: 21.4% (6/28) vs. 40% (4/10), OR 2.44 (95% CI 0.53 to 11.57), p=0.260 AIS grade C vs. grade D: 7.1% (1/14) vs. 37.5% (9/24), OR 7.80 (95% CI 0.87 to 70.08), p=0.067 Lower extremity motor score <26 vs. >25: 18.8% (3/16) vs. 31.8% (7/22), OR 2.02 (95% CI 0.43 to 9.46), p=0.371 >3 years vs. <3 years since injury: 15.8% (3/19) vs. 36.8% (7/19), OR 3.11 (95% CI 0.66 to 14.60), p=0.150 Functional walker at home (>0.4m/s) vs. Non–functional walker at home (<0.4 m/s): 22.2% (6/27) vs. 36.4% (4/11), OR 2.00 (95% CI 0.43 to 9.21), p=0.374	

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Jones, 2014a Jones, 2014b **(Continued)**			6MWT (positive response ≥45.11 meter increase) Tetraplegia vs. paraplegia: 25% (7/28) vs. 50% (5/10), OR 3.00 (95% CI 0.67 to 13.53), p=0.153 AIS grade C vs. grade D: 7% (1/14) vs. 53% (11/24), OR 11.00 (95% CI 1.24 to 97.97), p=0.032 Lower extremity motor score <26 vs. >25: 18.8% (3/16) vs. 40.9% (9/22), OR 3.00 (95% CI 0.66 to 13.66), p=0.156 >3 years vs. <3 years since injury: 15.8% (3/19) vs. 47.4% (9/19), OR 4.80 (95% CI 1.04 to 22.10), p=0.044 Functional walker at home (>0.4m/s) vs. Non–functional walker at home (<0.4 m/s): 25.9% (7/27) vs. 45.5% (5/11), OR 2.38 (95% CI 0.55 to 10.32), p=0.246 Odds of responding to Activity Based Therapy at 12-week followup (n=31) [% responding (n/N) vs. % responding (n/N), OR (95% CI)] 10MWT Tetraplegia vs. Paraplegia: 44% (11/25) vs. 83.3% (5/6), OR 6.36 (95% CI 0.65 to 62.69), p=0.113 AIS grade C vs. grade D: 16.7% (2/12) vs. 13.7% (14/19), OR 14.00 (95% CI 2.25 to 87.25), p=0.005 Lower extremity motor score <26 vs. >25: 28.6% (4/14) vs. 70.6% (12/17), OR 6.00 (95% CI 1.26 to 28.55), p=0.024 >3 years vs. <3 years since injury: 50% (8/16) vs. 33.3% (8/15), OR 1.14 (95% CI 0.28 to 4.68), p=0.853 Functional walker at home (>0.4m/s) vs. nonfunctional walker at home (<0.4 m/s): 42.9% (9/21) vs. 70% (7/10), OR 3.11 (95% CI 0.63 to 15.49), p=0.166 Reported exercise <3 hours/week vs. >3 hours/week: 44.4% (4/9) vs. 60% (9/15), OR 1.88 (95% CI 0.35 to 9.98), p=0.461	

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Jones, 2014a Jones, 2014b **(Continued)**			Reported no community walking vs. community walking: 44.4% (4/9) vs. 60% (9/15), OR 1.88 (95% CI 0.35 to 9.98), p=0.461 6MWT Tetraplegia vs. Paraplegia: 40% (10/25) vs. 33.3% (2/6), OR 1.33 (95% CI 0.20 to 8.70), p=0.764 AIS grade C vs. grade D: 8.3% (1/12) vs. 57.9% (11/19), OR 15.13 (95% CI 1.61 to 142.16), p=0.018 Lower extremity motor score <26 vs. >25: 7.1% (1/14) vs. 64.7% (11/17), OR 23.83 (95% CI 2.4 to 229.36), p=0.006 >3 years vs. <3 years since injury: 37.5% (6/16) vs. 40% (6/15), OR 1.11 (95% CI 0.26 to 4.72), p=0.887 Functional walker at home (>0.4m/s) vs. Non–functional walker at home (<0.4 m/s): 23.8% (5/21) vs. 70% (7/10), OR 0.019 (95% CI) Reported exercise <3 hours/week vs. >3 hours/week: 44.4% (4/9) vs. 46.7% (7/15), OR 1.09 (95% CI 0.21 to 5.76), p=0.916 Reported no community walking vs. community walking: 22.2% (2/9) vs. 60% (9/15), OR 5.25 (95% CI 0.80 to 34.43), p=0.084	
Jung, 2014 **Aerobic Exercise** Aquatics Postintervention, 0 weeks Fair	A. Aquatic exercise, 24 sessions over 8 weeks (n=10) B. Land exercise, 24 sessions over 8 weeks (n=10)	A vs. B Age (mean years): 42.1 vs. 51.1 Female: 3 (30%) vs. 5 (50%) Race: NR Ambulatory: NR Wheelchair user: NR	A vs. B FVC(L): 2.5 (0.7) vs. 3.0 (0.9) baseline 4.3 (1.4) vs. 3.4 (1.4); change values -1.8 (1.3) vs. -0.31 (1.6), p<0.01 (postintervention) FEV1(L): 2.1 (0.9) vs. 2.7 (1.0) baseline 3.2 (1.2) vs. 2.9 (1.0); change values -1.1 (1.2) vs. -0.21 (0.3); p<0.05 (postintervention) FER(L/sec) and FEV1/FVC: all NS	NA

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Jonsdottir, 2018 **Aerobic Exercise** Treadmill Postintervention, 0 weeks Fair	A. 30 minutes treadmill walking, 5 days a week for 8 weeks; 10 of the 30 minutes was doing other cognitive or motor tasks (dual tasking treadmill) B. Strength training 4 or 5 days a week, 3 sets with 10 reps/set multiple lifts	EDSS 5.53 (3.5-7) n=42 Mean age 54.05 years (n=38) 28 females and 10 males (26.3% males)	Pre, post 2 minute walk A. 89.1 (35.5) to 116.2 (21.5) B. 84.5 (34.7) to 87.9 (21.5) p=0.0006 95% CI -1.31 (-2.06, -0.57) Timed Up and Go A. 16.1 (7.8) to 11.9 (2.3) B. 17.4 (13.5) to 14.8 (2.9) p=0.009 95% CI 0.009 1.00 (.26, 1.85) DGI (Dynamic Gate Index) A. 15.2 (4.4) to 17.3 (2.7) B. 15 (5.22) to 17.2 (2.7) p=0.97 95% CI 0.00 (-0.77, 0.70) SF-12 mental A. 39.3 (8) to 42.6 (6.9) B. 42.0 (10.2) to 44.7 (8.8) p=0.34 95% CI 0.34 (-0.39, 1.09) SF-12 physical A. 33.8 (7.4) to -35.4 (5.3) B. 37.4 (11.3) to 33.6 (5.3) p=0.36 95% CI -0.34 (-1.06, 0.40) Berg Balance A. 42.9 (10.3) to 48.6 (3.7) B. 44.8 (9.4) to 47.4 (3.8) p=0.39 95% CI -0.30 (-0.98, 0.38)	NA

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Kalron, 2016 **Postural Control** Motion gaming Postintervention, 6 weeks Fair	A. Virtual reality (motion platform, VR 3D visuals and sound, plus balance training): 12 sessions over 6 weeks (n=16) B. Usual care control (conventional exercise, plus balance training): 12 sessions over 6 weeks (n=16)	A vs. B NR Age (mean years): 45.2 Female: 19 (63%) vs. 11 (37%) Race: NR Ambulatory: NR Wheelchair user: NR EDSS, mean (SD): 4.1 (1.3)	A. vs. B., mean (SD) FSST: 16.2 (7.0) vs. 14.2 (7.1), (baseline) 12.7 (6.4) vs. 11.7 (5.9) (postintervention) Mean difference −3.5 (6.1), F=9.011, p=0.031 FES-I: 36.4 (9.7) vs. 32.9 (10.3) (baseline) 29.4 (7.8) vs. 28.6 (5.8) (postintervention) Mean difference −4.3 (6.3), F=17.815, p=0.023	A. vs. B, mean (SD) BBS* 46.8 (9.6) vs. 43.3 (7.1) (baseline) 47.9 (6.4) vs. 44.6 (4.9) (postintervention) Mean difference 1.3 (5.2), F=1.541, p=0.215 *Labeled in the study as "BBT- Berg Balance Test"

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Kalron, 2017 **Muscle Strength** Postintervention, 0 weeks Fair	A. Pilates: 12 sessions over 12 weeks + 15-minute daily home exercise program (n=22) B. Standardized physical therapy (Usual care ?): 12 sessions over 12 weeks + 15-minute daily home exercise program (n=23)	A vs. B [not accounting for those lost to followup] Age (mean years): 42.9 vs. 44.3 Female: 14 (60.9%) vs. 15 (68.2%) Race: NR Ambulatory: NR (minimum ability to walk 100m with or without resting with the assistance of a walking aid was required for inclusion) Wheelchair user: NR Baseline EDSS (mean): 4.1 vs. 4.6 Disease duration (mean years): 12.4 vs. 11.3	Data reported as mean (SD) A vs. B TUG (seconds): 12.5 (3.5) vs. 11.6 (2.9) (baseline) 10.7 (3.3) vs. 9.9 (2.9) (postintervention) −1.8 (2.1) vs. −1.7 (2.1) (pre-post change) Time factor p=0.023 Time X Group interaction p=0.422 6MWT (meters): 405.6 (125.8) vs. 398.2 (105.3) (baseline) 444.7 (89.7) vs. 423.5 (119.2) (postintervention) 39.1 (78.3) vs. 25.3 (67.2) (pre-post change) Time factor p=0.017 Time X Group interaction p=0.341 2MWT (meters) 139.3 (41.5) vs. 135.7 (39.8) (baseline) 153.8 (43.6) vs. 147.9 (40.9) (postintervention) 14.5 (25.8) vs. 12.7 (23.0) (pre-post change) Time factor p=0.018 Time X Group interaction p=0.872 MSWS-12 (0-100, higher scores=decreased walking ability): 39.2 (12.7) vs. 37.2 (10.5) (baseline) 36.4 (11.8) vs. 34.8 (11.9) (postintervention) 2.8 (6.3) vs. 2.4 (5.9) (pre-post change) Time factor p=0.042 Time X Group interaction p=0.924	Data reported as mean (SD) A vs. B BBS (0-56, higher scores=better balance): 46.8 (9.6) vs. 43.3 (7.1) (baseline) 47.9 (6.4) vs. 44.6 (4.9) (postintervention) 1.1 (4.2) vs. 1.3 (5.2) (pre-post change) Time factor p=0.215 Time X Group interaction p=0.561

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Kara, 2017 **Aerobic Exercise** Aerobics Postintervention, 0 weeks Poor	A. Pilates: 16 sessions over 8 weeks (n=27) B. Aerobic exercise: 16 sessions over 8 weeks (n=28)	A vs. B Age: 50 vs. 43 Female: 67% vs. 65% EDSS: 2.85 vs. 3.2	Data reported as mean (SD) A vs. B TUG right 11.75 (3.38) vs. 10.33 (6.32), p<0.001 (baseline) 10.51 (2.69) vs. 9.56 (6.04), p=0.075 (postintervention) TUG left: 12.74 (3.32) vs. 10.33 (6.28), p=0.001 (baseline) 9.73 (3.17) vs. 10.39 (7.09), p=0.515 (postintervention) BDI: 11.44 (6.52) vs. 8.92 (6.49), p=0.001 (baseline) 9.77 (5.26) vs. 7.15 (6.35), p=0.156 (postintervention)	Data reported as mean (SD) A vs. B 44.66 (10.98) vs. 46.11 (12.44), p=0.028 (baseline) 47.77 (13.89) vs. 48.57 (16.02), p=0.243 (postintervention) 3.11 (NR) vs. 2.46 (NR), p=NR (pre-post change)
Kara, 2020 **Strength** Immediately postintervention, 12 weeks Fair	A. Strength and power training, 36 sessions over 12 weeks (n=15) B. Usual care; occupational therapy, 36 sessions over 12 weeks (n=15)	A vs. B Age: 12.3 vs. 11.8 Female: 53% vs. 53% Race: NR Ambulatory: NR Wheelchair: NR Manual ability classification system (MACS) Level I: 47% vs. 40% II: 27% vs. 33% III: 27% vs. 27% GMFCS Level I: 87% vs. 87% II: 13% vs. 13%	A vs. B, Mean (SD), p-value for between group difference QUEST total 8.88 (6.51) vs. 2.22 (4.74), MD 6.65 (95% CI 2.4 to 10.9), p=0.001 (pre-post change)	A vs. B, Mean (SD), p-value for between group difference COMP total 6.12 (2.33) vs. 0.41 (1.56), MD 5.71 (95% CI 4.2 to 7.2), p<0.001 (pre-post change)

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Kargarfard, 2017 **Aerobic Exercise** Aquatics Postintervention, 0 weeks Fair	A. Aquatic exercise, 24 sessions over 8 weeks (n=17), plus 2-3 sessions per week with neurologic PTs and once weekly educational session B. 2-3 sessions per week with neurologic PTs and once weekly educational session, 16-24 sessions over 8 weeks (n=15)	A vs. B Age (mean years): 36.5 (9.0) vs. 36.2 (7.4) Female: 20 (100%) vs. 15 (100%) Race: NR Ambulatory: NR Wheelchair user: NR Other: MS: subtypes NR	A vs. B, mean (SD) 6MWT: 451 (58) vs. 447 (30) (baseline) 503 (57) vs. 418 (29); p<0.001 (postintervention) Sit to Stand: 21.0 (5.7) vs. 21.4 (4.7) (baseline) 16.8 (5.1) vs. 27.3 (4.8); p<0.001 (postintervention) Calculated A vs. B, Mean change scores: 6MWT: -52 vs. 29, p<0.001 Sit to Stand: 4.2 vs. -5.9, p<0.001 BBS: -1.6 vs. 2.1, p<0.001	A vs. B, mean (SD) Pushup: 17 (9) vs. 18 (7) (baseline) 26 (11) vs. 10 (5); p<0.001 (postintervention) BBS: 53.6 (1.7) vs. 52.3 (3.3) (baseline) 55.2 (1.2) vs. 50.2 (4.6); p<0.001 (postintervention)
Kaya Kara, 2019 **Multimodal Exercise** Immediately postintervention, 12 weeks Fair	A. Strength training (progressive resistance exercise) + balance, 36 sessions over 12 weeks (n=17) B. Usual care, 36 sessions over 12 weeks (n=16)	A vs. B Age: 11.8 vs. 11.3 Female: 53% vs. 60% Ambulatory: 100% Manual ability classification system level: I: 47% vs. 47% II: 33% vs. 27% III: 20% vs. 27%	A vs. B, Mean change from baseline (SD) (data are for completers only; n=15 vs. 15) GMFM-88D 0.17 (0.67) vs. 0.32 (1.42), MD −0.15 (95% CI −0.93 to 0.63), p=0.632; effect size 0.13 GMFM-88E 2.31 (2.20) vs. −0.37 (2.59), MD 2.68 (95% CI 0.98 to 4.38), p=0.004; effect size 1.11 1 minute walk 7.76 (7.03) vs. 0.53 (3.37), MD 7.23 (95% CI NR), p=0.001; effect size 1.31 TUG −1.02 (0.45) vs. 0.08 (0.45), MD −1.10 (95% CI −1.42 to −0.78), p<0.001; effect size 2.42	A vs. B, mean difference, Effect size, p-value is between groups Affected lower leg 1 RM (kg): 54.33, ES 3.23, p<0.001 Unaffected lower leg 1 RM (kg): 44.33, ES 2.74, p<0.001

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Kerling, 2015 **Multimodal Exercise** Postintervention, 0 weeks Fair	A. Full body progressive resistance + aerobic training (n=30) B. Aerobic training (n=30) [36 sessions over 12 weeks for both groups]	A vs. B Age (mean years): 42.3 vs. 45.6 Female: 24 (80%) vs. 20 (67%) Race: NR Ambulatory: NR Wheelchair user: NR MS specific medication (yes): 20 (67%) vs. 20 (67%)	Data reported as mean (SD) A vs. B SF-36 PCS (0-100, higher=greater QOL) 44.9 (9.1) vs. 39.0 (10.8), p=NR (baseline) 46.2 (9.1) vs. 39.6 (11.3), p=NR (postintervention) Time X Group p=0.56 SF-36 MCS (0-100, higher=greater QOL) 44.9 (13.6) vs. 46.7 (11.7), p=NR (baseline) 45.4 (13.4) vs. 51.4 (8.6), p=NR (postintervention) Time X Group p=0.01 VO_2-peak (mL/min): 1684 (601) vs. 1632 (539), p=NR (baseline) 1756 (599) vs. 1676 (494), p=NR (postintervention) Time X Group p=0.71 VO_2-peak (ml/min/kg): 23.8 (7.8) vs. 23.5 (8.2), p=NR (baseline) 24.6 (7.4) vs. 23.7 (7.1), p=NR (postintervention) Time X Group p=0.72	Data reported as mean (SD) A vs. B Resting HR (bpm): 92 (12) vs. 88 (12), p=NR (baseline) 90 (11) vs. 85 (13), p=NR (postintervention) Time X Group p=0.63 Right knee extensor strength (hamstrings): 102.3 (23.5) vs. 91.4 (36.9), p=NR (baseline) 107.7 (28.0) vs. 99.3 (42.3), p=NR (postintervention) Time X Group p=0.50 Left knee extensor strength (hamstrings): 105.5 (28.1) vs. 92.7 (39.3), p=NR (baseline) 108.2 (33.1) vs. 95.6 (43.8), p=NR (postintervention) Time X Group p=0.95 Right knee flexor strength (quadriceps): 55.3 (16.0) vs. 51.0 (21.0), p=NR (baseline) 61.3 (18.7) vs. 55.9 (24.6), p=NR (postintervention) Time X Group p=0.72 Left knee flexor strength (quadriceps): 58.2 (20.2) vs. 48.7 (23.5), p=NR (baseline) 64.0 (23.7) vs. 51.7 (24.85), p=NR (postintervention) Time X Group p=0.31 Right extensor shoulder strength: 48.0 (13.9) vs. 45.5 (19.3), p=NR (baseline) 51.8 (14.9) vs. 49.9 (20.1), p=NR (postintervention) Time X Group p=0.85

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Kerling, 2015 **(Continued)**				Left extensor shoulder strength: 46.3 (17.5) vs. 43.3 (17.3), p=NR (baseline) 50.0 (18.9) vs. 46.9 (18.6), p=NR (postintervention) Time X Group p=0.98 Right flexor shoulder strength: 34.2 (9.6) vs. 35.3 (12.6), p=NR (baseline) 36.5 (10.0) vs. 36.9 (14.1), p=NR (postintervention) Time X Group p=0.67 Left flexor shoulder strength: 35.8 (13.9) vs. 34.0 (12.1), p=NR (baseline) 36.9 (12.4) vs. 35.9 (12.5), p=NR (postintervention) Time X Group p=0.60
Keser, 2011 **Aerobic Exercise** Aerobics Postintervention, 0 weeks Poor	A. Calisthenics, 18 sessions over 6 weeks (15) B. Routine neurorehabilitation (strength, balance, coordination, anti-spasticity exercises) 18 sessions over 6 weeks (15)	A vs. B Age: 36 vs. 35 Female: 53% vs. 47% EDSS: 2.9 vs. 2.8	A vs. B mean Difference MSFC: -0.002 (0.44) vs. 0.02 (0.23), p>0.05 SF-36: 0.20 (5.67) vs. 1.73 (7.75), p>0.05 HADS-A: -2.26 (3.23) vs. -0.80 (2.40), p>0.05 HADS-D: 0.20 (2.65) vs. 1.46 (2.19), p>0.05	A vs. B mean Difference BBS: -1.73 (3.03) vs. -1.80 (2.67), p>0.05 Strength UE right: 8.67 (10.17) vs. 15.19 (7.77), p<0.05 Strength UE left: 7.86 (11.97) vs. 16.25 (10.95), p<0.05 Strength LE right: 15.76 (11.17) vs. 20.66 (6.18), p>0.05 Strength LE left: 18.54 (7.59) vs. 24.17 (16.69), p>0.05

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Khalil, 2018 **Postural Control** Motion gaming Postintervention, 6 weeks Fair	A. Nintendo Wii balance board and VR scenarios with tasks to complete, 12 sessions over 6 weeks (n=16) B. Balance training at home, 18 sessions over 6 weeks (n=16)	A vs. B Age (mean years): 39.8 vs. 34.9 Female: 12 (75%) vs. 10 (63%) Race: NR Ambulatory: NR Wheelchair user: NR Duration of MS (mean years) 8.38 vs. 10.43 EDSS: 2.9 (1.4) vs. 3.1 (1.1) *EDSS = a lower score indicates a better performance	A. vs. B., mean (SD), mean difference (95% CI) TUG 13.93 (5.00) vs. 18.01 (15.03) (baseline) 13.38 (5.88) vs. 17.42 (14.66) (postintervention) Mean difference 0.04 (95% CI -2.24 to 2.32) 10MWT 12.43 (2.86) vs. 12.11 (3.71) (baseline) 11.35 (2.66) vs. 19.69 (27.23) (postintervention) Mean difference 8.48 (95% CI -5.16 to 22.12) 3 min walk test 148.75 (58.60) vs. 144.75 (63.64) (baseline) 142.31 (64.64) vs. 140.00 (70.21) (postintervention) Mean difference -7.11 (95% CI -34.18 to 19.95) PCS 54.7 (17.69) vs. 56.91 (18.38) (baseline) 68.17 (13.20) vs. 57.99 (18.26) (postintervention) Mean difference -11.62 (95% CI -22.27 to -0.99) SF-36, MCS 57.00 (16.58) vs. 67.56 (11.24) 52.37 (18.73) (baseline) 52.37 (18.73) 67.56 (11.24) vs. 51.94 (18.97) (postintervention) Mean difference -13.60 (95% CI -23.66 to -3.55)	A. vs. B., mean (SD), mean difference (95% CI) BBS 43.69 (6.58) vs. 42.31 (10.82) (baseline) 50.44 (3.76) vs. 45.19 (8.64) (postintervention) Mean difference - 4.52 (95% CI -7.90 to -1.09)
Kim 2015 **Aerobic Exercise** Treadmill Postintervention, 0 weeks Fair	A. Conventional physical therapy plus 30 minutes of treadmill walking for 20 sessions (3 to 5 sessions a week for 1 to 2 months) B. Conventional physical therapy for similar number of sessions	Mean age 27.2 years 11 males and 10 females (52% male) A. n=14 B. n=7	Pre, post 6 minute walk (meters) A. 151.29 (91.79) to 193.93 (79.01) B. 162.14 (81.85) to 180.71 (61.40) A. Significantly increased after training p<0.05 and B. Did not significantly change; direct comparison changes in A and B NR	NR

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Kim, 2017 **Postural Control** Balance Social activity/exercise (Boccia) Postintervention, 0 weeks Poor	A. Group boccia: 12 sessions over 6 weeks (n=11) B. Usual care (n=12)	A vs. B Age (mean years): 22.36 vs. 21.83 Female: 5 (45%) vs. 5 (42%) Race: NR Ambulatory: NR Wheelchair user: NR	NR	Data reported as mean (SD) A vs. B Modified Barthel Index (0–100, higher=greater independence completing ADLs) 39.00 (9.34) vs. 35.67 (11.41), p=NR (baseline) 41.81 (10.24) vs. 37.25 (11.77), p=NR (postintervention) 2.82 (1.25) vs. 1.58 (1.38), p<0.05, MD 1.24 (95% CI 0.09 to 2.34), p=0.0352 (post-pre change)

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Kirk, 2016 **Muscle Strength** Postintervention, 0 weeks Poor	A. Progressive resistance: 36 sessions over 12 weeks (n=11) B. Usual care (n=21)	A+B (data across all patients) Age (mean years): 36.5 Female: 15 (43%) Race: NR Ambulatory: NR Wheelchair user: 6 (17%)	Data reported as mean (SD) A vs. B 10MWT (seconds) 7.76 (1.23) vs. 8.83 (0.78) (baseline) 7.49 (1.10) vs. 8.47 (0.86) (postintervention) 6MWT (meters) 481 (30) vs. 400 (32) (baseline) 510 (33) vs. 416 (33) (postintervention) Timed Stair Test (seconds) 30.69 (4.92) vs. 49.82 (7.27) (baseline) 29.15 (4.62) vs. 45.01 (6.57) (postintervention)	Data reported as mean (SD) A vs. B There was a statistically significant Groups X Time interaction for the 1RM measurements of all exercises. Ankle dorsiflexion 1RM for most affected leg (kg) 5.7 (0.6) vs. NR (baseline) 10.4 (1.1) vs. NR (postintervention) 83% vs. NR (pre-post % change) Ankle plantarflexion 1RM for most affected leg (kg) 30.3 (4.9) vs. NR (baseline) 71.8 (6.7) vs. NR (postintervention) 137% vs. NR (pre-post % change) Knee flexion 1RM for most affected leg (kg) 16.3 (2.0) vs. NR (baseline) 29.5 (3.1) vs. NR (postintervention) 82% vs. NR (pre-post % change) Knee extension 1RM for most affected leg (kg) 72.3 (5.8) vs. NR (baseline) 104.5 (6.7) vs. NR (postintervention) 45% vs. NR (pre-post % change)

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Kjolhede, 2016 **Muscle Strength** Postintervention, 0 weeks Fair	A. Progressive resistance: 48 sessions over 24 weeks (n=16) B. Usual care (habitual lifestyle) (n=14)	A vs. B Age (mean years): 44.6 vs. 42.2 Female: 12 (75%) vs. 12 (75%) Race: NR Ambulatory: NR Wheelchair user: NR EDSS: 2.9 (1) vs. 2.9 (1) Disease Duration (mean years): 6.7 (7.8) vs. 7.2 (6) Medication (n) (Rebif/Avonex/Extavia/Betaferon): 5/7/4/0 vs. 8/6/1/0	Data reported as mean (SD) A vs. B 25 foot walk test (m/s): 1.66 (95% CI 1.5 to 1.8) vs. 1.79 (95% CI 1.6 to 2.0) (baseline) 1.82 (95% CI 1.7 to 2.0) vs. 1.80 (95% CI 1.6 to 2.0) (postintervention) Time × group interaction p-value=0.0009 2 minute walk test (m/s): 1.61 (95% CI 1.4 to 1.8) vs. 1.66 (95% CI 1.5 to 1.8) (baseline) 1.77 (95% CI 1.6 to 2.0) vs. 1.69 (95% CI 1.5 to 1.9) (postintervention) Time × group interaction p-value=0.0111 2 minute walk test (meters) - calculated by AAI 193.2 (95% CI 168 to 216) vs. 199.2 (95% CI 180 to 216) (baseline) 212.2 (95% CI 192 to 240) vs. 202.8 (95% CI 180 to 228) (postintervention)	NA

Klobucka, 2020 **Aerobic Exercise** Robot-Assisted Gait Training Immediately Postintervention, and 12-16 weeks Poor	A. RAGT, 20 sessions, over 12 weeks, (n=21) B. Usual care, conventional therapy: 20 sessions, over 12 weeks, (n=26)	A vs. B Age (mean years): 18 vs. 23 Female: 47% vs. 38% Race: NR Ambulatory: 4.8% vs. 11.5% Wheelchair user: 23.8% vs. 53.8% Mechanical wheelchair: 23.8% vs. 53.8% Electric wheelchair: 0% vs. 15.3% GMFCS levels I-IV (%): Level I: 4.8% vs. 0% Level II: 14.3% vs. 15.4% Level III: 42.9% vs. 46.2% Level IV: 38.1% vs. 38.5%	A vs. B, mean change scores, p=between groups: Total GMFM: MD 9.43, 95% CI 6.989 to 11.891 vs. MD 0.80, 95% CI 0.154 to 1.446, p<0.001 GMFM D: MD 8.30, 95% CI 4.699 to 11.901 vs. MD 1.09, 95% CI -0.438 to 2.619, p<0.001 GMFM E: MD 9.32, 95% CI 5.329 to 13.310 vs. MD 0.53, 95% CI -0.208 to 1.268, p<0.001 A vs. B., Mean (SD) GMFM-88 A (lying and rolling): 73.29 (16.53) vs. 77.83 (22.49) (baseline) 84.59 (11.58), p=0.000 vs. 77.98 (22.61), p=0.157 (postintervention) GMFM-88 B (sitting): 52.22 (34.56) vs. 60.63 (35.23) (baseline) 61.58 (33.12), p=0.000 vs. 62.05 (34.44), p=0.063 (postintervention) GMFM-88 C (crawling and kneeling): 49.09 (32.08) vs. 52.56 (32.55) (baseline) 57.26 (34.05), p=0.000 vs. 53.40 (32.85), p=0.027 (postintervention) GMFM-88 D (standing): 30.03 (30.48) vs. 28.69 (34.12) (baseline) 38.34 (34.38), p=0.001 vs. 29.78 (34.92), p=0.180 (postintervention) GMFM-88 E (walking): 25.06 (23.18) vs. 24.36 (34.23) (baseline) 34.39 (29.11), p=0.000 vs. 24.89 (35.27), p=0.180 (postintervention) GMFM-88 Total (walking, running and jumping): 45.79 (26.05) vs. 50.27 (27.01) (baseline) 55.23 (26.70), p=0.000 vs. 51.07 (27.26), p=0.028 (postintervention) A vs. B. Change, Mean (SD), 95% CI Overall improvement in GMFM-88 score GMFM-88 A: 11.29 (9.03) vs. 0.15 (0.53), 1.847 (95% CI 1.161–2.532), p=0.000	NA

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
			GMFM-88 B: 9.36 (7.48) vs.1.42 (3.38), 1.421 (95% CI 0.778–2.064), p=0.000 GMFM-88 C: 8.17 (8.69) vs.0.84 (1.89), 1.229 (95% CI 0.603–1.856), p=0.000 GMFM-88 D: 8.30 (8.42) vs.1.09 (3.98), 1.136 (95% CI 0.516–1.755), p=0.000 GMFM-88 E: 9.32 (9.33) vs.0.53 (1.92), 1.377 (95% CI 0.738–2.016), p=0.000 GMFM-88 Total: 9.43 (5.73) vs. 0.80 (1.68), 2.147 (95% CI 1.426–2.867), p=0.000	
Kooshiar, 2015 **Aerobic Exercise** Aquatics Postintervention, 0 weeks Fair	A. Aquatic exercise, 24 sessions over 8 weeks (n=20) B. Usual care (n=20)	A vs. B Age (mean years): Only given as mean of all participants, 29.24 Female: 20 (100%) vs. 20 (100%) Race: NR Ambulatory: NR Wheelchair user: NR MS: all participants, RRMS 28 (75.7%), PPMS 6 (16.2%), SPMS 3 (8.1%)	A vs. B, mean (SD) MQLIM: 80.06 (11.53) vs. 66.52 (6.22) 65.48 (9.74) vs. 63.13 (13.02) baseline; p<0.001 (postintervention) Calculated A vs. B, Mean change scores: MQLIM: -16.93 vs. -1.04, p<0.001	NA

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Kressler, 2013 Companion to: Field-Fote, 2011 **Aerobic Exercise** Robot-Assisted Gait Training Postintervention, 12 weeks Poor	A. RAGT (DGO), 60 sessions over 12 weeks (n=14) *guidance force at 100% B. Treadmill Gait Training with E-Stim (TS), 6 sessions over 12 weeks (n=18) C. Manual Assisted Treadmill Gait Training (TM), 6 sessions over 12 weeks (N=17) D. Overground Gait Training with E-stim (OG), 60 sessions over 12 weeks (n=15)	NR (no demographics table)	Walking speed pertaining to post training (m/s): Slow: DGO: 0.08 (0.05) to 0.09 (0.06), p=0.233 TS: 0.09 (0.07) to 0.10 (0.07), p=0.170 TM: 0.10 (0.07) to 0.10 (0.06), p=0.955 OG: 0.06 (0.04) to 0.11 (0.09), p=0.001 Moderate: DGO: 0.14 to 0.14 (0.07), p=0.572 TS: 0.14 (0.12) to 0.20 (0.15), p=0.007 TM: 0.17 (0.13) to 0.19 (0.14), p=0.194 OG: 0.13 (0.15) to 0.25 (0.27) p=0.002 Fast: DGO: 0.20 (0.13) to 0.20 (0.11), p=0.814 TS: 0.22 (0.22) to 0.28 (0.27), p=0.003 TM: 0.23 (0.18) to 0.26 (0.19), p=0.232 OG: 0.32 (0.62) to 0.35 (0.42), p=0.084) VO_2 (peak) Ln[L/m] Moderate Pace: DGO: 1.11 (0.37) to 1.05 (0.40), p=00.046 TS: 0.91 (0.28) to 1.01 (0.28), p=0.041 TM: 0.90 (0.27) to 1.07 (0.34), p=0.035 OG: 0.90 (0.27) to 1.07 (0.34), p=0.033 Maximal Pace: DGO: 1.32 (0.40) to 1.28 (0.40), p=0.439 TS: 1.07 (0.36) to 1.17 (0.44), p=0.060 TM: 0.97 (0.25) to1.17 (0.35), p=0.017 OG: 1.00 (0.39) to 1.13 (0.45), p=0.038	NA

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Kumru, 2016 **Aerobic Exercise** Robot-Assisted Gait Training Postintervention, 8 weeks Fair	A. RAGT with rTMS, 20 sessions over 4 weeks , then 20 sessions without rTMS for 4 weeks (n=15) B. RAGT alone, 40 sessions over 8 weeks (n=16)	A vs. B Age (mean years): 51 vs. 49 Female: 5 (33%) vs. 2 (13%) Race: NR Ambulatory: NR Wheelchair user: NR Other: Time since SCI (months) 2.8 vs. 2.8 Level of Injury Cervical or Thoracic Cervical: 8 (53%) vs. 6 (38%)	10MWT number able to perform test 2 at baseline, 6 after last session, 10 at followup 2 at baseline, 4 after last session, 6 at followup LEMS mean change score after last stimulation session (4 weeks) 8 vs. 4 at followup 10 vs. 6 UEMS mean change score after last stimulation session (4 weeks) 5 vs. 1 at followup 8 vs. 5 Modified Ashworth Score 1.1 (0.8) to 1.1 (0.9) vs. 1.3 (1.3) to 1.1 (1.1)	NA

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Kwon, 2011 **Postural Control** Hippotherapy Postintervention, 0 weeks (End of treatment after 8-week intervention) Fair	A. Hippotherapy-plus-conventional-physiotherapy group (hippotherapy group), 16 hippotherapy sessions over 8 weeks and conventional physiotherapy (n=16) B. Conventional-physiotherapy group (Control group), 2 sessions per week (n=16)	A vs. B Age (mean years): 6.4 vs. 6.1 Female: 5 (31%) vs. 6 (38%) Race: NR Ambulatory: 100% Wheelchair user: NR GMFCS level: GMFCS level I: 4 (25%) vs. 4 (25%) GMFCS level II: 12 (75%) vs. 12 (75%) Body weight (mean kg): 21.8 vs. 19.8 Height (mean cm): 113.5 vs. 111.0 Previous surgery: 3 (19%) vs. 4 (25%)	A vs. B, mean (SD) 8 weeks GMFM-66: 70.4 (7.4) vs. 69.8 (8.7) (baseline) 73.7 (8.3) vs. 70.1 (8.1), p=0.003 (postintervention)	A vs. B, mean (SD) 8 weeks PBS: 41.7 (8.8) vs. 41.0 (10.4) (baseline) 45.8 (8.6) vs. 41.5 (10.6), p=0.004 (postintervention)

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Kwon, 2015 **Postural Control** Hippotherapy Postintervention, 0 weeks (after 8-week intervention) Good	A. Hippotherapy group, 16 sessions over 8 weeks (n=46) B. Control group (home-based aerobic exercise with conventional physiotherapy), 16 aerobic exercise sessions over 8 weeks with conventional physiotherapy (n=46)	A vs. B Age (mean years): 5.7 vs. 5.9 Female: 25 (56%) vs. 17 (37%) Race: NR Ambulatory: NR Wheelchair user: NR GMFCS level: GMFCS level I: 12 (27%) vs. 12 (26%) GMFCS level II: 12 (27%) vs. 12 (26%) GMFCS level III: 11 (24%) vs. 12 (26%) GMFCS level IV: 10 (22%) vs. 10 (22%) Neuromotor type: Spastic: 41 (91%) vs. 43 (93%) Dyskinetic: 2 (4%) vs. 2 (4%) Ataxic: 2 (4%) vs. 1 (2%) Unilateral: 4 (9%) vs. 6 (13%) Previous surgery: 6 (13%) vs. 7 (15%) Body weight (mean kg): 18.7 vs. 19.9 Height (mean cm): 107.7 vs. 110.1 Physiotherapy time (mean hours per week): 3.3 vs. 31	A vs. B, mean (SD) 8 weeks GMFM-66: 60.8 (14.9) vs. 61.4 (14.8) (baseline) 63.5 (15.8) vs. 61.8 (15.0), p<0.01 (postintervention)	A vs. B, mean (SD) 8 weeks PBS: 25.1 (18.9) vs. 26.9 (18.3) (baseline) 28.9 (18.8) vs. 27.1 (18.3), p<0.01 (postintervention)

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Lai, 2010 **Aerobic Exercise** Cycling Postintervention, 12 weeks Fair	A. Functional electrical stimulation cycling exercises, 36 sessions over 12 weeks (n=12) B. Control group (n=12)	A vs. B Age (mean years): 28.9 vs. 28.3 Female: 2 (17%) vs. 2 (17%) Race: NR Ambulatory: 0 (0%) vs. 0 (0%) Wheelchair user: NR Other: SCI: Quadriplegia: 5 (33%) vs. 5 (33%) Paraplegia: 10 (67%) vs. 10 (67%)	NA	A vs. B (SD) BMD femoral neck (g/cm2) 0.927(0.189) vs. 0.913(0.097) (baseline) 0.884(0.171) vs. 0.867(0.095); p<0.050 for difference between 1st and 2nd measurements (postintervention) 0.842 (0.168) vs. 0.825 (0.092); p<0.050 for difference between 2nd and 3rd measurements (3 months postintervention) BMD distal femur (g/cm2) 1.003 (0.064) vs. 1.003 (0.110) (baseline) 0.981 (0.063) vs. 0.936 (0.103); p<0.050 for difference between 1st and 2nd measurements (postintervention) 0.913 (0.058) vs. 0.868 (0.097); p<0.050 for difference between 2nd and 3rd measurements (3 months postintervention)
Lai, 2015 **Aerobic Exercise** Aquatics Postintervention, 0 weeks Fair	A. Aquatic therapy plus traditional rehabilitation, 24 sessions over 12 weeks (n=11) B. Traditional rehabilitation, average 2-3 sessions over 12 weeks (n=13)	A vs. B Age (mean years): 7.6 vs. 6.6 Female: 7 (64%) vs. 4 (31%) Race: NR Ambulatory: NR Wheelchair user: NR N (%) vs. N (%) Other: CP subtypes: Diplegia: 3 (27.3) vs. 6 (46.2) Quadriplegia 5 (45.5) vs. 4 (30.8) Hemiplegia 3 (27.3) vs. 3 (23.1)	A vs. B, Mean difference between groups: <u>GMFM-66:</u> 5.0 vs. 0.7, p=0.007 GMFM-66: 61.2 (18.7) vs. 64.6 (19.4) (baseline) 66.2 (18.2) vs. 65.3 (19.1); p=0.007 (postintervention) CPQoL scales for Social, Functioning, Participation, Emotional, Access, Pain and Disability, and Family Health: All NS	A vs. B. mean (SD) MAS: Ankle, Knee, Wrist, Elbow: all NS Vineline Adaptive Beh Scale for Daily Living: NS

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Lavado, 2012 **Aerobic Exercise** Hand cycling Postintervention, 0 weeks Fair	A. Cycloergometer with strength and stretching exercises 32 to 48 sessions over 16 weeks (21) B. Maintain current activities (21)	A vs. B Age: 34 vs. 39 Female: 14% vs. 19% BMI: 24.1 vs. 27.1 Injury C8-T12: 100%	A vs. B median VO_2 peak in mL min-1 baseline: 939 (714-1215) vs. 896 (677-1158), p=0.529 VO_2 peak in mL min-1 Endpoint: 1154 (1005-1351) vs. 834 (711-1005), p<0.001 CAB baseline: 52.3% vs. 61.9%, p=0.755 CAB endpoint: 14.2% vs. 71.4%, p<0.001 RR 0.20, 95% CI 0.07 to 0.54 Absolute risk reduction: 57.1%, 95% CI 32.7 to 81.6 NNT 2, 95% CI 1 to 3	NA
Lee, 2013 **Postural Control** Whole body vibration Postintervention, 0 weeks Fair	A. Whole body vibration + conventional physical therapy: 24 sessions of vibration over 8 weeks (n=15) B. Conventional physical therapy (n=15)	A vs. B Age (mean years): 10.00 vs. 9.66 Female: 9 (60%) vs. 6 (40%) Race: NR Ambulatory: 15 (100%) vs. 15 (100%) Wheelchair user: NR Baseline GMFM: 78.4 vs. 79.53	A vs. B Walking speed (meters/second): 0.37 (0.04) vs. 0.39 (0.05) (baseline) 0.48 (0.06) vs. 0.40 (0.05) (postintervention) Group effect p=0.189 Group X Time interaction p=0.001	NR
Lee, 2014 **Postural Control** Hippotherapy Postintervention, 0 weeks End of treatment (12-week intervention) Poor	A. Hippotherapy group, 36 sessions over 12 weeks (n=13) B. Horseback riding simulator group, 36 sessions over 12 weeks (n=13)	A vs. B Age (mean years): 10.8 vs. 10.0 Female: 5 (38%) vs. 4 (31%) Race: NR Ambulatory: NR Wheelchair user: NR Height: (mean cm): 125.8 vs. 122.6 Weight (mean kg): 25.2 vs. 25.5	NR	A vs. B, mean (SD) 12 weeks PBS: 35.6 (3.8) vs. 41.2 (4.7) (baseline) 35.8 (4.7) vs. 38.5 (5.3) (postintervention) No significant difference was found between the two groups.

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Liu, 2019 **Multimodal Exercise** Immediately postintervention, 12 weeks Fair	A. Strength exercise + treadmill + core stability training on a stable support surface, 60 sessions over 12 weeks (n=20) B. Strength exercise + treadmill + core stability training on an unstable support surface, 60 sessions over 12 weeks (n=20)	A vs. B (data are for completers only; n=14 vs. 15) Age: 43 vs. 46 Female: 21% vs. 27% Ambulatory: 100% -paraplegia: 36% vs. 40% -tetraplegia: 64% vs. 60%	A vs. B, Mean (SD), data for completers only): Stride length (units NR) 0.564 (0.189) vs. 0.454 (0.173), p=0.025 (post-intervention) 0.09 (0.26) vs. 0.06 (0.24), MD 0.03 (95% CI –0.16 to 0.22), p=NR (pre-post change) Walking speed (units NR) 0.350 (0.226) vs. 0.209 (0.171), p=0.0196 (post-intervention) 0.09 (0.30) vs. 0.03 (0.23), MD 0.06 (95% CI –0.14 to 0.26), p=NR (pre-post change)	NA

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Lorentzen, 2015 **Postural Control** Balance Postintervention, 20 weeks Poor	Interactive computer training vs. usual care A. Interactive computer training (home-based): 140 sessions over 20 weeks, 40 hours of total training time. (n=34) B. Usual care control: (n=12)	A vs. B Age (mean years): 10.9 vs. 11.3 Female: 11 (32%) vs. 5 (42%) Race: NR Ambulatory: NR Wheelchair user: NR	A. vs. B., mean (SD) Sit-to-stand 16.1 (0.7) vs. 14.5 (1.0), baseline 20.0 (0.9) vs. 15.1 (0.9), 20 weeks Mean difference, (p=0.04) A. Sit-to-stand, baseline vs. 20 weeks 16.1 (0.7) vs. 19.2.0 (0.9), (p=0.01) B. Sit-to-stand, baseline vs. 20 weeks 14.5 (1.0) vs. 15.1 (0.9), (p=0.33) A. Sit-to-stand, 20 weeks vs. 34 weeks 20.0 (0.9) vs. 18.7 (1.0), (p=0.58) Lateral step-up (LSU) left leg 17.9 (1.1) vs. 16.9 (1.8) (baseline) 23.5 (1.4) vs. 17.8 (2.2) (20 weeks) Mean difference, (p=0.004) Lateral step-up (LSU) right leg 16.7 (1.1) vs. 18.1 +/− 2.1 (baseline) 22.1 +/− (1.4) vs. 18.0 +/− 2.0 (20 weeks) Mean difference, (p<0.001) A. LSU, baseline vs. 20 weeks (left) 17.9 (1.1) vs. 23.5 (1.4), (p<0.001) B. LSU, baseline vs. 20 weeks (left) 16.9 (1.8) vs. 17.8 (2.2), (p=0.44) A. LSU, baseline vs. 20 weeks (right) 16.7 (1.1) vs. 22.1 (1.4), (p<0.001) B. LSU, baseline vs. 20 weeks (right) 18.1 (2.1) vs. 18.0 (2.0), (p=0.93) A. LSU, 20 vs. 34 weeks (left) 23.5 (1.4) vs. 24.1 (1.3), (p=0.63)	A. vs. B., mean (SD) Romberg Balance Test: C90 (mm2) 427.2 (57.6) vs. 310.9 (131.9) (intro) 462.2 (62.5) vs. 314.6 (104.9) (test1) Mean difference, (p=0.18) Romberg Balance Test: velocity (mm/s) 13.4 (0.7) vs. 10.6 (1.4) 14.1 (0.7) vs. 11.7 (1.7) Mean difference, (p=0.59) Romberg Balance Test: trace length (mm) 403.1 (21.3) vs. 317.4 (43.0) 422.8 (19.9) vs. 351.6 (50.2) Mean difference, (p=0.9)

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Lorentzen, 2015 **(Continued)**			A. LSU, 20 vs. 34 weeks (right) 22.1 (1.4) vs. 23.6 (1.5), (p=0.17) AMPS A. vs. B. (motor) 1.34 (0.09) vs. 1.21 (0.12) (baseline) 1.57 (0.11) vs. 1.26 (0.14) (20 weeks) Mean difference, (p=0.049) AMPS A. vs. B. (process) 0.85 (0.09) vs. 0.82 (0.13) (baseline) 1.10 (0.09) vs. 0.82 (0.10) (20 weeks) Mean difference, (p=0.04) A. AMPS (motor), baseline vs. 20 weeks 1.34 (0.09) vs. 1.57 (0.11), (p<0.001) B. AMPS (motor), baseline vs. 20 weeks 1.21 (0.12) vs. 1.26 (0.14), (p=0.48) A. AMPS (motor), 20 vs. 34 weeks 1.57 (0.11) vs. 1.65 (0.06), (p=0.84) A. AMPS (process), baseline vs. 20 weeks 0.85 (0.09) vs. 1.10 (0.09), (p<0.001) B. AMPS (process), baseline vs. 20 weeks 0.82 (0.13) vs. 0.82 (0.10), (p=0.95) A. AMPS (process), 20 vs. 34 weeks 1.10 (0.09) vs. 1.09 (0.07), (p=0.58)	NA

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Lucena-Anton, 2018 **Postural Control** Hippotherapy Postintervention, 1 week (13 weeks total including 12-week intervention) Fair	A. Intervention group (hippotherapy and conventional therapy), 12 sessions over 12 weeks (n=22) B. Control group (conventional therapy), 24 sessions over 12 weeks (n=22)	A vs. B Age (mean years): 9.500 vs. 8.227 Female: 9 (41%) vs. 7 (32%) Race: NR Ambulatory: 0% Wheelchair user: NR SLLA: 2.773 vs. 2.591 SLRA: 2.227 vs. 2.409	A vs. B, mean (SD) 13 weeks MAS: Left adductors: 2.77 (1.15) vs. 2.59 (1.22) (baseline) 2.50 (1.05) vs. 2.54 (1.22), p=0.040 (postintervention) Right adductors: 2.22 (1.26) vs. 2.40 (1.14) (baseline) 1.77 (1.26) vs. 2.31 (1.24), p=0.047 (postintervention)	NR
Makhov, 2018 **Multimodal exercise** Immediately postintervention, 15 weeks Poor	A. Therapeutic gymnastics + strength 94 sessions over 15 weeks (n=18) B. Therapeutic gymnastics (passive exercises only) (n=17)	A vs. B Age: 7-9 years Female: Spastic diplegia or spastic tetra paresis: 100%	A vs. B, Mean (SD), p-value is between groups Strength quadriceps femoris: 1.29 (0.49) to 1.92 (0.38) vs. 1.36 (0.56) to 1.61 (0.61), p<0.05	NA

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Marandi, 2013a Has companion: Marandi, 2013b **Aerobic Exercise** Aquatics Postintervention, 0 weeks Poor	A. Pilates: 36 sessions over 12 weeks (n=15) B. Aquatics: 36 sessions over 12 weeks (n=15) C. Usual care (n=15)	A vs. B Age (mean years): NR Female: 15 (100%) vs. 15 (100%) Race: NR Ambulatory: 15 (100%) vs. 15 (100%) Wheelchair user: 0 (0%) vs. 0 (0%)	A vs. B, Six Spot Step Test: Adjusted Mean Difference between groups: Right leg dynamic balance: -5.88 (SE 1.4), p<0.001 Left leg dynamic balance: -6.23 (SE 1.2), p<0.001	Data reported as mean (SD), unless otherwise noted A vs. C Right leg Six Spot Step Test (seconds): 9.82 (2.87) vs. 10.64 (4.17) (baseline) 6.54 (1.93) vs. 12.65 (6.05); adj. MD -5.96 (SE, 1.4), p=0.000 (postintervention) Left leg Six Spot Step Test (seconds): 9.07 (2.53) vs. 10.16 (3.76) (baseline) 6.25 (2.16) vs. 12.49 (4.63); adj. MD -6.23 (SE, 1.2), p=0.000 (postintervention) B vs. C Right leg Six Spot Step Test (seconds): 8.57 (3.64) vs. 10.64 (4.17) (baseline) 6.40 (1.82) vs. 12.65 (6.05); adj. MD -5.88 (SE, 1.4), p=0.000 (postintervention) Left leg Six Spot Step Test (seconds): 9.12 (4.31) vs. 10.16 (3.76) (baseline) 6.26 (1.95) vs. 12.49 (4.63); adj. MD -6.23 (SE, 1.2), p=0.000 (postintervention) A vs. B Right leg Six Spot Step Test (seconds): 9.82 (2.87) vs. 8.57 (3.64) (baseline) 6.54 (1.93) vs. 6.40 (1.82); adj. MD -0.08 (SE, 1.4), p=0.955 (postintervention) Left leg Six Spot Step Test (seconds): 9.07 (2.53) vs. 9.12 (4.31) (baseline) 6.25 (2.16) vs. 6.26 (1.95), adj. MD 0.00 (SE, 1.2), p=0.997 (postintervention)

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Marandi, 2013b Companion to: Marandi, 2013a **Aerobic Exercise** Aquatics Postintervention, 0 weeks Poor	A. Pilates: 36 sessions over 12 weeks (n=15) B. Aquatics: 36 sessions over 12 weeks (n=15) C. Usual care (n=15)	B vs. C Age (mean years): 40 Female: 15 (100%) vs. 15 (100%) Race: NR Ambulatory: 15 (100%) vs. 15 (100%) Wheelchair user: 0 (0%) vs. 0 (0%)	B vs. C Right leg dynamic balance: 8.57 (3.64) vs. 10.64 (4.17) (baseline) 6.40 (1.82) vs. 12.65 (6.05); adj. MD -5.88 (SE, 1.4), p=0.000 (postintervention) Left leg dynamic balance: 9.12 (4.31) vs. 10.16 (3.76) (baseline) 6.26 (1.95) vs. 12.49 (4.63); adj. MD -6.23 (SE, 1.2), p=0.000 (postintervention)	NR
Matusiak-Wieczorek, 2016 **Postural Control** Hippotherapy Postintervention, 0 weeks End of treatment (after 12-week intervention) Poor	A. Intervention group (hippotherapy), 12 sessions over 12 weeks (n=19) B. Control group (maintain current activities) (n=20)	A vs. B Age (mean years): 8.42 vs. 8.3 Female: 9 (47%) vs. 9 (45%) Race: NR Ambulatory: 100% Wheelchair user: NR Diplegia: 6 (32%) vs. 5 (25%) Hemiplegia: 13 (68%) vs. 15 (75%) GMFCS level: GMFCS level I: 12 (63%) vs. 11 (55%) GMFCS level II: 7 (37%) vs. 9 (45%)	NR	A vs. B, mean (SD) 12 weeks SAS: 14.42 (4.39) vs. 15.50 (3.14) (baseline) 15.63 (3.65) vs. 15.75 (3.19) (postintervention) 1.21 (1.18) vs. 0.25 (0.44) (difference in pre- and postintervention scores)

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Matusiak-Wieczorek, 2020 **Postural Control** Hippotherapy Immediately Postintervention, 12 weeks Fair	A. Hippotherapy, 24 sessions over 12 weeks (n=15) B. Hippotherapy, 12 sessions over 12 weeks (n=15) C. Waitlist control (n=15)	A vs. B vs. C Age (mean years): 7.9 vs. 8.6 vs. 8.3 Female: 40% vs. 46% vs. 46% GMFCS, level I: 67% vs. 80% vs. 47% GMFCS, level II: 33% vs. 20% vs. 53%	NA	A vs. B vs. C, mean (SD), p=between groups SAS: 10.93 (3.97) vs. 15.93 (4.17) vs. 14.87 (3.27) (baseline) 11.53 (3.74) vs. 16.53 (3.50) vs. 14.93 (3.35) (4 weeks) 12.40 (3.70) vs. 16.93 (3.24) vs. 15.00 (3.30) (8 weeks) 13.13 (3.46) vs. 17.27 (2.76) vs. 15.13 (3.36) (postintervention) 2.20 (1.42) vs. 1.33 (0.76) vs. 0.27 (0.46) (difference in pre- and postintervention scores) A vs. C: MD 1.93, 95% CI 0.94 to 2.92, p<0.001 B vs. C: MD 1.06, 95% CI 0.61 to 1.51, p<0.001 A vs. B: MD 0.87, 95% CI 0.06 to 1.69, p=0.036
Midik, 2020 **Aerobic Exercise** Robot-Assisted Gait Training Postintervention, and 12 weeks Fair	A. RAGT plus conventional rehab, 25 sessions over 5 weeks (n=15) B. Conventional rehab only, 25 sessions over 5 weeks (n=15)	A vs. B Age: 35.4 vs. 37.9 Female: 0% Race: NR AIS C: 40% vs. 67% AIS D: 60% vs. 33%	A vs. B, mean change (SE), p=between groups: WISCI: 3.9 (0.8) vs. 2.5 (0.5), p=0.178 SCIM: 9.9 (2.5) vs. 7.0 (1.3), p=0.326 LEMS: 1.8 (0.4) vs. 0.6 (0.2), p=0.061 At 3 month followup, change from baseline: WISC: 4.3 (1.0) vs. 2.5 (0.5), p=0.139 SCIM: 16.5 (3.2) vs. 7.6 (1.5), p=0.127 LEMS: 2.1 (0.5) vs. 0.6 (0.2), p=0.049	NA

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Mogharnasi, 2018 **Muscle Strength exercise** Postintervention, 0 weeks Poor	A. Upper body resistance training: 24 sessions over 8 weeks (n=10) B. Usual care (n=10)	A vs. B Age (mean years): 25.33 vs. 25.50 Female: 0 (0%) vs. 0 (0%) Race: NR Ambulatory: 0 (0%) vs. 0 (0%) Wheelchair user: 100 (100%) vs. 100 (100%) Duration of paralysis (mean months): 117 vs. 111 Smoking (yes): 1 (10%) vs. 3 (30%) Etiology -Motor vehicle accident: 8 (80%) vs. 9 (90%) -Fall: 2 (20%) vs. 1 (10%) Neurological status -T9: 1 (10%) vs. 2 (20%) -T10: 2 (20%) vs. 2 (20%) -T11: 2 (20%) vs. 0 (0%) -T12: 5 (50%) vs. 6 (60%)	Data reported as mean (SD) A vs. B BMI (kg/m^2): 25.33 (1.37) vs. 24.91 (0.98), p>0.05 (baseline) 24.73 (1.24) vs. 25.14 (1.01), p>0.05 (postintervention)	Data reported as mean (SD) A vs. B % Body fat: 32.20 (2.08) vs. 32.60 (2.17), p>0.05 (baseline) 31.30 (2.21) vs. 32.90 (2.23), p>0.05 (postintervention) Total cholesterol (mg/dl) 180.30 (7.02) vs. 185 (4), p>0.05 (baseline) 165.50 (5.89) vs. 186.50 (4.24), p<0.05 (postintervention) High density lipoprotein cholesterol (mg/dl) 43.20 (2.25) vs. 44.60 (4.32), p>0.05 (baseline) 47.90 (3.63) vs. 45.10 (4.45), p>0.05 (postintervention) Low density lipoprotein cholesterol (mg/dl) 108.70 (3.74) vs. 109 (4.59), p>0.05 (baseline) 104 (1.94) vs. 110.80 (3.76), p<0.05 (postintervention) Triglyceride (mg/dl) 158.20 (6.28) vs. 159.80 (9.70), p>0.05 (baseline) 134.30 (7.58) vs. 161.20 (9.78), p<0.05 (postintervention)
Moraes, 2020 **Postural Control** Hippotherapy Postintervention, 0 weeks Fair	A. Hippotherapy, 16 sessions over 8 weeks (n=17) B. Waitlist control (n=16)	A vs. B Age: 45.5 vs. 48.4 Female: 94% vs. 94% Race: NR EDSS, median: 2.0 vs. 1.75 RRMS: 100%	A vs. B, mean (SD): 6MWT: 459.06 (118.34) to 503.59 (126.38) vs. 513.00 (101.97) to 497.13 (88.88), p<0.001 25FWT: 6.37 (1.70) to 5.36 (1.43) vs. 5.82 (1.29) to 5.84 (1.08), p<0.001	NA

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Mutoh, 2019 **Postural Control** Hippotherapy Postintervention, 12 weeks (post 48-week intervention) Fair	A. Hippotherapy, 48 sessions over 48 weeks (n=12) B. Outdoor recreation 48 sessions over 48 weeks (n=12)	A vs. B Age: 8 vs. 9 Female: 58% vs. 50% GMFCS II: 42% vs. 42% GMFCS III: 58% vs. 58%	A vs. B, Mean (SD), p=between groups GMFM-66: 56.6 (9.2) to 62.8 (10.8) vs. 57.4 (7.9) to 57.9 (9.2), p<0.05 GMFM-66E: 45.4 (7.0) to 49.7 (7.6) vs. 46.0 (6.3) to 46.5 (6.6), p<0.05 5MWT (m/min): 31.9 (10.7) to 38.8 (13.5) vs. 31.1 (11.3) to 32.3 (11.6), p<0.05 WHOQOL (positive feelings): 3.1 (1) to 4.1 (1) vs. 3.1 (0.9) to 3.4 (1), p<0.05 WHOQOL (self-esteem): 2.9 (1.2) to 4.0 (0.7) vs. 3.3 (1.1) to 3.7 (0.7), p<0.05 WHOQOL (negative feelings): 2.9 (0.8) to 2.8 (0.7) vs. 2.8 (0.8* to 2.8 (0.8), p>0.05	NA
Najafidoulataba, 2014 **Postural Control** Postintervention, 12 weeks Poor	Yoga vs. usual care A. Yoga: 24 sessions over 12 weeks (n=30) B. Usual care control: (n=30)	A vs. B Age (years): "mean age in the case group 31.6" Female: 30 (100%) vs. 30 (100%) Race: NR Ambulatory: NR Wheelchair user: NR	A. vs. B., mean (SD) Physical activity QoL 23.7 (4.25) vs. 20.5 5 (3.5) (95% CI –2.42 to 0.42), p=0.001 (baseline) 24.7 (3.94) vs. 19.45 (4.1) (95% CI 0.49 to 1.7), p=0.00 (postintervention) Sexual satisfaction QoL 1.8 (2.0 vs. 2.1 (1.2) (95% CI –0.09 to 0.89), p=0.01 (baseline) 1.4 (1.5) vs. 2.1 (1.2) (95% CI NR), p=NR (postintervention)* * stated as not significant	NA

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Negaresh, 2018 **Aerobic Exercise** Cycling Postintervention, 0 weeks Fair	A. vs. B. A. Normal BMI cycling UE/LE, 24 sessions over 8 weeks (n=18) B. Normal BMI Control (n=15) C vs. D: C: Overweight BMI cycling UE/LE, 24 sessions over 8 weeks (n=18) D: Overweight BMI Control (n=15)	A vs. B Age (mean years): 31.2 vs. 29.1 Female: 6 (35%) vs. 9 (64%) Race: NR Ambulatory: 17 (100%) vs. 14 (100%) Wheelchair user: NR Other: MS RRMS 18 (100%) vs. 15 (100%) C vs. D Age (mean years): 32.1 vs. 32.2 Female: 6 (35%) vs. 4 (29%) Race: NR Ambulatory: 17 (100%) vs. 13 (100%) Wheelchair user: NR Other: RRMS 17 (100%) vs. 13 (100%)	A vs. B vs. C vs. D, Mean difference between groups (scores are estimates from graph): TUG: -3.8 vs. -0.1 vs. -2.5 vs. 0, p=0.001 Interaction between Weight and Exercise p=0.52 A vs. B (scores are estimates from graph) BDI changes (score): -5 vs. 0, p=0.005 TUG changes (sec): -4 vs. 0, p=0.001 VO_2 peak changes (mg/kg/min): 2.5 vs. 0), p=0.001	A vs. B BMI: NS

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Nilsagard, 2012 **Postural Control** Motion gaming Postintervention, 7 weeks Fair	A. Play games using Nintendo Wii Fit Plus® Balance Board for balance, yoga, strength and aerobics, 12 sessions over 6 weeks (n=42) B. No balance exercise during routine physical therapy (42)	A vs. B Age (mean years): 50.0 vs. 49.4 Female: 32 (76%) vs. 32 (76%) Race: NR Ambulatory no use of assistive devices: Indoors - 32 (76%) vs. 37 (88%) Outdoors - 22 (52%) vs. 21 (50%) Wheelchair user: 3 (7%) vs. 4 (10%) MS subtype Relapsing–remitting: 26 (62%) vs. 28 (67%) Secondary progressive: 13 (31%) vs. 13 (31%) Primary progressive: 3 (7%) vs.1 (2%) MS Impact Scale (total score) (mean, SD) 72.1 (19.7) vs. 73.8 (21.2)	A. vs. B.*, mean (SD) TUG 12.4 (6.9) vs. 11.3 (5.0) (baseline) –0.8 (2.4) vs. 0.1 (2.1) (postintervention) Between groups comparison pre-post: p=0.10 4SST (Four Square Step Test) 16.8 (12.2) vs. 17.7 (13.8) (baseline) –1.6 (2.1) vs. B –2.0 (6.6) (postintervention) Between groups comparison pre-post: p=0.64 25-foot walk test 6.56 (3.4) vs. 6.47 (3.1) (baseline) –0.3 (1.1) vs. B 0.0 (1.4) (postintervention) Between groups comparison pre-post: p=0.51 DGI Dynamic Gait Index 17.1 (4.6) vs.17.1 (4.7) (baseline) 1.78 (2.3) vs. 1.0 (2.0) (postintervention) Between groups comparison pre-post: p=0.21 MS Walking scale 50.5 (25.8) vs. 52.3 (25.0) (baseline) –5.9 (11.5) vs. –3.95 (18.1) (postintervention) Between groups comparison pre-post: p=0.76 *A. analyzed n=41, B. analyzed n=39	NA

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Niwald, 2017 **Aerobic Exercise** Cycling Postintervention, 0 weeks Fair	A. Cycle ergometry Intervention + complex rehabilitation 120 min/wk, 20 sessions over 4 weeks (n=21) B. Control intervention of complex rehabilitation 120 min/wk (n=32)	A vs. B Age (mean years): 57 vs. 60 Female: 13 (62%) vs. 21 (65%) Race: NR Ambulatory: 21 (100%) vs. 32 (100%) Wheelchair user: NR Other: MS subtypes NR	A vs. B (SD)WHOQOL Physical 20.05(3.58) vs. 19.5(2.9) (baseline) 23.1(2.83) vs. 21.1(2.5); p=0.001 (postintervention) WHOQOL Psychological 18.05(3.67) vs. 17.6(3.2) (baseline) 21.7(3.13) vs. 18.2(1.7); p=0.001 (postintervention) WHOWOL Environmental 23.76(4.15) vs. 24.85(5.2) (baseline) 26.57(3.78) vs. 25.1(3.97); p=0.030 (postintervention) Calculated A vs. B, Mean difference between groups: EDDS: 0.01, 95% CI -0.61 to 1.29, p=0.48 WHOQOL-Bref Physical: 1.45, 95% CI -0.72 to 3.62, p=0.19 WHOQOL-Bref Psychological: 3.05, 95%CI 1.30 to 4.80 to, p=0.001 WHOQOL-Bref Social: 0.60, 95% CI -0.64 to 1.84, p=0.34 WHOQOL-Bref Environmental: 2.56, 95% CI 0.20 to 4.92, p=0.03	EDSS: NS
Norouzi, 2019 **Postural Control** Balance exercises Immediately postintervention, 4 weeks Fair	A. Cawthorne/ Cooksey exercises, 12 sessions over 4 weeks (n=10) B. Usual care, 4 sessions over 4 weeks (n=10)	A vs. B Age: NR Female: 0% L3-L4: 100%	NA	A vs. B, Mean (SD), p-value=between groups BBS: 38.36 (6.01) to 48.39 (4.01) vs. 37.67 (6.07) to 43.20 (4.05), MD 4.5, 95% CI -0.17 to 9.17, p=0.059* *authors report p<0.05 but unclear if this value also includes a third, neurofeedback group

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Nsenga, 2013 **Aerobic Exercise** Cycling Postintervention, 0 weeks Fair	A. Cycle ergometry, 24 sessions over 8 weeks (n=10) B. Control with CP, no training (n=10)	A vs. B Age (mean years): 14.2 vs. 14.2 Female: 4 (40%) vs. 4 (40%) Race: NR Ambulatory: 10 (100%) vs. 10 (100%) Wheelchair user: NR Other: CP: Hemiplegia: 8(80%) vs. 8 (80%) Diplegia: 2 (20%) vs. 2 (20%)	A Baseline vs. A After Training Period (SD) VO_2 peak (ml/kg/min): 35.6 (5.6) vs. 43.7(4.7) (p<0.050)	NA
Nsenga Leunkeu, 2012 **Aerobic Exercise** Treadmill Postintervention, 0 weeks Fair	A. 40 minutes treadmill walking 3 times a week for 8 weeks Walking (n=12) B. Usual care (no training) (n=12)	A vs. B Age (mean years): 14.2 vs. 14.2 Female: 6 (50%) vs. 6 (50%) Race: NR Ambulatory: 12 (100%) vs. 12 (100%) Wheelchair user: 0 (0%) vs. 0 (0%) Hemiplegia: 10 (83%) vs. 10 (83%) Diplegia: 2 (17%) vs. 2 (17%) GMFCS -I: 8 (67%) vs. 8 (67%) -II: 4 (33%) vs. 4 (33%)	A vs. B 6MWT (meters): 490 (NR) vs. 450 (NR), p>0.05 (baseline) 600 (NR) vs. 450 (NR), p<0.05 (postintervention) VO_2 peak: 32 (NR) vs. 32.5 (NR), p>0.05 (baseline) 40 (NR) vs. 32.5 (NR), p<0.05 (postintervention) Measured peak oxygen uptake during incremental cycle ergometry (ml/kg/min) A. 32.5 to 39.0 B. 32.5 to 32.5 (data estimated from bar graph) Significant increase for those trained (A) p=0.046) and no significant change in B; comparison beween groups NR	NR

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Ortiz-Rubio, 2016 **Muscle Strength** Postintervention, 0 weeks Good	A. Upper extremity strength + coordination: 16 sessions over 8 weeks (n=19) B. Booklet with exercise info (n=18)	A vs. B Age (mean years):42.21 vs. 44.89 Female: 5 (26%) vs. 6 (33%) Race: NR Ambulatory: NR Wheelchair user: NR MS type -Relapsing-remitting 4 (21.05%) vs. 4 (22.22%) -Primary progressive 3 (15.79%) vs. 2 (11.11%) -Secondary progressive 12 (63.16%) vs. 12 (66.67%) EDSS (mean): 5.71 vs. 6.04	Data reported as mean (SD) A vs. B ARAT most affected upper limb (scale unclear): 54.68 (1.82) vs. 54.27 (0.95), p=0.803 (baseline) 56.89 (0.31) vs. 54.11 (1.07), p<0.001 (postintervention) 2.21 (95% CI -2.95 to -1.46) vs. 0.16 (95% CI -0.29 to 0.62), p=NR (post-pre change) ARAT least affected upper limb (scale unclear): 56.31 (1.24) vs. 56.33 (0.68), p=0.895 (baseline) 57.17 (0.00) vs. 56.16 (0.78), p<0.001 (postintervention) 0.68 (95% CI -1.28 to -0.08) vs. 0.16 (95% CI -0.08 to 0.42), p=NR (post-pre change)	No adverse effects were reported by any patient.
Ozkul, 2020 **Postural Control** Balance Exercises Motion Gaming Postintervention, 0 weeks Fair	A. Immersive virtual reality, 16 sessions over 8 weeks (n=13) B. Relaxation exercises at home, 16 sessions over 8 weeks (n=13)	A vs. B Age: 29 vs. 34 Female: 69% vs. 77% Race: NR EDSS median: 1 vs. 2 Number of relapses: 3 vs. 2	Pre-post median (IQR): BBS: 52 (42.5, 56) to 54 (44.5, 56) vs. 55 (53, 56) to 56 (53.5, 56), p>0.05 TUG: 7.6 (6.9, 8) to 6.3 (5.7, 7.2) vs. 6.9 (6.5, 7.5) to 7.4 (6.4, 7.7), p<0.017	NA

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Ozkul, 2020b **Multimodal Exercise** Immediately Postintervention, 8 weeks Fair	A. Aerobics + Pilates, 24 sessions (3 per week) over 8 weeks (n=17) B. Control group, relaxation exercise at home, 24 sessions (3 per week) over 8 weeks (n=17)	A vs. B Age (mean years): 35.8 vs. 36.7 (mean years): Female: 76% vs. 76% Race: NR Ambulatory: 100% Wheelchair user: NR EDSS (score): 1.5 vs. 1.71 GMFM: NR BMI (kg/m2) 23.75 vs. 25.39 Disease duration (years): 7.18 vs. 5.71 Number of relapses 2.88 vs. 2.71	A vs. B, Mean (SD), change mean (SD), p=within groups 6MWT (meters): 539.94 (50.21) vs. 513.82 (50.96) (baseline) 587.92 (51.44) vs. 502.75 (53.54) (postintervention); change mean (SD) 47.98 (23.34) vs. −11.07(36.40), p<0.001 MSQOL-54-MCS: 62.74 (19.37) vs. 56.29 (16.47) (baseline) 74.24 (14.83) vs. 50.91 (20.42) (postintervention) change mean (SD) 11.50 (15.94) vs. −5.38 (17.37), p=0.006 MSQOL-54-PCS: 120.54 (29.32) vs. 109.67(27.89) (baseline) 140.08 (18.42) vs. 97.83 (35.58) (postintervention) change mean (SD) 19.54 (14.42) vs. −11.84 (28.36), p<0.001 Beck's Depression Inventory (BDI 0-63, higher=worse depression): 11.06 (8.05) vs. 15.18 (8.68) (baseline) 9.18 (5.48) vs. 18.41 (7.77) (postintervention) change mean (SD) 1.88 (5.35) vs. −3.24 (8.86), p=0.152	Fatigue Impact Scale (FIS-Total score): 53.35 (29.64) vs. 68.12 (36.84) (baseline) 36.18 (21.57) vs. 78.88 (39.72) (postintervention) change mean (SD) −17.18 (22.24) vs. 10.76 (28.01), p=0.006

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Park, 2014 Postintervention, 8 weeks (within 2 months after 8-week intervention) **Postural Control** Hippotherapy Poor	A. Intervention group (hippotherapy), 16 sessions over 8 weeks (n=34) B. Control group (waitlist)	A vs. B Age (mean years): 6.68 vs. 7.76 Female: 19 (56%) vs. 11 (52%) Race: NR Ambulatory: NR Wheelchair user: NR Bilateral CP: 32 (94%) vs. 19 (90%) Unilateral CP: 2 6%) vs. 2 (10%) GMFCS level: GMFCS level I: 8 (24%) vs. 6 (29%) GMFCS level II: 11 (32%) vs. 4 (19%) GMFCS level III: 5 (15%) vs. 6 (29%) GMFCS level IV: 10 (29%) vs. 5 (24%)	A vs. B, mean (SD) within 2 months after 8-week intervention GMFM-66: 58.49 (13.40) vs. 61.20 (21.69) (baseline) 61.43 (14.78) vs. 62.46 (21.70) (postintervention) 2.93 (3.95) vs. 1.25 (1.99), p<0.05 (pre-postintervention difference) PEDI: Intervention group: n=28; Control group: n=21 116.32 (48.61) vs. 112.52 (64.98) (baseline) 127.21 (46.89) vs. 114.52 (64.53) (postintervention) 10.89 (11.94) vs. 2.00 (4.93), p<0.05 (pre-post intervention difference)	NR

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Peri, 2017 **Aerobic Exercise** Robot-Assisted Gait Training Postintervention, 4-10 weeks Poor	A. RAGT plus TOP (task oriented physical therapy), 2+2 sessions/week over 10 weeks (n=10) B. RAGT plus TOP (task oriented physical therapy), 5+5 sessions/week over 4 weeks (n=10) C. TOP 4 sessions/wk over 10 weeks (n=10) D. RAGT 4 sessions/wk over 10 weeks	A vs. B vs. C vs. D Age (mean years): 6.8 vs. 10.8 vs. 9.3 vs. 8 Female: 6 (60%) vs. 5 (42%) vs. 5 (50%) vs. 6 (50%) Race: NR Ambulatory: NR Wheelchair user: NR Other: GMFCS (I/II/III) 3/4/3 vs. 5/2/5 vs.3/5/2 vs. 3/5/4	A vs. B vs. C vs. D, mean (SD) 6MWT (meters, T0 to T1 to T2) 285.2 (219.2) to 300.9 (201.9) to 309.0 (214.9) vs. 222.1 (237.6) to 208.5 (252.7) to 225.0 (193.7) vs. 378.2 (182.6) to 381.7 (159.3) to 364.1 (179.8) vs. 324.4 (110.2) to 345.0 (92.4) to 346.5 (84.3) GMFM-66 66.0 (12.1) to 67.0 (12.7) to 69.2 (10.4) vs. 66.2 (6.3) to 67.1 (6.2) to 68.1 (6.3) vs. 66.4 (13.4) to 68.2 (11.9) to 69.2 (9.7) vs. 68.5 (8.8) to 68.9 (8.6) to 69.2 (9.7)	A vs. B, mean (SD)

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Pompa, 2017 **Aerobic Exercise** Robot-Assisted Gait Training Postintervention, 4 weeks Fair	A. RAGT, 12 sessions over 4 weeks (n=21) B. Conventional Walking Training, 12 sessions over 4 weeks (n=22)	A vs. B Age (mean years): 47 vs. 50 Female: 10 (48%) vs. 12 (55%) Race: NR Ambulatory: NR Wheelchair user: NR Other: disease duration (years) 17.05 vs. 14.09 Primary Progressive/Secondary Progressive MS 0/21 vs. 3/22 EDSS 6.62 vs. 6.50	2MWT 33.71 (15.43) to 42.59 (20.79) p=0.001 vs. 40.91 (22.45) to 43.72 (24.50) p=0.076 FAC 3.10 (1.51) to 3.76 (1.04) p=0.017 vs. 3.50 (1.10) to 3.50 (1.10) p=0.999 EDSS 6.62 (0.42) to 6.48 (0.37) p=0.014 vs. 6.50 (1.10) to 6.50 (0.49) p=0.999 Rivername Mobility index 5.76 (2.05) to 7.76 (2.62) p<0.001 vs. 6.14 (3.11) to 7.41 (2.58) p<0.001 LE Spasticity VAS 5.05 (1.01) to 3.40 (1.24) p=0.007 vs. 5.31 (2.52) to 5.23 (2.29) p=0.693 Modified Barthel Index 63.43 (18.51) to 77.43 (15.91) p<0.001 vs. 64.09 (20.60) to 74.10 (14.72) p<0.001	A vs. B, mean (SD)
Pourazar, 2020 **Postural Control** Motion Gaming Postintervention, 0 weeks Fair	A. Virtual reality Xbox 360 Kinect, 20 sessions over 6 weeks (n=10) B. Encouraged to do typical physical activity at home (n=10)	A vs. B Age: 9.2 vs. 9.6 Female: 100% Race: NR GMFCS !: 50% vs. 60% GMFCS II: 20% vs. 30% GMFCS III: 30% vs. 10%	Dynamic balance was improved in the anterior, posterolateral, and posteromedial directions with virtual reality dance game compare with the control group, p=0.001 all comparisons	NA

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Qi, 2018 **Postural Control** Tai Chi Postintervention, 6 weeks Fair	Tai Chi vs. usual care A. Tai Chi: 60 sessions (2 sessions/day, 5 days/week) over 6 weeks (n=20) B. Usual care control: (n=20)	A vs. B Age (mean years): 38.3 vs. 43.05 Female: 5 (25%) vs. 4 (20%) Race: NR Ambulatory: NR Wheelchair user: 100% BMI: 24.46 vs. 24.28 Injury level C6-T1: 3 vs. 4 T2-T5: 5 vs. 6 T6-T12: 8 vs.7 Below L1: 4 vs.3	A. vs. B., mean (SD) WHOQOL-BREF (5-point scale, higher score=higher QOL) Quality of life - Physical: 11.40 (1.25) vs. 10.94 (1.15), p=0.24 (baseline) Quality of life - Psychological 10.95 (1.57) vs. 10.87 (1.08), p=0.09 (postintervention) Quality of life - Physical: 11.80 (1.33) vs. 11.09 (1.29), p=0.85 (baseline) Quality of life - Psychological: 12.23 (1.65) vs. 10.87 (1.08), p=0.04 (postintervention)	NA
Qi, 2018a **Muscle Strength** Immediately postintervention, 6 weeks Fair	A. Strength + neuromuscular electrical stimulation: 30 sessions over 6 weeks, electrodes were placed on extensor of acrotarsium with a current intensity used just strong enough to cause muscle contraction, which continued for 20 minutes (n=50) B. Neuromuscular electrical stimulation: same stimulation as above (n=50)	A vs. B Age (mean years): 5.8 vs. 6.0 Female: 24 (48%) vs. 23 (46%) Race: NR Ambulatory: NR Wheelchair user: NR	Data reported as mean (SD) A vs. B GMFM-D/E (0-100, higher=increased motor function): 44.5 (13.2) vs. 44 (12.6), p>0.05 (baseline) 70.6 (15.2) vs. 56.7 (14.3), p<0.05 (postintervention) 71.0 (16.4) vs. 58.0 (15.6), p<0.05 (6 weeks) CSS (<7=spasm, 7-9=mild spasm, 10-12=moderate spasm, 13-16=severe spasm): 12.0 (3.4) vs. 12.3 (3.6), p>0.05 (baseline) 7.6 (3.0) vs. 9.5 (2.8), p<0.05 (postintervention) 7.4 (2.4) vs. 9.4 (2.6), p<0.05 (6 weeks)	NR

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Razazian, 2016 **Aerobic Exercise** Aquatics Postintervention, 8 weeks Poor	Yoga vs. Aquatics A. Yoga: 24 sessions over 8 weeks (n=18) B. Aquatic exercise: 24 sessions over 8 weeks (n=18) C. Usual care control: met 2-3 times a week in hospital for usual care, over 8 weeks (n=18)	A vs. B vs. C Age (mean years): 33 vs. 35 vs. 33 Female: 18 (100%) vs. 18 (100%) vs. 18 (100%) Race: NR Ambulatory: NR Wheelchair user: NR Duration of MS (years) 6.90 vs. 7.11 vs. 6.78 EDDS: 3.89 vs. 3.44 vs. 3.25 MS (primary-progressive): 0 (0%) vs. 0 (0%) vs. (0%) MS (secondary-progressive): 1 (.5%) vs. 2 (11%) vs. 2 (11%) MS (relapsing-remitting): 13 (72%) vs. 11(61%) vs. 12 (66%) MS (progressive-relapsing): 4 (22%) vs. 5 (27%) vs. 4 (22%)	A. vs. B. vs. C, mean (SD) Beck Depression Inventory (BDI: 0–9=no or minimal to 30–63=severe depression) 19.72 (7.04) vs. 19.17 (7.83) vs. 20.78 (6.22), (baseline) 5.06 (2.92) vs. 4.78 (3.42) vs. 21.33 (6.88), (postintervention), p=0.000	NA
Roppolo, 2013 **Multimodal Exercise** Immediately postintervention, 12 weeks Fair	A. Combination therapy (aerobic + strength training) 12 weeks 24 sessions over 12 weeks (n=17) B. Control group (activity not specified) (n=18)	A vs. B Age: 40 vs. 40 Female: 100% EDSS: 1.5 vs. 2.0	A vs. B, Mean (SD), p=between groups BDI: 8.8 (5.8) to 3.4 (2.9) vs. 9.2 (3.7) to 17.0 (7.0), MD 13.2, 95% CI 9.86 to 16.55, p<0.001 MSQOL-54: 202.7 (7.9) vs. 139.3 (32.4), MD 63.4 (7.86) (95% CI 47.43 to 79.4), p<0.001 (post-intervention); 29.5 (36.17) vs. −22.5 (55.57), MD 52.0, 95% CI 20.8 to 83.2, p=NR (pre-post change)	NA

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Russo, 2018 **Aerobic Exercise** Robot-Assisted Gait Training Postintervention, 18 weeks Fair	A. RAGT, 18 sessions over 6 weeks followed by usual 12 weeks (36 sessions) of traditional training (n=30) B. Usual care (traditional rehabilitation training), 54 sessions over 18 weeks (n=15)	A vs. B Age (mean years): 42 vs. 41 Female: 16 (53%) vs. 10 (67%) Race: NR Ambulatory: N (%) vs. N (%) Wheelchair user: N (%) vs. N (%) Other: Disease duration 11.4 years vs. 12.3 years	TUG change in score (seconds) Post training 11.4, p<0.001 vs. 11.2, p<0.001; At followup 8.9, p<0.001 vs. 5.1, p<0.001 EDSS 5.5 to 5.0, p=0.026 vs. 4.5 to 4.0, p=0.003 Tinetti Balance Scale change in score Post training -1.2, p<0.001 vs. -.7, p<0.01; At followup -1.0, p<0.001 vs. -0.1 p=0.71 FIM Change in score Post training -2.2, p<0.001 vs. -1.7, p<0.001 At followup -1.8, p<0.001 vs. -1.5, p<0.001	HRSD 10.0 to 7.0, p=0.004 vs. 12.5 to 7.0, p=0.004
Sadeghi Bahmani, 2019 **Aerobic Exercise** Aerobics **Postural Control** Balance Postintervention, 8 weeks Fair	A. Endurance training (treadmill, cycling, walking, jogging), 24 sessions over 8 weeks (n=26) B. Balance and coordination exercises, 24 sessions over 8 weeks (n=24) C. Attention control, 24 sessions over 8 weeks (n=21)	A vs. B vs. C Age: 38 vs. 39 vs. 38 Female: 100% EDSS: 2.46 vs. 3.38 vs. 2.02	A vs. B vs. C, Mean (SD), p=between groups: BDI-FS: 7.92 (5.11) to 5.12 (4.65) vs. 7.96 (6.67) to 5.29 (5.75) vs. 6.24 (4.47) to 6.52 (4.91) A vs. C: MD 3.08, 95% CI 0.33 to 5.84, p=0.028 B vs. C: MD 2.95, 95% CI –0.26 to 6.16, p=0.072 A vs. B: MD 0.13, 95% CI –3.00 to 3.26, p=0.935	A vs. C, Mean (SD), p=between groups: EDSS - Expanded Disability status: 3.38 (1.87) to 3.10 (1.86) vs. 2.02 (1.84) to 1.98 (1.70), p>0.05 ISI = Insomnia Severity Index; 13.46 (5.81) to 10.13 (4.92) vs. 1.71 (5.43) to 11.14 (5.39), p>0.05

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Sadeghi Bahmani, 2020a (aquatic) **Aerobic Exercise** Aquatic Postintervention, 5 weeks Fair	A. Aquatic exercise for two weeks (n=21) B. Aquatic exercise for three weeks (n=19) C. Control (n=22)	Age: 39 vs. 41 vs. 34 Female: 100% Race: NR Ambulatory: 100% vs. 100% vs. 100% Wheelchair user: NR Median EDSS score: 3.00 vs. 1.50 vs. 1.50 Baseline Female Sexual Function Index (FSFI), mean: 41.40 vs. 45.67 vs. 50.59	A vs. B, adjusted mean (SE): FSFI: 52.14 (1.2) vs. 48.80 (1.2) vs. 42.80 (1.1) After controlling for baseline values, the highest scores were achieved in the group that exercised 2 times weekly (52.14) followed by three times weekly (48.80) and active control (42.80), p<0.001 Correlation coefficients between sexual function, EDSS EDSS: -0.29, p<0.05 (baseline) -0.4, p=NR (postintervention) Correlation coefficients between sexual function, Depression Depression: -0.17 (baseline) -0.09; p< 0.01 (postintervention)	Correlation coefficients between sexual function, Fatigue Fatigue: -0.33; p< 0.01 (baseline) -0.14 (postintervention) Correlation coefficients between sexual function, Couple satisfaction Couple satisfaction: 0.48 (baseline) 0.64; p< 0.001 (postintervention)
Sadowsky, 2013 **Aerobic Exercise** Cycling Postintervention, 0 weeks Poor	A. FES cycle ergometry, 3 sessions per week over range of 3-168 months (n=25) B. Standard rehabilitation care, not specified (n=20)	A vs. B Age (mean years): 37.2 vs. 34.6 Female: 4 (12%) vs. 4 (20%) Race: NR Ambulatory: NR Wheelchair user: NR Other: Quadriplegia 13 (52%) vs. 15 (75%) Paraplegia 12(48%) vs. 5(25%)	Calculated A vs. B, Mean change scores: Total FIM: 80% vs. 60%, p<0.001 With significant improvement with FES in subscales: self-care, sphincter control, transfer, and locomotion SF-36: total and composite scores NR Significant improvement in physical function and role limit physical with FES, no difference in mental health subscales	A vs. B (SD) Body Fat Volume (cc): 450 vs. 800 (est), p<0.010

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Salci, 2016 **Postural Control** Balance Postintervention, 6 weeks Fair	A. Balance training (plus Lumbar stabilization):18 sessions over 6 weeks (n=14)* B. Lumbar stabilization (transversus abdominis muscle contractions): 18 sessions over 6 weeks (n=14)* C. Task oriented training (Individualized exercises plus Lumbar stabilization): 18 sessions over 6 weeks (n=14)* *Only 14 per group received the intervention postrandomization	A vs. B vs. C Age (mean years): 35.36 vs. 37.29 vs. 34.36 Female: 6 (43%) vs. 9 (62%) vs. 10 (71%) Race: NR Ambulatory: 100% Wheelchair user: NR BMI (kg/m^2) 22.62 vs. 24.45 vs. 23.73 MS duration (years): 6.18 vs. 8.54 vs. 5.82 EDSS, median (interquartile range): 3.5 (3–4) vs. 3.5 (3–4) vs. 3.5 (3.5–4) EDSS 1.0-4.5=fully ambulatory EDSS 5.0-9.5=impairment on ambulation Relapsing Remitting: 11 vs. 11 vs. 12 Primary Progressive: 1 vs. 1 vs. 0 Secondary Progressive: 2 vs. 2 vs. 2	A. vs. B. vs. C., mean (SD), (95% CI) 2-Minute Walk Test (2MWT) , 25-meter A. 158.(34.14), (95% CI 138.92 to 178.34), (baseline) vs. B. 151.32 (37.76), (95% CI 129.51 to 173.12), (baseline) vs. C. 151.05, (31.52) (95% CI 132.84 to 169.25), (baseline) A. 169.39 (30.67) (95% CI 151.67 to 187.10), (postintervention) vs. B. 176.87 (36.64) (95% CI 155.71 to 198.02), (postintervention) vs. C. 169.74 (31.25) (95% CI 151.69 to 187-78) (postintervention) Change in 2MWT: 10.75 (9.97) (95% CI 4.99 to 16.51) vs. 25.55 (16.90) (95% CI 15.79 to 35.31) vs. 18.69 (14.24) (95% CI 10.46 to 26.91), p=0.023 (pre-post change)	A. vs. B. vs. C., mean (SD), (95% CI) BBS A. 49.14 (5.98), (95% CI 45.68 to 52.58), (baseline) vs. B. 48.50 (6.03), (95% CI 45.01 to 51.98), (baseline) vs. C. 48.64 (6.10) (95% CI 45.11 to 52.17), (baseline) A. 52.71 (5.36) (95% CI 49.61 to 55.81), (postintervention) B. 54.28 (3.42) (95% CI 52.30 to 56.26), (postintervention) C. 54.21 (3.37) (95% CI 52.26 to 56.16) (postintervention) Change in BBS: 3.57 (2.20) (95% CI 2.29 to 4.84) vs. 5.78 (3.40) (95% CI 3.82 to 7.74) vs. 5.57 (3.73) (95% CI 3.41 to 7.72), p=0.156 (pre-post change)

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Samaei 2014 **Aerobic Exercise** Treadmill Postintervention, 0 weeks Fair	A. 30 minutes walking at 10 degrees downgrade 3 times a week for 4 weeks B. 30 minutes walking at 10 degrees elevation 3 times a week for 4 weeks	Score greater than 3 on GNDS limb score n=34 Mean age 33.03 years 28 females and 6 males (17.6% males)	Pre, post 25 foot walk A. 8.7 (2.4) to 6.1 (1.8) p=0.002 (within group differences) B. 7.9 (1.1) to 7.0 (1.6) p=0.048 p=0.001 2 minute walk A. 120.01 (23.6) to 160.1 (35.7) p=0.001 B. 132.6 (32.3) to 147.5 (29.8) p=0.026 p=0.0001 Timed Up and Go A. 98. (1.7) to 7.5 (1.8) p=0.008 B. 9.4 (2.3) to 8.9 (0.9) p=0.039 p=0.041 GNDS A. 35.4 (9.1) to 21.8 (5.3) p=0.006 B. 32.1 (8.6) to 27.5 (6.1) p=0.041 p=0.12 Modified Riverman Mobility Index A. 10.6 (3.2) to 14.3 (2.7) p=0.009 B. 10.5 (2.3) to11.9 (2.1) p-=0.038 p=0.005	NA

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Sandroff, 2017 **Multimodal Exercise** Mid-intervention (12 weeks into intervention); Immediately postintervention Fair	A. Resistance + aerobics + balance: 72 sessions over 24 weeks. Approximately equal durations of aerobic, lower-extremity resistance, and balance training (n=43) B. Stretching and toning (n=40) 72 sessions over 24 weeks for both groups	A vs. B Age (mean years): 49.8 vs. 51.2 Female: 36 (83.7%) vs. 35 (87.5%) Race: NR Ambulatory: NR Wheelchair user: NR BMI: 29.2 vs. 31.2	Data reported as mean (SD) A vs. B VO_2 peak (ml/kg/min) 16.5 (6.5) vs. 15.4 (6.2), p=NR (baseline) 16.6 (5.6) vs. 15.6 (4.9), p=NR (mid-intervention) 17.1 (5.9) vs. 15.9 (5.5), p=NR (postintervention) Time X Group interaction p>0.20 6MWT (feet) 1073.1 (529.0) vs. 1097.5 (493.3), p=NR (baseline) 1142.6 (570.3) vs. 1123.6 (488.6), p=NR (mid-intervention) 1185.5 (600.5) vs. 1115.1 (512.7), p=NR (postintervention) 112 feet vs. 18 feet, p=NR (post-pre change) +10.5% vs. +1.6%, p=NR (post-pre % change) Time X Group interaction p=0.05 25 foot walk test (feet/second) 3.7 (1.8) vs. 4.0 (1.4), p=NR (baseline) 3.8 (1.8) vs. 4.0 (1.4), p=NR (mid-intervention) 59.0 (23.4) vs. 49.3 (27.1), p=NR (postintervention) Time X Group interaction p>0.11	NR

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Sangelaji, 2014 **Multimodal Exercise** Postintervention, 0 weeks Poor	A. Strength + aerobics + balance: 30 sessions over 10 weeks (n=35) B. Usual care (n=20)	A vs. B [according to those with followup data] Age (mean years): 33.05 vs. 7.68 Female: 24 (61.5%) vs. 15 (68.2%) Race: NR Ambulatory: NR Wheelchair user: NR	Data reported as mean (SD) A vs. B [according to those with followup data] 6MWT (meters) 487.69 (NR) vs. 597.36 (NR),p=NR (baseline) 586.2 (NR) vs. 560.14 (NR), p=NR (postintervention) 443.29 (NR) vs. 409.7 (NR), p=NR (followup) NR vs. NR, MD 137.2 (24.54), p<0.0001 (pre-post change) NR vs. NR, MD 47.07 (45.34), p=0.30 (postfollowup change) NR vs. NR, MD 184.3 (51.1), p=0.001 (prefollowup change) MSQoL-PCS (0-100, higher=increased QOL) 58.46 (NR) vs. 66.33 (NR),p=NR (baseline) 65.78 (NR) vs. 61.47 (NR), p=NR (postintervention) 60.56 (NR) vs. 57.53 (NR), p=NR (followup) NR vs. NR, MD 12.17 (3.62), p=0.001 (pre-post change) NR vs. NR, MD -1.27 (3.61), p=0.73 (postfollowup change) NR vs. NR, MD 10.90 (4.55), p-0.02 (prefollowup change) MSQoL-MCS, (0-100, higher=increased QOL) 57.92 (NR) vs. 70.2 (NR), p=NR (baseline) 68.52 (NR) vs. 64.45 (NR), p=NR (postintervention) 63.73 (NR) vs. 62.47 (NR), p=NR (followup) NR vs. NR, MD 16.36 (4.46), p=0.001 (pre-post change) NR vs. NR, 2.82 (4.85), p=0.56 (postfollowup change) NR vs. NR, MD 13.54 (5.37), p=0.02 (prefollowup change)	Data reported as mean (SD) A vs. B [according to those with followup data] EDSS (1-10, higher scores=greater disability) 1.7 (NR) v. 1.96 (NR),p=NR (baseline) 1.7 (NR) vs. 2.06 (NR), p=NR (postintervention) 2.2 (NR) vs. 2.74 (NR), p=NR (followup) NR vs. NR, MD -0.13 (0.23), p=0.60 (pre-post change) NR vs. NR, MD -0.15 (0.21), p=0.50 (postfollowup change) NR vs. NR, MD -0.28 (0.29), p=0.35 (prefollowup change) BBS (0-56, higher scores=better balance) 48.47 (NR) vs. 46.68 (NR), p=NR (baseline) 51.41 (NR) vs. 46.28 (NR), p=NR (postintervention) 48.52 (NR) vs. 42.53 (NR), p=NR (followup) NR vs. NR, MD 3.34 (0.87), p<0.0001 (pre-post change) NR vs. NR, MD -0.14 (1.32), p=0.92 (postfollowup change) NR vs. NR, MD 3.21 (1.44), p=0.03 (prefollowup change)

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Sangelaji, 2016 **Multimodal Exercise** Postintervention, 0 weeks Fair	A. 1 aerobic + 3 resistance training exercises per week for 8 weeks (32 total sessions) (n=10) B. 2 aerobic + 2 resistance training exercises per week for 8 weeks (32 total sessions) (n=10) C. 3 aerobic vs. 1 resistance training exercises per week for 8 weeks (32 total sessions) (n=10) D. Control group (n=10)	A vs. B vs. C vs. D Age (mean years): 35.80 vs. 31.33 vs. 33.91 vs. 33.63 Female: 4 (60%) vs. 4 (60%) vs. 4 (60%) vs. 4 (60%) Race: NR Ambulatory: NR Wheelchair user: NR Baseline EDSS (mean): 1.33 vs. 2.06 vs. 1.95 vs. 1.81	Data reported as mean (SD) A vs. D 10MWT (seconds): 9.828 (4.89645) vs. 15.217 (18.94777), p=NR (baseline) 7.422 (2.42591) vs. 15.122 (19.02946), p=NR (postintervention) −2.4056 (NR) vs. −0.095 (NR); MD 2.31 (SE, 1.04), p=0.030 (post-pre change) −0.624281255% (NR) vs. −24.47750259% (NR), p=NR (post-pre % change) 6MWT (meters): 380.222 (136.77790) vs. 361.500 (238.86757), p=NR (baseline) 461.444 (139.61206) vs. 367.500 (258.75692), p=NR (postintervention) 81.2222 (NR) vs. 6.0000 (NR); MD −75.22 (SE, 28.21), p=0.010 (post-pre change) 21.36177674% (NR) vs. 1.659751037% (NR), p=NR (post-pre % change)	Data reported as mean (SD) BBS (0-56, higher scores=better balance) A vs. D 43.111 (4.96096) vs. 45.000 (10.04277), p=NR (baseline) 49.000 (2.34521) vs. 45.000 (9.74500), p=NR (postintervention) 5.8889 (NR) vs. 0 (NR); MD −5.88 (SE, 1.80), p<0.001 (post-pre change) 13.65982311% (NR) vs. 0% (NR), p=NR (post-pre % change) B vs. D 49.375 (3.06769) vs. 45.000 (10.04277), p=NR (baseline) 50.625 (1.84681) vs. 45.000 (9.74500), p=NR (postintervention) 1.25 (NR) vs. 0 (NR); MD −1.25 (SE, 1.85), p=0.500 (pre-post change) 2.53164557% (NR) vs. 0% (NR), p=NR (post-pre % change) C vs. D 45.400 (8.93433) vs. 45.000 (10.04277), p=NR (baseline) 48.500 (4.99444) vs. 45.000 9.74500, p=NR (postintervention) 3.1 (NR) vs. 0 (NR); MD −3.10 (SE, 1.75), p=0.090 (pre-post change) 6.828193833% (NR) vs. 0% (NR), p=NR (post-pre % change)

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Sangelaji, 2016 **(Continued)**			B vs. D 10MWT (seconds): 8.109 (2.08783) vs. 15.217 (18.94777), p=NR (baseline) 6.567 (1.29852) vs. 15.122 (19.02946), p=NR (postintervention) −1.5413 (NR) vs. −0.095 (NR); MD 1.45 (SE, 1.07), p=0.190 (post-pre change) −19.00774467% (NR) vs. −0.624281255% (NR), p=NR (post-pre % change) 6MWT (meters): 422.500 (106.39012) vs. 361.500 (238.86757), p=NR (baseline) 491.500 (108.79338) vs. 367.500 (258.75692), p=NR (postintervention) 69.0000 (NR) vs. 6.0000 (NR); MD −63.00 (SE, 29.03), p=0.040 (post-pre change) 16.33136095% (NR) vs. 1.659751037% (NR), p=NR (post-pre % change) C vs. D 10MWT (seconds): 9.874 (5.56309) vs. 15.217 (18.94777), p=NR (baseline) 7.949 (5.55153) vs. 15.122 (19.02946), p=NR (postintervention) −1.925 (NR) vs. −0.095 (NR); MD 1.83 (SE, 1.01), p=0.080 (post-pre change) −19.49564513% (NR) vs. −0.624281255 (NR), p=NR (post-pre % change) 6MWT (meters): 363.000 (159.48319) vs. 361.500 (238.86757), p=NR (baseline) 396.500 (154.32739) vs. 367.500 (258.75692), p=NR (postintervention) 33.5000 (NR) vs. 6.0000 (NR); MD −27.50 (SE, 27.54), p=0.330 (post-pre change) 9.228650138% (NR) vs. 1.659751037% (NR), p=NR (post-pre % change)	Left knee extension strength (kg) A vs. D 12.000 (5.3619) vs. 10.667 (5.04645) (baseline) 20.444 (6.12599) vs. 11.333 (6.43946) (postintervention) 8.4444 vs. 0.6666 (pre-post change) 70.37% vs. 6.249355471% (pre-post % change)B vs. D 19.000 (10.01428) vs. 10.667 (5.04645) (baseline) 24.750 (10.93814) vs. 11.333 (6.43946) (postintervention) 5.75 vs. 0.6666 (pre-post change) 30.26315789 vs. 6.249355471% (pre-post % change) C vs. D 14.580 (7.16377) vs. 10.667 (5.04645) (baseline) 23.200 (8.70249) vs. 11.333 (6.43946) (postintervention) 8.62 vs. 0.6666 (pre-post change) 59.12208505% vs. 6.249355471% (pre-post % change) Left knee flexion strength (kg) A vs. D 7.422 (3.50955) vs. 5.346 2.761 (baseline) 13.000 (4.03113) vs. 4.917 2.61566 (postintervention) 5.5778 vs. −0.42897 (pre-post change) 75.150225 vs. −8.024625538% (pre-post % change)

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Sangelaji, 2016 **(Continued)**				B vs. D 12.375 (4.89716) vs. 5.346 2.761 (baseline) 15.500 (5.47723) vs. 4.917 2.61566 (postintervention) 3.125 vs. −0.42897 (pre-post change) 25.25252525% vs. −8.024625538% (pre-post % change) C vs. D 7.060 (2.49275) vs. 5.346 2.761 (baseline) 12.600 (2.79682) vs. 4.917 2.61566 (postintervention) 5.54 vs. −0.42897 (pre-post change) 78.47025496% vs. −8.024625538% (pre-post % change) Right knee extension strength (kg) A vs. D 12.111 (5.1099) vs. 14.667 (3.26599) (baseline) 19.000 (6.61438) vs. 16.667 (7.44759) (postintervention) 6.8889 vs. 2 (pre-post change) 56.88087787% vs. 13.63633264% (pre-post % change) B vs. D 21.375 (9.31876) vs. 14.667 (3.26599) (baseline) 25.000 (10.91526) vs. 16.667 (7.44759) (postintervention) 3.625 vs. 2 (pre-post change) 16.95906433% vs. 13.63633264% (pre-post % change)

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Sangelaji, 2016 **(Continued)**				C vs. D 16.000 (6.8313) vs. 14.667 (3.26599) (baseline) 24.300 (8.53815) vs. 16.667 (7.44759) (postintervention) 8.3 vs. 2 (pre-post change) 51.875% vs. 13.63633264% (pre-post % change) Right knee flexion strength (kg) A vs. D 7.722 3.(64958) vs. 8.205 (3.55624) (baseline) 12.333 (4.74342) vs. 7.750 (2.80624) (postintervention) 4.6111 vs. −0.4555 (pre-post change) 59.71225816% vs. −5.551154713% (pre-post % change) B vs. D 13.375 (5.15302) vs. 8.205 (3.55624) (baseline) 17.250 (5.94619) vs. 7.750 (2.80624) (postintervention) 3.875 vs. −0.4555 (pre-post change) 28.97196262% vs. −5.551154713% (pre-post % change) C vs. D 8.850 (2.80921) vs. 8.205 (3.55624) (baseline) 12.900 (3.38132) vs. 7.750 (2.80624) (postintervention) 4.05 vs. −0.4555 (pre-post change) 45.76271186% vs. −5.551154713% (pre-post % change)

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Scholtes, 2010 Scholtes, 2011 Scholtes, 2008 **Muscle Strength** Postintervention, 6 weeks Fair	A. Progressive resistance (n=26): 36 sessions over 12 weeks B. Usual care (n=25)	A vs. B [data for completers only] Age (mean years): 10.33 vs. 10.25 Female: 8 (33%) vs. 12 (50%) Race: NR Ambulatory: 24 (100%) vs. 25 (100%) Wheelchair user: NR Limb distribution -unilateral: 29% vs. 40% -bilateral: 71% vs. 60% GMFM Classification Level -I: 54% vs. 48% -II: 33% vs. 36% -III: 13% vs. 16%	Data reported as mean (SD) A vs. B 10MWT (meters/second) 0.95 (0.29) vs. 0.95 (0.28) (baseline) 1.06 (0.32) vs. 1.00 (0.33), effect 0.05 (95% CI −0.07 to 0.16), p=0.44 (mid-intervention) 1.03 (0.33) vs. 1.07 (0.38), effect −0.04 (95% CI −0.18 to 0.10), p=0.56 (postintervention) 1.00 (0.28) vs. 1.06 (0.34), effect −0.06 (95% CI −0.17 to 0.04), p=0.25 (6 weeks) 1-minute fast walking test (meters/second) 1.29 (0.45) vs. 1.25 (0.39) (baseline) 1.33 (0.44) vs. 1.24 (0.47), effect 0.04 (95% CI −0.04 to 0.13), p=0.31 (mid-intervention) 1.34 (0.48) vs. 1.23 (0.43), effect 0.04 (95% CI −0.04 to 0.12), p=0.30 (postintervention) 1.30 (0.45) vs. 1.26 (0.44), effect −0.01 (95% CI −0.08 to 0.06), p=0.78 (6 weeks) Timed Stair Test (seconds) 10.75 (15.93) vs. 14.08 (17.50) (baseline) 10.75 (13.31) vs. 12.86 (15.13), effect 1.38 (95% CI −1.39 to 4.12), p=0.33 (mid-intervention) 9.63 (12.06) vs. 12.14 (11.22), effect 0.83 (95% CI −2.64 to 4.30), p=0.64 (postintervention) 11.25 (17.34) vs. 11.71 (8.51), effect 2.87 (95% CI −2.41 to 8.16), p=0.29 (6 weeks) Sit-to-Stand (reps) 12.9 (2.8) vs. 10.8 (3.0), p<0.05 (baseline) 13.3 (3.2) vs. 12.1 (4.2), effect −0.47 (95% CI −2.28 to 1.33), p=0.61 (postintervention) 13.6 (3.0) vs. 12.7 (4.3), effect −0.75 (95% CI −2.21 to 0.72), p=0.32 (6 weeks)	Data reported as mean (SD) A vs. B Knee extensors strength (Newton/kg) 4.78 (1.12) vs. 4.36 (1.05) (baseline) 5.39 (1.10) vs. 4.48 (1.21), effect 0.56 (95% CI 0.13 to 0.99), p=0.01 (postintervention) 5.20 (1.04) vs. 4.46 (1.20), effect 0.35 (95% CI −0.16 to 0.85), p=0.16 (6-weeks) Knee flexors strength (Newton/kg) 2.73 (0.79) vs. 2.25 (0.96) (baseline) 2.76 (0.75) vs. 2.27 (1.02), effect 0.05 (95% CI −0.25 to 0.36), p=0.71 (postintervention) 2.67 (0.86) vs. 2.33 (0.90), effect −0.10 (95% CI −0.43 to 0.24), p=0.58 (6-weeks) Hip flexor strength (Newton/kg) 3.96 (0.75) vs. 3.76 (0.99) (baseline) 24 4.43 (0.99) vs. 4.12 (0.99), effect 0.16 (95% CI −0.22 to 0.55), p=0.41 (postintervention) 4.46 (0.90) vs. 4.43 (0.86), effect −0.12 (95% CI −0.50 to 0.27), p=0.55 (6-weeks) Hip abductor strength (Newton/kg) 2.66 (0.76) vs. 2.41 (0.74) (baseline) 2.78 (0.85) vs. 2.28 (0.70), effect 0.27 (95% CI 0.00 to 0.54), p=0.05 (postintervention) 2.90 (0.99) vs. 2.45 (0.94), effect 0.23 (95% CI −0.10 to 0.56), p=0.17 (6-weeks)

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Scholtes, 2010 Scholtes, 2011 Scholtes, 2008 **(Continued)**			Lateral step-up test (reps): 15.6 (4.0) vs. 13.3 (5.4), p=0.95 (baseline) 15.2 (3.9) vs. 13.7 (4.3), effect −0.05 (95% CI −1.87 to 1.77), p=0.95 (mid-intervention) 17.0 (5.1) vs. 15.4 (4.3), effect 0.48 (95% CI −1.45 to 2.40), p=0.63 (postintervention) 17.5 (4.8) vs. 15.8 (6.6), effect 0.13 (95% CI −1.84 to 2.10), p=0.9 (6-weeks) GMFM-66 (0-100, higher=increased motor function): 76.1 (12.8) vs. 71.8 (12.5) (baseline) 76.1 (11.8) vs. 73.1 (12.4), effect −0.56 (95% CI −2.11 to 0.99), p=0.48 (postintervention) 76.6 (13.0) 24 72.7 (12.8), effect 0.26 (95% CI −1.23 to 1.76), p=0.73 (6 weeks) Spasticity (0-5, higher=greater spasticity): T0 24 1.00 (1.32) vs. 2.00 (1.32) (baseline) T1 23 2.00 (1.41) vs. 2.00 (1.39), effect 0.02 (95% CI −0.99 to 1.02), p=0.97 (mid-intervention) T2 23 2.00 (1.11) vs. 1.50 (1.10) 0.46 (95% CI −0.34 to 1.26), p=0.26 (postintervention) T3 22 1.00 (0.87) vs. 1.00 (0.87) −0.22 (95% CI −0.92 to 0.49), p=0.55 (6 weeks)	Leg power - Six-repetition maximum on leg press (% body weight) 112.78 (21.28) vs. 93.76 (20.18), p<0.05 (baseline) 119.38 (26.61) vs. 100.80 (23.72), effect 1.97 (95% CI −8.45 to 12.41), p=0.71 (mid-intervention) 135.63 (31.87) vs. 102.88 (26.76), effect 14.17 (95% CI 1.99 to 26.35) ,p=0.02 (postintervention) 129.90 (32.15) vs. 111.99 (26.17), effect 3.42 (95% CI −8.62 to 15.46), p=0.58 (6 weeks)

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Shin, 2014 **Aerobic Exercise** Robot-Assisted Gait Training Postintervention, 4 weeks Fair	A. RAGT, 12 sessions over 4 weeks, plus usual physiotherapy 2 times per day 5 days per week, 40 sessions over 4 weeks (N=27) B. Conventional Overground Training, 2 times per day 5 days per week, 40 sessions over 4 weeks (n=26)	A vs. B Age (mean years): 43 vs. 48 Female: 7 (26%) vs. 12 (46%) Race: NR Ambulatory: N (%) vs. N (%) Wheelchair user: N (%) vs. N (%) Other: Cervical SCI 15 (52%) vs. 16 (62%) Months since injury 3.33 vs. 2.73	A vs. B, mean WISCI-II change in score 8 vs. 5 (intergroup p=0.01) LEMS change in score 6 vs. 4 (intergroup p=0.24) SCiM3-M 6 vs. 3 (intergroup p=0.13) All intragroup p-values <0.001	A vs. B, mean (SD)
Silva e Borges, 2011 Postintervention, 0 weeks (after 6-week intervention) **Postural Control** Hippotherapy Fair	A. Riding simulator (RS) group, 12 sessions over 6 weeks (n=20) B. Conventional physical therapy (CT) group, 12 sessions over 6 weeks (n=20)	A vs. B Age (mean years): 5.65 vs. 5.77 Female: 12 (60%) vs. 11 (55%) Race: NR Ambulatory: NR Wheelchair user: NR	A vs. B, number of people (%) GMFCS: GMFCS level III (baseline) to level II (postintervention): 2 (10%) vs. 1 (5%) GMFCS level IV (baseline) to level III (postintervention): 1 (5%) vs. 1 (5%) GMFCS level V (baseline) to level IV (postintervention): 2 (10%) vs. 0 (0%) Children in RS group had 1.63 times more chances to show a better GMFCS score after the treatment than before the treatment (p=0.0110). Children in CT group had 1.22 times more chances to obtain a better score after treatment than before the treatment (p=0.1510).	NR

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Slaman, 2014a Slaman, 2014b Slaman, 2015 Slaman, 2010 **Multimodal Exercise** Mid-intervention (12 weeks into intervention); Immediately postintervention; 24 weeks Fair	A. Strength training + cardiopulmonary fitness: (n=29) The intervention consisted of 3 parts over 6 months. 1) Supervised center and home-based physical fitness training (24 sessions over 12 weeks) 2) Counseling on daily physical activity, based on motivational interviewing (6 sessions over 24 weeks) 3) Counseling on sports participation, (2 required sessions - up to 4 offered- over 24 weeks) B. Usual care (n=28) (Entire intervention period was 24 weeks)	A vs. B Age (mean years): 20 vs. 20 Female: 14 (48.3%) vs. 16 (57.1%) Race: NR Ambulatory: 28 (96.6%) vs. 25 (89.3%) Wheelchair user: 1 (3.3%) vs. 3 (10.7%) CP distribution -unilateral: 15 (51.7%) vs. 14 (50%) -bilateral: 14 (48.3%) vs. 13 (46.4%) -unknown: 0 (0%) vs. 1 (3.4%) baseline VO_2 peak (mean mL/min): 2533 vs. 2260 Waist circumference (mean cm): 79 vs. 87, p<0.04 Total lower-extremity muscle strength (mean): 1482 vs. 1307 Total upper-extremity muscle strength (mean): 466 vs. 448 Gross Motor Function Classification System Level (I/II/III/IV): 16/9/3/1 vs. 17/9/2/0	Data reported as mean (SD) A vs. B [for those with followup data] GMFM-66 (0-100, higher=increased motor function): 82.57 (12.07) vs. 83.76 (14.38), p=NR (baseline) 82.44 (11.48 vs. 85.22 (11.62), p=NR (postintervention) 85.50 (12.41) vs. 85.22 (11.62), p=NR (24 weeks) VO_2 Peak (mL/min): 2260 (725) vs. 2533 (824), p=NR (baseline) 2515 (737) vs. 2553 (862), p=NR(mid-intervention) 2456 (583) vs. 2396 (861), p=NR (postintervention) 2315 (519) vs. 2549 (864), p=NR (24 weeks) NR vs. NR; adj. MD 89.3 (95% CI -98.8 to 277.4), p=0.35 (pre-mid change) NR vs. NR; adj. MD 195.2 (95% CI 57.3 to 333.1), p<0.01 (pre-post change) NR vs. NR; adj. MD -118.2 (95% CI -274.5 to 40.1), p=0.14 (postfollowup change) Waist Circumference (cm): 87 (15) vs. 79 (12), p=NR (baseline) 86 (15) vs. 82 (13), p=NR (mid-intervention) 86 (14) vs. 82 (13), p=NR (postintervention) 84 (13) vs. 80 (15), p=NR (24 weeks) NR vs. NR; adj. MD -3.7 (95% CI -7.2 to -0.2), p=0.04 (pre-mid change) NR vs. NR; adj. MD -2.6 (95% CI -6.1 to 0.9), p=0.15 (pre-post change) NR vs. NR; adj. MD 0.4 (95% CI -3.9 to 4.7), p=0.85 (postfollowup change)	Data reported as mean (SD) A vs. B [for those with followup data] Hip flexion strength (units NR): 417 (15) vs. 477 (20), p=NR (baseline) 449 (160) vs. 474 (139), p=NR (mid-intervention) 429 (12) vs. 443 (153), p=NR (postintervention) 501 (187) vs. 486 (118), p=NR (24 weeks) NR vs. NR; adj. MD -16.1 (95% CI -81.3 to 49.2), p=0.63 (pre-mid change) NR vs. NR; adj. MD 1.4 (95% CI -63.0 to 66.0), p=0.97 (pre-post change) NR vs. NR; adj. MD 29.0 (-56.5 to 114.5), p=0.51 (postfollowup change) Hip abduction strength (units NR): 461 (15) vs. 483 (24), p=NR (baseline) 482 (143) vs. 449 (176), p=NR (mid-intervention) 469 (128) vs. 480 (195), p=NR (postintervention) 476 (108) vs. 508 (215), p=NR (24 weeks) NR vs. NR; adj. MD 2.4 (95% CI -59.6 to 64.5), p=0.94 (pre-mid change) NR vs. NR; adj. MD -38.6 (95% CI -93.1 to 15.9), p=0.17 (pre-post change) NR vs. NR; adj. MD -10.8 (95% CI -68.1 to 46.5), p=0.71 (postfollowup change)

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Slaman, 2014a Slaman, 2014b Slaman, 2015 Slaman, 2010 **(Continued)**			Weight (kg): 70.3 (18.4) vs. 64.6 (17.6), p=NR (baseline) 74.0 (18.5) vs. 66.0 (18.2), p=NR (mid-intervention) 72.9 (17.8) vs. 66.5 (18.7), p=NR (postintervention) 70.7 (15.0) vs. 67.4 (19.9), p=NR (24 weeks) NR vs. NR; adj. MD 0.5 (95% CI -1.1 to 2.2), p=0.51 (pre-mid change) NR vs. NR; adj. MD -0.6 (95% CI -2.2 to 0.9), p=0.46 (pre-post change) NR vs. NR; adj. MD -0.8 (95% CI -4.0 to 2.4), p=0.62 (postfollowup change) SF-36 subscale – Physical functioning 64.81 (26.44) vs. 76.72 (20.54) (baseline) 78.86 (18.96) vs. 77.50 (27.11) (postintervention) 79.72 (19.44) vs. 76.90 (26.34) (24 weeks) NR vs. NR; adj. MD 3.11 (95% CI –8.31 to 14.53), p>0.05 (pre-post change) NR vs. NR; adj. MD 5.45 (95% CI –5.13 to 16.04), p>0.05 (prefollowup change) SF-36 subscale – Role Physical 80.56 (27.15) vs. 75.00 (34.72) (baseline) 78.41 (35.60) vs. 73.96 (37.94) (postintervention) 84.72 (33.36) vs. 69.05 (46.03) (24 weeks) NR vs. NR; adj. MD 4.15 (95% CI –15.10 to 23.40), p>0.05 (pre-post change) NR vs. NR; adj. MD 16.27 (95% CI –8.65 to 41.20), p>0.05 (prefollowup change) SF-36 subscale – bodily pain 82.59 (21.60) vs. 80.75 (23.75) (baseline) 82.09 (25.07) vs. 75.78 (22.45) (postintervention) 88.61 (18.39) vs. 73.55 (19.29) (24 weeks) NR vs. NR; adj. MD 5.47 (95% CI –7.12 to 18.06), p>0.05 (pre-post change) NR vs. NR; adj. MD 15.14 (95% CI 3.44 to 26.85), p<0.05 (prefollowup change)	Knee extension strength (units NR): 463 (12) vs. 522 (25), p=NR (baseline) 494 (126) vs. 484 (136), p=NR (mid-intervention) 468 (124) vs. 457 (147), p=NR (postintervention) 494 (144) vs. 516 (211), p=NR (24 weeks) NR vs. NR; adj. MD 17.8 (95% CI 95% CI -56.7 to 92.4), p=0.64 (pre-mid change) NR vs. NR; adj. MD 23.7 (95% CI -58.6 to 106.1), p=0.57 (pre-post change) NR vs. NR; adj. MD 37.7 (95% CI -38.0 to 113.4), p=0.33 (postfollowup change) Shoulder abduction strength (units NR): 222 vs. 267 (67), p=NR (baseline) 250 vs. 167 (41), p=NR (mid-intervention) 250 vs. 105 (25), p=NR (postintervention) 282 vs. 139 (27), p=NR (24 weeks) Elbow extension strength (units NR): 226 vs. 198 (60), p=NR (baseline) 179 vs. 221 (68), p=NR (mid-intervention) 191 vs. NA, p=NR (postintervention) 263 vs. 232 (43), p=NR (24 weeks) Total cholesterol (mmol/L): 4.17 (0.54) vs. 4.58 (0.61), p=NR (baseline) 4.19 (0.52) vs. 4.30 (0.63), p=NR (mid-intervention) 3.68 (0.51) vs. 4.46 (0.94), p=NR (postintervention) 3.27 (0.67) vs. 4.32 (0.86), p=NR (24 weeks) NR vs. NR; adj. MD -0.18 (95% CI -0.50 to 0.14), p=0.27 (pre-mid change) NR vs. NR; adj. MD -0.50 (95% CI -3.22 to -0.01), p=0.07 (pre-post change) NR vs. NR; adj. MD -0.55 (-1.04 to -0.07), p=0.05 (postfollowup change)

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Slaman, 2014a Slaman, 2014b Slaman, 2015 Slaman, 2010 **(Continued)**			SF-36 subscale – general health 71.08 (18.39) vs. 69.90 (23.19) (baseline) 75.18 (17.39) vs. 66.09 (23.57) (postintervention) 74.50 (18.22) vs. 66.85 (22.80) (24 weeks) NR vs. NR; adj. MD 7.41 (95% CI –3.81 to 18.62), p>0.05 (pre-post change) NR vs. NR; adj. MD 10.28 (95% CI –1.42 to 21.98), p>0.05 (prefollowup change) SF-36 subscale – vitality 54.44 (15.53) vs. 55.54 (11.25) (baseline) 58.41 (8.78) vs. 57.71 (14.37) (postintervention) 53.61 (11.22) vs. 54.00 (12.73) (24 weeks) NR vs. NR; adj. MD 1.64 (95% CI –4.96 to 8.23), p>0.05 (pre-post change) NR vs. NR; adj. MD −0.40 (95% CI –6.92 to 7.71), p>0.05 (prefollowup change) SF-36 subscale – social functioning 85.19 (13.44) vs. 82.76 (21.24) (baseline) 90.34 (11.53) vs. 89.06 (17.02) (postintervention) 86.03 (15.23) vs. 90.00 (17.01) (24 weeks) NR vs. NR; adj. MD 1.76 (95% CI –5.88 to 9.41), p>0.05 (pre-post change) NR vs. NR; adj. MD −3.08 (95% CI –12.64 to 6.49), p>0.05 (prefollowup change)	High-density lipoprotein cholesterol (mmol/L): 1.29 (0.28) vs. 1.44 (0.31), p=NR (baseline) 1.37 (0.22) vs. 1.36 (0.33), p=NR (mid-intervention) 1.42 (0.35) vs. 1.36 (0.26), p=NR (postintervention) 1.41 (0.21) vs. 1.44 (0.25), p=NR (24 weeks) NR vs. NR; adj. MD 0.12 (95% CI -0.03 to 0.26), p=0.13 (pre-mid change) NR vs. NR; adj. MD 0.01 (95% CI -0.21 to 0.21), p=0.38 (pre-post change) NR vs. NR; adj. MD 0.09 (95% CI -0.09 to 0.26), p=0.34 (postfollowup change) Systolic blood pressure (mmHg): 119.9 (17.7) vs. 119.4 (17.6), p=NR (baseline) 121.1 (12.3) vs. 117.0 (16.8), p=NR (mid-intervention) 119.2 (13.6) vs. 116.0 (16.4), p=NR (postintervention) 115.9 (14.2) vs. 22.9 (15.1), p=NR (24 weeks) NR vs. NR; adj. MD 2.9 (95% CI -3.7 to 9.5), p=0.40 (pre-mid change)

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Slaman, 2014a Slaman, 2014b Slaman, 2015 Slaman, 2010 **(Continued)**			SF-36 subscale – role emotional 87.65 (22.92) vs. 79.31 (37.18) (baseline) 96.97 (9.81) vs. 90.28 (28.62) (postintervention) 98.15 (7.86) vs. 87.30 (32.45) (24 weeks) NR vs. NR; adj. MD 5.94 (95% CI –5.01 to 16.90), p>0.05 (pre-post change) NR vs. NR; adj. MD 11.09 (95% CI –1.22 to 23.39), p>0.05 (prefollowup change) SF-36 subscale – mental health 75.26 (13.90) vs. 76.69 (16.32) (baseline) 82.36 (8.52) vs. 74.67 (15.99) (postintervention) 81.56 (10.81) vs. 73.40 (15.59) (24 weeks) NR vs. NR; adj. MD 8.00 (95% CI 0.96 to 15.05), p<0.05 (pre-post change) NR vs. NR; adj. MD 8.80 (95% CI 0.99 to 16.61), p<0.05 (prefollowup change)	NR vs. NR; adj. MD 1.5 (95% CI -5.6 to 8.6), p=0.68 (pre-post change) NR vs. NR; adj. MD -10.0 (95% CI -19.2 to -1.2), p=0.03 (postfollowup change) Diastolic blood pressure (mmHg): 78.0 (9.3) vs. 75.2 (8.6), p=NR (baseline) 76.0 (8.0) vs. 69.9 (11.7), p=NR (mid-intervention) 77.2 (8.3) vs. 77.5 (9.2), p=NR (postintervention) 74.8 (11.8) vs. 73.9 (10.6), p=NR (24 weeks) NR vs. NR; adj. MD 5.2 (95% CI -0.3 to 10.6), p=0.10 (pre-mid change) NR vs. NR; adj. MD -3.0 (95% CI -7.9 to 1.9), p=0.24 (pre-post change) NR vs. NR; adj. MD 0.7 (95% CI -6.1 to 7.5), p=0.83 (postfollowup change)

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Straudi, 2016 **Aerobic Exercise** Robot-Assisted Gait Training Postintervention, 6 weeks Fair	A. RAGT, 12 sessions over 6 weeks (n=27) B. Conventional physiotherapy, 12 sessions over 6 weeks (n=25)	A vs. B Age (mean years): 52 vs. 54 Female: 17 (63%) vs. 17 (68%) Race: NR Ambulatory: NR Wheelchair user: NR Other: EDSS (mean): 6.43 vs. 6.46 MS type: primary progressive 9 (33%) vs. 7 (28%), remainder secondary progressive	PHQ-9 T1-T0: -1.19 (3.26) vs. -1.88 (5.92), p=0.25 T2-T0: -1.7 (3.24) vs. -3.04 (4.66), p=0.213 T3-T0: -0.78 (3.31) vs. -2.20 (4.49), p=0.44 SF 36-PCS T1-T0: 1.85 (6.92) vs. 0.72 (5.63), p=0.50 T2-T0: 1.67 (7.74) vs. 1.84 (6.77), p=0.99 T3-T0: 5.11 (16.60) vs. 1.04 (6.24), p=0.91 SF 36-MCS T1-T0: 3.33 (8.77) vs. -1.16 (8.88), p=0.08 T2-T0: 5.37 (9.58) vs. 1.60 (9.41), p=0.14 T3-T0: -2.52 (14.11) vs. 1.08 (8.74) p=0.34 TUG (s) T1-T0: -1.11 (6.73) vs. -0.09 (7.04), p=0.76 T2-T0: 2.66 (13.79) vs. -3.96 (10.50), p=0.95 T3-T0: -4.16 (15.30) vs. -3.63 (10.61) p=0.24 6MWT (m) T1-T0: 16.94 (18.96) vs. -6.02 (27.70), p=0.003 T2-T0: 23.22 (32.23) vs. -0.75 (26.40), p=0.01 T3-T0: 10.64 (35.07) vs. 4.51 (33.59) p=0.55 BBS T1-T0: 2.44 (3.98) vs. -0.22 (4.48), p=0.043 T2-T0: 3.24 (4.99) vs. 0.87 (6.45), p=0.19 T3-T0: 1.72 (6.05) vs. -0.17 (6.04) p=0.37	NA

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Straudi, 2019 **Aerobic Exercise** Robot-Assisted Gait Training Postintervention, 12 weeks Good	A. Robot-assisted gait training (RAGT), 12 sessions over 4 weeks (n=36) B. Overground walking, 12 sessions over 4 weeks (n=36)	A vs. B Age: 56 vs. 55 Female: 67% vs. 69% EDSS: 6.5 vs. 6.5 PPMS: 50% vs. 45% SPMS: 50% vs. 55%	A vs. B, mean difference between groups: 6MWT: 4, 95% CI –10 to 18, p=0.86 25FWT: 0, 95% CI –0.06 to 0.05, p=0.98 TUG: 7.8, –0.2 to 15.8, p=0.25 MSIS-29 motor: –3, 95% CI –9 to 3, p=0.31 MSIS-29 psychological: –2, 95% CI –5 to 1, p=0.22S SF-36 PCS: –1, 95% CI –4 to 3, p=0.13 SF-36 MCS: 1, 95% CI –2 to 4, p=0.94	A vs. B, Mean difference between groups: BBS: 0, 95% CI –2 to 2, p=0.91 PHQ-9: -0.4, 95% CI -2.3 to 1.4, p=0.86
Swe 2015 **Aerobic Exercise** Treadmill Pre to post only Good	A. Partial body weight supported treadmill walking 30 minutes twice a week for 8 weeks B. Overground walking similar duration and number of sessions	GMFCS II or III (II/III 70/25) N=95 Mean age 16.6 years 61 males and 34 females (64% males)	Pre to week 8 10 meter walk test (meters/second) A 0.922 (0.316) to 1.082 (0.352) B. 0.805 (0.248) to 0.978 (0.299) 6 minute walk test (meters) A. 223.33 (94.62) to 250.60 (110.86) B. 205.00 (88.58) to 249.27 (107.84) Gross Motor Function Measure-88 (D) (standing) A. 66.07 (22.28) to 77.73 (21.73) B. 64.53 (16.29) 79.13 (14.22) Gross Motor Function Measure-88 (E) (walking) A. 41.07 (24.60) to 54.13 (28.25) B. 40.47 (19.17) to 56.33 (23.05) Outcome measures all showed an improvement over time (p<0.001); no effect of group allocation on any parameter	NA

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Tak, 2015 **Postural Control** Motion gaming Immediately postintervention, 6 weeks Fair	A. Nintendo-Wii, 18 sessions over 6 weeks + conventional rehabilitation (n=13) B. Conventional rehabilitation (n=13)	A vs. B Age: 50 vs. 43 Cervical: 31% vs. 38% ASIA (A): 77% vs. 77% ASIA (B): 23% vs. 23%	A vs. B Mean (SD), p=between groups T-shirt test (s): 29.5 (10.95) to 22.60 (8.28) vs. 23.59 (11.35) to 22.15 (12.28), p<0.05 Change 6.90 (3.55) vs. 1.44 (1.51), p<0.05	NA

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Tarakci, 2013 **Multimodal Exercise** Postintervention, 0 weeks Fair	A. Group exercise: 36 sessions over 12 weeks (n=55) B. Waitlist (n=55)	A vs. B Age (mean years): 41.49 vs. 39.65 Female: 34 (67%) vs. 30 (48%) Race: NR Ambulatory: NR Wheelchair user: NR Mean EDSS: 4.38 vs. 4.21 MS type –Relapsing Remitting: 32 (62.7%) vs. 33 (68.7%) –Primary Progressive: 10 (19.6%) vs. 8 (16.6%) –Secondary Progressive: 9 (17.6%) vs. 7 (14.5%)	Data reported as mean (SD) A vs. B 10MWT (seconds): 17.97 (2.89) vs. 17.17 (3.89), p=0.274 (baseline) 15.24 (2.51) vs. 18.62 (4.21) MD 0.98, p=NR (postintervention) Difference between groups pre-post change scores: p<0.001 Stair Climbing Test (seconds): 12.00 (3.57) vs. 13.92 (4.54), p=0.290 9.53 (3.49) vs. 18.46 (16.34), MD 0.290, p=NR (postintervention) Difference between groups pre-post change scores: p<0.001 MUSIQoL (0-100, higher-increased QOL): 74.41 (9.20) vs. 73.42 (9.73), p=0.628 (baseline) 76.39 (9.53) vs. 73.02 (10.30), MD 0.34, p=NR (postintervention) Difference between groups pre-post change scores: p=0.02 Right hip flexors MAS (0-4, higher=increased spasticity): 1.35 (1.33) vs. 1.52 (1.03), p=0.508 (baseline) 0.68 (0.83) vs. 1.65 (1.09), MD 1.01, p=NR (postintervention) Difference between groups pre-post change scores: p<0.001 Left hip flexors MAS (0-4, higher=increased spasticity): 1.29 (1.15) vs. 1.13 (1.18), p=0.518 (baseline) 1 (0.87) vs. 1.31 (1.21), MD 0.3, p=NR (postintervention) Difference between groups pre-post change scores: p=0.015	Data reported as mean (SD) A vs. B BBS (0-56, higher scores=better balance): 37.68 (9.91) vs. 36.94 (12.55), p=0.757 (baseline) 42.01 (9.32) vs. 34.81 (12.85), MD 0.64, p=NR (postintervention) Difference between groups pre-post change scores: p=0.003

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Tarakci, 2013 **(Continued)**			Right hamstring MAS (0-4, higher=increased spasticity): 1.35 (1.18) vs. 1.28 (0.89), p=0.782 (baseline) 0.70 (0.75) vs. 1.47 (0.92), MD 0.92, p=NR (postintervention) Difference between groups pre-post change scores: p<0.001 Left hamstring MAS (0-4, higher=increased spasticity): 1.01 (1.15) vs. 1.02 (0.88), p=0.976 (baseline) 0.54 (0.70) vs. 1.26 (1.08), MD 0.8, p=NR (postintervention) Difference between groups pre-post change scores: p<0.001 Right Achilles MAS (0-4, higher=increased spasticity): 0.86 (0.87) vs. 0.94 (0.61), p=0.611 (baseline) 0.68 (0.73) vs. 1.10 (0.83), MD 0.54, p=NR (postintervention) Difference between groups pre-post change scores: p=0.014 Left Achilles MAS (0-4, higher=increased spasticity): 0.58 (0.82) vs. 0.81 (0.69), p=0.173 (baseline) 0.27 (0.53) vs. 0.89 (0.76), MD 0.95, p=NR (postintervention) Difference between groups pre-post change scores: p<0.001	NA

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Tarakci, 2016 **Postural Control** Motion gaming Postintervention, 12 weeks Fair	A. Nintendo Wii-Fit balanced gaming, 24 sessions over 12 weeks (n=15) B. Conventional balance training, 24 sessions over 12 weeks (n=15)	A vs. B Age (mean years): 10.46 vs. 10.53 Female: 5 (33%) vs. 6 (40%) Race: NR Ambulatory: NR Wheelchair user: NR Assistive devices: 0 (0%) vs. 3 (20%) Orthesis: 9 (16%) vs. 10 (67 %) Type of CP: Hemiplegic: 7 (47%) vs. 7 (47%) Diplegic: 7 (47%) vs. 5 (33%) Dyskinetic: 1 (.06%) vs. 3 (20%) GMFCS median (min–max): 2 vs. 2	A. vs. B., mean (SD) TUG (seconds) 12.96 (3.65) vs. 15.77 (4.52) (baseline) 10.62 (3.30) vs. 14.67 (4.54) (postintervention): Difference between groups pre-post change scores: p=0.001 10 MWT 10MWT (seconds) 13.25 (3.56) vs. 13.77 (4.72) (baseline) 11.04 (3.46) vs. 12.96 (4.64) (postintervention) Difference between groups pre-post change scores: p=0.001 Wee FIM 95.73 (10.10) vs. 94.40 (10.70) (baseline) 100.26 (8.75) vs. 95.50 (10.47) (postintervention) Difference between groups pre-post change scores: p=0.001 Sit-to-Stand Test (number of stands in 30 seconds) 6.13 (1.55) vs. 5.60 (1.50) (baseline) 8.73 (2.08) vs. 6.13 (1.68) (postintervention) Difference between groups pre-post change scores: p=0.001 10-stair climbing test 10.32 (3.81) vs. 12.03 (4.91) (baseline) 8.42 (3.57) vs. 11.12 (4.27) (postintervention) Difference between groups pre-post change scores: p=0.001	NA

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Taylor, 2013 Bania, 2016 **Muscle Strength** Immediately postintervention, 12 weeks Taylor, 2013: Good Bania, 2016: Fair	A. Progressive resistance: 24 sessions over 12 weeks (n=23) B. Usual care (n=25)	A vs. B Age (mean years): 18.17 vs. 18.58 Female: 10 (44%) vs. 12 (48%) Race: NR Gait aid use -No gait aid 13 (57%) vs. 15 (60%) -Sticks 5 (22%) vs. 5 (20%) -Crutches 1 (4%) vs. 3 (12%) -Walker 4 (17%) vs. 2 (8%) Orthotics use: 8 (35%) vs. 11 (44%) Previous single-event multi-level surgery: 11 (48%) vs. 11 (44%) Hip morphology -Grade I, normal hip: 1 (2%) vs. 3 (7%) -Grade II, near normal hip: 23 (52%) vs. 27 (59%) -Grade III, dysplastic hip: 19 (43%) vs. 16 (35%) -Grade IV, subluxated hip: 1 (2%) vs. 0 (0%)	Data reported as mean (SD) A vs. B 6MWT (meters): 380.7 (117.8) vs. 377.4 (114.4), p=NR (baseline) 389.3 (120.4) vs. 386.0 (110.7); MD 0.1 (95% CI –20.6 to 20.9), p>0.05 (postintervention) 387.7 (121.9) vs. 395.1 (123.9); MD –12.3 (95% CI –34.8 to 10.2), p>0.05 (12 weeks) GMFM-66-D (0-100, higher=increased motor function): 81.4 (13.0) vs. 78.9 (12.5), p=NR (baseline) 80.8 (13.1) vs. 80.2 (9.7); MD –1.3 (95% CI –4.9 to 2.4), p>0.05 (postintervention) 83.7 (12.6) vs. 78.7 (13.7); MD 2.5 (95% CI –1.8 to 6.9), p>0.05 (12 weeks) GMFM-66-E (0-100, higher=increased motor function): 70.2 (22.6) vs. 66.6 (20.7), p=NR (baseline) 72.1 (21.7) vs. 67.9 (20.6); MD 0.9 (95% CI –3.0 to 4.7), p>0.05 (postintervention) 71.9 (23.4) vs. 66.3 (20.2); MD 1.0 (95% CI –2.6 to 4.5), p>0.05 (12 weeks) Gait Profile Score (°): 9.9 (2.6) vs. 10.6 (3.0) (baseline) 10.2 (3.0) vs. 10.7 (3.1); MD 0.2 (95% CI –0.6 to 0.9), p>0.05 (postintervention) 10.0 (2.9) vs. 10.5 (3.0); MD 0.2 (95% CI –0.8 to 1.2), p>0.05 (12 weeks) Timed Stair Test (seconds): 21.1 (28.9) vs. 13.8 (11.7) (baseline) 19.2 (28.5) vs. 13.3 (10.1), MD –0.9 (95% CI –4.7 to 2.9) (postintervention) 17.9 (23.2) vs. 12.6 (9.1), MD –0.6 (95% CI –4.2 to 3.0) (12 weeks)	Data reported as mean (SD) A vs. B Max leg press (1RM; kg): 84.7 (34.9) vs. 78.4 (31.7), p=NR (baseline) 99.5 (37.4) vs. 79.1 (31.2); MD 14.8 (95% CI 4.3 to 25.3), p<0.05 (postintervention) 97.7 (41.1) vs. 83.0 (29.7); MD 10.0 (95% CI –3.6 to 23.6), p>0.05 (12 weeks) Reverse leg press (1RM; kg): 14.8 (10.7) vs. 14.2 (10.4), p=NR (baseline) 12.8 (10.4) vs. 14.2 (11.2); MD –0.7 (95% CI –4.3 to 2.8), p>0.05 (postintervention) 12.4 (11.2) vs. 10.3 (10.8); MD 1.6 (95% CI –2.3 to 5.6), p>0.05 (12 weeks)

Author, Year **Intervention Type** **Duration of Postintervention Followup** **Quality** **(See Appendix B for Full Citation)**	**Intervention and Comparison**	**Population** **Age (Mean)** **Gender (% Female)** **Race (%)** **Ambulatory (%)** **Wheelchair User (%)** **Condition Specific (%)** **Other (%)**	**Prioritized Outcomes**	**Other Outcomes**
Tedla, 2014 **Strength interventions** Muscle Strength Exercises Immediately postintervention, 6 weeks Poor	A. Strength training 18 sessions over 6 weeks + conventional PT 1-2 days/week (n=31) B. Conventional physical therapy 3-5 sessions/per for 6 weeks (n=31)	A vs. B (data are for completers only; n=30 vs. 30) Age: 9.1 vs. 8.9 years Female: 33% vs. 33% Gross motor function classification system: I: 7% vs. 3% II: 20% vs. 27% III: 37% vs. 27% IV: 37% vs. 43%	A vs. B, Mean change from baseline (SD): PBS total score 7.23 (3.350) vs. 1.87 (1.074), p<0.001 GMFM-total score 9.9 (NR) vs. 2.2 (NR), p=NR	Change in Strength of Trunk, Hip, Knee, Ankle: significantly better in group A than B, p<0.05

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Teixeira-Machado, 2017 **Aerobic Exercise** Aerobics (Dance) Postintervention, 12 weeks Fair	A. Dance (somatic dance therapy): 24 sessions, over 12 weeks, (n=13) B. Usual care control (n=13)	A vs. B Age (mean years): 18 vs. 17 Female: 54% vs. 62 % Race: NR Ambulatory: NR Wheelchair user: NR BMI (cm/Kg^2): GMFCS Level II: 6 vs. 3 Level III: 3 vs. 5 Level IV: 3 vs. 4 Level V: 1 vs. 1	A vs. B, mean (SD) FIM 3.68 (0.50) vs. 3.61 (0.38) (baseline) 5.38 (0.50) vs. 3.64 (0.38) (postintervention) Total scores post intervention, p=0.0006 FIM - Self care 3.17 (0.48) vs. 3.21 (0.49) (baseline) 4.50 (0.59) vs. 3.28 (0.50) (postintervention) FIM - Sphincter control 5.00 (0.78) vs. 4.84 (0.77) 4.84 (0.77) (baseline) 5.30 (0.66) vs. (postintervention) FIM - Mobility 3.25 (0.44) vs. 3.23 (0.45) (baseline) 4.71 (0.67) vs. 3.30 (0.41) (postintervention) FIM - Locomotion 3.19 (0.42) vs. 3.07 (0.43) (baseline) 4.50 (0.55) vs. 3.11 (0.41) (postintervention) FIM - Communication 4.76 (0.66) vs. 4.61 (0.58) (baseline) 5.57 (0.46) vs. 2.69 (0.41) (postintervention) FIM - Psychosocial adjustments 2.71 (0.46) vs. 2.69 (0.41) (baseline) 5.38 (0.50) vs. 2.69 (0.41) (postintervention) FIM - Cognitive function 2.71 (0.46) vs. 2.69 (0.41) (baseline) 5.38 (0.50) vs. 2.69 (0.41) (postintervention) WHODAS-IFC, overall scores 84.56 (4.62) vs. 84.45 (4.05) (baseline) 39.90 (5.80) vs. 69.55 (4.39) (postintervention) Overall scores, p=0.0002	NA

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Tollar, 2020 **Aerobic Exercise** Cycling **Postural Control** Balance Exercises Motion Gaming **Strength** proprioceptive neuromuscular facilitation (PNF) Immediately postintervention,5 weeks Fair	A. Exergaming: Xbox 360, Adventure video game, 25 sessions over 5 weeks (n=14) Sensorimotor and visuomotor agility training using each of the three modules of the Xbox 360 core system (n=14) B. Balance exercises: dynamic and static balance and stepping exercises performed in multiple directions (n=14) C. Cycling (n=14) D. Proprioceptive neuromuscular facilitation (n=14) E. Usual care: continuation of standard physical therapy and habitual activity (n=12) All interventions consisted of 25, 1 hour sessions over 5 weeks	Age: 48 vs. 47 vs. 48 vs. 47 vs. 44 Female: 86% vs. 86% vs. 93% vs. 93% vs. 92% Race: NR Ambulatory: 100% vs. 100% vs. 100% vs. 100% vs. 100% Wheelchair user: NR RRMS: 50% vs. 64% vs. 64% vs. 64% vs. 66% PPMS: 50% vs. 36% vs. 36% vs. 36% 34% Median EDSS score: 5.0 vs. 5.0 vs. 5.0 vs. 5.0 vs. 5.0	A vs. B, mean difference between groups: MSIS-29: -10.8 (6.09) vs. 1.0 (3.46), p<0.001 6MWT: 57.4 (52.09) vs. 6.3 (49.27), p=0.017 BBS: 6.1 (3.52) vs. -0.2 (2.62), p<0.001 EQ-5 Sum score:-2.3 (1.44) vs. 0.0 (1.13), p<0.001 Data are reported as Mean (SD) [MDs calculated by EPC] A vs. E MSIS-29 109.1 (8.60) vs. 109.8 (10.67) (baseline) -10.8 (6.09) vs. 1.0 (3.46), MD -11.8 (95% CI -15.9 to -7.7) (pre-post change) EQ5D sum score 13.9 (2.18) vs. 13.3 (0.89) (baseline) -2.3 (1.44) vs. 0.0 (1.3), MD -2.3 (95% CI -3.4 to -1.2) (pre-post change) BDI 12.6 (3.23) vs. 14.3 (3.22) (baseline) -0.2 (2.67) vs. -0.4 (2.94), MD 0.20 (95% CI -2.1 to 2.5) (pre-post change) BBS 21.7 (3.56) vs. 22.5 (4.38) (baseline) 6.1 (3.52) vs. -0.2 (2.62), MD 6.3 (95% CI 3.8 to 8.8) (pre-post change) 6MWT (meters) 235.8 (35.48) vs. 243.3 (39.56) (baseline) 57.4 (52.09) vs. 6.3 (49.27), MD 51.1 (95% CI 9.8 to 92.4) (pre-post change)	A. Exergaming: sensorimotor and visuomotor agility training using each of the three modules of the Xbox 360 core system (n=14) B. Balance exercises: dynamic and static balance and stepping exercises performed in multiple directions (n=14) C. Cycling (n=14) D. Proprioceptive neuromuscular facilitation (n=14) E. Usual care: continuation of standard physical therapy and habitual activity (n=12) All interventions consisted of 25, 1 hour sessions over 5 weeks

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Tollar, 2020 **(Continued)**			B vs. E MSIS-29 106.0 (10.35) vs. 109.8 (10.67) (baseline) -6.3 (4.36) vs. 1.0 (3.46), MD -7.3 (95% CI -10.5 to-4.1) (pre-post change) EQ5D sum score 13.6 (0.93) vs. 13.3 (0.89) (baseline) -0.6 (1.15) vs. 0.0 (1.3), MD -0.6 (95% CI -1.6 to 0.40) (pre-post change) BDI 11.6 (2.56) vs. 14.3 (3.22) (baseline) 0.1 (1.86) vs. -0.4 (2.94), MD 0.5 (95% CI -1.4 to 2.5) (pre-post change) BBS 21.9 (2.32) vs. 22.5 (4.38) (baseline) 3.9 (2.25) vs. -0.2 (2.62), MD 4.1 (95% CI 2.1 to 6.1) (pre-post change) 6MWT (meters) 230.4 (30.03) vs. 243.3 (39.56) (baseline) 19.2 (35.4) vs. 6.3 (49.27), MD 12.9 (95% CI -21.5 to 47.3) (pre-post change) C vs. E MSIS-29 110.7 (9.76) vs. 109.8 (10.67) (baseline) -6.3 (8.07) vs. 1.0 (3.46), MD -7.3 (95% CI -12.5 to -2.1) (pre-post change) EQ5D sum score 13.4 (1.83) vs. 13.3 (0.89) (baseline) -1.4 (1.7) vs. 0.0 (1.3), MD -1.4 (95% CI -2.6 to -0.2) (pre-post change)	

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Tollar, 2020 **(Continued)**			BDI 13.6 (3.43) vs. 14.3 (3.22) (baseline) -1.0 (2.75) vs. -0.4 (2.94), MD -0.60 (95% CI -2.9 to 1.7) (pre-post change) BBS 20.7 (3.79) vs. 22.5 (4.38) (baseline) 2.5 (2.62) vs. -0.2 (2.62), MD 2.7 (95% CI 1.1 to 4.3) (pre-post change) 6MWT (meters) 245.7 (41.08) vs. 243.3 (39.56) (baseline) 32.1 (44.58) vs. 6.3 (49.27), MD 25.8 (95% CI -12.2 to 63.8) (pre-post change) D vs. E MSIS-29 109.8 (10.67) vs. 109.8 (10.67) (baseline) -1.9 (2.8) vs. 1.0 (3.46), MD -2.9 (95% CI -5.4 to -0.4) (pre-post change) EQ5D sum score 13.9 (1.44) vs. 13.3 (0.89) (baseline) -0.5 (1.16) vs. 0.0 (1.3), MD -0.5 (95% CI -1.5 to 0.5) (pre-post change) BDI 12.3 (2.55) vs. 14.3 (3.22) (baseline) -0.6 (1.87) vs. -0.4 (2.94), MD -0.2 (95%CI -2.2 to 1.8) (pre-post change) BBS 21.1 (1.51) vs. 22.5 (4.38) (baseline) 1.6 (3.52) vs. -0.2 (2.62), MD 1.8 (95% CI -0.7 to 4.3) (pre-post change) 6MWT (meters) 244.3 (52.98) vs. 243.3 (39.56) (baseline) 5.5 (34.64) vs. 6.3 (49.27), MD -0.8 (95% CI -34.9 to 33.3) (pre-post change)	

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Totosy de Zepetnek, 2015 **Multimodal Exercise** Immediately postintervention, 16 weeks Fair	A. Progressive resistance + aerobic training, 32 sessions over 16 weeks (n=12) B. Maintain existing physical activity levels (n=11)	A vs. B Age: 39 vs. 42 Female: 0% vs. 18% AIS A-B: 25% vs. 45% AIS C-D: 75% vs. 55%	A vs. B, Mean (SD), p-value between groups: Systolic blood pressure: 116 (18) to 116 (15) vs. 118 (18) to 116 (17), p>0.05 Diastolic blood pressure: 68 (9) to 67 (9) vs. 74 (13) to 72 (11), p>0.05 Heart rate: 75 (13) to 71 (13) vs. 75 (10) to 74 (10), p>0.05 HbA1c (mmol/mol): 35.7 (11.6) to 36.6 (11.2) vs. 34.9 (4.8) to 34.7 (3.9), p>0.05 BMI: 27.3 (5.2) to 27.0 (5.0) vs. 25.7 (4.9) to 26.6 (4.7), p<0.05	A vs. B, Mean (SD), p-value between groups: Total cholesterol (mmol/L): 1.5 (0.9) to 4.3 (1.0) vs. 4.1 (0.9) to 4.1 (0.9), p>0.05 Low-density lipoprotein cholesterol (mmol/L): 2.9 (0.9) to 2.7 (0.7) vs. 2.5 (0.7) to 2.4 (0.6), p>0.05 High density lipoprotein cholesterol (mmol/L): 1.01 (0.2) to 1.01 (0.3) vs. 1.13 (0.2) to 1.17 (0.3), p>0.05 Triglyceride: 1.3 (0.6) to 1.4 (0.6) vs. 1.1 (0.7) to 1.0 (0.7), p>0.05

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Valent, 2010 **Aerobic Exercise** Hand cycling Postintervention, 0 weeks Fair	A. Hand cycle ergometry, 15-72 sessions over 9-39 weeks (n=20) B. Active rehabilitation, sessions unclear (matched control) (n=17)	A vs. B Age (mean years): 46 vs. 40 Female: 4 (24%) vs. 4(24%) Race: NR Ambulatory: NR Wheelchair user: NR Other: Paraplegia: 10 (59%) vs. 11 (65%) Tetraplegia: 7(41%) vs. 6(35%)	A vs. B (SD) FVC%, PEF%, VO_2 Peak (ml/min), VO_2 Peak (ml/kg/min): all NS Elbow R Flexion 253(94) vs. 213(73) (baseline) 283(91) vs. 233(72); p=0.168 (postintervention)	Elbow L Flexion 255(76) vs. 235(75) (baseline) 300(84) vs. 233(65); p=0.0.010(postintervention) Shoulder R Exorotation 126(47) vs. 130(43) (baseline) 150(49) vs. 134(33); p=0.011 (postintervention) Shoulder L Exorotation 124(47) vs. 129(43) (baseline) 154(51) vs. 133(43); p=0.0.001 (postintervention) Shoulder R Endorotation 158(71) vs. 149(54) (baseline) 191(70) vs. 160(61); p=0.025(postintervention) Shoulder L Endorotation 165(62) vs. 158(61) (baseline) 195(62) vs. 163(67); p=0.0.026 (postintervention) Elbow R Flexion, Elbow R Extension, Elbow L Extension, Shoulder R Abduction, Shoulder L Abduction: All NS

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
van der Scheer 2016 **Aerobic Exercise** Treadmill 16 week intervention Postintervention, 0 weeks Fair	A. Low-intensity wheelchair training in a treadmill for 30 minutes 2 times a week for 16 weeks B. Usual care	Mean age 56.0 years 22 males and 7 females (76% males)	Peak oxygen uptake (median) A. 1.02 to 1.01 B. 1.09 to 1.07 No differences	NA

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Van Wely, 2014a Van Wely, 2014b Van Wely, 2010 **Multimodal Exercise** Mid-intervention (16 weeks into trial); Immediately postintervention, 24 weeks Van Wely, 2014a: Good Van Wely, 2014b: Fair	A. Strength + aerobics + physiotherapy + counseling: 24 sessions of fitness training over 16 weeks (n=25) B. Physiotherapy (n=25)	A vs. B Age (mean years): 9.5 vs. 10.0 Female: 13 (52%) vs. 8 (33%) Race: NR Ambulatory: 25 (100%) vs. 24 (100%) Wheelchair user for long distances: 5 (20%) vs. 5 (21%) GMFCS -I: 15 (60%) vs. 13 (54%) -II: 6 (24%) vs. 6 (25%) -III: 4 (16%) vs. 5 (21%) Laterality -Unilateral: 12 (48%) vs. 11 (46%) -Bilateral: 13 (52%) vs. 13 (54%) Orthoses (yes): 17 (68%) vs. 15 (62%)	Data reported as mean (SD) A vs. B GMFM-66 (0-100, higher=increased motor function): 77 (14) vs. 80 (14), p=NR (baseline) 79 (13) vs. 79 (14), p=NR (postintervention) 79 (14) vs. 82 (14), p=NR (24 weeks) 1.7 (4.5) vs. −1.4 (4.2); adj. MD 2.8 (95% CI 0.2 to 5.4), p=0.03 (post-pre change) 1.2 (4.4) vs. 2.0 (3.1); adj. MD −0.9 (95% CI −3.3 to 1.4), p>0.05 (24 weeks-pre change) 1 min walk test (meters): 86.0 (20.0) vs. 92.0 (20.0), p=NR (baseline) 92.0 (22.0) vs. 94.0 (20.0), p=NR (mid-intervention) 92.0 (25.0) vs. 96.0 (17.0), p=NR (postintervention) 91.0 (25.0) vs. 93.0 (19.0), p=NR (24 weeks) 6.0 (7.0) vs. 1.0 (9.0); adj. MD 5.0 (95% CI 0.0 to 9.0), p=0.06 (mid-pre change) 6.0 (11.0) vs. 3.0 (9.0); adj. MD 2.0 (95% CI −4.0 to 9.0), p>0.05 (post-pre change) 5.0 (11.0) vs. 2.0 (10.0); adj. MD 3.0 (−43.0 to 10.0), p>0.05 (24 weeks-pre change) Functional strength (repetitions) 43 (16) 42 (18) (baseline) 48 (18) 48 (22) (mid-intervention) 51 (20) 53 (21) (postintervention) 53 (18) 56 (22) (24-week followup) 4 (8) 4 (8), MD 0 (95% CI −5 to 5) (pre-mid change) 9 (10) 10 (9), MD 0 (95% CI −5 to 5) (pre-post change) 9 (8) 13 (9), MD −4 (95% CI −9 to 2) (prefollowup change)	NR

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Van Wely, 2014a Van Wely, 2014b Van Wely, 2010 **(Continued)**			CP-QOL Social well-being and acceptance (0-100, higher=increased QOL) 75.9 (8.4) vs. 75.4 (11.9) (baseline) 72.9 (9.6) vs. 75.5 (9.4) (24 weeks) NR vs. NR, MD –3.1 (95% CI –7.9 to 1.7), p=0.19 (prefollowup change) CP-QOL Functioning (0-100, higher=increased QOL) 71.1 (8.6) vs. 71.3 (11.4) (baseline) 72.9 (9.6) vs. 75.5 (9.4) (24 weeks) NR vs. NR, MD –2.5 (95% CI –7.3 to 2.3), p=0.30 (prefollowup change) CP-QOL Participation & Physical Health (0-100, higher=increased QOL) 65.5 (11.6) vs. 67.2 (16.5) (baseline) 68.9 (9.3) vs. 70.7 (14.0) (24 weeks) NR vs. NR, MD –0.8 (95% CI –5.7 to 4.1) p=0.75 (prefollowup change) CP-QOL Emotional well-being and self-esteem (0-100, higher=increased QOL) 77.7 (8.2) vs. 79.7 (15.1) (baseline) 78.2 (7.1) vs. 79.6 (12.7) (24 weeks) NR vs. NR, MD –0.3 (95% CI –5.3 to 4.7), p=0.90 (prefollowup change) CP-QOL pain and impact on disability (0-100, higher=more bothered by disability) 30.5 (16.8) vs. 32.9 (21.0) (baseline) 34.4 (16.4) vs. 28.4 (14.8) (24 weeks) NR vs. NR, MD 5.0 (95% CI –5.2 to 15.2), p-0.33 (prefollowup change)	

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Vermohlen, 2018 Protocol: Wollenweber, 2016 **Postural Control** Hippotherapy End of treatment (after 12-week intervention) Fair	A. Hippotherapy plus standard care, 12 sessions over 12 weeks (n=32) B. Control group (standard care), 12 weeks (n=38)	A (n=30) vs. B (n=37) Age (median years): 50 vs. 51 Female: 27 (90%) vs. 27 (73%) Race: NR Ambulatory: NR Wheelchair user: NR EDSS at inclusion (mean): 5.4 vs. 5.3 Weight (mean kg): 67 vs. 70.6 Median time from onset of MS to inclusion (IQR years): 16.5 vs. 17.6 Physiotherapy: 29 (97%) vs. 35 (95%)	A vs. B 12 weeks MSQoL-54: A (n=30) vs. B (n=36), mean (SD) Mental health subscale score: 62.6 (18.0) vs. 67.1 (17.2) (baseline) 75.7 (15.0) vs. 64.2 (19.9) (postintervention) Mean difference in change between groups at 12 weeks: 14.4 (95% CI 7.5 to 21.3), p<0.001 A (n=25) vs. B (n=31), mean (SD) Physical health subscale score: 46.0 (14.2) vs. 53.7 (14.6) (baseline) 57.0 (15.1) vs. 51.3 (15.9) (postintervention) Mean difference in change between groups at 12 weeks: 12.0 (95% CI 6.2 to 17.7), p<0.001 A (n=30) vs. B (n=36), mean (SD) NRS: 4.6 (2.1) vs. 4.4 (2.2) (baseline) 2.9 (2.1) vs. 3.8 (2.3) (postintervention) Mean difference in change between groups at 12 weeks: −0.9 (95% CI −1.9 to −0.1), p=0.031	A (n=30) vs. B (n=37), mean (SD) 12 weeks BBS: LOCF ANCOVA: 40.6 (11.5) vs. 42.1 (10.9) (baseline) 47.0 (8.7) vs. 45.1 (10.9) (postintervention) Mean difference in change between groups at 12 weeks: 2.33 (95% CI 0.03 to 4.63), p=0.047 MMRM: Mean difference in change between groups at 12 weeks: 3.07 (95% CI 1.00 to 5.14), p=0.004
Wallard, 2017 Wallard, 2018 **Aerobic Exercise** Robot-Assisted Gait Training Postintervention, 4 weeks Poor	A. RAGT, 20 sessions over 4 weeks (n=14) B. Usual care, 20 sessions over 4 weeks (n=16)	A vs. B Age (mean years): 8.3 vs. 9.6 Female: 6 (43%) vs. 9 (56%) Race: NR Ambulatory: NR Wheelchair user: NR	GMFM-66 D (%), mean (SD) 53.89 (16.02) to 60.68 (14.71) vs. 53.81 (14.67) to 55.74 (15.02), p=0.048 GMFM-66 E 42.23 (14.65) to 50.87 (15.82) vs. 42.51 (13.09) to 43.61 (12.59), p=0.026	A vs. B, mean (SD)

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Williams, 2020 **Multimodal** Immediately postintervention and 8 weeks Fair	A. Center-baesd group exercise (n=26) B. Home-based exercise (n=24) The exercise program for both groups included two, 60-minute sessions per week, held at least 2 days apart for 8 weeks.	Age: 53 vs. 51 Female: 65% vs. 88% Race: NR Abulatory: 100% vs. 100% Wheelchair user: NR Aid use None: 27% vs. 58% Unilateral: 42% vs. 29% Bilateral: 31% vs. 13% Type of MS RRMS: 58% vs. 67% PPMS: 19% vs. 8% SPMS: 15% vs. 8% Benign: 4% vs. 8% Unknown/NR: 4% vs. 8%	A vs. B, Mean (SD) [baseline to 8-week followup change scores and MDs calculated by EPC] 10MWT (m/s) All patients 0.83 (0.5) vs. 1.1 (0.4) (baseline) 0.95 (0.5) vs. 1.25 (0.5) (immediately postintervention) 0.11 (0.6) vs. 0.11 (0.6), MD 0.01 (95% CI −0.36 to 0.37) (pre-post change) 0.86 (0.4) vs. 1.2 (0.4) (8 weeks postintervention) 0.03 (0.30) vs. 0.10 (5.23), MD -0.07 (95% CI -0.22 to 0.08) (pre-8 week postintervention change) Low disability patients (Disease Step Rating Scale 0-2) 1.37 (0.38) vs. 1.37 (0.32) (baseline) 1.28 (0.33) vs. 1.52 (0.46) (immediately postintervention) −0.1 (1.04) vs. 0.15 (0.63), MD 0.24 (95% CI −0.61 to 1.08) (pre-post change) 1.22 (0.06) vs. 1.41 (0.37) (8 weeks postintervention) -0.15 (0.33) vs. 0.04 (0.22), MD -0.19 (95% CI -0.41 to 0.03) (pre-8 week postintervention change) High disability patients (Disease Step Rating Scale 3-5) 0.71 (0.39) vs. 0.81 (0.28) (baseline) 0.86 (0.46) vs. 0.89 (0.36) (immediately postintervention) 0.16 (0.59) vs. 0.07 (0.85) MD 0.8 (95% CI −0.47 to 0.64) (pre-post change) 0.76 (0.41) vs. 0.92 (0.33) (8 weeks postintervention) 0.05 (0.25) vs. 0.11 (0.20), MD -0.06 (95% CI -0.24 to 0.12) (pre-8 week postintervention change) 6MWT (meters) 216.4 (128.4) vs. 301.3 (108.4) (baseline) 248.7 (125.3) vs. 312.3 (121.9) (immediately postintervention) 31.2 (163.2) vs. 12.5 (166.6), MD 18.67 (95% CI −78.22 to 115.56) (pre-post change) 236.3 (115.2) vs. 300.7 (119.4) (8 weeks postintervention) 19.9 (78.04) vs. -0.60 (72.79), MD -20.5 (95% CI -60.21 to 19.21) (pre-8 week postintervention change)	NA

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Williams, 2020 **(Continued)**			Low disability patients (Disease Step Rating Scale 0-2) 372.5 (61.5) vs. 359.36 (85.6) (baseline) 378 (63.3) vs. 382.4 (103) (immediately postintervention) 5.5 (248.8) vs. 23.1 (151.5), MD 17.6 (95% CI −184.2 to 219.26) (pre-post change) 352 (67.2) vs. 367 (97.4) (8 weeks postintervention) -20.5 (41.06) vs. 7.64 (58.94), MD 28.14 (95% CI -8.26 to 64.54) (pre-8 week postintervention change) High disability patients (Disease Step Rating Scale 3-5) 178.6 (102.1) vs. 216.5 (84.6) (baseline) 214.5 (111.5) vs. 221.2 (93.7) (immediately postintervention) 35.9 (151.7) vs. 4.7 (211.80), MD 31.17 (95% CI −108.37 to 170.72) (pre-post change score) 204.1 (105.2) vs. 212.2 (85.1) (8 weeks postintervention) 25.5 (65.6) vs. -4.3 (53.7), MD -29.8 (95% CI -77.21 to 17.61) (pre-8 week postintervention change) BBS 42 (16.7) vs. 50.9 (6) (baseline) 43.5 (14.9) vs. 50.7 (7.9) (immediately postintervention) 1.5 (17.02) vs. −0.18 (17.37), MD 1.70 (95% CI −8.4 to 11.80) (pre-post change) 44 (15.4) vs. 51 (6.9) (8 weeks postintervention) 2.0 (10.23) vs. 0.1 (4.17), MD -1.9 (-6.44 to 2.64) (pre-8 week postintervention change) Low disability patients (Disease Step Rating Scale 0-2) 53.8 (0.8) vs. 53.3 (3.6) (baseline) 54.2 (1.9) vs. 53.8 (3.5) (immediately postintervention) 0.4 (9.7) vs. 0.56 (5.9), MD 0.2 (95% CI −7.69 to 8.01) (pre-post change) 54 (1.9) vs. 53.5 (3.9) (8 weeks postintervention) 0.20 (1.35) vs. 0.20 (2.39), MD 0.0 (-1.37 to 1.37) (pre-8 week postintervention change)	

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Williams, 2020 **(Continued)**			High disability patients (Disease Step Rating Scale 3-5) 39.1 (17.5) vs. 47.6 (7.3) (baseline) 40.7 (15.5) vs. 46.7 (10.2) (immediately postintervention) 1.6 (22.3) vs. −0.9 (31.2), MD 2.54 (95% CI −18.01 to 23.08) (pre-post change) 41.2 (16.4) vs. 47.7 (8.7) (8 weeks postintervention) 2.10 (10.77) vs. 0.10 (5.23), MD -2.0 (95% CI -9.31 to 5.31) (pre-8 week postintervention change)	
Wens, 2015a "Impact of 24 weeks of resistance and endurance exercise on glucose tolerance in persons with multiple sclerosis" **Multimodal Exercise** Postintervention, 0 weeks Poor	A. Progressive resistance + aerobics, 60 sessions over 24 weeks (n=29) B. Nonexercise control (n=15)	A vs. B Age (mean years): 48 vs. 49 Female: 17 (59%) vs. 8 (53%) Race: NR Ambulatory: NR Wheelchair user: NR MS type: RRMS: 17 (59%) vs. 11 (73%) CPMS: 12 (41%) vs. 4 (27%) EDSS (mean): 3.25 vs. 3.36	A vs. B, Mean difference between groups: 24 weeks (end of treatment) Body weight (kg): 1.9, 95% CI -0.124 to 0.07 No differences in glucose and insulin	A vs. B, Mean difference between groups: 24 weeks (end of treatment) Resting HR: 9.0, 95% CI 6.57 to 11.43, $p<0.001$ Body fat %: 2.0, 95% CI 0.67 to 3.33, p=0.003 Knee extension and flexion improved with exercise. Group X Time interaction $p<0.05$

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Wens, 2015b **Multimodal Exercise** Postintervention, 0 weeks Fair	A. Resistance Training + High Intensity Interval Training (n=12) B. Resistance Training + High intensity continuous cardiovascular training (n=11) C. No intervention - "sedentary control" (n=11) [30 sessions over 12 weeks for both groups]	A vs. B vs. C Age (mean years): 43 vs. 47 vs. 47 Female: 5 (42%) vs. 5 (45%) vs. 9 (82%) Race: NR Ambulatory: NR Wheelchair user: NR EDSS (mean score): 2.3 vs. 2.7 vs. 2.5	Data reported as mean (SD) A vs. C VO_2 Max (ml/min) 2031 (186) vs. 1647 (133) (baseline) 2379 (197) vs. 1645 (160) (postintervention) 17.8% (4.6%) vs. 2.5% (4.1%), p<0.01 (pre-post % change) VO_2 Max (ml/min/kg) 26.6 (2.2) vs. 21.9 (1.8) (baseline) 30.7 (2.1) vs. 23.6 (2.1) (postintervention) 17.8% (4.6%) vs. 2.5% (4.1%), p<0.01 (pre-post % change) B vs. C VO_2 Max (ml/min) 1870 (238) vs. 1647 (133) (baseline) 1969 (230) vs. 1645 (160) (postintervention) 7.5% (5.8%) vs. 2.5% (4.1%), p<0.01 (pre-post % change) VO_2 Max (ml/min/kg) 26.3 (3.1) vs. 21.9 (1.8) (baseline) 28.2 (3.0) vs. 23.6 (2.1) (postintervention) 7.5% (5.8%) vs. 2.5% (4.1%), p<0.01 (pre-post % change)	Data reported as mean (SD) A vs. C Resting HR (BPM): 75 (3) vs. 75 (4) (baseline) 84 (3) vs. 87 (4) (postintervention) 12.5% (4.6%) vs. 14.3% (3.8%), p>0.05 (pre-post % change) % body fat: 36.2% (1.9%) vs. 38.2% (2.1%) (baseline) 34.3% (2.0%) vs. 37.3% (2.2%) (postintervention) −3.9% (2.0%) vs. −2.8% (1.6%), p>0.05 (pre-post % change) B vs. C Resting HR (BPM): 76 (3) vs. 75 (4) (baseline) 80 (4) vs. 87 (4) (postintervention) 7.0% (5.8%) vs. 14.3% (3.8%), p>0.05 (pre-post % change) % body fat 33.6% (2.8%) vs. 38.2% (2.1%) (baseline) 32.6% (2.8%) vs. 37.3% (2.2%) (postintervention) −2.5% (1.2%) vs. −2.8% (1.6%) (pre-post % change)

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Willoughby, 2010 **Aerobic Exercise** Treadmill RCT Postintervention, 10 weeks after intervention Fair	A. Partial body weight supported treadmill training 30 minutes 2 times a week for 9 weeks B. Overground walking with walker or assist device comparable duration and number of sessions	GMFCD III or IV n=33 randomized and 26 analyzed Mean age 10.8 years 15 males and 11 females (54% males)	Pre, post, 10 weeks after training 10 minute walk test (10MWT) (walking endurance) (meters) A. 244.33 (115.41) to 218.38 (123.71) to 215.67 (142.99) B. 118.36 (89.89) to 135.82 (95.65) to 148.43 (103.52) Pre to post trend for between groups F=3.004 p=0.097 favoring B Pre to 24 week trend for between groups F=2.992 p=0.098 favoring B	NA
Wu, 2017a "Robotic resistance treadmill training improves locomotor function in children with cerebral palsy: a randomized controlled pilot study" **Aerobic Exercise** Robot-Assisted Gait Training Postintervention,8 weeks (after 6-week intervention) Fair	A. Robotic resistance treadmill training, 18 sessions over 6 weeks (n=12) B. Robotic assistance treadmill training, 18 sessions over 6 weeks (n=11)	A vs. B Age (mean years): 10.6 vs. 10.8 Female: 6 (50%) vs. 6 (55%) Race: -week followupwhite: 6 (50%) vs. 6 (55%) Ambulatory: NR Wheelchair user: NR Other: GMFCS I: 1 (8%) vs. 0 (0%) GMFCS II: 5 (42%) vs. 5 (45%) GMFCS III: 5 (42%) vs. 4 (36%) GMFCS IV: 1 (8%) vs. 2 (5%)	A vs. B, pre to post followup mean (SD), p-value 10MWT (m/s) Fast: 0.98 (0.39) to 1.13 (0.38) to 1.09 (0.35), p=0.01 vs. 0.84 (0.34) to 0.84 (0.37) to 0.77 (0.36), p=0.19 Self-selected: 0.63 (0.30) to 0.72 (0.24) to 0.71 (0.22), p=0.22 vs. 0.54 (0.22) to 0.52 (0.18) to 0.50 (0.19), p=0.61 6MWT (m) 272.7 (113.0) to 336.3 (104.9) to 353.9 (125.8), p=0.001 vs. 216.3 (116.8) to 230.1 (119.2) to 224.7 (118.7), p=0.63 GMFM-66 63.7 (8.7) to 63.4 (8.2) to 64.9 (9.4), p=0.02 vs. 60.0 (9.2) to 59.8 (9.6) to 60.3 (9.4), p=0.69 PODCI, self 23.0 (17.2) to 23.0 (18.0) to 24.5 (12.2), p=0.84 vs. 23.0 (23.6) to 19.5 (12.1) to 24.0 (16.0), p=0.74 PODCI, parent 7.5 (16.2) to 19.1 (15.5) to 19.0 (16.8), p=0.002 vs. 7.9 (22.8) to 9.8 (16.4) to 3.9 (24.5), p=0.83	NR

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Wu, 2017b "The effects of the integration of dynamic weight shifting training into treadmill training on walking function of children with cerebral palsy– a randomized controlled study" **Aerobic Exercise** Robot-Assisted Gait Training Postintervention,8 weeks (after 6 weeks intervention) Fair	A. Robotic treadmill training, 18 sessions over 6 weeks (n=11) B. Treadmill only training, 18 sessions over 6 weeks (n=12)	A vs. B Age (mean years): 11.3 vs. 10.5 Female: 5 (45%) vs. 4 (33%) Race: -week followup white: 6 (55%) vs. 7 (58%) Ambulatory: 100% Wheelchair user: NR Other: GMFCS I: 1 (9%) vs. 2 (17%) GMFCS II: 6 (55%) vs. 3 (25%) GMFCS III: 3 (27%) vs. 5 (42%) GMFCS IV: 1 (9%) vs. 2 (17%)	A vs. B, pre to post to followup mean (SD), p-value GMFM-66B 64.0 (8.3) to 64.7 (9.2) to 64.7 (9.4), p=0.57 vs. 62.6 (10.7) to 64.5 (11.1) to 63.8 (10.5), p=0.08 PODCI self 10.0 (14.6) to -1.0 (24.8) to 16.0 (17.45), p=0.52 vs. 23.0 (23.6) to 19.5 (12.1) to 24.0 (16.0), p=0.73 PODCI parent 12.9 (16.2) to 19.4 (12.9) to 17.2 (16.0), p= 0.17 vs. 17.2 (17.6) to 18.2 (19.4) to 21.4 (21.2), p=0.34 MAS 0.62 (0.46) to 0.67 (0.60) to 0.41 (0.38), p=0.18 vs. 0.65 (0.36) to 0.48 (0.47) to 0.58 (0.44), p=0.19	NA

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Yang 2013 **Aerobic Exercise** Treadmill Pre to post, crossover with 2 months rest between 8 week intervention Fair	A. Walking on a track while stepping over individualized series of obstacles and on targets (precision training) one hour a day for 5 days a week for 8 weeks B. Walking on a treadmill with body weight support if needed (used by 5 of 10 participants) at faster than their overground walking speed for one hour a day for 5 days a week for 8 weeks Crossover trial with 2 months rest between	Spinal cord injury n=22 randomized and 20 analyzed Mean age 46 years 14 males and 6 females (70% males)	Pre to post change scores 6 minute walk test (meters) (change scores) A. 10 B. 29 Both groups achieved significant improvement p<0.05 Improvement significantly greater with treadmill training p=0.045 10 meter walk test (meters/second) A. 0.025 B. 0.070 Both groups achieved significant improvement p<0.05 No difference between groups Spinal Cord Injury Functional Ambulatory Profile (measures walking skills in daily life) A. -42 B. -75 Both groups achieved significant improvement p<0.05 No difference between groups	CES-D (change scores) A=-2.5 B=-2.3 Both groups achieved significant improvement p<0.05 No difference between groups
Yazgan 2020 **Postural Control** Motion Gaming Postintervention, 0 weeks Fair	A. Nintendo Wii Fit, 16 sessions over 8 weeks (n=15) B. Balance Trainer motion gaming, 16 sessions over 8 weeks (n=12) C. Waitlist control (n=15)	A vs. B vs. C Age: 47.5 vs. 43.1 vs. 40.7 Female: 86.7% vs. 100% vs. 86.7% EDSS: 4.16 vs. 3.83 vs. 4.06 RRMS: 73.3% vs. 66.7% vs. 93.3%	A vs. C, Mean change scores: BBS: 5.8 vs. 0.93, p<0.05 TUG: -1.54 vs; 0.05, p<0.05 6MWT: 42.71 vs. 7.59 p<0.05 MusiQoL: 12.61 vs. -0.19, p<0.05 B vs. C, Mean change scores: BBS: 2.66 vs. 0.93, p<0.05 TUG: -0.64 vs; 0.05, p<0.05 6MWT: 23.25 vs. 7.59 p>0.05 MusiQoL: 5.32 vs. -0.19, p<0.05 A vs. C, Mean change scores: p<0.05 in favor of group A for BBS and MusiQoL	NA

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Yazici, 2019 **Aerobic Exercise** Robot-Assisted Gait Training Immediately postintervention, 12 weeks Poor	A. Robot-assisted gate (RAGT), 36 sessions over 12 weeks (n=12) B. Physiotherapy assumed, 36 sessions over 12 weeks assumed (n=12)	A vs. B Age: 8.8 vs. 9.5 Female: 50% vs. 50% GMFCS I or II: 100%	A vs. B, Mean or Median (SD), MD calculated as if all are means, p=between groups 6MWT: 409.58 (49.1) to 475.17 (47.7) vs. 437.00 (55.0) to 459.17 (53.75); MD 43.42, 95% CI 19.64 to 67.21, p<0.001 GMFM-88: 253.00 (8.81) to 256.17 (8.23) vs. 253.67 (7.70) to 255.25 (7.94), MD 1.59, 95% CI -2.19 to 5.37, p=0.410 GMFM-88D: 36.08 (2.27) to 36.92 (1.73) vs. 36.75 (2.22) to 37.42 (1.98), MD 0.17, 95% CI -0.79 to 1.13, p=0.729 GMFM-88E: 6 4.00 (6.90) to 66.25 (6.78) vs. 64.08 (6.43) to 64.92 (6.72), MD 1.14, 95% CI -1.69 to 4.51, p=0.373	BBS: 50.08 (2.43) to 52.08 (2.68) vs. 50.25 (2.93) to 51.00 (3.30), MD 1.25, 95% CI -0.07 to 2.57, p=0.064
Yildirim, 2019 **Aerobic Exercise** Robot-Assisted Gait Training Immediately postintervention, 8 weeks Fair	A. Robot-assisted gate (RAGT), 16 sessions over 8 weeks + conventional therapy (n=44) B. Conventional therapy (n=44)	A vs. B Age: 32 vs. 37 Female: 39% vs. 36% Tetraplegia: 20% vs. 16% ASIA Complete: 48% vs. 41%	A vs. B, Median (Interquartile range), p-value=between groups: Functional Independence Measure (FIM): 69 (31) to 85 (35) vs. 67 (36) to 77 (24), p=0.022 Walking Index for Spinal Cord Injury (WISCI II): 5 (9) to 9 (7) vs. 5 (6.7) to 6.5 (5), p=0.011	NA

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Intervention and Comparison	Population Age (Mean) Gender (% Female) Race (%) Ambulatory (%) Wheelchair User (%) Condition Specific (%) Other (%)	Prioritized Outcomes	Other Outcomes
Young, 2019 **Aerobic Exercise** Aerobics Postintervention, 0 weeks Fair	A. Movement to Music 36 sessions over 12 weeks (27) B. Adapted Yoga (26) C. Waitlist control (28)	A vs. B vs. C Age: 50 vs. 48 vs. 47 Female: 81% vs. 77% vs. 86% White: 44 vs. 58% vs. 61% Patient Determined Disease Steps (PDDS): PDDS 0: 30% vs. 46% vs. 21% PDDS 3: 15% vs. 8% vs. 14% PDDS 6: 11% vs. 4% vs. 11%	A vs. B vs. C TUG A vs. C: -1.89, 95% CI -3.30 to -0.48, p=0.01 TUG B vs. C: -1.20, 95% CI -2.58 to 0.18, p=0.09 TUG B vs. A: 0.69, 95% CI -0.71 to 2.08, p=0.33 6MWT A vs. C: 40.98, 95% CI 2.21 to 79.75 6MWT B vs. C: 22.83, 95% CI -16.67 to 6.2, p=0.25 6MWT B vs. A: -18.15, 95% CI -56.36 to 20.05 5xSit-to-Stand A vs. C: -1.00, 95% CI -2.58 to 0.55, p=0.20 5xSit-to-Stand B vs. C: -0.70, 95% CI -2.17 to 0.77, p=0.34 5xSit-to-Stand B vs. A: 0.30, 95% -1.21 to 1.82, p=0.69	NA
Zoccolillo, 2015 **Postural Control** Motion gaming Postintervention, 8 weeks Poor	A. X-box with Kinect (3D motion capture) gaming plus neuro-developmental treatment, 16 sessions over 8 weeks (n=15) B.Neurodevelopmental treatment, 16 sessions over 8 weeks (n=16)	A and B (combined) Age (mean years): 6.89 Female: NR Race: NR Ambulatory: NR Wheelchair user: NR GMFM88=84.6±19.8%	NA	A. vs. B., mean (SD) QUEST (Quality of Upper Extremities Skills Test) A. 76 (21) (baseline) 81 (20), p=0.003 (postintervention) B. NR (baseline) (postintervention) NR, p=0.056

Abbreviations: BMD = bone mineral density; BMI = body mass index; CAB = Chronic Asymptomatic Bacturia; CHART = Craig Handicap and Assessment Reporting Technique; CP = cerebral palsy; EDSS = Expanded Disability Status Scale; FAC = functional ambulation category; FES-I = Falls Efficacy Scale International; FIM=Functional Independence Measure; FSS = Fatigue Severity Scale; FSST = Four Square Step Test; GNDS = Guy's Neurologic Disability Scale; GMFCS = Gross Motor Function Classification System; HADS-A = Hospital Anxiety Depression Scale-Anxiety; HADS-D=Hospital Anxiety Depression Scale-Depression; HRSD = Hamilton Depression Rating Scale; MAS = Modified Ashworth Scale; MCS = Mental Component Summary; MS = multiple sclerosis; MSIS = Multiple Sclerosis Impact Scale; MMT = Maximal Muscle Testing combined upper and lower limb strength; MusiQoL = MS international Quality of Life; NA = not applicable; NR = not reported; PCS = General Health Perception; SAWS = Satisfaction with Abilities and Well-Being Scale; SD = standard deviation; SCI = spinal cord injury; SCIM = Spinal Cord Independence Measure; WHODAS IFC=The International Classification of Functioning, Disability and Health

See Appendix B. Included Studies for full study citation.

Table F-2. Harms and study characteristics (continuation of Table F-1 results by study)

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
Acar, 2016 **Postural Control** Motion gaming Postintervention, 6 weeks Poor	NR	Cerebral palsy	Children with spastic hemiparesis, 6 and 15 years old, 1–3 Manual Ability Classification System, level 1or 2 of the GMFCS and ability to grasp and release an object.	Randomized:30 Analyzed:3 0 Attrition: 0% (0/30)	Turkey Outpatient clinic RCT	NR
Abbasi, 2019 **Postural Control** Whole body vibration Immediately postintervention, 6 weeks Fair	NR	Multiple sclerosis	Inclusion Criteria: 20-50 years old with MS, ambulatory, EDSS 1-4.5 with no relapse in the past 2 months	Randomized: 50 Analyzed:46 Attrition: 8.7% (4/46)	Iran Rehabilitation Clinic RCT	NR
Adar, 2017 **Aerobic Exercise** Aquatics Postintervention, 0 weeks Fair	NR	Cerebral palsy	Inclusion Criteria: Diagnosis of CP, Age 4-18 years. Grade >1 in lower extremities according to MAS, being able to being medically able to participate in an exercise program (no severe medical illness other than CP), being able to follow directions, and adherence to the exercise program.	Randomized: N=32 Analyzed: 32 Attrition: 0% (0/32)	Turkey Outpatient clinic RCT	None

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
Afrasiabifar, 2018 **Postural Control** Balance Postintervention, 12 weeks Good	No adverse events reported Cawthorne-Cooksey Group: Lost to followup after 8 weeks (n=1) -Unable to participate regularly (n=1) Frankel Group: Lost to followup after 8 weeks (n=2) -Unable to participate regularly (n=1) -Disease relapses (n=1)	Multiple sclerosis	Patients with confirmed MS for 6 months, in remission, aged 15 to 55 years, ability to stand for 30 seconds and to walk a distance of 6 meters without any assistance, and BBS score of 21–40.	Randomized: 75 Analyzed: 72 Attrition: 4% (3/75)	Iran Outpatient clinic RCT	University This work was supported by a Master thesis grant from the Deputy of Research and Technology of Yasuj University of Medical Sciences, Iran
Ahmadi, 2013 **Aerobic Exercise** Treadmill **Postural Control** Yoga Immediately postintervention, 8 weeks Fair	None	Multiple sclerosis	Inclusion Criteria: Women aged 19 to 54 with EDSS score 1-4	Randomized: 31 Analyzed: 31 Attrition: NR	Iran Outpatient clinic RCT	NR
Ahmadizadeh, 2020 **Postural Control** Whole Body Vibration Postintervention, 6 weeks Fair	NR	Cerebral Palsy	Children with CP, up to 12 years old; able to walk without falling or without walking aids, ability to follow orders and to be at the level of 1, 2 and 3 GMFCS	Randomized: 20 Analyzed: 20 Attrition: 0% (0/20)	Iran Outpatient rehabilitation RCT	Neuromuscular Rehabilitation Research Center of Semnan University of Medical Sciences

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
Akkurt, 2017 **Aerobic Exercise** Hand cycling Postintervention, 0 weeks Fair	NR	Spinal cord injury	Participants were included if: 1) they were aged between 15 and 65 years; 2) all lesions were traumatic; 3) lesion levels were C7-L5; 4) they were at least 1 month postinjury; 5) they were physically active in training and outdoor mobility less than two hours a week; 6) they received medical approval for participation in physical activity; 7) they had the ability to read and write the Turkish language.	Randomized: N=40 Analyzed:33 Attrition: 18% (7/40)	Turkey Outpatient clinic RCT	NR
Alexeeva 2011 **Aerobic Exercise** Treadmill Pre to post Fair	2 experienced an increase in spasticity with slower walking times after training	Spinal cord injury	Injury at T10 or below 17-60 years old Able to rise from sitting with minimal assistance and independently advance at least one leg	Randomized 40 Analyzed 35 Attrition 5/35=12.5% (13 w intervention)	USA (author), states recruited nationally to internationally but does not provide details Coordinated at large spinal cord injury rehabilitation hospital RCT	Government funding
Al-Sharman, 2019 **Aerobic Exercise** Aerobics Postintervention, 6 weeks Poor	N=1 patient broke a leg.	Multiple sclerosis	Multiple sclerosis patients attending neurology clinics with EDSS 3-5.5>5	Randomized: 40 Analyzed: 30 Attrition: 25% (10/40)	Jordan Neurological hospital clinic RCT	NR

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
Amiri, 2019 **Postural Control** Balance exercises **Strength interventions** Muscle Strength Exercises Postintervention,10 weeks Fair	NR	Multiple sclerosis	Inclusion Criteria: Women with relapse MS, subgroup scores of EDSS 2.5 to 5.5	Randomized: 69 (in abstract (72, Figure 1) Analyzed: 69 Attrition: 4% (3/69)	Iran Outpatient clinic for sports injury RCT	NR
Aras, 2019 **Aerobic Exercise** Robot-Assisted Gait Training Postintervention, 4 weeks, and 6 month followup Fair	None reported	Cerebral Palsy	Children with CP, 6 to 14 years; Level II-III GMFCS and able to ambulate at least 10 meters with or without an assistive device	Randomized: 30 Analyzed: 29 Attrition: 3% (1/30)	Turkey Outpatient rehabilitation RCT	No funding received
Arntzen, 2019 Arntzen, 2020 **Postural Control** Balance exercises Postintervention, 7 weeks, plus 18 and 30 weeks Good	None	Multiple sclerosis	Diagnosis of MS; Patients with expanded disability scores of 1 to 6.5	Randomized: 80 Analyzed: 80 Attrition: 0% (80/80) post intervention	Norway Setting Outpatient clinic RCT	Norway Regional Health Authority

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
Aviram 2017 **Aerobic Exercise** Treadmill Postintervention, 6 months Fair	None reported	Cerebral palsy	Recruited from adolescents from schools and clinics Ability to walk with or without assist device for at least 10 meters	95 randomized 95 assessed	Israel, Jordan, Palestine	Funding NR
Aydin, 2014 **Aerobic Exercise** Aerobics Postintervention, 12 weeks Fair	No harms reported. Note: Two patients discontinued due to "failure to adapt to the exercise"	Multiple sclerosis	Patients with relapsing-remitting type of MS and EESS scores above 4.5	Randomized: 40 Analyzed: 36 Attrition: 10% (4/40)	Germany Outpatient clinic RCT	NR
Azimzadeh, 2015 **Postural Control** Tai Chi Postintervention, 12 weeks Poor	NR	Multiple sclerosis	Women between 20 and 60 years old; diagnosed with MS by a physician specialist based on their medical records; EDSS scores equal to or less than 5/5 based on medical records; No other acute or chronic debilitating conditions such as lung and heart diseases, musculoskeletal disorders, mental or psychological problems based on patients' statements and medical records; Absence of any stage of pregnancy	Randomized: 36 Analyzed:34 Attrition: 5.5% (2/36)	Iran Group setting - location NR RCT	Unclear

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
Bahrami, 2019a **Aerobic Exercise** Treadmill Immediately postintervention, 8 weeks Fair	None - reported that no injury occurred that was due to the intervention.	Cerebral palsy	Inclusion Criteria: spastic CP patients aged 18-45 year old with GMFCS level I to III	Randomized: 35 Analyzed: 29 Attrition: 17% (6/35)	Iran Outpatient rehab clinic RCT	Iran University Grant
Baquet, 2018 **Aerobic Exercise** Cycling Postintervention, 12 weeks Fair	NR	Multiple sclerosis	Patients had to be diagnosed with RRMS according to the McDonald criteria 2010, an EDSS score <3.5, and currently in remission with no relapse or progression during the last 3 months. Patients had to be on stable immunotherapy for more than 3 months or without any planned change in disease-modifying therapies for the next 6 months.	Randomized: N=64	Germany Outpatient clinic RCT with 12 week extension	German Ministry of Research and Education

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
Bleyenheuft, 2017 **Postural Control** Balance Postintervention, 12 weeks Poor	NR	Cerebral palsy	Patients diagnosed with bilateral CP in GMFCS levels II to IV; age 6 to 16 years; an ability to grasp light objects and lift the more affected arm 15cm above a table surface, school level equal to that of typically developing peers; ability to follow instructions and complete testing	Randomized: 20 Analyzed:20 Attrition: 0% (0/20)	Belgium, USA Day camp Non randomized study (quasirandomized)	This study was a pilot for a larger trial (NCT02667613). The work was supported in part by Goldman Sachs Gives and by Mindy and Mark Dehnert. YB had a research grant from the Fonds de la recherche clinique, cliniques universitaires Saint-Luc, Brussels, Belgium.
Brichetto, 2015 **Postural Control** Balance Postintervention, 4 weeks Good	NR	Multiple sclerosis	Patients 18 years or older; stable without relapses or worsening in the last 3 months; history of falls (at least one fall in the last year)	Randomized: 32 Analyzed:32 Attrition: 0% (0/32)	Italy Outpatient clinic RCT	None
Bryant, 2013 **Aerobic Exercise** Cycling Postintervention, 12 weeks Fair	NR	Cerebral palsy	Children aged 8–17 years, with cerebral palsy at GMFCS levels IV and V, able to pedal on an adapted static bicycle and walk with partial body weight support on a treadmill	Randomized: N=23 Analyzed: 21 Attrition: 10% (2/21)	UK School RCT	National Institute for Health Research

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Bryant, 2013 **Aerobic Exercise** Cycling Postintervention, 12 weeks Fair	None reported	Cerebral palsy	Children aged 8–17 years, with cerebral palsy at GMFCS levels IV and V, able to pedal on an adapted static bicycle and walk with partial body weight support on a treadmill	Randomized: N=24 Analyzed: 22 Attrition: 8% (2/24)	UK School RCT	National Institute for Health Research
Bulguroglu, 2017 **Muscle Strength** Postintervention, 0 weeks Poor	NR	Multiple sclerosis	Being over 18 years of age; not having had an MS attack or any surgery in the last 6 months, being below 4.5 EDSS score	Randomized: 45 Analyzed: 38 Attrition: 15.6% (7/45)	Turkey Outpatient RCT	NR
Burschka, 2014 **Postural Control** Tai Chi Postintervention, 24 weeks Poor	NR (One patient in the Tai Chi withdrew due to unspecified health issues.)	Multiple sclerosis	MS patients able to walk without a walking aid, an EDSS score <5, relapse-free for the past 4 weeks	Randomized: 38 Analyzed: 32 Attrition: 15% (6/38)* *Six patients from the Tai Chi group withdrew from the study due to time issues (N=5) and (N=1) health problems, 32 patients was included in the final analysis	Germany Outpatient clinic RCT (two-arm trial)	Industry Novartis Pharma GmbH.

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Cakit, 2010 **Multimodal Exercise** Postintervention, 0 weeks Poor	NR	Multiple sclerosis	Clinically or laboratorially definite relapsing-remitting or secondary progressive MS, mild or moderate MS determined by Kurtzke Expanded Disability Status Scale scores of 6.0, and ability to stand independently in upright position for 3 secs and if they had been without steroid and immunosuppressive therapy within the past 4 weeks	Randomized: 45 Analyzed: 33 Attrition: 27% (12/45) [Across entire study - all 3 study arms]	Turkey Outpatient/home RCT	NR
Calabro, 2017 **Aerobic Exercise** Robot-Assisted Gait Training Postintervention, 8 weeks Good	NA	Multiple sclerosis	Inclusion Criteria: RRMS, Age 18-65, moderate to severe walking disability EDSS 4.0-5.5, Montreal Cognitive Score >24, no neurological or orthopedic co-morbidities that interfere with ambulation, stable medications for 6 months	Randomized: N=40 Analyzed: 40 Attrition: 0% (0/40)	Italy Outpatient Randomized Control Trial	None
Callesen, 2019 **Postural Control** Balance exercises **Strength interventions** Muscle Strength Exercises Postintervention,10 weeks Fair	PRT group reported three falls but they were not related to the intervention.	Multiple sclerosis	Inclusion Criteria: People 18 years or older, EDSS scale 2.0 to 6.5	Randomized: 71 Analyzed: 71 Attrition: 17% (12/71)	Denmark Outpatient clinic RCT	Danish foundation TrygFonden

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
Carling, 2017 **Postural Control** Balance Postintervention, 7 weeks Fair	Two adverse events (both falls) occurred during intervention, neither fall was injurious (cited from text). Note: Figure 1 indicates (n=2) Lost to followup due to fall related fractures in the early-intervention group Prospectively reported falls: The late-start group reported a total of 245 falls and 2220 near falls during the study period, giving a fall rate of 1.28/person/ month and a near fall rate of 11.64/ person/month	Multiple sclerosis	Walking ability not exceeding 200 m (with or without a walking aid)	Randomized: 51 Analyzed: 48 Attrition: 6% (3/51)	Sweden Outpatient RCT	Mixed Study was supported by grants from the Uppsala-Örebro Regional Research Committé, the research committee of Örebro County Council and the Norrbacka-Eugenia Foundation
Castro-Sanchez, 2012 **Aerobic Exercise** Aquatics Postintervention, 20 weeks, and 30 weeks Good	NR	Multiple sclerosis	Inclusion Criteria: People 18 to 75 years old, EDSS scale ≤ 7.5, VAS >4.	Randomized: 73 Analyzed: 71 Attrition: 2% (2/73)	Spain Outpatient therapy clinic RCT	NR
Chen, 2016 **Muscle Strength** 8 weeks – mid intervention 16 weeks – mid intervention Post-52-week intervention 4 weeks Fair	NR	Spinal cord injury	1. Injury located at C5–C7 (C: cervical spinal nerve), spinal injury of patients conformed to International Standards for Neurological Classification of Spinal Cord Injury (ASIA, 4th Edition, 1992); 2. Patients in stable condition and could cooperate to complete pulmonary function test and pulmonary rehabilitation	Randomized: 98 Analyzed: 98 Attrition: 0% (0/98)	China Inpatient RCT	NR

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
Cho, 2020 **Muscle Strength** Immediately Postintervention, 6 weeks Poor	No adverse events reported, (one patient dropped out “due to their health condition”.	Cerebral palsy	Inclusion Criteria: Children between the ages of 6 and 13 years diagnosed with diplegic CP, GMFCS level between I and III.	Randomized: 25* Analyzed: 25 Attrition: 0% (0/25) *Selected from 28,10% (3/28)	Korea Outpatient clinic RCT	Korean government grant
Chrysagis 2012 **Aerobic Exercise** Treadmill Postintervention, 0 weeks Fair	None reported	Cerebral palsy	Recruited at special school for children with disabilities Ambulatory (with or without aids) adolescents with tetra- or diplegia	Randomized 22 Analyzed 22	Greece RCT	NR
Claerbout, 2012 **Postural Control** Whole Body Vibration Postintervention, 0 weeks Fair	NR	Multiple sclerosis	Persons with clinically definite MS and an EDSS between 3 and 7	Randomized: 55 Analyzed: 47 Attrition: 14.5% (8/55)	Belgium Inpatient RCT	PF acknowledges the FWO Flanders for financial support during the study period.

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
Collett, 2010 **Aerobic Exercise** Cycling Postintervention, 12 weeks Poor	3 participants from the combined exercise group reported adverse events during the exercise intervention phase (tachycardia, leg pain, and exacerbation of a knee injury). Intermittent group 4 participants discontinued the intervention due to adverse events (two due to pain during cycling, one because of an exacerbation of MS symptoms and one due to a loss of consciousness during cycling). MS	Multiple sclerosis	People with MS over 18 years of age identified through local neurologists or self-referral.	Randomized: N=61 Analyzed:55 Attrition: 20% (12/61)	United Kingdon Gym Randomized comparator study	Multiple Sclerosis Society of Great Britain and Northern Ireland and Oxfordshire Primary Care Trust (PCT) extension to the MS funding National Institute of Health Research
Curtis, 2018 **Postural Control** Balance Postintervention, 24 weeks Fair	NR	Cerebral palsy	Diagnosis of CP classified as levels III–V of the Gross Motor Function Classification System, be aged between 2 and 15 years, and have trunk or head postural control deficits	Randomized: 28 Analyzed: 23 Attrition: 17.9% (5/28)	NR Outpatient clinic and home RCT	Nonprofit This trial was supported financially by grants from The Association of Danish Physiotherapist's Foundation for Research, Education and Development of Clinical Practice, Fund for Physiotherapy in Private Practice and the Britta Holles Fund.

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
Dalgas, 2009 Dalgas, 2010 **Muscle Strength** Immediately postintervention Dalgas, 2009: Fair to Good Dalgas, 2010: Poor	NR	Multiple sclerosis	Patients with definite relapsing-remitting MS according to Mc-Donald criteria, EDSS score between 3.0 and 5.5 with a pyramid function score 2.0, ability to walk 100m, no need for help with transportation to training facility, age 18 years, and acceptance of diagnosis and treatment.	Randomized: 38 Analyzed: 31 Attrition: 18.4% (7/38)	Denmark Outpatient clinic RCT	Supported by the National Multiple Sclerosis Society, The Research Foundation of the MS Clinic of Southern Denmark (Vejle, Esbjerg, and Soenderborg), Director Werner Richter and Wife's Grant, The Augustinus-Foundation, Engineer Bent Boegh and Wife Inge Boeghs Foundation, Vilhelm Bangs Foundation, Manufacturer Mads Clausen's Foundation, The Toyota Foundation, Mrs. Benthine Lund's Foundation, and AP Moeller's Foundation.
Demuth, 2012 Companion to: Fowler, 2010 **Aerobic Exercise** Cycling Postintervention, 0 weeks Fair	NR	Cerebral palsy	Inclusion criteria were: (1) spastic diplegic CP; (2) age between 7 and 18 years; (3) the ability to comply with simple verbal directions; (4) Gross Motor Function Classification System (GMFCS) levels I to III; and (5) selective motor control rating of good or fair for at least one leg.	Randomized: N=64 Analyzed: 58 Attrition:9 % (6/64)	USA Outpatient clinic RCT	Foundation for Physical Therapy

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Deutz, 2017 **Postural Control** Hippotherapy Middle of treatment (after 8-week observational phase and 16- to 20-week intervention) and end of treatment (after 16-week washout period, 16- to 20-week intervention, and 8-week observational phase) Poor	1 patient fell during hippotherapy and fractured humerus	Cerebral palsy	Inclusion Criteria: bilateral spastic CP, age 5 to 16 years, no HT and no major surgery during the preceding 12 months, no allergy to horse hair, informed consent of the parents available, gross motor function classification level (GMFCS) II to IV, and no achillotenotomy performed during the preceding 6 months	Randomized: 73 Analyzed: 66 (19 more did not finish the study, 47 analyzed) Attrition: 10% (7/73) or 36% (26/73) or 29% (19/66)	Germany Outpatient clinic Randomized crossover trial	Nonprofit
Dodd, 2011 **Muscle Strength** Immediately postintervention, 12 weeks Good	A vs. B Increases in any sensory symptoms characteristic of MS: 0 (0%) vs. 0 (0%) Any injury that required participants to miss a training session: 0 (0%) vs. 0 (0%) Reductions in symptoms of muscle spasm: -2.8 units (95% CI 5.6 to 0.3) vs. -2.4 units (95% CI 5.2 to 0.5), p>0.05 Short-term muscle soreness: 69% (25) vs. NR	Multiple sclerosis	Aged 18 years or more, have a confirmed diagnosis of relapsing–remitting MS, have an Ambulation Index score of 2, 3 or 4 (mild to moderate walking disabilities), and have received medical clearance to participate.	Randomized: 76 Analyzed: 67 Attrition: 11.8% (9/76)	Australia Community gymnasiums RCT	Supported by Multiple Sclerosis Research Australia.

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
Doulatabad, 2013 **Postural Control** Yoga Postintervention, 12 weeks Poor	NR	Multiple sclerosis	Women aged between 18-45 with at least 2 year MS history; and the ability to participate in Yoga exercise	Randomized: 60 Analyzed:60 Attrition: 0% (0/60)	Iran Group setting RCT	Nonprofit: Yasouj University of Medical Sciences
Duarte Nde, 2014 **Aerobic Exercise** Treadmill Postintervention, 3 weeks and 5 weeks Fair Note: May share participants with Grecco, 2014	NR	Cerebral palsy	Inclusion Criteria: Spastic cerebral palsy; GMFCS levels I, ii or iii;;between 5 and 10 years old; independent gate for at least 12 months; able to comprehend procedures	Randomized: 24 Analyzed: 24 Attrition: 0%	Brazil Outpatient physical therapy clinics RCT	Brazilian fostering agencies CAPES and FAPESP
Duff, 2018 **Muscle Strength** Postintervention, 0 weeks Fair	No adverse events were reported in either group during the intervention. However, one participant experienced severe muscle spasticity of the leg during the baseline stimulation protocol. This person fully recovered within 2 hours of the testing.	Multiple sclerosis	Definite diagnosis of MS, not restricted to a wheelchair or scooter, and the ability to travel to the assessment and intervention locations	Randomized: 30 Analyzed: 27 Attrition: 10% (3/30)	Canada Pilates studio RCT	This study was funded by a Hermes Canada MS Society of Canada Wellness Research Innovation grant.
Duffell, 2014 **Aerobic Exercise** Robot-Assisted Gait Training Postintervention, 4 weeks Poor	NR	Spinal cord injury	Inclusion Criteria: subjects with incomplete SCI	Randomized: 52 Analyzed: 52 Attrition: 0% (0/52)	USA Outpatient Rehabilitation Clinic RCT	NIH and Craig H Nelson Foundation

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
Ebrahimi, 2015 **Multimodal** Postintervention, 0 weeks Poor	NR	Multiple sclerosis	Definite MS according to McDonald's criteria, with relapsing–remitting form of the disease and EDSS 1.5 to 5.0	Randomized: 34 Analyzed: 30 Attrition: 11.8% (4/34)	Iran Outpatient RCT	NR
Elnaggar 2019 **Strength** Plyometric training Postintervention, 8 weeks Fair	NR	Cerebral palsy	Inclusion Criteria: Spastic unilateral CP as determined by a pediatric neurologist, 8-12 years of age, independent ambulators, categorized as level I according to Gross Motor Function Classification System, mild spastic (hypertonia less than 1+ grade as being measured by the Modified Ashworth Scale), ability to understand and follow instructions.	Randomized:44 Analyzed: 39 Attrition: 11.4% (5/44)	Saudi Arabia Outpatient RCT	NR
El-Shamy, 2018 **Postural Control** Motion gaming Postintervention, 12 weeks Fair	NR	Cerebral palsy	Inclusion Criteria: children 6-8 years old with hemiplegic CP, MACS I-III, able to hear/see and follow directions	Randomized: 30 Analyzed: 30 Attrition: 0% (0/30)	Saudi Arabia Children's Hospital RCT	NR

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
Emara, 2016 **Aerobic Exercise** Treadmill Postintervention, 12 weeks Fair	NR	Cerebral palsy	Inclusion Criteria: Children 6 to 8 years old with spastic diplegia, gross motor function classification system (GMFCS) level lll.	Randomized: N=22 Analyzed: 20 Attrition: .09% (2/22)	Saudi Arabia Outpatient clinic RCT	Nonprofit Taibah University, Al Madinah Al-Munawara, Saudi Arabia (Grant Number 6093/1435).
Faramarzi, 2020 Has companion: Banitalebi, 2020 **Multimodal Exercise** Immediately Postintervention, 12 weeks Fair	No adverse events were reported.	Multiple sclerosis	Inclusion Criteria: Women aged 18 to 50 with MS, with no relapse or acute exacerbation the past 6 months.	Randomized: 94 Analyzed: 89 Attrition: 5% (5/94)	Iran Outpatient clinic RCT	NR
Esclarin-Ruz, 2014 **Aerobic Exercise** Robot-Assisted Gait Training Postintervention, 8 weeks Fair	NA	Spinal cord injury	Inclusion Criteria: C2 to L3 SCI, ASIA C or D, onset <6 months, ago 16-70, able to stand with external support	Randomized: N=88 Analyzed: 81 Attrition: 7.9%	Spain Hospital RCT	Research Grant

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
Field-Fote, 2011 Has companions: Kressler, 2013; Sandler, 2017 **Aerobic Exercise** Robot-Assisted Gait Training Postintervention, 12 weeks Fair	NA	Spinal cord injury	Inclusion Criteria: Asia classification C or D Spinal Cord Injury at T10 or higher, able to take 1 step with 1 leg, and ability to rise to standing position with at most moderate (50%) assistance	Randomized: N=74 Analyzed: 64 Attrition: 14% (10/74)	USA Outpatient Randomized Control Trial	Funding: National Institutes of Health and Miami Project to Cure Paralysis
Forsberg, 2016 **Postural Control** Balance Postintervention, 8 weeks Fair	Two adverse events were reported: one participant lost balance during challenging tasks in standing and fell on a soft carpet, and one fell while standing on his/her knees. No injuries were reported.	Multiple sclerosis	Patients with MS able to walk 100 meters but unable to maintain tandem stance ≥30 seconds	Randomized: 87 Analyzed:73 (week 8) Attrition: 16.1% (14/87 - week 8) Analyzed: 66 (week 24) Attrition: 24% (21/87 - week 24)	Sweden Hospital RCT	Government: supported by the Uppsala- ¨Orebro Regional Research Council (RFR-306241), the Norrbacka-Eugenia Foundation (Grant no. 814/12), and the Research Committee of Region ¨ Orebro County (Grants nos.OLL-216421 and OLL-317511)
Fosdahl, 2019b **Multimodal Exercise** Postintervention, 16 weeks and 32 weeks Fair	NR	Cerebral palsy	Inclusion Criteria: Spastic bilateral CP patients GMFCS levels I-III	Randomized: 37 Analyzed: 34 Attrition: 9% (34/37)	Norway Pediatric outpatient clinic RCT	Sophies Minde Ortopedi AS, Oslo University Hopsital

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
Fowler, 2010 Has companion: Demuth, 2012 **Aerobic Exercise** Cycling Postintervention, 0 weeks Fair	NR	Cerebral palsy	Inclusion criteria were: (1) between 7 and 18 years of age; (2) ability to follow simple verbal directions (3) ability to walk independently, with or without an assistive device, for short distances (Gross Motor Function Classification System levels I–III); and (4) good or fair selective voluntary motor control for at least one limb.	Randomized: N=64 Analyzed:58 Attrition: 9% (6/64)	USA Outpatient clinic RCT	Corporate donations or discounts: Biodex Inc, Freedom Concepts, Helen's Cycles, Santa Monica, National AMBUCS Inc, and Sam's Club. Volunteers and foundations: Caitlin Fowler, Ernie Meadows, Sidney Stern Memorial Trust, Steinmetz Foundation, Sykes Family Foundation, and United Cerebral Palsy Research and Education Foundation.
Fox, 2016 **Muscle Strength** Postintervention, 4 weeks Fair	Four adverse events occurred: a fractured ankle (Pilates group) and a fractured humerus (standardized exercise group) (both as a result of falls in the snow, unrelated to the exercise sessions) and pneumonia and pancreatitis (relaxation group) (unrelated to the exercise sessions)	Multiple sclerosis	Aged over 18 years, had a definite diagnosis of MS according to McDonald's criteria, and had an EDSS score of 4.0 to 6.5, meaning that, at best, they were able to walk independently without use of an aid or rest for 500 m (EDSS score 4.0) and, at worst, they required 2 walking aids (pair of crutches or canes) to walk about 20 m without resting.	Randomized: 100 Analyzed: 84 Attrition: 16% (16/100)	England Outpatient clinic RCT	NR

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
Galea, 2018 **Multimodal Exercise** Postintervention, 12 weeks Fair	A vs. B Withdrawals due to AE or SAE: 3.3% (2/60) vs. 1.8% (1/56) Other AEs (only most common are specifically called out) Definitely related (n events) All: 85 vs. 28 -Skin abrasion/ bruising: 25 vs. 2 -Autonomic dysreflexia: 19 vs. 4 -Pain: 17 vs. 19 Probably related (n events) All: 53 vs. 40 -Skin abrasion/ bruising: 16 vs. 0 -Autonomic dysreflexia: 7 vs. 3 -Pain: 17 vs. 27 -Headache: 0 vs. 3 Possibly related (n events) All: 56 vs. 64 -Skin abrasion/ bruising: 0 vs. 4 -Pain: 20 vs. 34 -Headache: 0 vs. 12 -Dizziness/ nausea: 5 vs. 0 -Bladder/bowel problems: 5 vs. 0 -Fatigue: 0 vs. 4	Spinal cord injury	More than 18 years of age, had sustained a motor complete or incomplete traumatic SCI above the level of T12 at least 6 months prior to consent, and had medical clearance to participate.	Randomized: 116 Analyzed: 86 Attrition: 25.9% (30/116)	Australia and New Zealand Outpatient clinic RCT	The study was funded by the Transport Accident Commission (Victorian Neurotrauma Initiative), the Lifetime Care and Support Authority NSW, the University of Melbourne and The University of Western Australia.
Gandolfi, 2015 **Postural Control** Balance Postintervention, 5 weeks Fair	7 patients in the experimental group 8.8% (7/80) withdrew for medical reasons or because of difficulty arranging transportation to the study site. No adverse events were reported during the study period	Multiple sclerosis	Patients diagnosed with MS aged ≤65 years; EDSS22 score 1.5≥ × ≤6.0; Mini-Mental State Evaluation score ≥24; subjective symptoms of balance impairments; fear of falling and/or history of falls as defined by at least one fall within the last year	Randomized: 80 Analyzed:80 Attrition: 0% (0/80)	Italy Outpatient clinic RCT	Nonprofit: Fondazione Italiana Sclerosi Multipla onlus (FISM) grant no. FISM 2009/R/27

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
Garrett, 2013a Garrett, 2013b (same author group a as Hogan 2014) **Postural Control** Yoga Postintervention, 12 weeks	NR	Multiple sclerosis	Over 18 years of age and had a diagnosis of MS that was confirmed by a consultant physician or neurologist.	Garrett 2013a (3 intervention groups, 1 control group, postintervention followup, ITT analysis) Randomized: 372 Analyzed: 242 Attrition: 34.9% (130/372) Garrett 2013b (3 intervention groups, 12-week followup, no ITT analysis) Randomized: 243 Analyzed: 121 Attrition: 50% (122/243)	Ireland Community gyms, hotels, health centers RCT	This work, designated the 'Getting the Balance Right project,' was supported by the Multiple Sclerosis Society of Ireland (MSI) through the Tesco Charity of the Year funding and the Pobal, Dormant Accounts Flagship Fund. In addition, the lead author was an EMBARK PhD Scholar who was supported by the Irish Research Council for Science Engineering and Technology.
Gervasoni 2014 **Aerobic Exercise** Treadmill Postintervention, 0 weeks Fair	None reported	Multiple sclerosis	Able to walk 6 meters with or without assist device	30 randomized 30 analyzed	Iran RCT	Government funded

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
Giangregorio 2012 (Body composition) Hitzig 2013 (quality of life) Kapadia 2014 (walking capacity) Craven 2017 (bone markers) **Aerobic Exercise** Treadmill Postintervention, 6 months Fair	None reported	Spinal cord injury	Incomplete injuries from C2 to T12 American Spinal Injury Association Impairment Scale C or D	34 randomized 28 analyzed 6/34=18% attrition	Canada Rehabilitation hospital	Ontario Neurotrauma Foundation
Gibson, 2018 **Aerobic Exercise** Aerobics Postintervention, 12 weeks Good	NR	Cerebral palsy	Inclusion Criteria: CP patients 9 to 18 years old with GMFCS levels I-III	Randomized: 43 Analyzed: 42 Attrition: 2% (1/43)	Australia Outpatient therapy clinic RCT	Non-government Centre and Princess Margaret Hospital Foundation
Gorman, 2019 **Aerobic Exercise** Aquatics Postintervention, 12 weeks Fair	(N=1, treatment related)	Spinal cord injury	SCI ASIA C or D, age 18-65, tolerate 30 minutes standing frame	Randomized: N=37 Analyzed 32 Attrition: 13.5%)	USA Outpatient RCT	Funding: US Department of Defense SCI Research Program

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Grecco 2013 **Aerobic Exercise** Treadmill RCT Postintervention, 3 weeks Fair	None reported	Cerebral palsy	Recruited children from specialized outpatient clinics Children	24 randomized 24 analyzed	Brazil	Government funded
Grecco 2014 **Aerobic Exercise** Treadmill RCT Postintervention, 4 weeks Fair	None reported	Cerebral palsy	Recruited from outpatient clinics Children	35 randomized 35 analyzed at post 33 analyzed at 1-month followup 2/35=6%	Brazil RCT	Government funded
Harness, 2008 **Multimodal Exercise** Postintervention, 0 weeks Fair	NR	Spinal cord injury	Age 18–70 years, SCI greater than 2 months prior that resulted in paraplegia or quadriplegia between C2 and T12, and ASIA Impairment Scale A, B, C, or D	Randomized: NA Analyzed: 29 Attrition: 6.5% (2/31)	USA Outpatient clinic Comparative Cohort	Funds provided by the National Center of Research Resources, 5M011 RR- 00827-29, US Public Health Service.

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
Hasanpour-Dehkordi, 2014 "Comparison of regular aerobic and yoga on the quality of life in patients" Has companions: Hasanpour-Dehkordi, 2016; Hasanpour-Dehkordi, 2016 (2) **Postural Control** Yoga Postintervention, 12 weeks Poor	NR	Multiple sclerosis	Diagnosis of MS and ability to perform the exercise program after the medication therapy; having no difficulty with movement; having no advanced heart failure	Randomized: 61 Analyzed: 61 Attrition: 0% (0/61)	Iran Hospital RCT	Nonprofit: Research and Technology Deputy of Shahrekord University of Medical Sciences grant no. 419
Hasanpour-Dehkordi, 2016 (2) "Influence of yoga and aerobics exercise on fatigue, pain and psychosocial status…" **Postural Control** Yoga Companion to: Hasanpour-Dehkordi, 2014 Postintervention, 12 weeks Poor	NR	Multiple sclerosis	Diagnosis of MS; consent to participate in the study; and the ability to speak and to move	Randomized: 61 Analyzed:61 Attrition: 0% (0/61)	Iran Gym RCT	Nonprofit: Research and Technology Deputy of Shahrekord University of Medical Sciences

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	**Harms**	**Condition**	**Inclusion Criteria**	**Number Randomized Analyzed Attrition**	**Country Setting Study Design**	**Funding Source**
Hasanpour-Dehkordi, 2016 "Effects of Yoga on Physiological Indices, Anxiety and Social Functioning" **Postural Control** Yoga Companion to: Hasanpour-Dehkordi, 2014 Poor	NR	Multiple sclerosis	Diagnosis of MS; consent to participate in the study; and the ability to speak and to move	Randomized: 60 Analyzed: 60 Attrition: 0% (0/60) *During the study, 10 from case group and 10 from control group were excluded	Iran Gym RCT	Nonprofit: Research and Technology Deputy of Shahrekord University of Medical Sciences
Hebert, 2011 **Aerobic Exercise** Cycling Postintervention, 4 weeks Fair	One patient in the exercise control group had a minor ankle sprain (1/13).	Multiple sclerosis	MS patients 18 to 65 years old; able to walk 100 m with or without a single-sided device; a score of 45 out of 84 on the Modified Fatigue Impact Scale questionnaire; composite score of 72 on the computerized SOT	Randomized: 38 Analyzed: 38* Attrition: 0% (0/38) *ITT	US Outpatient clinic	National Multiple Sclerosis Society, Pilot Project no. PP1501
Hebert, 2009 Companion to: Hebert, 2011 Balance Postinterventon, 14 weeks Fair	NR	Multiple sclerosis	Ambulation of 100 m with no greater than intermittent or unilateral constant use of an assistive device, age 18 to 60 years	Randomized: 88 Analyzed: 6 weeks: 81 Analyzed: 14 weeks: 76 Attrition: 15% (13/88)	USA Outpatient RCT	Nonprofit

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Heine, 2017 **Aerobic Exercise** Cycling 16 weeks Postintervention, 36 weeks Fair	Odds of self- reported relapse in patients with RRMS (adjusted for disease severity) was 0.28, 95% CI 0.10 to 0.789, p=0.016 in favor of aerobic training	Multiple sclerosis	Male and female between 18 and 70 years, ambulant without MS exacerbation or steroid treatment <3 months.	Randomized: 89 Analyzed: 80 Attrition at end of treatment: 9/43 (21%) vs. 15/46 (33%) Attrition at 1 year followup: 17/43 (40%) vs. 38/46 (83%)	The Netherlands Outpatient RCT	Nonprofit
Herrero, 2012 **Postural Control** Hippotherapy Postintervention, 12 weeks Fair	A vs. B	Cerebral palsy	Inclusion Criteria: Children 4 and 18 years old with cerebral palsy, Gross Motor Function Classification System levels I–V.	Randomized: N=38 Analyzed: 38* Attrition:.5% (4/38) *ITT	Spain Outpatient clinic RCT	Government

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
Hochsprung, 2017 **Aerobic Exercise** Cycling Postintervention, 0 weeks Poor	NR	Multiple sclerosis	Inclusion criteria: (1) referral by the neurologist to our hospital's multiple sclerosis unit; (2) diagnosis of definite MS according to the McDonald criteria at least 2 years previously; (3) EDSS score ≤7 (established by a neurologist); (4) age between 20 and 70 years; (5) clinical stability during the 3 months previous to recruitment; (6) no cognitive impairment according to the Mini-Mental State Examination; (7) willingness to sign an informed consent form; and (8) EDSS score between 2 and 6.5.	Randomized: N=61 Analyzed:61 Attrition: 0% (0/61)	Spain Outpatient clinic RCT	NR

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Hogan, 2014 (same author group and protocol as Garrett 2013a and 2013b - see notes) **Postural Control** Yoga Postintervention, 0 weeks	Main problems reported by participants, n -Mobility/walking problems: 49 -Fatigue: 41 -Balance: 36 -Weakness: 34 -Bladder/bowel: 29 -Pain: 16 -Stiffness/spasms: 16 -Vision: 9 -Sensation: 6 -Falls: 3 -No problems: 2	Multiple sclerosis	Over 18 years of age and had a diagnosis of MS that was confirmed by a consultant physician or neurologist.	Randomized: 146 Analyzed: 111 Attrition: 24% (35/146)	Ireland Community gyms, hotels, health centers RCT	This work, designated the 'Getting the Balance Right project,' was supported by the Multiple Sclerosis Society of Ireland (MSI) through the Tesco Charity of the Year funding and the Pobal, Dormant Accounts Flagship Fund. In addition, the lead author was an EMBARK PhD Scholar who was supported by the Irish Research Council for Science Engineering and Technology.
Hota, 2020 **Postural Control** Balance Exercises Postintervention, 4 weeks Fair	None reported	Spinal Cord Injury	Patients 10 years old or more, admitted with cervical injury, > 30 days post injury	Randomized: 40 Analyzed: 40 Attrition: 0% (0/40)	India Spinal injury center inpatient rehabilitation RCT	Funding NR
Hsieh, 2018 **Postural Control** Motion gaming Postintervention, 12 weeks Fair	NR	Cerebral palsy	Diagnosis of CP resulting in hemiparesis, or a deficit in movement and balance	Randomized: 40 Analyzed:40 Attrition: 0% (0/40)	Taiwan Outpatient clinic RCT	NR

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Hsieh, 2020 **Postural Control** Motion Gaming Postintervention, 0 weeks Fair	No adverse effect “was expected” but results NR.	Cerebral Palsy	Children between 6 and 10 years old with cerebral palsy and motor problems GMFCS category level = I–III	Randomized: 56 Analyzed: 56 Attrition: 0% (0/56)	Taiwan Pediatric rehabilitation RCT	Funding NR
Huang, 2015 **Aerobic Exercise** Robot-Assisted Gait Training Postintervention, 4 weeks Fair	none	Spinal cord injury	Inclusion Criteria: Incomplete SCI, T8 to L2, injury within 6 months	Randomized: N=24 Analyzed: 24 Attrition: 0%	China outpatient (?) RCT	Research on Design Theory and Compliant Control for Underactuated Lower Extremity Rehabilitation Robotic Systems
In, 2018 **Postural Control** Whole body vibration Postintervention, 0 weeks Fair	None reported.	Spinal cord injury	(1) diagnosed with cervical level 6 or 7 incomplete SCI, (2) onset ≥6 months, (3) American Spinal Injury Association Impairment Scale (AIS) grade D motor and sensory scores, (4) ability to stand for at least 5 min, (5) ability to understand and follow verbal commands, (6) medical referral by a physician for physical therapy, and (7) ability to complete designed WBV training session.	Randomized: 32 Analyzed: 28 Attrition: 12.5% (4/32)	South Korea Outpatient RCT	This work was supported by the 2016 Gimcheon university Research Grant.

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Johnston 2011 **Aerobic Exercise** Treadmill Postintervention, 4 weeks Fair	None reported	Cerebral palsy	Recruited from Shriners' outpatient clinics children with diplegia, triplegia or quadriplegia GMFCS III or IV Able to take 8 steps 6 to 13 years old	34 randomized 26 analyzed 8/34=23.5% attrition	USA Physical therapists and home setting RCT	funded by Shriners (Foundation)
Jones, 2014a Jones, 2014b **Multimodal Exercise** Postintervention, 12 weeks (for ALL patients completing the Activity Based Therapy intervention) Poor (for both)	Withdrawals due to injuries related to participation in intensive exercise: 7.7% (2/26) vs. 0% (0/22)	Spinal cord injury	AIS classification of C or D, upper motor neuron injury, preserved tendon reflexes in the lower extremities, at least 1 year postinjury, and ages 18 to 66 years.	Randomized: 48 Analyzed: 41 Attrition: 14.6% (7/48)	USA Outpatient RCT	Supported in part by the National Institute on Disability and Rehabilitation Research (NIDRR), U.S. Department of Education (grant no. H133G080031–10).
Jonnsdottir, 2018 **Aerobic Exercise** Treadmill Postintervention, 0 weeks Fair	None reported	Multiple sclerosis	Recruited inpatient rehab service, able to walk 10 meters	42 randomized 38 analyzed 4/42=9.5% attrition	Italy Rehabilitation center RCT	Government

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Jung, 2014 **Aerobic Exercise** Aquatics Postintervention, 0 weeks Fair	NR	Spinal cord injury	Diagnosis of American Spinal Injury Association (ASIA) grade B, C, or D spinal cord injury at the levels of C8 to L5.	Randomized: N=20 Analyzed: 20 Attrition: 0% (0/20)	Korea Inpatient RCT	NR
Kalron, 2016 **Postural Control** Motion gaming Postintervention, 6 weeks Fair	NR	Multiple sclerosis	Diagnosis of definite relapsing remitting MS; 25–55 years of age; moderate neurological disability as scored by the EDSS; ranging from 3.0 to 6.0 inclusive with a pyramidal functional score of at least 3	Randomized: 32 Analyzed:30 Attrition: 6.3% (2/32)	Israel Outpatient clinic RCT	Nonprofit: supported by a Pilot Research Award from the National Multiple Sclerosis Society (PP2208)
Kalron, 2017 **Muscle Strength** Postintervention, 0 weeks Fair	No adverse or harmful events were reported in both groups	Multiple sclerosis	(1) diagnosis of definite relapsing-remitting multiple sclerosis according to the revised McDonald criteria (2) age range from 25-55 years; and (3) the EDSS score ranging from 3.0 to 6.0. Additionally, only patients receiving disease-modifying drugs based on interferon beta-1a for at least 3 months.	Randomized: 50 Analyzed: 45 Attrition: 10% (5/50)	Israel Outpatient clinic RCT	This work was supported by a grant (EMR200136_642) from the Merk KGaA, Damstadt, Germany.

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Kara, 2017 **Aerobic Exercise** Aerobics Muscle Strength Postintervention, 0 weeks Poor	NR	Multiple sclerosis	Older than 18 years, EDSS <6 – Being diagnosed with definite MS according to McDonald criteria, an-EDSS of ≥6 – Being older than 18 years – Not having an acute attack.	Randomized: NA Analyzed: 35 (64%) Attrition: 22 (40%)	Turkey Outpatient Quasiexperimental, nonrandomized	No funding received
Kara, 2020 **Strength** Immediately postintervention, 12 weeks Fair	No adverse events occurred in either group.	Cerebral palsy	(1) age between 7 and 16 years; (2) classification as levels I-III on the Manual Ability Classification System (MACS); and (3) the ability to follow and accept verbal instructions.	Randomized: 34 Analyzed: 30 Attrition: 12% (4/34)	Turkey Outpatient RCT	NR
Kargarfard, 2017 **Aerobic Exercise** Aquatics Postintervention, 0 weeks Fair	NR	Multiple sclerosis	Inclusion Criteria: MS of a minimum of 2 years, had no relapses in the past month, and were able to exercise regularly.	Randomized: N=40 Analyzed: 32 Attrition: 20% (8/40)	Iran Outpatient clinic RCT	NR
Kaya Kara, 2019 **Multimodal Exercise** Immediately postintervention, 12 weeks Fair	No adverse events reported, although one person in the exercise group had ankle pain following a fall while playing basketball.	Cerebral palsy	Inclusion Criteria: GMFCS levels I, ages 7 to 16 years old	Randomized: 33 Analyzed: 30 Attrition: 9% (3/33)	Turkey Physical therapy clinic RCT	NR

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Kerling, 2015 **Multimodal Exercise** Postintervention, 0 weeks Fair	NR	Multiple sclerosis	Diagnosed MS, adult age (18–65 years), and mobility with a maximum value of 6 (low to moderate disability) on the EDSS	Randomized: 60 Analyzed: 37 Attrition: 38.3% (23/60)	Germany Outpatient RCT	The study was supported by Sanofi Aventis.
Keser, 2011 **Aerobic Exercise** Aerobics Postintervention, 0 weeks Poor	NR	Multiple sclerosis	EDSS between 1 and 5.5	Randomized: NA Analyzed: 30 Attrition: 0	Turkey Outpatient Quasiexperimental, nonrandomized	NR
Khalil, 2018 **Postural Control** Motion gaming Postintervention, 6 weeks Fair	NR	Multiple sclerosis	Diagnosis of MS, relapsing remitting type of MS; age of above 18 years, EDSS score of 3 to 6.5; being relapse free for 30 days prior to participation or to completing testing	Randomized:40 Analyzed: 32 Attrition: 20% (8/40)	Jordan University RCT	Government: funding support from EU commission for funding support (grant number: AR- 42).
Kim 2015 **Postural Control** Balance Postintervention, 0 weeks Fair	None reported	Cerebral palsy	Ambulatory adults (without support)	Randomized 21 Analyzed 21	Korean RCT	Government funding

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
Kim, 2017 **Postural Control** Balance Social activity/exercise (Boccia) Postintervention, 0 weeks Poor	NR	Cerebral palsy	Adults with CP in the age bracket of 18 to 30 years diagnosed with disability of levels 1 to 2 encephalopathy by medical specialists in the areas of rehabilitation medicine and neurosurgery. Those who can sustain seated posture on supplementary wheelchair, those capable of performing boccia exercise, those who achieved more than 18 points in the Mini–Mental Status Examination and had no difficulties in communicating and interacting with the researcher and participants, those who consented to voluntarily participate in the experiment on their own will.	Randomized: N/A Analyzed: 23 Attrition: 0% (0/23)	South Korea NR Prospective Comparative Cohort	This work was supported by the Research Fund of Ulsan College in Korea
Kirk, 2016 **Muscle Strength** Postintervention, 0 weeks Poor	Most subjects that received the PRT intervention reported delayed onset of muscle soreness during the first couple of training sessions, and 3 subjects reported irritation in tendon tissue surrounding the knee.	Cerebral palsy	Diagnosed with CP, age 18–65 years, and gait function with or without walking aids	Randomized: N/A Analyzed: 32 Attrition: 8.6% (3/35)	Denmark Gymnasium Comparative cohort	The study was supported by a grant from the Ludvig and Sara Elsass Foundation and the Association of Danish Physiotherapists

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
Kjolhede, 2016 **Muscle Strength** Postintervention, 0 weeks Fair	NR	Multiple sclerosis	18–60 years, a definite relapsing-remitting MS diagnosis according to the McDonald criteria, EDSS 2.0–5.5 with a "pyramidal functions" subscore ≥2 and receiving IFN-β 1a or 1b (Rebif, Avonex, Extavia, or Betaferon) for at least 3 months (IFN-β and Copaxone are the first line of recommended medication for relapsing-remitting MS in Denmark).	Randomized: 35 Analyzed: 30 Attrition: 16.7% (5/30)	Denmark Outpatient clinic RCT	This study was supported by The Augustinus Foundation, Hestehandler Ole Jacobsen Mindelegat, and Biogen Idec.
Klobucka, 2020 **Aerobic Exercise** Robot-Assisted Gait Training Immediately Postintervention, and 12-16 weeks Poor	No adverse events were reported.	Cerebral palsy	Adolescent and adults with bilateral spastic CP, ages 15 years and older with GMFCS levels I-IV.	Randomized: 47 Analyzed: 47 and 45 Attrition: 10% (5/47)	Slovakia Outpatient rehabilitation Clinic RCT	This work was supported by KREATON Project.
Kooshiar, 2015 **Aerobic Exercise** Aquatics Fair	NR	Multiple sclerosis	Inclusion Criteria: Female patients affected by MS, certified with a medical documentation and with a neurologist approval; cognitive competency to give informed consent; citizen of Iran and residing in Mashhad; age ranging from 19 to 45 years; and Kurtzke EDSS 9 Score of 1-5.5.	Randomized: N=40 Analyzed: 37 Attrition: 0.8% (3/40)	Iran Outpatient clinic RCT	NR

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
Kressler, 2013 Companion to: Field-Fote, 2011 **Aerobic Exercise** Robot-Assisted Gait Training Postintervention, 12 weeks Poor	None	Spinal cord injury	Inclusion Criteria: chronic motor-incomplete spinal cord injury, minimal walking ability	Randomized: N=74 Analyzed: 64 Attrition: 13.5%	US Outpatient (Academic medical center research lab) RCT	NR
Kumru, 2016 **Aerobic Exercise** Robot-Assisted Gait Training Postintervention, 8 weeks Fair	9 mild treatment-related adverse effects (facial twitching, headache)	Spinal cord injury	Inclusion Criteria: ASIA C or D Cerivial or Thoracic SCI, no limitation in passive range of motion, no changes in medical treatment	Randomized: N=34 Analyzed: 31 Attrition: 9%	Spain Inpatient rehabilitation hospital RCT	Foundation La Marato and Instituto de Salud Carlos
Kwon, 2011 **Postural Control** Hippotherapy Postintervention, 0 weeks (End of treatment after 8-week intervention) Fair	NR	Cerebral palsy	Inclusion Criteria: diagnosis of bilateral spastic cerebral palsy, GMFCS level I or II, body weight less than 35kg, and age of 4 to 10 years	Randomized: NA Analyzed: 32 Attrition: 0% (0/32)	Republic of Korea Gym and outpatient clinic Quasiexperimental, nonrandomized	Nonprofit

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
Kwon, 2015 **Postural Control** Hippotherapy Postintervention, 0 weeks (End of treatment after 8-week intervention) Good	2 participants (2%) fell during the study period. One participant returned to the therapy, while the other dropped out. A vs. B Falls: 2% (1/46) vs. 0% (0/46)	Cerebral palsy	Inclusion Criteria: diagnosis of CP, body weight less than 35 kg, and age between 4 and 10 years	Randomized: 92 Analyzed: 91 Attrition: 1% (1/92)	Republic of Korea Home and outpatient clinic RCT	Nonprofit
Lai, 2010 **Aerobic Exercise** Cycling Postintervention, 12 weeks Fair	NR	Spinal cord injury	Having a neurologically complete SCI motor lesion (American Spinal Cord Association (ASIA) impairment scale (17) grade A) between C5 andT10; having muscle responses to trial electrical stimulation; and never having undergone FES therapy	Randomized: N=24 Analyzed:24 Attrition: 0% (0/24)	Taiwan Inpatient RCT	National Science Council
Lai, 2015 **Aerobic Exercise** Aquatics Postintervention, 0 weeks Fair	None	Cerebral palsy	Diagnosis of spastic cerebral palsy; age of 4 to 12 years; Gross Motor Function Classification System levels of I to IV16; and ability to follow instructions	Randomized: N=27 Analyzed: 24 Attrition: 11% (3/27)	Taiwan Outpatient clinic RCT	National Science Council and Chang Gung Memorial Hospital

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
Lavado, 2012 **Aerobic Exercise** Hand cycling Postintervention, 0 weeks Fair	NR	Spinal cord injury	EDSS between 1 and 5.5 Injury between C5 and L2, excluded community ambulators and those unable to arm cycle	Randomized: 42 Analyzed: 42 (100%) Attrition: 0	Brazil Outpatient RCT	No funding received
Lee, 2013 **Postural Control** Whole body vibration Postintervention, 0 weeks Fair	NR	Cerebral palsy	(1) cerebral palsy diagnosed by both a pediatric neurological doctor and a physical therapist; (2) no history of serious surgery on the spine; (3) diagnosis of weak muscles in at least one of the evaluated leg muscles; muscle weakness was determined by symptoms of the muscle's inability to perform rising from a chair (difficulty with movements) – symptoms include: fatigue, numbness in muscles, inability to support one's arms and legs, drowsiness, prolonged tiredness and lethargy; (4) no drug being taken for spasticity control; (5) good vision; (6) ability to comprehend instructions; and (7) ability to walk without the use of walking aids.	Randomized: 30 Analyzed: 30 Attrition: 0% (0/30)	South Korea Outpatient RCT	This research received no specific grant from any funding agency in the public, commercial, or not–for–profit sectors.

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
Lee, 2014 **Postural Control** Hippotherapy End of treatment (12-week intervention) Poor	NR	Cerebral palsy	Inclusion Criteria: MAS grade less than +1, perform more than 10 m independent walking, available for more than 30-minute training per day	Randomized: 26 Analyzed: 26 Attrition: 0% (0/26)	Republic of Korea Outpatient clinic RCT	NR
Liu, 2019 **Multimodal Exercise** Immediately postintervention, 12 weeks Fair	Reported no adverse events occurred.	Spinal cord injury	Inclusion Criteria: Ambulatory SCI patients, 18-50 years old	Randomized: 40 Analyzed: 29 Attrition: 27% (11/40)	China Rehab center RCT	The Special Fund for Basic Scientific Research of Central Public Institutes
Lorentzen, 2015 **Postural Control** Balance Postintervention, 20 weeks Poor	NR	Cerebral palsy	Diagnosis pf spastic cerebral palsy (GMFCS I-II; MACS I-II) based on medical records and classification by the therapists participated in the study	Non Randomized: 34 Analyzed:34 Attrition: 0% (0/34)	Denmark Outpatient Clinic Quasiexperimental, nonrandomized	Nonprofit: Ludvig and Sara Elsass foundation
Lucena-Anton, 2018 **Postural Control** Hippotherapy Postintervention, 1 week (13 weeks total including 12-week intervention) Fair	No adverse effects were reported.	Cerebral palsy	Inclusion Criteria: prior diagnosis of spastic CP, nonwalking children (GMFCS levels: IV-V), and children aged 3 to 14 years	Randomized: 48 Analyzed: 44 Attrition: 4% (2/48)	Spain Outpatient clinic RCT	NR

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
Makhov, 2018 **Multimodal exercise** Immediately postintervention, 15 weeks Poor	NR	Cerebral palsy	Inclusion Criteria: CP patients 7 to 9 years old with spastic diplegia or spastic tetra paresis	Randomized: 35 Analyzed: 35 Attrition: 0 % (0/35)	Russia Setting Outpatient clinic RCT	NR
Marandi, 2013a **Aerobic Exercise** Aquatics Has companion: Marandi, 2013b Postintervention, 0 weeks Poor	NR	Multiple sclerosis	Women with MS and a EDSS score of less than 4.5 who visited Kashai hospital in Esfahan	Randomized: 57 Analyzed: 45 Attrition: 21% (12/57)	Iran NR RCT	This study was conducted as a thesis funded by Isfahan University, Isfahan, Iran
Marandi, 2013b Companion to: Marandi, 2013a **Aerobic Exercise** Aquatics Postintervention, 0 weeks Poor	NR	Multiple sclerosis	Women with MS and a EDSS score of less than 4.5 who visited Kashai hospital inEsfahan	Randomized: 57 Analyzed: 45 Attrition: 21% (12/57)	Iran NR RCT	This study was conducted as a thesis funded by Isfahan University, Isfahan, Iran

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
Matusiak-Wieczorek, 2016 **Postural Control** Hippotherapy End of treatment (after 12-week intervention) Poor	NR	Cerebral palsy	Inclusion criteria: children aged 6-12 years with spastic diplegia or spastic hemiplegia CP, GMFCS level 1 or 2, able to understand and follow simple verbal instructions	Randomized: NA Analyzed: 39 Attrition: 0% (0/39)	Poland Outpatient clinic Quasiexperimental, nonrandomized	NR
Matusiak-Wieczorek, 2020 **Postural Control** Hippotherapy Immediately Postintervention, 12 weeks Fair	Not reported	Cerebral Palsy	Children with CP, aged 6–12 years, classified as Gross Motor Function Classification System (GMFCS) level I or II, with spastic diplegia or hemiplegia.	Randomized: 45 Analyzed: 45 Attrition: 0% (0/45)	Poland Outpatient rehabilitation (Indoor riding arena) RCT	None
Midik, 2020 **Aerobic Exercise** Robot-Assisted Gait Training Postintervention, and 12 weeks Fair	None reported	Spinal Cord Injury	Male patients 19 to 53 years old with traumatic incomplete SCI for at least 12 weeks	Randomized: 30 Analyzed: 30 Attrition: 0% (0/30)	Turkey Inpatient rehabilitation RCT	None

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
Mogharnasi, 2018 **Muscle Strength exercise** Postintervention, 0 weeks Poor	NR	Spinal cord injury	1) All lesions were complete and lesion levels were T9-T12; 2) all lesions were traumatic duo to physical trauma; 3) all subjects were physically inactive in training after occurrence of lower limb paralysis; 4) all participants were examined by a physician and received medical approval for participation in physical activities; 5) they were able to sit down while maintaining upper-body balance; and 6) all participants only used wheelchairs without any short leg braces þ crutches, long leg braces þ walker and crutches. They were free from pressure sores, bladder infections, and potentially damaging metabolic and cardiovascular limitations.	Randomized: 20 Analyzed: 20 Attrition: 0% (0/20)	Iran NR RCT	This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.
Moraes, 2020 **Postural Control** Hippotherapy Postintervention, 0 weeks Fair	None reported	Multiple Sclerosis	Diagnosis of relapsing-remitting MS; 18 years or older, able to walk with an assistive device; have EDSS ≤6.0; have PDDS ≤5, have not had a relapse for more than 6 mon	Randomized: 33 Analyzed: 33 Attrition: 0% (0/33)	Brazil Outpatient rehabilitation RCT	None

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
Mutoh, 2019 **Postural Control** Hippotherapy Postintervention, 12 weeks (post 48 week intervention) Fair	NR	Cerebral palsy	Inclusion Criteria: CP patients 4 to 14 years old with GMFCS levels II-III	Randomized: 24 Analyzed: 24 Attrition: 0% (0/x24)	United Kingdom Outpatient RCT	Grants-in-Aid for Scientific Research
Najafidoulataba, 2014 **Postural Control** Postintervention, 12 weeks Poor	NR	Multiple sclerosis	Women aged 18 years and older, diagnosed with MS disease for the last 2 years; no history of other disabling diseases; physically able to participate in the study and perform yoga exercises	Randomized: 60 Analyzed:60 Attrition: 0% (0/60)	Iran Unclear (not specified) RCT	Nonprofit: financial support from Yasuj University of Medical Sciences
Negaresh, 2018 **Aerobic Exercise** Cycling Postintervention, 0 weeks Fair	NR	Multiple sclerosis	Inclusion based on the following criteria: (a) RRMS type (revised McDonald criteria19), (b) general BMI ranging between 20 to 30 kg/m^2, EDSS: 4, and (d) age >22 years.	Randomized: N=66 Analyzed:61 Attrition: 9% (5/66)	Iran Outpatient clinic RCT	NR
Nilsagard, 2012 **Postural Control** Motion gaming Postintervention, 7 weeks Fair	At the final data collection, the balance exercise group reported 10 falls during the study period compared with 14 in the nonexercise group. No falls occurred during balance exercise, data collection or travelling to or from the appointments. No other adverse events were reported.	Multiple sclerosis	Patients diagnosed with MS in accordance with the revised McDonald criteria; subjectively perceived impaired balance function in standing or walking activities; and the ability to walk 100 m without resting	Randomized: 84 Analyzed:80 Attrition: 4.8% (4/84)	Sweden Unclear (Home or Clinic) RCT	Nonprofit: funded by the Uppsala-Örebro Regional Research Council, the Research Committee of Örebro County Council, and the Norrbacka-Eugenia Foundation

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
Niwald, 2017 **Aerobic Exercise** Cycling Postintervention, 0 weeks Fair	NR	Multiple sclerosis	Diagnosed MS Age >18 years Informed consent to participate in the study Ability to perform aerobic exercises	Randomized: N=53 Analyzed: NR Attrition: NR	Poland Inpatient Pre-post	Young Scientists of the Medical University of Lodz
Norouzi, 2019 **Postural Control** Balance exercises Immediately postintervention, 4 weeks Fair	NR	Spinal cord injury	Inclusion Criteria: Paraplegic veterans with SCI at L3, L4 (ASIA B-D)	Randomized: 30 Analyzed: 30 Attrition: 0% (0/30)	Iran Setting Outpatient clinic RCT	NR
Nsenga, 2013 **Aerobic Exercise** Cycling Postintervention, 0 weeks Fair	NR	Cerebral palsy	CP (Gross Motor Function Classification System (GMFCS) levels I and II	Randomized: N=24 Analyzed: 20 Attrition: 17% (4/24)	France School Pre-Post	NR
Nsenga-Leunkeu 2012 **Aerobic Exercise** Treadmill Postintervention, 0 weeks Fair	None reported	Cerebral palsy	Convenience sample children from special education school 10 to 16 years old	28 randomized 24 analyzed 4/28=14% attrition	Canada RCT	NR

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
Nsenga–Leunkeu, 2012 **Aerobic Exercise** Treadmill Postintervention, 0 weeks Fair	None of this group experienced any limitation of walking because of pain.	Cerebral palsy	Children and adolescents with CP (GMFCS27 levels I or II; age range, 10 to 16 years)	Randomized: N/A Analyzed: 24 Attrition: 14.3% (4/28)	NR Outpatient clinic Matched pairs cohort	NR
Ortiz-Rubio, 2016 **Muscle Strength** Postintervention, 0 weeks Good	NR	Multiple sclerosis	Diagnosis of relapsing-remitting MS, secondary progressive MS, or primary progressive MS according to the criteria formulated by McDonald et al; adults between the ages of 18 and 65 years; patients with an Expanded Disability Status Scale <7.5; and patients with a Mini-Mental State Examination >24. Patients reported upper limb impairment and had at least on 1 hand a pathological Nine Hole Peg Test with 2 standard deviations above the mean normal values published by Oxford Grice et al at screening.	Randomized: 37 Analyzed: 37 Attrition: 0% (0/37)	Spain Home-based RCT	NR

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
Ozkul, 2020 **Postural Control** Balance Exercises Motion Gaming Postintervention, 0 weeks Fair	None reported (No adverse or harmful events in both groups)	Multiple Sclerosis	Diagnosis of MS; 18–65 years old a, Expanded Disability Status Scale (EDSS) score under 6	Randomized: 54 (51 assigned to intervention) Analyzed: 39 Attrition: 24% (13/54)	Turkey Outpatient rehabilitation RCT	None
Ozkul, 2020b **Multimodal Exercise** Immediately Postintervention, 8 weeks Fair	Reported no adverse or harmful events occurred.	Multiple sclerosis	Diagnosis of relapsing-remitting MS, adults age 18–65 with EDSS score < 4, relapse-free for the last 3 months, with cognitive impairment values that were below at least one.	Randomized: 34 Analyzed: 34 Attrition: 0% (0/34)	Turkey Outpatient Neurorehabilitation Clinic RCT	None
Park, 2014 Postintervention, 8 weeks (within 2 months after 8-week intervention) **Postural Control** Hippotherapy Poor	NR	Cerebral palsy	Inclusion Criteria: age 3 to 12 years, body weight less than 40 kg, and gross motor function classification system (GMFCS) level I to IV	Randomized: NA Analyzed: 55 Attrition: 17% (11/66)	Republic of Korea Outpatient clinic Cohort	NR

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
Peri, 2017 **Aerobic Exercise** Robot-Assisted Gait Training Postintervention, 4-10 weeks Poor	NR	Cerebral palsy	Inclusion criteria: age 4-17, spastic bilateral CP, able to communicate, able to walk independently, femur length >21cm	Randomized: N=44 Analyzed: 44 Attrition: 0%	Italy Outpatient Quasiexperimental, nonrandomized	NR
Pourazar, 2020 **Postural Control** Motion Gaming Postintervention, 0 weeks Fair	NR	Cerebral Palsy	Girls with 7 to 12 years with Spastic Hemiplegic Cerebral Palsy, levels I and II (MACS), GMFCS score range 1 to 3 and able to walk without an assistive device	Randomized: 20 Analyzed: 20 Attrition: 0% (0/20)	Iran Outpatient rehabilitation RCT	None
Pompa, 2017 **Aerobic Exercise** Robot-Assisted Gait Training Postintervention, 4 weeks Fair	NR	Multiple sclerosis	Diagnosis of MS, age 25-65, EDSS 6-7.5, Mini Mental State Exam >24	Randomized: N=50 Analyzed: 43 Attrition: 14%	Italy Inpatient Rehabilitation RCT	Santa Lucia Foundation and Italian Ministry of Health

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
Qi, 2018 **Postural Control** Tai Chi Postintervention, 6 weeks Fair	NR	Spinal cord injury	Right-handed SCI patients who met the diagnostic criteria for SCI according to the American Spinal Injury Association; between 20 and 70 years old; able to communicate and follow instructions, and able to maintain a sitting posture for more than 30 min in a wheelchair	Randomized: 40 Analyzed:40 Attrition: 0% (0/40)	China Unclear RCT	Government: Financially supported by Research Project of Shanghai Administration of Sports (16Z015)
Qi, 2018a **Muscle Strength** Immediately postintervention, 6 weeks Fair	NR	Cerebral palsy	NR (Children with spastic CP)	Randomized: 100 Analyzed: 100 Attrition: 0% (0/100)	China NR RCT	None
Razazian, 2016 **Aerobic Exercise** Aquatics Postintervention, 8 weeks Poor	NR	Multiple sclerosis	Women diagnosed with primary-progressive secondary-progressive MS or relapsing-remitting progressive-relapsing MS as diagnosed by neurologists, aged between 25 and 50 years, Expanded Disability Status Scale e6, receiving stable, regular, and monitored pharmacological treatment of MS (immune modulatory treatments)	Randomized: 54 Analyzed:54 Attrition: 0% (0/54)	Iran Gym, aquatic rehab. center RCT	Nonprofit

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
Roppolo, 2013 **Multimodal Exercise** Immediately postintervention, 12 weeks Fair	NR	Multiple sclerosis	Inclusion Criteria: Women with relapsing MS mean ages 18 to 60 years old, and EDSS scores 0 to 3	Randomized: 35 Analyzed: 35 Attrition: 2% (1/35)	Italy Outpatient clinic Quasiexperimental study	NR
Russo, 2018 **Aerobic Exercise** Robot-Assisted Gait Training Postintervention, 18 weeks Fair	None	Multiple sclerosis	Inclusion Criteria: relapsing-remitting MS, EDSS 3.0-5.5, Montreal Cognitive Assessment Score at least 24, no other neurological or orthopedic comorbidities, stable medication for 6 months	Randomized: N=45 Analyzed: 45 Attrition: 0%	Italy Outpatient RCT	NR
Sadeghi Bahmani, 2019 **Aerobic Exercise** Aerobics **Postural Control** Balance Postintervention, 8 weeks Fair	NR	Multiple sclerosis	Inclusion Criteria: Women with MS 18 to 65 years old, EDSS score <6	Randomized: 92 Analyzed: 71 Attrition: 23% (21/92)	Iran Outpatient clinic RCT	NR

Author, Year **Intervention Type** **Duration of Postintervention Followup** **Quality** **(See Appendix B for Full Citation)**	**Harms**	**Condition**	**Inclusion Criteria**	**Number Randomized** **Analyzed** **Attrition**	**Country** **Setting** **Study Design**	**Funding Source**
Sadeghi Bahmani, 2020a (aquatic) **Aerobic Exercise** Aquatic Postintervention, 5 weeks Fair	NR	Multiple Sclerosis	Diagnosis of MS;18 to 65 year old women, EDSS score < 6	Randomized: 62 Analyzed: 39 Attrition: 24% (13/54)	Iran Setting (outpatient, rehabilitation) RCT	Not reported
Sadowsky, 2013 **Aerobic Exercise** Cycling Postintervention, 0 weeks Poor	NR	Spinal cord injury	Diagnosed with chronic SCI, defined as >16 months following injury at the time of initial evaluation at the center.	Randomized: This was a nonrandomized study	USA Outpatient clinic Retrospective analysis	Deans Fund at Washington University School of Medicine, Barnes-Jewish Hospital Foundation, the Barnes-Jewish Hospital Auxiliary Foundation , Christopher Reeve Paralysis Foundation, the Nextsteps Foundation, the Sam Schmidt Foundation, Gateway to a Cure Foundation, and the Eric Westacott Foundation and, in part, by the Intramural Research Program at the NIH Clinical Center.

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
Salci, 2016 **Postural Control** Balance Postintervention, 6 weeks Fair	4.2% (2/48) discontinued intervention reported acute exacerbation and femur fracture after fall 4.2% (2/48) discontinued intervention reported acute exacerbation and traffic accident 4.2% (2/48) discontinued intervention without any reason Study states: "No adverse effects of training were reported in the groups".	Multiple sclerosis	Diagnosis of MS (McDonald criteria); older than 18 years, an EDSS score between 3 and 5 with prominently ataxic problems; discontinuing the use of corticosteroids for 3 months prior to the study; and having no acute exacerbations and no change in MS-specific medications within 3 months of the study	Randomized: 48 Analyzed: 42* Attrition: 11% (6/48) *Studies states that n=0 were excluded from the analysis yet the n-analyzed was 42/48, so there was no ITT.	Turkey University RCT	None
Samaei 2014 **Aerobic Exercise** Treadmill Postintervention, 0 weeks Fair	None reported	Multiple sclerosis	Able to walk 10 meters in less than 10 minutes Score greater than 3 on GNDS limb score	34 randomized 31 analyzed 3/34=9% attrition	Iran	Government/university

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
Sandroff, 2017 **Multimodal Exercise** Mid-intervention (12 weeks into intervention); Immediately postintervention Fair	NR	Multiple sclerosis	Between 18 and 64 years of age; definite MS diagnosis based on neurologist's verification using standard diagnostic criteria; neurologist's verification of EDSS score between 4.0 and 6.0 based on the participant's most recent neurologist administered score (i.e., onset of substantial MS-related mobility disability); engaging in low levels of physical activity (i.e., participating in <2 days of at least 30 min of aerobic and/or resistance exercise per week); being relapse-free over the past 30 days; and low risk for contraindications for exercise testing and training based on no more than one “yes” response on all Physical Activity Readiness Questionnaire items.	Randomized: 83 Analyzed: 62 Attrition: 25.3% (21/83)	USA Outpatient clinic RCT	This paper was supported by a grant from the National Multiple Sclerosis Society (RG 4991A3/1).
Sangelaji, 2014 **Multimodal Exercise** Postintervention, 0 weeks Poor	NR	Multiple sclerosis	Suffering from recurrent and improving type of MS, 18 to 50 years old, not having had any MS attack in the last 3 months and consuming various types of interferon for prevention of MS attacks, EDSS scores of 0-4	Randomized: 72 Analyzed: 55 Attrition: 23.6%% (17/72)	Iran PT clinic RCT	The study is self-funded

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
Sangelaji, 2016 **Multimodal Exercise** Postintervention, 0 weeks Fair	NR	Multiple sclerosis	1. Definite relapse-remaining MS 2. Adults between 18 and 50 years of age 3. An EDSS level of 0-5 4. Right-handed 5. No history of systemic disease, concomitant neurological disorders, epilepsy, heart diseases, anemia, or severe depression.	Randomized: 40 Analyzed: 40 Attrition: 0% (0/40)	Iran PT clinic RCT	The study is funded by Sport Science Research Institute of Iran.
Scholtes, 2010 Scholtes, 2011 Scholtes, 2008 (check QR, only 2 studies listed - 2010, 2012) **Muscle Strength** Postintervention, 6 weeks Fair	NR	Cerebral palsy	(1) age between 6 and 13 years, (2) able to accept and follow verbal instructions, (3) able to walk independently indoors, with or without walking aids (Gross Motor Function Classification System [GMFCS] levels I–III), and (4) able to participate in a group training program.	Randomized: 51 Analyzed: 49 Attrition: 3.9% (2/51)	Netherlands School RCT	Study was supported financially by a grant from the Johanna Kinder-Fonds (2005⁄0123-357), the Adriaanstichting, and the Phelps Stichting (2006016).
Shin, 2014 **Aerobic Exercise** Robot-Assisted Gait Training Postintervention, 4 weeks Fair	NR	Spinal cord injury	Inclusion Criteria: SCI <6 months, ASIA D, age 20-65	Randomized: N=60 Analyzed: 53 Attrition: 11.7%	Korea Inpatient Rehabilitation RCT	NR

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
Silva e Borges, 2011 Postintervention, 0 weeks (after 6-week intervention) **Postural Control** Hippotherapy Fair	NR	Cerebral palsy	Inclusion Criteria: CP spastic diplegia	Randomized: 40 Analyzed: 40 Attrition: 0% (0/40)	Brazil Outpatient clinic RCT	NR
Slaman, 2014a Slaman, 2014b Slaman, 2015 Slaman, 2010 (check QR study dates - Slaman 2014, 2015a, 2015b listed) **Multimodal Exercise** Mid-intervention (12 weeks into intervention); Immediately postintervention, 24 weeks Fair	NR	Cerebral palsy	Diagnosed with spastic unilateral or bilateral CP; age 16 to 24 years old; and GMFCS levels I to IV.	Randomized: 57 Analyzed: 42 Attrition: 26.3% (15/57)	Netherlands outpatient clinic RCT	NR
Straudi, 2016 **Aerobic Exercise** Robot-Assisted Gait Training Postintervention, 6 weeks Fair	none	Multiple sclerosis	Primary or secondary progressive MS, 18 or older, and severe gait impairment EDSS 6.0-7.0	Randomized: N=58 Analyzed: 54 Attrition: 6.9%	Italy 2 outpatient treatment centers RCT	Multiple Sclerosis Italian Society

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
Straudi, 2019 **Aerobic Exercise** Robot-Assisted Gait Training Postintervention, 12 weeks Good	NR	Multiple sclerosis	Inclusion Criteria: People with MS, 18-65 years old, EDSS of 6.0-7.0	Randomized: 72 Analyzed: 64 Attrition: 12.5% (8/64)	Italy University Hospital RCT	Research Programme of Emilia Romagna Region
Swe 2015 **Aerobic Exercise** Treadmill Pre to post only Good	None reported	Cerebral palsy	Recruited from adolescents from schools and clinics Ability to walk with or without assist device for at least 10 meters	30 randomized 30 analyzed	Done in Singapore. Author in Australia RCT	Funding NR
Tak, 2015 **Postural Control** Motion gaming Immediately postintervention, 6 weeks Fair	NR	Spinal cord injury	Inclusion Criteria: At least 6 months since injury; able to sit independently for at least 30 seconds and absence pain sitting for 2 hours; able to lift arms to head; no musculoskeletal deformities; less than 5 points each leg on American Spinal Cord Injury Association Scale	Randomized: 26 Analyzed: 26 Attrition: 0%	South Korea Rehabilitation hospital RCT	Sahmyook Univerisity

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
Tarakci, 2013 **Multimodal Exercise** Postintervention, 0 weeks Fair	No adverse events occurred during the training period of the current study. There were no deleterious effects of the group exercise training on balance, fatigue and quality of life parameters.	Multiple sclerosis	Diagnosis of definite MS by McDonald criteria, EDSS score between 2.0 and 6.5, no relapse within 30 days, ability to adapt to exercises, having stability in medication and no difficulty in the transportation to the hospital.	Randomized: 110 Analyzed: 99 Attrition: 10% (11/110)	Turkey Outpatient RCT	This research received no specific grant from any funding agency in the public, commercial, or not–for–profit sectors.
Tarakci, 2016 **Postural Control** Motion gaming Postintervention, 12 weeks Fair	NR	Cerebral palsy	Diagnosis of CP (diplegic, hemiplegic, dyskinetic type); age 5–18 years of age; GMFCS level 1, level 2 or level 3; no history of epilepsy; no botulinum toxin A treatment for the lower extremities in the previous 6 months; no excessive spasticity in any joint (score >2 on the MAS); and confirmed mental ability to be able adapt to exercise	Randomized: 38 Analyzed:30 Attrition: 21% (8/38)	Turkey University rehab. center RCT	NR
Taylor, 2013 Bania, 2016 **Muscle Strength** Immediately postintervention, 12 weeks Taylor, 2013: Good Bania, 2016: Fair	A vs. B Short-term muscle soreness was reported by most participants in group A. Minor calf strain: 4.3% (1/23) vs. 0% (0/25) Minor discomfort due to plantar fascia: 4.3% (1/23) vs. 0% (0/25)	Cerebral palsy	Patients with spastic diplegic CP, aged between 14 and 22 years, be classified as level II or III on the GMFCS, and be able to follow simple instructions.	Randomized: 49 Analyzed: 48 Attrition: 2% (1/49)	Australia Local gymnasiums RCT	This trial was supported financially by a grant from the National Health and Medical Research Council of Australia (ID 487321).

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
Tedla, 2014 **Strength interventions** Muscle Strength Exercises Immediately postintervention, 6 weeks Poor	Strong pressure from hand held dynameters was applied but reported to not hurt the skin.	Cerebral palsy	Inclusion Criteria: CP patients 5 to 14 years old with spastic diplegia, GMFCS I - IV	Randomized: 60 Analyzed: 60 Attrition: 3% (2/60)	Saudi Arabia Rehabilitation hospital RCT	NR
Teixeira-Machado, 2017 **Aerobic Exercise** Aerobics (Dance) Postintervention, 12 weeks Poor	NR	Cerebral palsy	Patient 15-29 years old, diagnosed with cerebral palsy, increased muscle tone and no cardiopathy or neoplasy	Randomized: 26 Analyzed: 26 Attrition: 0% (0/26)	Italy Outpatient clinic RCT	NR
Tollar, 2020 **Aerobic Exercise** Cycling **Postural Control** Balance Exercises Motion Gaming **Strength** proprioceptive neuromuscular facilitation (PNF) Immediately postintervention, 5 weeks Fair	NR	Multiple Sclerosis	Diagnosis of MS; male or female sex, age ≥30 years, EDSS score of 4 to 6, a relapse frequency ≤1 per year over the past 5 years to minimize a change in medication, and Mini-Mental State Examination score ≥24	Randomized: 70 Analyzed: 68 Attrition: 3% (2/70)	Hungary and The Netherlands Outpatient clinic RCT	None

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
Totosy de Zepetnek, 2015 **Multimodal Exercise** Immediately postintervention, 16 weeks Fair	NR, one adverse event not related to the study reported.	Spinal cord injury	Inclusion Criteria: People with chronic SCI 1 year post injury, 18 to 65 years old	Randomized: 23 Analyzed: 17 Attrition: 7% (2/23)	Canada Outpatient clinic RCT	Ontario Neurotrauma Foundation Grant
Valent, 2010 **Aerobic Exercise** Hand cycling Postintervention, 0 weeks Fair	NR *this is questionable as one subject dropped out due to elbow tendonitis	Spinal cord injury	Included subjects met the following criteria: (1) had an acute SCI; (2) had a prognosis of 'remaining mainly wheelchair-bound'; (3) had a lesion level of C5 or lower (and consequently were expected to be able to propel a hand cycle); (4) were aged between 18 and 65 years; (5) had sufficient knowledge of the Dutch language; (6) did not have a progressive disease or psychiatric problem; (7) were free of halo-frames or corset; (8) were made familiar with hand cycling and agreed to participate according the training protocol.	Randomized: Nonrandomized study	Netherlands Inpatient rehabilitation Retrospective analysis	Netherlands Organisation for Health, Research and Development

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
van der Scheer 2016 **Aerobic Exercise** Treadmill 16-week intervention Postintervention, 0 weeks Fair	None	Spinal cord injury	Community dwelling inactive manual wheelchair users with SCI	n=29 randomized 27 analyzed 2/29 attrition	The Netherlands RCT Trained in rehabilitation center	Government
Van Wely, 2014a Van Wely, 2014b Van Wely, 2010 **Multimodal Exercise** Mid-intervention (16 weeks into trial); Immediately postintervention, 24 weeks Van Wely, 2014a: Good Van Wely, 2014b: Fair	NR	Cerebral palsy	Children with spastic cerebral palsy, aged 7–13 years who could walk, classification in GMFCS level I–III, understanding of the Dutch language and fulfilling at least one of the following criteria as determined in a telephone interview: less active than the international physical activity norm of less than 1 hour daily at >5 metabolic equivalents, which is moderate or vigorous intensity; no regular participation in sports or (physiotherapeutic) fitness program (i.e., less than three times a week for at least 20 minutes); and experience of problems related to mobility in daily life or sports.	Randomized: 50 Analyzed: 47 Attrition: 6.0% (3/50)	Netherlands Outpatient clinic and participants home RCT	This project is part of the Dutch nationalLEARN 2 MOVE research program and is supported financially by ZonMw (grant number 89000002), Johanna Kinderfonds, Stichting Rotterdams Kinderrevalidatie Fonds Adriaanstichting, Revalidatie-fonds, Phelps Stichting, Revalidatie Nederland, and the Nederlandse Vereniging van Revalidatieartsen.

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
Vermohlen, 2018 Protocol: Wollenweber, 2016 **Postural Control** Hippotherapy End of treatment (after 12-week intervention) Fair	A (n=30) vs. B (n=37) Patients with adverse events: 13 (43%) vs. 15 (41%) Number of patients with adverse events that are considered serious adverse events: 1 (3%) vs. 2 (5%)	Multiple sclerosis	Inclusion Criteria: confirmed multiple sclerosis with spasticity of the lower limbs, EDSS score between 4 and 6.5, written informed consent of the patient, approval of the responsible study physician, legal competence, minimum age of 18 years	Randomized: 70 Analyzed: 41 (67 analyzed for modified ITT) Attrition: 41% (29/70)	Germany Outpatient clinic RCT	Nonprofit
Wallard, 2017 Wallard, 2018 **Aerobic Exercise** Robot-Assisted Gait Training Postintervention, 4 weeks Poor	NR	Cerebral palsy	Inclusion Criteria: children 8-10 years old with bilateral spastic CP GMFCS Level II, walk 60m with or without assistive device	Randomized: N=30 Analyzed:30 Attrition: 0%	France Outpatient RCT	NR
Wens, 2015b **Multimodal Exercise** Postintervention, 0 weeks Fair	No dropout or adverse events were reported during the trial period	Multiple sclerosis	MS patients diagnosed according to McDonald criteria (EDSS range 1–5), aged >18 years	Randomized: 34 Analyzed: 34 Attrition: 0% (0/34)	NR NR RCT	Nonprofit MS Fund, Limburg, Flanders, Belgium
Williams, 2020 **Multimodal** Postintervention, 0 weeks and 8 weeks Fair	No adverse events were reported as a result of the intervention by either group.	Multiple sclerosis	Diagnosis of MS made by a neurologist, able to walk 10 meters with or without an aid within 2 minutes, no relapse of their MS in the past 4 weeks, and no other neurological or orthopedic condition that would affect their function.	Randomized: 50 Analyzed: 44 Attrition: 12% (6/50)	Australia Outpatient and home RCT	Nonprofit agency

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
Willoughby 2010 **Aerobic Exercise** Treadmill Postintervention, 10 weeks Fair	One B child dropped out due to back pain	Cerebral palsy	Recruited children from school for children with disabilities	33 randomized 26 analyzed 7/33=21% attrition for 9-week study	Done in Singapore, Author Australia Done at schools RCT	NR
Wu, 2017a "Robotic resistance treadmill training improves locomotor function in children with cerebral palsy: a randomized controlled pilot study" **Aerobic Exercise** Robot-Assisted Gait Training Postintervention,8 weeks (after 6-week intervention) Fair	NR	Cerebral palsy	Inclusion Criteria: bilateral spastic CP, aged 4 to 14 years, without botulinum toxin treatment and orthopedic surgery or neurosurgery in the 6 months before the onset of training, GMFCS I to IV, able to signal pain, fear, or discomfort reliably, with mild scoliosis (Cobb angle <20), passive range of motion within functional limits, and able to follow instructions on behavior tests	Randomized: N=23 Analyzed: 20 Attrition: 13% (3/23)	US Outpatient clinic RCT	Government

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
Wu, 2017b "The effects of the integration of dynamic weight shifting training into treadmill training on walking function of children with cerebral palsy– a randomized controlled study" **Aerobic Exercise** Robot-Assisted Gait Training Postintervention,8 weeks (after 6-week intervention) Fair	NR	Cerebral palsy	Inclusion Criteria: bilateral spastic CP, age 4 to 16 years, GMFCS I-IV, able to signal pain, fear or discomfort reliably, passive range of motion within functional limits (ankle dorsiflexion = neutral; knee flexion = 0–120°; hip flexion = 0–90°; and hip extension = 0–10°), if scoliosis is present, Cobb angle < 20°, no Botulinum toxin treatment within past 3 months, no orthopedic surgery or neurosurgery within the past 6 months	Randomized: N=23 Analyzed: 21 Attrition: 8.7% (2/23)	US Outpatient RCT	NIDRR/RERC Government
Yang 2013 **Aerobic Exercise** Treadmill Pre to post, crossover with 2 months rest between 8 week intervention Fair	One drop out due to wrist pain worsening during use of walker	Spinal cord injury	SCI C1 to L1 > 7 months ago Able to walk > 5 meters with walking aid or braces Able to attend 5x/week training Recruitment occurred over 5 years	n=22 randomized and 20 analyzed 2/22	Canada RCT, single blind, cross over design with 2 months rest between	Government and Foundation

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
Yazgan 2020 **Postural Control** Motion Gaming Postintervention, 0 weeks Fair	None reported	Multiple Sclerosis	Diagnosis of MS; 25 to 60 years old, ambulatory without relapses in 3 months, EDSS between 2.5 and 6	Randomized: 47 Analyzed: 42 Attrition: 10% (5/47)	Turkey Setting (outpatient, rehabilitation) RCT	University
Yazici, 2019 **Aerobic Exercise** Robot-Assisted Gait Training Immediately postintervention, 12 weeks Poor	NR	Cerebral palsy	Children with GFMS I-II hemiplegic cerebral palsy, no vision or hearing impairment who were attending a physiotherapy rehabilitation program	Randomized: 24 Analyzed: 22 Attrition: 9.1% (2/22)	Turkey University Rehabilitation Clinic Cohort study	NR
Yildirim, 2019 **Aerobic Exercise** Robot-Assisted Gait Training Immediately postintervention, 8 weeks Fair	NR	Spinal cord injury	18-65 years olds with SCI ASIA A-D complete or incomplete, injury within 6 months, ambulatory pre-injury	Randomized: 88 Analyzed: 88 Attrition: 0% (0/88)	Turkey Rehbialita-tion hospital RCT	NR

Author, Year Intervention Type Duration of Postintervention Followup Quality (See Appendix B for Full Citation)	Harms	Condition	Inclusion Criteria	Number Randomized Analyzed Attrition	Country Setting Study Design	Funding Source
Young, 2019 **Aerobic Exercise** Aerobics 12 weeks 0 weeks Fair	A vs. B vs. C Total AEs: 3 vs. 1 vs. 0 Falls: 0 vs. 0 vs. 0 MSK-related: 3 vs. 0 vs. 0 CV-related: 0 vs. 1 vs. 0	Multiple sclerosis	PDSS between 0 to 6 (8=bedridden)	Randomized: 81 Analyzed: 81 presumed (100%) Attrition: 20 (25%)	USA Outpatient RCT	Government
Zoccolillo, 2015 **Postural Control** Motion gaming Postintervention, 8 weeks Poor	1 patient withdrew due to adverse event not related to the intervention (external exoskeleton for standing up in front of the Kinect was broken, damage occurred outside of the study.	Cerebral palsy	Clinical diagnosis of CP; age between 4 and 14 years; level of GMFC between I and IV	Randomized: 22 Analyzed: 15 Attrition: 31.8% (7/22)	Italy Outpatient clinic Crossover RCT	Government Italian Ministry of Health

Abbreviations: AE = Adverse Events; BAI = Beck Anxiety Inventory; BBS = Berg Balance Scale; BMD = bone mineral density; BDI = Beck Depression Inventory; BMI = body mass index; CAB = Chronic Asymptomatic Bacturia; CAPES = Coordenac¸a˜o de Aperfeic¸oamento de Pessoal de Nı´vel Superior; CES-D = Center for Epidemiologic Studies Depression Scale; CHART = Craig Handicap and Assessment Reporting Technique; CP = cerebral palsy; EESS = ENLIST ENL Severity Scale; EDSS = Expanded Disability Status Scale; FAC = functional ambulation category; FAFESP = Fundac¸a˜o de Amparo a´ Pesquisa; FES-I = Falls Efficacy Scale International; FIM=Functional Independence Measure; FISM = Fondazione Italiana Sclerosi Multipla FSS = Fatigue Severity Scale; FSST = Four Square Step Test; GMFM-88= The Gross Motor Function Measure-88; GNDS = Guy’s Neurologic Disability Scale; GMFCS = Gross Motor Function Classification System; HADS-A = Hospital Anxiety Depression Scale-Anxiety; HADS-D = Hospital Anxiety Depression Scale-Depression; HRSD = Hamilton Depression Rating Scale; MACS = Manual Ability Classification System; MAS = Modified Ashworth Scale; MCS = Mental Component Summary; MS = multiple sclerosis; MSI = Multiple Sclerosis Society of Ireland; MSIS = Multiple Sclerosis Impact Scale; MSQOL= Multiple Sclerosis Quality; MMT = Maximal Muscle Testing combined upper and lower limb strength; MusiQoL = MS international Quality of Life; NA = not applicable; NR = not reported; PCS = General Health Perception; PPMS = Primary progressive MS ; NIH = National Institutes of Health; PRT = progressive resistance training RCT = Randomized controlled trial; RRMS = Relapsing-remitting MS; SAE = Serious Adverse Events; SAWS = Satisfaction with Abilities and Well-Being Scale; SD = standard deviation; SCI = spinal cord injury; SCIM = Spinal Cord Independence Measure; SCPE = Surveillance of Cerebral Palsy in Europe; SOT = Sensory Organization Test; SPMS = Secondary progressive MS; TUG= Timed Up and Go Test; WHODAS IFC=The International Classification of Functioning, Disability and Health

See Appendix B. Included Studies for full study citation.

Appendix G. Quality Assessment

Table G-1. Quality assessment of randomized controlled trials

Author, Year (See Appendix B for Full Citation)	Randomization Adequate	Allocation Concealment Adequate	Groups Similar at Baseline (10% or Less Difference)	Outcome Assessors Masked	Care Provider Masked	Patients Masked	Intent-to-Treat Analysis (at Least 95% Analyzed)	Overall Loss to Followup Acceptable/ Differential Loss to Followup Acceptable	Quality Rating
Abbasi, 2019	Yes	Unclear	Yes	Yes	No	No	Yes	Yes/Yes	Fair
Acar, 2016	Unclear	Unclear	No	Unclear	No	No	Yes	Yes/Yes	Poor
Adar, 2017	Unclear	Unclear	No	Yes	No	No	Yes	Yes/Yes	Fair
Afrasiabifar, 2018	Yes	Unclear	No	Yes	No	No	Yes	Yes/Yes	Good
Ahmadi, 2013	Unclear	Unclear	Yes	Unclear	No	No	Yes	Yes/Yes	Fair
Ahmadizadeh, 2020	Unclear	Unclear	Yes	Yes	Unclear	No	Yes	Yes/Yes	Fair
Akkurt, 2017	Unclear	Unclear	No	Yes	No	No	Yes	Yes/Yes	Fair
Al-Sharman, 2019	Unclear	Unclear	No	Yes	No	No	No	No/No	Poor
Alexeeva, 2011	Yes	Yes	No	Yes	No	No	Yes	Yes/No	Fair
Amiri, 2019	Unclear	Unclear	Yes	Unclear	No	No	Yes	Yes/Yes	Fair
Aras, 2019	Unclear	Unclear	Unclear	Unclear	No	No	Yes	Yes/Yes	Fair
Arntzen, 2019	Yes	Unclear	Yes	Yes	No	No	Yes	Yes/Yes	Good
Aydin, 2014	Yes	Unclear	Yes	Unclear	No	No	No	Yes/No (20% vs. 0%)	Fair
Azimzadeh, 2015	No	No; small numbers	Yes	Unclear	No	No	Unclear	Yes	Poor
Bahrami, 2019a	Unclear	Unclear	Yes	Unclear	No	No	No	Yes/Yes	Fair
Baquet, 2018	Yes	Unclear	No	Yes	No	No	Yes	Yes/Yes	Fair
Brichetto, 2015	Unclear	Yes	Yes	Yes	No	No	Yes	Yes	Good
Bryant, 2013	Unclear	Unclear	No	Yes	No	No	Yes	Yes/Yes	Fair
Bulguroglu, 2017	Unclear	Unclear	No	Yes	No	No	No	Yes/Unclear	Poor
Cakit, 2010	Yes	Unclear	No	Yes	No	No	Unclear	No/No	Poor
Calabro, 2017	Yes	Yes	Yes	Yes	No	No	Yes	Yes/Yes	Good
Callesen, 2019	Unclear Cluster randomized	Unclear	Yes	Yes	No	No	No	Overall, Yes (17%) Differential, No: strength (26%) vs. WL (10%); Yes: strength (26%) vs. balance (16%) and balance (16%) vs. WL (10%)	Fair
Carling, 2017	Yes	Yes	No	Yes	No	No	Yes	Yes/Yes	Fair
Castro-Sanchez, 2012	Yes	Yes	Unclear	Yes	No	No	Yes	Yes/Yes	Good

Chen, 2016	Unclear	Unclear	No for smoking but had similar baseline PFTs and QoL scores	Unclear	No	No	Yes based on SF-36 answered questionnaires	Yes/Yes	Fair
Cho, 2020	Unclear	Unclear	No	Unclear	Unclear	No	No	Yes/Yes	Poor
Chrysagis, 2012	Unclear	Yes	No	Yes	No	No	Yes	Yes/Yes	Fair
Claerbout, 2012	Unclear	No	Yes	Yes	No	Unclear	Yes	Yes/Yes	Fair
Collett, 2011	Yes	Unclear	No (DMT, Leg power)	Yes	No	No	Yes (imputed)	No (75% completed 12 weeks) No (53%, 95%, 72%)	Poor
Curtis, 2018	Yes	Unclear	No - gender	Yes	No	No	No	No control lost more	Fair
Dalgas, 2009 Dalgas, 2010	Unclear	Unclear	Yes	No	No	No	No	Yes	Fair
Demuth, 2012	Unclear	Unclear	Yes	Yes	No	No	No	Yes	Fair
Deutz, 2018	Unclear	Unclear	Unclear	Unclear	No	No	Unclear	No (29%)	Poor
Dodd, 2011	Yes	Yes	Yes	Yes	No	No	Yes LVCF	Yes	Good
Doulatabad, 2012	Unclear	Unclear	Unclear	Unclear	No	No	No	Unclear	Poor
Duarte Nde, 2014	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	Yes/Yes	Fair
Duff, 2018	Yes	Unclear	No	Yes	No	No	Yes	Yes	Fair
Duffell, 2014	Unclear	Unclear	Unclear	Unclear	No	No	Unclear	Unclear	Poor
Ebrahimi, 2015	Unclear	Unclear	No	Yes	No	No	No (88%)	Yes/No (6% vs. 18%)	Poor
Elnaggar, 2019	Yes	Yes	No	Yes	No	No	No	Yes/Yes	Fair
El-Shamy, 2018	Yes	Yes	No	Yes	No	No	Yes	Yes/Yes	Fair
Emara, 2016	Yes	Unclear	Yes	Yes	No	No	No (91%)	Yes	Fair
Esclarin-Ruz, 2014	Unclear	Unclear	No	Yes	No	No	Unclear	Yes/Yes	Fair
Faramarzi, 2020 (Banitalebi, 2020)	Unclear	Unclear	Unclear-characteristics based on disability levels	No	No	No	Yes	Yes/Yes	Fair
Field-Fote, 2011 (Sandler, 2017)	Unclear	Unclear	Yes	Yes	No	No	No	Yes	Fair
Forsberg, 2016	Yes	Yes	Yes	Yes	No	No	No	Yes	Fair
Fosdahl, 2019b	Unclear	No	No	Yes	No	No	Yes (imputation for 6MWT)	Yes	Fair
Fowler, 2010	Unclear	Unclear	No - vision	Yes	No	No	No	Yes	Fair
Fox, 2016	Yes	Yes	No	Yes	No	No	No	Yes	Fair
Galea, 2018	Yes	Yes	Yes	Yes	No	No	Yes	No/No	Fair
Gandolfi, 2015	Yes	Yes	Yes	Yes	No	No	No	Yes	Fair

Garrett, 2013a "Exercise in the community for people with minimal gait..." (Garrett, 2013b)	Yes	Yes	No	Yes	No	No	No	No	Poor
Gervasoni, 2014	Unclear	Unclear	Yes	NR	No	No	No	Yes	Fair
Giangregorio, 2012 (Hitzig, 2013; Craven, 2017;Kapadia, 2014)	Yes	Yes	Yes	Yes	No	No	Yes	No	Fair
Gibson, 2018	Yes	Yes	Yes	Yes	No	No	Yes	No	Good
Gorman, 2019	Yes	Yes	No	No (not at both sites)	No	No	Yes	Yes/Yes	Fair
Grecco, 2013	Unclear	Unclear	Yes	Yes	No	No	No	Yes	Fair
Grecco, 2014	Yes	Yes	Yes	Unclear	Unclear	No	Yes	Yes	Fair
Hasanpour Dehkordi, 2016 "Influence of…"	Yes	Unclear	Unclear	Unclear	No	No	Unclear	Unclear	Poor
Hasanpour-Dehkordi, 2016 "Effects of…"	No	No	Unclear	Yes	No	No	Unclear	Unclear	Poor
Hassanpour-Dehkordi, 2014	Unclear	Unclear	Unclear	Unclear	No	No	Unclear	Unclear	Poor
Hebert, 2011 (Hebert, 2009)	Yes	Yes	Yes	Yes (except patient-reported)	Unclear	No	Yes	Yes	Fair
Heine, 2017	Yes	Yes	No	Yes	No	No	Unclear	2 mos: Yes 4 mos: Yes 6 mos: Yes/No 12 mos: No	Fair
Herrero, 2012	Yes	Yes	Yes	Yes	No	No	Yes	Yes/Yes	Fair
Hochsprung, 2017	Yes	Unclear	No	Yes	No	No	No	Yes/Unclear	Poor
Hogan, 2014	No	Unclear	No	Yes	No	No	No	No/No	Poor
Hota, 2020	Unclear	Unclear	No	Unclear	Unclear	No	Yes	Yes/Yes	Fair
Hsieh, 2018	Unclear	Unclear	Yes	Yes	No	No	Unclear	Yes/Yes	Fair
Hsieh, 2020	Yes	Unclear	Unclear	Unclear	No	No	Yes	Yes/Yes	Fair
Huang, 2015	Unclear	Unclear	Yes, but few variables	No	No	No	Yes	Yes/Yes	Fair
In, 2018	Unclear	Unclear	Yes	Yes	No	No	No	Yes/Yes	Fair
Johnston, 2011	Yes	Unclear	Unclear (some differences)	Unclear (2 sites yes, 1 site no)	No	No	No	No (23%)/Yes	Fair
Jones, 2014a "...results from a randomized clinical trial"	Unclear	Unclear	No (several differences)	No	No	No	Unclear	Unclear	Poor
Jones, 2014b "…results from a secondary analysis…"	Unclear	Unclear	Unclear	NR	NR	No	No 41/48 analyzed	No 38/48 for 6 months	Poor
Jonsdottir, 2018	Yes	Yes	No	Yes	No	No	Yes	Yes	Fair
Jung, 2014	Unclear	Unclear	Unclear (some differences)	No	No	No	Yes	Yes/Yes	Fair

Kalron, 2016	Unclear	Yes	Yes	Unclear	Unclear	No	Yes (6.6% missing)	Yes/Yes	Fair
Kalron, 2017	Yes	Yes	Yes	Yes (except patient-reported)	Unclear	No	No	Yes	Fair
Kara, 2020	Yes	Unclear	Yes	Yes	No	No	No	Yes/Yes	Fair
Kargarfard, 2018	Yes	Unclear	Yes	Unclear	No	No	Yes (LOCF)	Yes	Fair
Kaya Kara, 2019	Yes	Unclear	Yes	Yes	No	No	Yes	Yes	Fair
Kerling, 2015	Unclear	Yes	No	Yes (primary outcomes objective)	No	No	Yes (LOCF)	No/Yes	Fair
Khalil, 2018	Unclear	Unclear	No	Yes	No	No	No	Yes	Fair
Kim, 2015	Yes	Yes	No	Unclear	No	No	Unclear	Unclear	Fair
Kjolhede, 2016	Unclear	Unclear	Yes	No	No	No	No	Yes	Fair
Klobucka, 2020	Unclear	Unclear	No	NR	No	No	Yes (immediately after treatment); at 3-4 month LTF only RAGT reported	Yes (immediately post treatment); No 3-4 month 24% LTF in RAGT	Poor
Kooshiar, 2015	No	No	Yes	Unclear	No	No	Yes	Yes/Yes	Fair
Kressler, 2013	Unclear	Unclear	Unclear (no demographics)	Unclear	No	No	Yes	Unclear	Fair
Kumru, 2016	Unclear	Unclear	Yes	Yes	No	Yes	Yes	Yes/Yes	Fair
Kwon, 2015	Yes	Yes	Yes	Yes	No	No	Yes	Yes/Yes	Good
Lavado, 2013	Yes	No	Unclear	Yes	No	No	Yes	Yes/Yes	Fair
Lee, 2013	Unclear	Unclear	Yes (limited)	Yes	No	No	Yes	Unclear	Fair
Lee, 2014	Unclear	Unclear	Yes (limited)	Unclear	No	No	Yes	Unclear	Poor
Liu, 2019	Unclear Unclear	Unclear Unclear	No Yes	Unclear Unclear	No No	No No	No No	Overall: No Differential: Yes No	Fair
Lucena-Anton, 2018	Yes	Unclear	Yes	Yes	No	No	Yes	Yes/Yes	Fair
Makhov, 2018	Unclear	Unclear	Unclear	Unclear	No	No	Unclear	Unclear	Poor
Marandi, 2013a "A comparison of 12 weeks…"	Unclear	Unclear	No	Unclear	No	No	No (79%)	No (21%), Yes	Poor
Marandi, 2013b "A comparison between pilates…"	Unclear	Unclear	No	Unclear	No	No	No	No	Poor
Matusiak-Wieczorek, 2020	Unclear	Unclear	No	Unclear	No	No	Yes	Yes/Yes	Fair
Midik, 2020	Unclear	Unclear	No	No	Yes	No	Yes	Yes/Yes	Fair
Mogharnasi, 2019	Unclear	Unclear	Yes	Unclear	No	No	Yes	Yes	Poor
Moraes, 2020	Unclear	Unclear	Yes	Yes	No	No	Yes	Yes, Yes	Fair

Musselman, 2014 (companion to Yang, 2014)	Yes	Yes	Yes except for self-selected speed for endurance training	Yes	No	No	Yes	Yes	Fair
Mutoh, 2019	Yes	Unclear	Yes	Yes	No	No	Yes	Yes/Yes	Fair
Najafidoulatabad, 2014	Unclear	Unclear	Yes	Unclear	No	No	Unclear (# eligible, LTF NR)	Unclear (# eligible, LTF NR)	Poor
Negaresh, 2019	Unclear	Unclear	Yes	Yes	No	No	No	Yes	Fair
Nilsagard, 2013	Yes	Yes	No	Yes	No	No	Yes 95% analyzed	Yes	Fair
Norouzi, 2019	Yes	Unclear	Unclear	Unclear	No	No	Yes	Yes/Yes	Fair
Ortiz-Rubio, 2016	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Good
Ozkul, 2020	Yes	Yes	No	Unclear	Unclear	No	No	No/Yes	Fair
Ozkul, 2020b	Yes	Unclear	Yes	Yes	Unclear	No	Yes	Yes/Yes	Fair
Pompa, 2017	Yes	No	No	Yes	No	No	No	Yes	Fair
Pourazar, 2020	Unclear	Unclear	Yes	Unclear	Unclear	No	Yes	Yes/Yes	Fair
Qi, 2018a "Therapeutic…"	Unclear	Unclear	Yes	Unclear	Unclear	No	Yes	Unclear	Fair
Qi, 2018b "The effect…"	Yes	Unclear	Yes	No	No	No	Yes	Yes/Yes	Fair
Razazian, 2016	No	Unclear	No	Yes	No	No	Unclear	Unclear	Poor
Russo, 2018	Yes	Yes	Unclear	Yes	No	No	Yes	Yes	Fair
Sadeghi Bahmani,2019a	Yes	Yes	No	Unclear	No	No	Yes	Yes/Yes	Fair
Sadeghi Bahmani,2019b	Yes	Yes	Yes	Unclear	No	No	No	Yes/Yes	Fair
Salci, 2017	Unclear	Unclear	Yes	No	No	No	No	Yes	Fair
Samaei, 2016	Unclear	Unclear	Yes	No	No	No	No	Yes	Fair
Sandroff, 2017	Unclear	Unclear	Yes	No	No	No	No	No	Fair
Sangelaji, 2014	No	Unclear	Yes	Yes	No	No	No	No	Poor
Sangelaji, 2016	Unclear	Unclear	Yes	Yes	No	No	No	Yes	Fair
Scholtes, 2010	Unclear	Unclear	Yes	Yes	No	No	No	Yes	Fair
Shin, 2014	Unclear	Unclear	Yes	No	No	No	No	Yes	Fair
Silva e Borges, 2011	Unclear	Unclear	Yes	Yes	No	No	Yes	Yes/Yes	Fair
Slaman, 2014	Unclear	Unclear	Yes	Unclear	No	No	No	Yes	Fair
Slaman, 2015a "A lifestyle…"	Yes	Unclear	Yes	No	No	No	No	Yes	Fair
Slaman, 2015b "Can a lifestyle…"	Yes	Unclear	Yes	Unclear	No	No	No	No	Fair
Straudi, 2016	Yes	Yes	No	Yes	No	No	Yes	Yes	Good
Straudi, 2019	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Good
Swe, 2015	Yes	Yes	Yes	Yes	No	No	No	Yes	Good
Tak, 2015	Yes	Unclear	Yes	Unclear	No	No	Yes	Yes/Yes	Fair
Tarakci, 2013	Yes	Unclear	Yes	Yes	No	No	No	Yes	Fair
Tarakci, 2016	Yes	Unclear	Yes	No	No	No	No	No	Fair

Taylor, 2013 and Bania, 2016	Yes	Yes	Yes	Yes	No	No	No	Yes	Good
Tedla, 2014	Unclear	Unclear	Unclear	No	No	No	Yes	Yes (97%)	Poor
Teixeira-Machado, 2017	Yes	Unclear	Yes	Unclear	Unclear	No	Yes	Yes/Yes	Fair
Tollar, 2020	Yes	Unclear	No	Yes	Unclear	No	Yes	Yes/Yes	Fair
Totosy de Zepetnek, 2015	Yes	Unclear	No	Unclear	No	No	No	No/Yes	Fair
van der Scheer, 2016	Unclear	Unclear	No (time since injury)	No	No	No	Yes	Yes/Yes	Fair
Van Wely, 2014a, 2014b	Yes	Yes	No for gender	Unclear	No	No	Yes	Yes/Yes	Fair
Vermohlen, 2018	Yes	Yes	Yes	Yes (except patient-reported)	Unclear	No	Yes	Yes	Fair
Wallard, 2017	Unclear	Unclear	Yes	Yes	No	No	Unclear	Unclear (NR)	Poor
Wallard, 2018	Unclear (NR)	Unclear	Unclear (few variables reported)	Unclear	No	No	Unclear	Unclear (NR)	Poor
Wens, 2015a "Impact…"	Unclear	Unclear	No	Yes	No	No	Unclear	Unclear	Poor
Wens, 2015b "High intensity…"	Unclear	Unclear	Yes, but BMI d= overweight for 2 groups, healthy weight for 1	No	No	No	Yes	Yes/Yes	Fair
Williams, 2020	Yes	Yes	No	Yes	No	No	Yes	Yes/Yes	Fair
Willoughby, 2010	Yes	Yes	Yes	Yes	No	No	No	No (24%)/Yes	Fair
Wu, 2017a "Robotic…"	Yes	Unclear	Unclear (numerous but small differences favoring one group)	Unclear	Unclear	No	No (13% missing)	Yes	Fair
Wu, 2017b "Effects…"	Unclear	Yes	Yes	No	No	No	Yes	Yes/Yes	Fair
Yang, 2014	Unclear	Unclear	Yes	Yes	No	No	No	Yes/Yes	Fair
Yazgan, 2020	Yes	Unclear	No	No	No	No	No	Yes//No	Fair
Yildirim, 2019	No	No	Yes	Unclear	No	No	Yes	Yes	Fair
Young, 2019	Yes	Yes	Yes	Yes	No	No	Yes	No (25%)/Yes	Fair
Zoccolillo, 2015	Unclear	Unclear	Unclear	No	No	No	No	No/No (41%)/Yes	Poor

Table G-2. Quality assessment of quasiexperimental studies

Author, Year (See Appendix B for Full Citation)	Did the Study Attempt To Enroll a Random Sample or Consecutive Patients Meeting Inclusion Criteria (Inception Cohort)?	Were the Groups Comparable at Baseline?	Did the Study Use Accurate Methods for Ascertaining Exposures, Potential Confounders, and Outcomes?	Were Outcome Assessors and/or Data Analysts Blinded to Treatment?	Did the Article Report Attrition?	Did the Study Perform Appropriate Statistical Analyses on Potential Confounders?	Overall Loss to Followup Acceptable? Differential Loss to Followup Acceptable?	Were Outcomes Prespecified and Defined, and Ascertained Using Accurate Methods?	Quality Rating
Aviram, 2017	Unclear	No	Yes	No	Yes	No	Yes	Yes	Fair
Bleyenheuft, 2017	No (quasiexperimental)	No	Yes	Yes (2 outcomes)	No	No	Yes	Yes/Yes	Poor
Burschka, 2014	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	No	Yes	Poor
Kara, 2017	Unclear	Unclear	Unclear	Yes	Yes	No	No (36%)/(63%)	Yes	Poor
Keser, 2011	Unclear	Yes	Yes	Unclear	No	No	Unclear	Yes	Poor
Kirk, 2016	No	unclear	Yes	No	No	No	Unclear	Yes	Poor
Kwon, 2011	No	Yes (limited variables)	Yes	Yes	No	Unclear; at least they did repeated measures analysis	Unclear	Yes	Fair
Lai, 2010	No	No; small numbers	Yes	Yes	Yes	Yes; ANCOVA	Yes	Yes	Fair
Lorentzen, 2015	No	No; n's in Gr 1=34, Gr 2=12; diff % but small #s	Yes	Unclear	No	Unclear; model appears to focus on interaction; they do correct for multiple comparisons.	Unclear	Yes	Poor
Matusiak-Wieczorek, 2016	No	Yes	No	No	Yes	No	Yes	Yes	Poor
Niwald, 2017	Unclear	Yes	Yes	No	No, but same number enrolled reported for outcomes	No	NR	Yes	Fair
Nsenga Leunkeu, 2012	No (convenience sample)	Unclear	Yes	No	Yes	No	Yes/Unclear	Yes	Fair
Nsenga, 2013	No	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Fair
Peri, 2017	Unclear	No	Unclear	Unclear	No	No	Unclear	Yes	Poor
Roppolo, 2013	Unclear	Yes	Yes	Unclear	Yes	Yes	Unclear	Yes	Fair

Table G-3. Quality assessment of cohort studies

Author, Year (See Appendix B for Full Citation)	Did the Study Attempt To Enroll a Random Sample or Consecutive Patients Meeting Inclusion Criteria (Inception Cohort)?	Were the Groups Comparable at Baseline?	Did the Study Use Accurate Methods for Ascertaining Exposures, Potential Confounders, and Outcomes?	Were Outcome Assessors and/or Data Analysts Blinded to Treatment?	Did the Article Report Attrition?	Did the Study Perform Appropriate Statistical Analyses on Potential Confounders?	Overall Loss to Followup Acceptable? Differential Loss to Followup Acceptable?	Were Outcomes Prespecified and Defined, and Ascertained Using Accurate Methods?	Quality Rating
Harness, 2008	Yes	Yes	Yes	No	Yes	No	Yes/Yes	Yes	Fair
Kim, 2017	Unclear	No	Yes	Unclear	No	No	Unclear	Yes	Poor
Lai, 2015	No	No; small numbers	Yes	Yes	Yes	Yes; ANCOVA	Yes	Yes	Fair
Park, 2014	No	No	Yes	Unclear	Yes	No	Yes (17%), No (24% vs. 0%)	Yes	Poor
Sadowsky, 2013	Unclear	No	Yes	Unclear	No	No	Unclear	Yes	Poor
Yazici, 2019	No	Unclear	Yes	Unclear	Yes	No	Yes/No	Yes	Poor
Valent, 2010	Unclear	Yes	Yes	Unclear	Yes	No	Yes/unclear	Yes	Fair

Appendix H. Strength of Evidence

Table H-1. Strength of evidence for Key Question 2: aerobic exercise for multiple sclerosis

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Aerobic Exercise Aerobics	*Home exercise with DVD or Attention control*	Sleep	2 (N=77) Al-Sharman, 2019 Sadeghi Bahmani, 2019b	Moderate	Consistent	Imprecise	Undetected	Low for benefit	PSQI: 8.0 (3.8) to 4.6 (2.3) vs. 8.9 (4.3) to 7.1 (3.2), p<0.001 Pooled ISI: 3.33, 95% CI 1.03 to 5.64, p=0.005 Total Sleep Time: 333.38 (84.6) to 372.4 (59.4) vs. 325.9 (84.5) to 320 (54), p=0.05
Aerobic Exercise Aerobics	*Attention control*	Function	1 (N=47) Sadeghi Bahmani, 2019b	Moderate	Unknown	Imprecise	Undetected	Insufficient	EDSS: 2.46 (1.50) to 2.27 (1.64) vs. 2.02 (1.84) to 1.98 (1.70), p>0.05
Aerobic Exercise Aerobics	*Pilates*	Function	1 (N=55) Kara, 2017	High	Unknown	Imprecise	Undetected	Insufficient	TUG right: MD -0.47, 95% CI -2.975 to 2.035, p=0.71 TUG left: MD -3.07, 95% CI -6.341 to 0.201, p=0.07
Aerobic Exercise Aerobics	*Pilates*	Balance	1 (N=55) Kara, 2017	High	Unknown	Imprecise	Undetected	Insufficient	BBS: MD -0.67, 95% CI -10.56 to 9.22, p=0.89
Aerobic Exercise Aerobics	*Neuro-rehabilitation*	Function	1 (N=30) Keser, 2011	High	Unknown	Imprecise	Undetected	Insufficient	MSFC: MD -0.002 (0.44) vs. 0.02 (0.23), p>0.05
Aerobic Exercise Aerobics	*Neuro-rehabilitation*	Quality of Life	1 (N=30) Keser, 2011	High	Unknown	Imprecise	Undetected	Insufficient	SF-36 total: MD 0.20 (5.67) vs. 1.73 (7.75), p>0.05
Aerobic Exercise Aerobics	*Neuro-rehabilitation*	Balance	1 (N=30) Keser, 2011	High	Unknown	Imprecise	Undetected	Insufficient	BBS: MD -1.73 (3.03) vs. -1.80 (2.67), p>0.05

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Aerobic Exercise Aquatics	*Usual care, previous activity level or attention control*	Function	1 (N=32) Kargarfard, 2018	Moderate	Unknown	Imprecise	Undetected	Insufficient	Mean (SD) 6MWT: 451 (58) vs. 447 (30) (baseline) 503 (57) vs. 418 (29) (postintervention) Between group difference p<0.001 Sit to Stand: 21.0 (5.7) vs. 21.4 (4.7) (baseline) 16.8 (5.1) vs. 27.3 (4.8) (postintervention) Between group difference p<0.001
Aerobic Exercise Aquatics	*Usual care, previous activity level or attention control*	Quality of Life	1 (N=40) Kooshiar, 2015	Moderate	Unknown	Imprecise	Undetected	Insufficient	Mean (SD) MQLIM: 63.13 (13.02) vs. 65.48 (9.74) (baseline) 80.06 (11.53) vs. 66.52 (6.22) (post-intervention) Between group difference, p<0.001
Aerobic Exercise Aquatics	*Ai-Chi exercises on mat*	ADLs	1 (N=73) Castro-Sanchez, 2012	Low	Unknown	Imprecise	Undetected	Low for benefit	MSIS-29 Physical: 48 (15.91) to 41 (12.37) vs. 46 (18.34) to 45 (17.14), p=0.014 MSIS-29 Psychological: 34 (29.47) to 21 (15.73) vs. 30 (23.53) to 25 (19.36), p=0.023 Differences in MSIS-29 maintained at 30 weeks Barthel Index: 91 (7.12) to 86 (9.23) vs. 87 (10.34) to 88 (8.92), p>0.05

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Aerobic Exercise Aquatics	*Usual care, previous activity level or attention control*	Balance	2 (N=62) Kargarfard, 2018 Marandi, 2013	Moderate	Consistent	Imprecise	Undetected	Low for benefit	Six Spot Step Test, N=30: Right leg dynamic balance: 8.57 (3.64) vs. 10.64 (4.17) (baseline) 6.40 (1.82) vs. 12.65 (6.05) (post-intervention) Adjusted MD -5.88 (SE 1.4), p<0.001 Left leg dynamic balance: 9.12 (4.31) vs. 10.16 (3.76) (baseline) 6.26 (1.95) vs. 12.49 (4.63) (post-intervention) Adjusted MD -6.23 (SE 1.2), p<0.001 BBS, N=32 53.6 (1.7) vs. 52.3 (3.3) (baseline) 55.2 (1.2) vs. 50.2 (4.6) (post-intervention) Between group difference p<0.001
Aerobic Exercise Aquatics	*Usual care, previous activity level or attention control*	Female Sexual Function Index	1 (60) Bahmani, 2020	Moderate	Unknown	Imprecise	Undetected	Low for benefit	Exercise 2x/week vs. 3x/week vs. active control: FSFI: 52.14 vs. 48.80 vs. 42.80, p<0.001

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Aerobic Exercise Cycling	*Usual care, previous activity level or attention control*	Function	6 (n=277) Negaresh, 2018 Hochsprung, 2017 Baquet, 2018 Hebert, 2011 Tollar, 2020 Heine, 2017	Moderate	Consistent	Imprecise	Undetected	Low-strength evidence of no clear benefit	TUG: -3.8 vs. -0.1, favors cycling UE/LE 6MWT: MD 4.0, 95% CI -36.5 to 44.5 32.1 (44.58) vs. 6.3 (49.27), p=0.174 MD 62.7, 95% CI -87 to 2.7, p=1.00 25 foot walk: MD: -0.1, 95% CI -0.4 to 0.2, p=0.49 MSWS: -0.3, 95% CI -2.1 to 1.6, p=0.78 MSIS-29: -6.3 (8.07) vs. 1.0 (3.46), p=0.008 FAP: 3.036 vs. -1.06, no between group comparison provided IPA autonomy indoors: –0.11 (0.088), p=0.203 IPA family role: –0.082 (0.1222), p=0.502 IPA autonomy outdoors: –0.097 (0.125), p=0.438 IPA Social Relations: –0.138 (0.092), p=0.135 IPA Work/education: 0.225 (0.167), p=0.181
Aerobic Exercise Cycling	*Usual care, previous activity level or attention control*	Quality of Life	2 (n=94) Baquet, 2018 Tollar, 2020	Moderate	Inconsistent	Imprecise	Undetected	Insufficient	HAQUAMS: -0.4, 95% CI -4.5 to 3.7, p=0.84 EQ-5 Sum Score: -1.4 (1.7) vs. 0.0 (1.13), p=0.023
Aerobic Exercise Cycling	*Usual care, previous activity level or attention control*	ADLs	1 (89) Heine, 2017	Moderate	Unknown	Imprecise	Undetected	Insufficient	IPA: Autonomy indoors: -0.11 (0.088), p=0.203 Family role: -0.082 (0.1222), p=0.502 Autonomy outdoors: -0.097 (0.125), p=0.438 Social Relations: -0.138 (0.092), p=0.135 Work/education: 0.225 (0.167), p=0.181

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Aerobic Exercise Cycling	*Usual care, previous activity level or attention control*	Balance	1 (26) Tollar, 2020	Moderate	Unknown	Imprecise	Undetected	Insufficient	BBS: 2.5 (2.62) vs. -0.2 (2.62), p=0.015
Aerobic Exercise Robot-Assisted Gait Training	*Usual care, previous activity level or attention control*	Walking	2 (95) Straudi, 2016 Pompa, 2017	Moderate	Inconsistent	Imprecise	Undetected	Insufficient	6MWT: 23.22 (32.23) vs. -0.75 (26.40), p=0.01 10MWT: 0.07 (0.15) vs. 0.01 (0.10), p=0.29 2MinWT: 8.88 vs. 2.81, p>0.05 FAC (functional ambulation category): 6.86 vs. 0.00, p>0.05
Aerobic Exercise Robot-Assisted Gait Training	*Usual care, previous activity level or attention control*	Function	2 (97) Russo, 2018 Straudi, 2016	Moderate	Consistent	Imprecise	Undetected	Low-strength evidence of no clear benefit	TUG: 0.20, 95% CI -3.40 to 3.80, p=0.91 TUG: 2.66 (13.79) vs. -3.96 (10.50), p=0.95
Aerobic Exercise Robot-Assisted Gait Training	*Usual care, previous activity level or attention control*	Quality of Life	1 (52) Straudi, 2016	Low	Unknown	Imprecise	Undetected	Insufficient	SF 36-PCS: 1.67 (7.74) vs. 1.84 (6.77), p=0.99 SF 36-MCS: 5.37 (9.58) vs. 1.60 (9.41), p=0.14
Aerobic Exercise Robot-Assisted Gait Training	*Usual care, previous activity level or attention control*	Balance	2 (97) Straudi, 2016 Russo, 2018	Moderate	Consistent	Imprecise	Undetected	Low for benefit	TBS: 0.48 (SE 0.22), p=0.04 BBS: 3.24 (4.99) vs. 0.87 (6.45), p=0.19
Aerobic Exercise Robot-Assisted Gait Training	*Usual care, previous activity level or attention control*	ADLs	1(43) Pompa, 2017	Moderate	Unknown	Imprecise	Undetected	Insufficient	Rivermean Mobility Index: 0.73, 95% CI -0.85 to 2.31, p=0.37
Aerobic Exercise Robot-Assisted Gait Training	*RAGT without VR*	Function	1 (40) Calabro, 2017	Low	Unknown	Imprecise	Undetected	Insufficient	TUG: -0.064, 95% CI -0.408 to 0.536, p=0.3
Aerobic Exercise Robot-Assisted Gait Training	*RAGT without VR*	Balance	1 (40) Calabro, 2017	Low	Unknown	Imprecise	Undetected	Insufficient	BBS: -0.019, 95% CI -2.403 to 2.365, p=0.8

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Aerobic Exercise Robot-Assisted Gait Training	*RAGT with assistance*	Function	1 (23) Wu, 2017a	Moderate	Unknown	Imprecise	Undetected	Insufficient	6MWT: 49.8, 95% CI -49.85 to 149.45, p=0.33 GMFM-66 total: 0.10, 95% CI -7.74 to 7.94, p=0.98 GMFM-66D: 0.10, 95% CI -8.55 to 8.75, p=0.98 GMFM-66E: 0.10, 95% CI -16.32 to 16.52, p=0.99
Aerobic Exercise Robot-Assisted Gait Training	*Treadmill or Overground walking*	Function	2 (95) Wu, 2017b Straudi, 2019	Low	Consistent	Imprecise	Undetected	Low-strength evidence of no clear benefit	GMFM-66 total: -5.1, 95% CI 13.62 to 3.42, p=0.24 GMFM-66D: 3.6, 95% CI -5.40 to 12.60, p=0.43 GMFM-66E: 0.2, 95% CI -17.79 to 19.19, p=0.98 6MWT: MD 4, 95% CI -10 to 18, p=0.86 25FWT: MD 0, 95% CI -0.06 to 0.05, p=0.98 TUG: MD 7.8, 95% CI -0.2 to 15.8, p=0.25
Aerobic Exercise Robot-Assisted Gait Training	*Overground walking*	QoL	1 (72) Straudi, 2019	Low	Unknown	Imprecise	Undetected	Low-strength evidence of no clear benefit	MSIS-29 motor: -3, 95% CI -9 to 3, p=0.31 MSIS-29 psychological: -2, 95% CI -5 to 1, p=0.22 SF-36 PCS: -1, 95% CI -4 to 3, p=0.13 SF-36 MCS: 1, 95% CI -2 to 4, p=0.94
Aerobic Exercise Robot-Assisted Gait Training	*Overground walking*	Balance	1 (72) Straudi, 2019	Low	Unknown	Imprecise	Undetected	Low-strength evidence of no clear benefit	BBS: 0, 95% CI -2 to 2, p=0.91

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Aerobic Exercise Treadmill	*All comparators*	Function	4(119) Gervasoni, 2014 Jonsdottir, 2018 Samaei, 2014 Ahmadi, 2013	Moderate	Consistent	Imprecise	Undetected	Low for benefit	DGI: 2.16 vs. 2.07, p=0.51 DGI: 0.2, 95% CI -1.95 to 2.27, p=0.87 TUG: -2.83, 95% CI -4.7 to -0.9, p=0.009 TUG: 9.8 (1.7) to 7.5 (1.8) vs. 9.4 (2.3) to 8.9 (0.9), p=0.041 10MWT: 8.68 (1.93) to 7.07 (1.03) vs. 9.16 (1.88) to 9.47 (1.92), p=0.001 2MWT: 120.40 (20.29) to 139.90 (20.78) vs. 121.50 (27.73) to 119.05 (27.12), p=0.001 2MWT: 28.3, 95% CI 13.04 to 43.60, p<0.001 2MinWT: 12.01 (23.6) to 160.1 (35.7) vs. 132.6 (32.3) to 147.5 (29.8), p<0.001 25-foot WT: 8.7 (2.4) to 6.1 (1.8) vs. 7.9 (1.1) to 7.0 (1.6), p=0.001 Modified Riverman Mobility Index: 10.6 (3.2) to 14.3 (2.7) vs.10.5 (2.3) to 11.9 (2.1), p=0.005
Aerobic Exercise Treadmill	*Usual care or waitlist*	Function/ Walking	2 (50) Gervasoni, 2014 Ahmadi, 2013	Moderate	Consistent	Imprecise	Undetected	Low for benefit	DGI: 0.2, 95% CI -1.95 to 2.27, p=0.87 TUG: -2.83, 95% CI -4.7 to -0.9, p=0.009 10MWT: 8.68 (1.93) to 7.07 (1.03) vs. 9.16 (1.88) to 9.47 (1.92), p=0.001 2MWT: 120.40 (20.29) to 139.90 (20.78) vs. 121.50 (27.73) to 119.05 (27.12), p=0.001 2MWT: 28.3, 95% CI 13.04 to 43.60, p<0.001

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Aerobic Exercise Treadmill	*Strength Training*	Function	1 (38) Jonsdottir, 2018	Moderate	Unknown	Imprecise	Undetected	Insufficient	TUG: -2.83, 95% CI -4.7 to -0.9, p=0.009 DGI: 0.2, 95% CI -1.95 to 2.27, p=0.87 2MWT: 28.3, 95% CI 13.04 to 43.60, p<0.001
Aerobic Exercise Treadmill	*Downhill vs. Uphill treadmill training*	Function	1 (31) Samaei, 2016	Moderate	Unknown	Imprecise	Undetected	Insufficient	25-foot WT: 8.7 (2.4) to 6.1 (1.8) vs. 7.9 (1.1) to 7.0 (1.6), p=0.001 2MinWT: 12.01 (23.6) to 160.1 (35.7) vs. 132.6 (32.3) to 147.5 (29.8), p<0.001 TUG: 9.8 (1.7) to 7.5 (1.8) vs. 9.4 (2.3) to 8.9 (0.9), p=0.041 Modified Riverman Mobility Index: 10.6 (3.2) to 14.3 (2.7) vs.10.5 (2.3) to 11.9 (2.1), p=0.005
Aerobic Exercise Treadmill	*Strength Training*	Quality of Life	1 (38) Johsdottir, 2018	Moderate	Unknown	Imprecise	Undetected	Insufficient	SF-12 mental: -3.0, 95% CI -9.43 to 3.38, p=0.34 SF-12 physical: 1.8, 95% CI -2.08 to 5.59, p=0.36
Aerobic Exercise Treadmill	*Strength Training*	Balance	1 (38) Jonsdottir, 2018	Moderate	Unknown	Imprecise	Undetected	Insufficient	BBS: 1.1, 95% CI -1.4 to 3.7, p=0.39
Aerobic Exercise Treadmill	*Usual care or waitlist*	Balance	2 (50) Ahmadi, 2013 Gervasoni, 2014	Moderate	Consistent	Imprecise	Undetected	Low for benefit	BBS: 4.01 vs. 3.15, p=0.33 BBS: 46.20 (6.32) to 53.80 (2.34) vs. 44.50 (9.43) to 41.70 (8.48), p=0.001

Abbreviations: 6MWT = 6-Minute Walking Test; 10MWT = 10-Meter Walking Test; 25FWT=25-Foot Timed Walking Test; BBS = Berg Balance Scale; DGI = Dynamic Gait Index; EDSS = Expanded Disability Status Scale; FAC = Functional Ambulation Category; FAP = Functional Ambulation Profile; GMFM-66 = The Gross Motor Function Measure-66; HAQUAMS = Hamburg Quality of Life Questionnaire in Multiple Sclerosis; IPA = Impact on Participation; MQLIM = Multicultural Quality of Life Index; MD = mean difference; MS = multiple sclerosis; MSFC = Multiple Sclerosis Functional Composite; MSIS = Multiple Sclerosis Impact Scale; NA = not applicable; PSQI = Pittsburgh Sleep Quality Index; RAGT = Robot-Assisted Gait Training; RCT = randomized controlled trial; SD = standard deviation; SF = Short Form; SF 36-MCS = Short Form 36 Mental Health Scores; SF 36-PCS = Short Form 36 Physical Component Score; TBS = Tinetti balance scale; TUG= Timed Up and Go Test

Table H-2. Strength of evidence for Key Question 2: aerobic exercise for cerebral palsy

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Aerobic Exercise Aerobics	*Usual care, previous activity level or attention control*	ADLs	1 (26) Teixeira-Machado, 2018	Moderate	Unknown	Imprecise	Undetected	Insufficient	ICF total change score: -44.56 vs. 14.90, p<0.001
Aerobic Exercise Aerobics	*Usual care*	Running/ mobility	1 (42) Gibson, 2018	Low	Unknown	Imprecise	Undetected	Insufficient	Shuttle Run Test (min): 0.9, 95% CI -0.3 to 2.2, p=0.142 HiMat: 0.8, 95% CI -2.7 to 4.3, p=0.651 10X5 sprint (sec): -1.3, 95% CI -5.4 to 2.8, p=0.535
Aerobic Exercise Aquatics	*Land-based exercise*	Function	(N=32) Adar, 2017	Moderate	Unknown	Imprecise	Undetected	Insufficient	Mean SD: TUG: -0.13 (0.14) vs. -0.16 (0.13), p=0.664 GMGM-88: 0.05 (0.05) vs. 0.05 (0.03), p=0.451 WeeFIM motor: 0.04 (0.04) vs. 0.06 (0.06),p=0.860 WeeFIM total: -0.13 (0.14) vs. -0.16 (0.13), p=0.287 N=24, Mean (SD)
Aerobic Exercise Aquatics	*Rehabilitation exercises*	Function	1 (24) Lai, 2015	Moderate	Unknown	Imprecise	Undetected	Insufficient	GMFM-66: 61.2 (18.7) vs. 64.6 (19.4) (baseline) 66.2 (18.2) vs. 65.3 (19.1) (postintervention) Difference in change score between groups:p=0.007
Aerobic Exercise Aquatics	*Rehabilitation exercises*	Quality of Life	1 (24) Lai, 2015	Moderate	Unknown	Imprecise	Undetected	Insufficient	Cerebral Palsy QoL Scale: for Social, Functioning, Participation, Emotional, Access, Pain and Disability, and Family Health: All NS

Intervention Category, Intervention	**Comparator**	**Outcome**	**Number of Studies (Participants) Author Year (See Appendix B for Full Citation)**	**Study Limitations**	**Consistency**	**Precision**	**Reporting Bias**	**Strength of Evidence**	**Findings, Direction and Magnitude of Effect**
Aerobic Exercise Aquatics	*Rehabilitation exercises*	ADLs	1 (24) Lai, 2015	Moderate	Unknown	Imprecise	Undetected	Insufficient	Vineline Adaptive Behavior Scale for Daily Living: 72.1 (48.5) vs. 93.7 (43.8) (baseline) 76.5 (7.6) vs. 76.4 (10.8) (post-intervention) Difference in change score between groups: p=0.393
Aerobic Exercise Cycling	*Usual care, previous activity level or attention control*	Function	2 (85) Fowler 2010 Bryant 2013	Moderate	Consistent	Imprecise	Undetected	Low for benefit	GMFM-66 pooled: 0.70, 95% CI -0.20 to 1.60, p=0.127 GMFM-88D: 5.4, 95% CI 1.23 to 9.57, p=0.01 GMFM-88E: 2.3, 95% CI 0.20 to 4.40, p=0.03 600-Yard Walk-Run Test: Change from baseline: 5.6, 95% CI 1.6 to 9.5 vs. 2.5, 95% CI -1.1 to 6.0, p=0.24
Aerobic Exercise Cycling	*Usual care, previous activity level or attention control*	Quality of Life	1 (62) Demuth, 2012	Moderate	Unknown	Imprecise	Undetected	Insufficient	Peds Quality of Life Total Score: 3.5, 95% CI -2.0 to 8.8, p=0.21

Intervention Category, Intervention	**Comparator**	**Outcome**	**Number of Studies (Participants) Author Year (See Appendix B for Full Citation)**	**Study Limitations**	**Consistency**	**Precision**	**Reporting Bias**	**Strength of Evidence**	**Findings, Direction and Magnitude of Effect**
Aerobic Exercise Robot-Assisted Gait Training	*Usual care, previous activity level or attention control*	Function	12 RCTs (77); 1 cohort study (24) Wallard, 2017 Wallard, 2018 Klobucka, 2020 Yazici, 2019	High	Consistent	Imprecise	Undetected	Insufficient	GMFM-66D: 4.73, 95% CI -6.14 to 15.60, p=0.39 GMFM-66E: 7.54, 95% CI -2.64 to 17.42, p=0.15 GMFM-88: 1.59, 95% CI -2.19 to 5.37, p=0.410 GMFM-88D: 0.17, 95% CI -0.79 to 1.13, p=0.729 GMFM-88E: 1.14, 95% CI -1.69 to 4.51, p=0.373 6MWT: 43.42, 95% CI 19.64 to 67.21, p<0.001 GMFM-88: MD 9.43, 95% CI 6.989 to 11.891 vs. MD 0.80, 95% CI 0.154 to 1.446, p<0.001 GMFM-88D: MD 8.30, 95% CI 4.699 to 11.901 vs. MD 1.09, 95% CI -0.438 to 2.619, p<0.001 GMFM-88E: MD 9.32, 95% CI 5.329 to 13.310 vs. MD 0.53, 95% CI -0.208 to 1.268, p<0.001
Aerobic Exercise Robot-Assisted Gait Training	*Usual care, previous activity level or attention control*	Balance	1 (24) Yazici, 2019	High	Unknown	Imprecise	Undetected	Insufficient	BBS: 1.25, 95% CI -0.07 to 2.57, p=0.064

Intervention Category, Intervention	**Comparator**	**Outcome**	**Number of Studies (Participants) Author Year (See Appendix B for Full Citation)**	**Study Limitations**	**Consistency**	**Precision**	**Reporting Bias**	**Strength of Evidence**	**Findings, Direction and Magnitude of Effect**
Aerobic Exercise Robot-Assisted Gait Training	*Treadmill training (Partial body-weight supported; Anti-gravity;)*	Function	2 (52) Aras, 2019 Wu, 2017b	Moderate	Consistent	Imprecise	Undetected	Insufficient	6MWT: 39.6 (40.4) vs. 37.6 (20.2) vs. 48.3 (25.1), p>0.05 for all pairwise comparisons 6MWT (3 mo followup): 45.2 (44.4) vs. 48.6 (37.8) vs. 58.2 (22.9), p>0.05 for all pairwise comparisons GMFM-D: 3.6 (2.5) vs. 4.6 (4.6) vs. 3.5 (2.5), p>0.05 for all pairwise comparisons GMFM-D (3 mo followup): 3.6 (2.5) vs. 4.6 (4.6) vs. 3.5 (2.5), p>0.05 for all pairwise comparisons GMFM-E: 2.4 (2.0) vs. 2.6 (1.7) vs. 3.7 (1.9), p>0.05 for all pairwise comparisons GMFM-E (3 mo followup): 2.6 (1.8) vs. 2.6 (1.7) vs. 3.7 (1.9), p>0.05 for all pairwise comparisons GMFM-66 total: –5.1, 95% CI 13.62 to 3.42, p=0.24 GMFM-66-D: 3.6, 95% CI –5.40 to 12.60, p=0.43 GMFM-66-E: 0.2, 95% CI –17.79 to 19.19, p=0.98

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Aerobic Exercise Treadmill	*Usual care, previous activity level or attention control*	Function	2 (53) Chrysagis, 2012 Bahrami, 2019a	Moderate	Consistent	Imprecise	Undetected	Low for benefit	GMFM-D+E: 3.87 vs. 0.69, p=0.007 Self-selected walking speed: 8.06 vs. 0.48, p=0.009 10MWT: 1.080 (0.47) to 1.22 (0.50) [22.46% change] vs. 0.99 (0.56) to 1.02 (0.61) [1.28% change], % change p<0.05 6MWT: 291.13 (160.28) to 342.63 (174.62) [23.68% change] vs. 276.10 (167.19) to 308.57 (181.22)[16.54% change], % change p>0.05
Aerobic Exercise Treadmill	*Usual care*	Quality of Life	1 (30) Bahrami, 2019a	Moderate	Unknown	Imprecise	Undetected	Insufficient	WHOQOL-Brief: 3.55 (.55) to 3.66 (0.59) [3.83% change] vs. 3.33 (0.69) 3.57 (0.67)[8.94% change], % change p>0.05
Aerobic Exercise Treadmill	*Overground walking*	Walking	5 (130) Willoughby, 2010 Swe, 2015 Grecco, 2013 Emara, 2016 Kim, 2015	Moderate	Inconsistent	Imprecise	Undetected	Low strength of evidence for no clear benefit	10MWT: 0.4 (0.04) to 0.5 (0.04) vs. 0.4 (0.03) to 0.6 (0.04), p=0.12 6MWT: 149.7 vs. 44.8, p<0.001 6MWT: -17.00, 95% CI -89.77 to 55.77, p=0.65 10MWT: -0.013, 95% CI -0.23, 0.21, p=0.91 10MWT: 244.33 (115.41) to 219.38 (123.71) vs. 118.36 (89.89) to 135.82 (95.65), p=0.097 6MWT on treadmill: 5.71, 95% CI -53.22 to 64.64, p=0.85 6MWT on overground walking: 24.07, 95% CI -46.80 to 94.94, p=0.51

Intervention Category, Intervention	**Comparator**	**Outcome**	**Number of Studies (Participants) Author Year (See Appendix B for Full Citation)**	**Study Limitations**	**Consistency**	**Precision**	**Reporting Bias**	**Strength of Evidence**	**Findings, Direction and Magnitude of Effect**
Aerobic Exercise Treadmill	*Overground walking*	Function	4 (109) Willoughby, 2010 Swe, 2015 Grecco, 2013 Emara, 2016	Moderate	Inconsistent	Imprecise	Undetected	Low strength of evidence for no clear benefit	5XSit-to-Stand: 21.5 (1.3) to 18.9 (1.0) vs. 21.7 (1.5) to 17.7 (0.8), p=0.26 GMFM-88 D: 12.5 (1.6) to 15.8 (1.5) vs.12.0 (0.7) to 19.2 (2.1), p=0.02, favors spider cage GMFM-88 E: 10.9 (1.3) to 14.8 (1.5) vs.10.4 (0.8) to 17.2 (2.1), p=0.05, favors spider cage TUG: -6.4 vs. -2.0, p=0.004, favors treadmill GMFM-88D: 23.9 vs. 8.1, p<0.001, favors treadmill GMFM-88E: 20.1 vs. 8.2, p<0.001, favors treadmill GMFM-88D: -2.94, 95% CI -16.42 to 10.64, p=0.67 GMFM-88E: -2.8, 95% CI -20.02 to 14.42, p=0.75
Aerobic Exercise Treadmill	*Treadmill training with TDC stim vs. Treadmill training with sham TDC*	Function	1 (24) Grecco, 2014	Moderate	Unknown	Imprecise	Undetected	Insufficient	6MWT: 102.4, 95% CI 33.16 to 171.64, p=0.004 GMFM-88D: 7.8, 95% CI 0.46 to 15.15, p=0.037 GMFM-88E: -3.39 to 12.99, p=0.251
Aerobic Exercise Treadmill	*Treadmill training with TDC stim vs. Treadmill training with sham TDC*	Balance	1 (24) Duarte Nde, 2014	Moderate	Unknown	Imprecise	Undetected	Insufficient	PBS: 40.5 (9.4) to 45.3 (7.9) vs.39.1 (9.8) to 39.7 (8.4); MD 4.2, 95% CI -2.88 to 11.28, p=0.245

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Aerobic Exercise Treadmill	*Treadmill training with TDC stim vs. Treadmill training with sham TDC*	ADLs	1 (24) Duarte Nde, 2014	Moderate	Unknown	Imprecise	Undetected	Insufficient	PEDI self-care: 46.1 (10) to 48.0 (9.5) vs. 45.0 (9.2) to 45.5 (9.3); MD 1.4, 95% CI -6.21 to 9.01, p=0.718 PEDI mobility: 38.0 (8.5) to 41.7 (7.4) vs. 38.3 (7.4) to 39.5 (7.6); MD 2.5, 95% CI -3.71 to 8.71, p=0.430
Aerobic Exercise Treadmill	*Individualized strength-based physical therapy*	Function	1 (26) Johnston, 2011	Moderate	Unknown	Imprecise	Undetected	Insufficient	GMFM: 62.7 (17.5) to 63.3 (16.2) vs. 58.4 (26.9) to 60.1 (25.1), p=0.66

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Aerobic Exercise Treadmill (for adults with CP)	*Strength Training or Usual care*	Function	2 RCTs (51) Kim, 2015 Bahrami, 2019a 1 quasiexperi-mental trial (95) Aviram, 2017	Moderate	Inconsistent	Imprecise	Undetected	Low-strength evidence for no clear benefit	6MWT on treadmill: 5.71, 95% CI -53.22 to 64.64, p=0.85 6MWT on overground walking: 24.07, 95% CI -46.80 to 94.94, p=0.51 6MWT: 20.9 (4.0) vs. 27.9 (6.7), p=0.31 TUG: -2.82 (0.51) vs. 3.52 (0.60), p=0.014, favors strength training GMFM-66: 1.98 (0.40) vs. 3.10 (0.44), p=0.001, favors strength training GMFM-66D: 5.53 (1.61) vs. 8.36 (1.24), p=0.013, favors strength training GMFM-66E: 4.80 (1.33) vs. 7.21 (0.96), p=0.81 10MWT-self-paced: 0.272 (0.045) vs. 0.276 (0.049), p=0.41 10MWT-fast: 0.387 (0.070) vs. 0.374 (0.069), p=0.30 10MWT: 1.080 (0.47) to 1.22 (0.50) [22.46% change] vs. 0.99 (0.56) to 1.02 (0.61) [1.28% change], % change p<0.05 6MWT: 291.13 (160.28) to 342.63 (174.62) [23.68% change] vs. 276.10 (167.19) to 308.57 (181.22)[16.54% change], % change p>0.05

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Aerobic Exercise Treadmill (for adolescents with CP)	*Physical Therapy or Overground Walking*	Function	2 RCTs (56) Chrysagis, 2012 Swe, 2015 1 Quasi-experimental study (24) Nsenga-Leunkau, 2012	Moderate	Consistent	Imprecise	Undetected	Low-strength evidence for no clear benefit	6MWT: -17.00, 95% CI -89.77 to 55.77, p=0.65 10MWT: -0.013, 95% CI -0.23, 0.21, p=0.91 GMFM-88D: -2.94, 95% CI -16.42 to 10.64, p=0.67 GMFM-88E: -2.8, 95% CI -20.02 to 14.42, p=0.75 10MWT: 244.33 (115.41) to 219.38 (123.71) vs. 118.36 (89.89) to 135.82 (95.65), p=0.097 6MWT: 480 to 601 vs. 450 to 450, no difference in baseline values, significant difference in post-intervention values favoring treatment

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Aerobic Exercise Treadmill (for children with CP)	*Overground walking with or without spider cage, treadmill walking with sham transcranial DC stim, Individual strength-based PT*	Function	4 (103) Johnston, 2011 Emara, 2016 Grecco, 2013 Grecco, 2014	Moderate	Inconsistent	Imprecise	Undetected	Low-strength evidence for no clear benefit	10MWT: 0.4 (0.04) to 0.5 (0.04) vs. 0.4 (0.03) to 0.6 (0.04), p=0.12 5XSit-to-Stand: 21.5 (1.3) to 18.9 (1.0) vs. 21.7 (1.5) to 17.7 (0.8), p=0.26 GMFM-88 D: 12.5 (1.6) to 15.8 (1.5) vs.12.0 (0.7) to 19.2 (2.1), p=0.02, favors spider cage GMFM-88 E: 10.9 (1.3) to 14.8 (1.5) vs.10.4 (0.8) to 17.2 (2.1), p=0.05, favors spider cage 6MWT: 102.4, 95% CI 33.16 to 171.64, p=0.004 GMFM-88D: 7.8, 95% CI 0.46 to 15.15, p=0.037 GMFM-88E: 4.8, 95% CI -3.39 to 12.99, p=0.251 6MWT: 149.7 vs. 44.8, p<0.001 TUG: -6.4 vs. -2.0, p=0.004 GMFM-88D: 23.9 vs. 8.1, p<0.001 GMFM-88E: 20.1 vs. 8.2, p<0.001 GMFM: 62.7 (17.5) to 63.3 (16.2) vs. 58.4 (26.9) to 60.1 (25.1), p=0.66

Abbreviations: 6MWT = 6-Minute Walking Test; 10MWT=10-Minute Walking Test; BBS = Berg Balance Scale; CI = confidence interval; CP = cerebral palsy; HiMat = High Level Mobility Assessment Tool; GMFM = The Gross Motor Function Measure; ICF = International Classification of Functioning, Disability and Health; NA = not applicable; PBS = Pediatric Balance Scale; PEDI = Pediatric Evaluation of Disability Inventory; RCT = randomized controlled trial; TUG= Timed Up and Go Test; WHOQOL = World Health Organization Quality of Life

Table H-3. Strength of evidence for Key Question 2: aerobic exercise for cerebral palsy and multiple sclerosis

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Aerobic Exercise Dance	*Usual care, previous activity level or attention control*	Function	2 (N=81) Teixera-Machado, 2017; Young, 2019	Moderate	Consistent	Imprecise	Undetected	Low for benefit	TUG: MD-1.89, 95% CI -3.30 to -0.48, p=0.01 6MWT: MD 40.98, 95% CI 2.21 to 79.75, p=0.04 5xSit-to-Stand: MD -1.00, 95% CI -2.58 to 0.55, p=0.38 FIM total change score: 1.7 vs. 0.03, p<0.001

Abbreviations: 6MWT = 6-Minute Walking Test; CP = cerebral palsy; FIM=Functional Independence Measure; MD = mean difference; MS = multiple sclerosis; TUG= Timed Up and Go Test

Table H-4. Strength of evidence for Key Question 2: aerobic exercise for spinal cord injury

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Aerobic Exercise Aquatics	*Rehabilita-tion exercises*	Pulmonary function	1 (20) Jung, 2014	Moderate	Unknown	Imprecise	Undetected	Insufficient	Difference in change scores between groups: FVC (L): MD -1.8 (1.3) vs. -0.31 (1.6), p=0.031 FEV1 (L): MD -1.1 (1.2) vs. -0.21 (0.3); p=0.038 FER (L/sec):-10.0 (9.7) vs. -5.4 (7.0, p=0.238 FEV1/FVC: -3.7 (2.3) vs. -2.1 (3.4), p=0.234
Aerobic Exercise Cycling (arm and leg)	*Usual care, previous activity level or attention control*	Function	1 RCT (33) Akkurt, 2017 1 cohort (45) Sadowsky, 2013	Moderate	Inconsistent	Imprecise	Undetected	Insufficient	A vs. B, Mean change scores: FIM: 0.5 vs. -0.5, p=1.00 FIM: 80% vs. 60%, p<0.001
Aerobic Exercise Cycling (arm and leg)	*Usual care, previous activity level or attention control*	Quality of Life	1 RCT (33) Akkurt, 2017 1 cohort (45) Sadowsky, 2013	Moderate	Inconsistent	Imprecise	Undetected	Insufficient	WHOQOL-Bref, p>0.05 SF-36: total and composite scores NR; Significant improvement in physical function and role limit physical with FES cycling, no difference in mental health subscales
Aerobic Exercise Cycling (hand)	*Usual care, previous activity level or attention control*	ADLs	1 (33) Akkurt, 2017	Moderate	Unknown	Imprecise	Undetected	Insufficient	CHART-sf, p>0.05
Aerobic Exercise Robot-Assisted Gait Training	*Usual care or overground walking without RAGT*	ADLs	2 (176) Yildirim, 2019 Esclarin-Ruz, 2014	Moderate	Consistent	Imprecise	Undetected	Low for benefit	FIM: 69 (31) to 85 (35) vs. 67 (36) to 77 (24), p=0.022 FIM/Motor: p=0.09, favors RAGT

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Aerobic Exercise Robot-Assisted Gait Training	*Head-to-head comparison (treadmill training, overground walking)*	Function	3 (141) Esclarin-Ruz, 2014 Kressler, 2013 Shin, 2014	Moderate	Consistent	Imprecise	Undetected	Low for benefit	6MWT: p=0.047, favors RAGT FIM/Motor: p=0.09, favors RAGT WISC-II: p=0.10, favors RAGT WISCI-II: p=0.01 , favors RAGT LEMS: p=0.24 LEMS: p<0.01, favors RAGT Velocity change: p>0.05, favors treadmill/ overground walking SCiM3-M: 6 vs. 3, p=0.13
Robot-Assisted Gait Training	*Sham transcranial magnetic stimulation*	Function	1 (31)	Moderate	Unknown	Imprecise	Undetected	Insufficient	10MWT: p=0.09, favors RAGT LEMS: p=0.001 UEMS: p=0.02 WISCI-II: p>0.05

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Aerobic Exercise Robot-Assisted Gait Training	*Usual care/no treatment*	Function	3 (170) Duffell, 2014 Yildirim, 2019 Midik, 2020	Moderate	Inconsistent	Imprecise	Undetected	Low-strength evidence for no clear benefit	WISCI II: 5 (9) to 9 (7) vs. 5 (6.7) to 6.5 (5), p=0.011 10MWT achieved MID (0.13m/s): 13% vs. 8%, p>0.05 6MWT and TUG: p>0.05 <u>WISCI:</u> 3.9 (0.8) vs. 2.5 (0.5), p=0.178 <u>SCIM</u>: 9.9 (2.5) vs. 7.0 (1.3), p=0.326 <u>LEMS</u>: 1.8 (0.4) vs. 0.6 (0.2), p=0.061 At 3 month followup, change from baseline: <u>WISC</u>: 4.3 (1.0) vs. 2.5 (0.5), p=0.139 <u>SCIM</u>: 16.5 (3.2) vs. 7.6 (1.5), p=0.127 <u>LEMS</u>: 2.1 (0.5) vs. 0.6 (0.2), p=0.049
Aerobic Exercise Treadmill	*Structured PT, Aerobic + Strength Training*	Function	2 (55) Alexeeva, 2011 Giangregorio, 2012 Hitzig, 2013 Kapadia, 2014 Craven, 2017	Moderate	Consistent	Imprecise	Undetected	Low-strength evidence for no clear benefit	<u>10MWT (m/s):</u> 0.30 (0.26) to 0.46 (0.40) vs. 0.41 (0.34) to 0.51 (0.36) <u>10MWT:</u> 42.8 (46.2) to 35.2 (40.8) to 42.2 (67.7) vs. 49.1 (41.7) to 28.7 (8.3) to 35.1 (18.8), p=0.829 <u>6MWT:</u> 187.9 (123.4) to 217.1 (134.4) to 232.5 (138.9) vs. 79.4 (83.9) to 130 (46.0) to 126.4 (63.8), p=0.096 <u>TUG:</u> 43.6 (25.5) to 33.0 (15.7) to 32.2 (19.1) vs. 61.6 (36.2) to 49.5 (21.9) to 51.3 (19.6), p=0.138 <u>FIM:</u> 4.7 (1.82) to 5.19 (1.80) to 5.19 (1.83) vs. 4.18 (2.14) to 4.82 (1.66) to 5.09 (2.98), p=0.115

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Aerobic Exercise Treadmill	*Track training, Physical therapy*	Quality of Life	1 (35) Alexeeva, 2011	Moderate	Unknown	Imprecise	Undetected	Insufficient	SAWS (Satisfaction with disabilities and well-being): 39.3 ((8.3) to 35.2 (8.7) vs. 35.9 (6.9) to 32.4 (7.6) vs. 36.6 (9.9) to 29.0 (7.9), p>0.05
Aerobic Exercise Treadmill	*Track training, Physical therapy*	Balance	1 (35) Alexeeva, 2011	Moderate	Unknown	Imprecise	Undetected	Insufficient	Tinetti Balance Scale (TBS): 9.8 (5.4) to 19.4 (5.0) vs. 10.5 (3.4) to 11.9 (2.5) vs. 10.1(3.6) to 12.9 (2.7), p<0.05, Improvement from baseline in track training and physical therapy groups but not treadmill group

Abbreviations: 6MWT = 6-Minute Walking Test; 10MWT = 10-Meter Walk Test; CHART = Craig Handicap and Assessment Reporting Technique; CI = confidence interval; FER= Forced Expiratory Flow Rate; FEV1 = Forced Expiratory Volume at one second; FEV1/FVC = Force Expiratory Volume at one second/Forced Vital Capacity; FIM=Functional Independence Measure; FVC = Forced Vital Capacity; LEMS = Lower Extremity Motor Score; MID = Minimal Important Difference; NA = not applicable; RAGT = Robot-Assisted Gait Training; RCT = randomized controlled trial; SAWS = Satisfaction with disabilities and well-being; SCI = spinal cord injury; SF-36 = Short Form 36; TBS = Tinetti Balance Scale; TUG= Timed Up and Go Test; UEMS = Upper Extremity Motor Score; WHOQOL = World Health Organization Quality of Life; WISCI II = Walking Index for Spinal Cord Injury II

Table H-5. Strength of evidence for Key Question 2: balance exercise for multiple sclerosis

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Postural Control Balance training	*Usual care*	Quality of life	2 (N=106) Gandolfi, 2015 Tollar, 2020	Moderate	Consistent	Imprecise	Undetected	Insufficient	Mean between-group difference: MSQoL-54: 5.02, 95% CI -1.12 to 9.92 EQ-5 Sum Score: -0.6 (1.15) vs. 0.0 (1.13), p=0.023
Postural Control Balance training	*Usual care or waitlist/no intervention*	Function	7 (N=369) Forsberg, 2016 Callesen, 2019 Carling, 2017 Amiri, 2019 Tollar, 2020 Ozkul, 2020 Arntzen, 2020	Moderate	Consistent	Imprecise	Undetected	Low strength of evidence for benefit	Pooled MSWS (4 studies): -4.66, 95% CI -6.65 to -2.67 Pooled TUG (3 studies): 0.45, 95% CI -1.92 to 2.82 2MWT: MD 16.7, 95% CI 8.15 to 25.25 10MWT: MD 0.48, 95% CI 0.11 to 0.85 25FWT (m/s): MD 0.10, 95% CI 0.00 to 0.20, p=0.04 FGA: 2.1, 95% CI 0.6 to 3.6, p=0.0079 2MWT: -3.24 (3.37), p=0.34 Sit-to-Stand: 0.24 (2.12), p=0.17 10MWT: 1.49 (3.84), p=0.70 Significant interaction between time and group according to baseline EDSS score for core muscle endurance and strength, p<0.05 MSIS-29: -6.3 (4.23) vs. 1.0 (3.46), p=0.008

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Postural Control Balance training	*Usual care or Waitlist*	Balance BBS	10 (N=553) Afrasiabifar, 2018 Brichetto, 2015 Gandolfi, 2015 Carling, 2017 Callesen, 2019 Arntzen, 2019 Forsberg, 2016 Amiri, 2019 Tollar, 2020 Ozkul, 2020	Moderate	Consistent	Imprecise	Undetected	Moderate for benefit	Pooled BBS (7 studies): MD -4.314 95% CI -5.57 to -2.70 Pooled MiniBEST) 2 studies: 2.40, 95% CI 1.10 to 3.70 1 study: Significant interaction between time and group according to baseline EDSS score for static and dynamic stability p<0.05
Postural Control Balance training	*Usual care or Waitlist*	Falls Near falls	2 (128) Carling, 2017 Gandolfi, 2015	Moderate	Consistent	Imprecise	Undetected	Low for benefit	<u>Falls</u>: -1.24 (1.66), p<0.001 <u>Near Falls</u>: -8.24 (14.78), p=0.002 <u># of Falls</u>: 0.59 (0.99) to 0.03 (0.16) vs. 0.37 (0.54) to 0.29 (0.34), p=0.005 (post-intervention); 0.59 (0.99) to 0.08 (0.27) vs. 0.37 (0.54) to 0.27 (0.55), p=0.53 (1 month post treatment)
Postural Control Balance training	*Attention control*	Sleep	1 (45) Sadeghi Bahmani, 2019b	Moderate	Unknown	Imprecise	Undetected	Insufficient	<u>ISI:</u> 13.46 (5.81) to 10.13 (4.92) vs. 1.71 (5.43) to 11.14 (5.39), p>0.05
Postural Control Balance training	*Other active interventions (lumbar stabilization and task-oriented training)*	Function 2-Minute Walk Test	1 (N=42) Salci, 2017	Moderate	Unknown	Imprecise	Undetected	Insufficient	Mean change from baseline: 10.75 m vs. 25.55 m vs. 18.69 m; p>0.05
Postural Control Balance training	*Other active interventions (lumbar stabilization and task-oriented training)*	Balance BBS	1 (N=42) Salci, 2017	Moderate	Unknown	Imprecise	Undetected	Insufficient	Mean change from baseline: 3.57 vs. 5.78 vs. 5.57; p=0.16

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Postural Control Hippotherapy	*Usual care, previous activity level or attention control*	Quality of life MSQoL-54	1 (N=70) Vermohlen, 2018	Moderate	Unknown	Imprecise	Undetected	Insufficient	Mental health score: mean difference 12.0, 95% CI 6.2 to 17.7 Physical health score: 14.4, 95% CI 7.5 to 21.3
Postural Control Hippotherapy	*Usual care, previous activity level or attention control*	Balance BBS	1 (N=70) Vermohlen, 2018	Moderate	Unknown	Imprecise	Undetected	Insufficient	Mean difference 3.07, 95% CI 1.00 to 5.14
Postural Control Hippotherapy	*Usual care, previous activity level or attention control*	Spasticity NSR	1 (N=70) Vermohlen, 2018	Moderate	Unknown	Imprecise	Undetected	Insufficient	Mean difference -0.9, 95% CI -1.9 to -0.1
Postural Control Hippotherapy	*Usual care, previous activity level or attention control*	Walking	1 (N=33) Moraes, 2020	Moderate	Unknown	Imprecise	Undetected	Insufficient	6MWT: 459.06 (118.34) to 503.59 (126.38) vs. 513.00 (101.97) to 497.13 (88.88), p<0.001 25FWT: 6.37 (1.70) to 5.36 (1.43) vs. 5.82 (1.29) to 5.84 (1.08), p<0.001
Postural Control Tai Chi	*Usual care*	Depression *Immediately Post-treatment*	1 QENR (N=32) Burschka, 2014	High	Unknown	Imprecise	Undetected	Insufficient	CES-D mean score 7.67 (5.12), p=0.007 vs. 16.13 (11.99), p=0.951; favors Tai Chi, interaction p=<0.05
Postural Control Tai Chi	*Usual care*	Quality of life *Immediately Post-treatment*	1QENR (N=32) Burschka, 2014	High	Unknown	Imprecise	Undetected	Insufficient	QLS mean score 232.57 (25.62), p=0.012 vs. 193.81 (36.2), p=0.290, Interaction p<0.01
Postural Control Tai Chi	*Usual care*	Balance *Immediately Post-treatment*	1 QENR (N=32) Burschka, 2014	High	Unknown	Imprecise	Undetected	Insufficient	14-task balance test: 9.33 (2.26), p=0.031, for the intervention vs. 6.53 (4.49), p=0.439; interaction p<0.05
Postural Control Tai Chi	*Psychological classes and physical therapy)*	Balance BBS *Immediately Post-treatment*	1 (N=34) Azimzadeh, 2015	High	Unknown	Imprecise	Undetected	Insufficient	BBS: 52.25 (3.39) to 53.94 (2.23) vs. 53.22 (2.23) to 53.61 (2.14), p>0.05

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Postural Control Motion gaming	*Usual care*	Function	4 N=(177) Nilsagard, 2013 Ozkul, 2020 Tollar, 2020 Yazgan, 2020	Moderate	Consistent	Imprecise	Undetected	Low for benefit	6MWT pooled 2 studies: MD -30.90, 95% CI -49.55 to -12.25 TUG pooled 3 studies: MD -1.06, 95% CI -1.43 to -0.69 25footWT: -0.3 (1.1) vs. -0.1 (1.4), p=0.51 DGI: 1.78 (2.3) vs. 1.0 (2.0), p=0.21 MS Walking Scale: -5.9 (11.5) vs. -3.95 (18.1), p=0.76 Four Square Step Test: -1.6(2.1) vs. -2.0 (6.6), p=0.64
Postural Control Motion gaming	*Different type balance exercises*	Function	2 (N=62) Kalron, 2016 Khalil, 2018	Moderate	Consistent	Imprecise	Undetected	Insufficient	Four Square Step Test: 16.2 (7.0) to 12.7 (6.4) vs. 14.2 (7.1) to 11.7 (5.9), p=0.361 TUG: 0.04, 95% CI –2.24 to 2.32, p=0.97 10MWT: 8.48, 95% CI –5.16 to 22.12, p=0.21 3MinWT: –7.11, 95% CI –34.18 to 19.95, p=0.59
Postural Control Motion gaming	*Different type balance exercises or usual care*	Quality of Life	2 (N=58) Khalil, 2018 Tollar, 2020	Moderate	Consistent	Imprecise	Undetected	Insufficient	SF-36 PCS: -11.62, 95% CI -22.27 to -0.99, p=0.03 SF-36 MCS: -13.60, 95% CI -23.66 to -3.55, p=0.01 EQ-5 Sum Score: -2.3 (1.44) vs. 0.0 (1.13), p<0.001
Postural Control Motion gaming	*Different type balance exercises*	Balance	2 (N=62) Khalil, 2018 Kalron, 2016	Moderate	Inconsistent	Imprecise	Undetected	Insufficient	BBS: 46.8 (9.6) to 47.9 (6.4) vs. 43.3 (7.1) to 44.6 (4.9), p=0.56 BBS: -4.52, 95% CI -7.90 to -1.09, p=0.01 Falls Efficacy Scale International: 36.4 (9/7) to 29.4 (7.8) vs. 32.9 (10.3) to 28.6 (5.8), p=0.021 FES-I: 3.86, 95% CI -0.062 to 8.34, p=0.08

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Postural Control Motion gaming	*Usual care*	Balance	3 (94) Tollar, 2020 Ozkul, 2020 Yazgan, 2020	Moderate	Consistent	Imprecise	Undetected	Low for benefit	BBS (pooled analysis 3 trials): MD -3.43, 95% CI -6.30 to -0.57
Postural Control Whole body vibration	*Usual Care*	Function	1 (N=47) Claerbout, 2012	Moderate	Unknown	Imprecise	Undetected	Insufficient	3MinWT: 45.0 (42.6) vs. 20.4 (27.95), p>0.05 TUG: 11.32 (5.21) to 11.16 (8.82) vs. 14.43 (3.20) to 14.57 (4.02), p=0.05, NS
Postural Control Whole body vibration	*Usual Care*	Balance	1 (N=47) Claerbout, 2012	Moderate	Unknown	Imprecise	Undetected	Insufficient	BBS: 3.9 (4.4) vs. 4.2 (6.1) vs. 0.2 (7.5), p>0.05 for all comparisons
Postural Control Whole body vibration	*No treatment*	QoL	1 (46) Abbasi, 2019	Moderate	Unknown	Imprecise	Undetected	Insufficient	QOL-54 (PCS): 4.20 (1.73, 8.40) vs. -1.26 (-3.28, 0), p<0.001 QOL-54 (MCS): 5.96 (2.71, 11.89) vs. -0.17 (-2.20, 0.07), p<0.001
Postural Control Yoga	*Usual care, previous activity level or attention control*	Function	4 (N=215) Garrett, 2013a/b Hogan, 2014 Young, 2019 Ahmadi, 2013	High	Consistent	Imprecise	Undetected	Low-strength evidence for no clear benefit	6MWT: Median Difference (SIQR): 0 (82) vs. -10 (91), p=0.73 6MWT: Median Difference: -25 vs. 6.5, NS 6MWT: Mean Difference: 22.83, 95% CI -16.67 to 6.2, p=0.25 TUG: MD:-1.20, 95% CI -2.58 to 0.18, p=0.09 5XSit to Stand: -0.70, 95% CI -2.17 to 0.77, p=0.34 10MWT: 12.45 (4.54) to 6.45 (3.61) vs. 9.16 (1.88) to 9.47 (1.92), p=0.11 2MWT: 109 (17.44) to 120.36 (20.62) vs. 121.50 (27.73) to 119.05 (27.12), p=0.11

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Postural Control Yoga	*Usual care, previous activity level or attention control*	Quality of Life	4 (N=241) Doulatabad, 2013 Hasanpour-Dehkordi, 2014 Garrett, 2013a/b Hogan, 2014	High	Inconsistent	Imprecise	Undetected	Insufficient	Mean (SD) MSQoL-54: 4.9±1.9 vs.6.9±1.5 (baseline); 7.4±2.16 vs. 6.8±1.9 (post-intervention), p=0.001 Mean Difference SF-36: 1106.41, p<0.001 Median Difference MSIS-psychological: –3.7 (22.2) vs. 0 (16.7), p=0.04 Median (SIQR) MSIS-psychological: 14 (2.2) baseline, 15 (4) post intervention vs. 17 (4) baseline, 15 (4.5) post-intervention, NS Mean Difference MSIS-physical: –4.0, 95% CI –7.5 to –0.5 vs. 0.3, 95% CI -4.0 to 4.6, p=0.12 Mean Difference MSIS-physical: 1.3, 95% CI -4.7 to 7.3 vs. -4.8, 95% CI -10.4 to -0.60, NS
Postural Control Yoga	*Usual care, previous activity level or attention control*	Balance	2 (N=49) Hogan, 2014	High	Unknown	Imprecise	Undetected	Insufficient	BBS: MD: 5.3, 95% CI -3.1 to 7.5 vs. -3.1, 95% CI -2.8 to 9.0, NS BBS: 47.72 (6.78) to 53.81 (3.40) vs. 44.50 (8.48) to 41.70 (8.48), p=0.07
Postural Control Yoga	Movement to Music (Dance)	Function	1 (N=53) Young, 2019	Moderate	Unknown	Imprecise	Undetected	Insufficient	6MWT: MD: -18.2, 95% CI -56.4 to 20.1, p=0.34 TUG: MD 0.69, 95% CI -0.71 to 2.08, p=0.33 5XSit to Stand: MD 0.30, 95% CI -1.21 to 1.82, p=0.69
Postural Control Yoga	Undescribed control	Quality of Life: Sexual Satisfaction	1 RCTs (N=60) Najafidoul-atabad, 2014	Moderate	Unknown	Imprecise	Undetected	Insufficient	Yoga baseline 1.8 (SD 2.0) to 1.4 (SD 1.5), p=0.001 versus women in the control group (baseline 2.1 (SD 1.2) to 2.1 (SD 1.2), p>0.05.
Postural Control Yoga	Aerobics	QoL	1 (N=40) Hasanpour-Dehkordi, 2014	High	Unknown	Imprecise	Undetected	Insufficient	SF-36: MD between groups: 229.32, p=0.07

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Postural Control Yoga	Physiotherapist-led exercise	Function	1 (N=126) Garrett, 2013a/b	High	Unknown	Imprecise	Undetected	Insufficient	6MWT: Median Difference (SIQR): 0 (82) vs. 10 (52), NS
Postural Control Yoga	Physiotherapist-led exercise	Quality of Life	1 (N=126) Garrett, 2013a/b	High	Unknown	Imprecise	Undetected	Insufficient	MSIS (psychological): Median Difference (SIQR): -3.7 (22.2) vs. -11.1 (25.9), NS MSIS (physical): : MD -4.0, 95% CI -7.5 to -0.5 vs. -6.9, 95% CI -10.8 to -2.9, NS
Postural Control Yoga	Group exercise	Qol	1 (N=61) Hogan, 2014	High	Unknown	Imprecise	Undetected	Insufficient	MSIS-29 (psychological): 18 (5.38) to 17 (4.8) vs. 8 (5.5) to 15 (5.7), p>0.05 MS-29 (physical): 54 (11.5) to 49.4 (12) vs. 50.5 (9.5) to 45.9 (10.5) vs, p=NR
Postural Control Yoga	Group exercise	Balance	1 (N=61) Hogan, 2014	High	Unknown	Imprecise	Undetected	Insufficient	BBS: 30.4 (11.6) to 34.2 (9.8) vs. 28.9 (9.5) to 34.5 (9.8), p<0.05
Postural Control Yoga	Group exercise	Function	1 (N=61) Hogan, 2014	High	Unknown	Imprecise	Undetected	Insufficient	6MWT: 83.9 (39.8) to 100 (55) vs. 101 (39.5) to 121.2 (47.4), p>0.05
Postural Control Yoga	One-on-one exercise	Qol	1 (N=48) Hogan, 2014	High	Unknown	Imprecise	Undetected	Insufficient	MSIS-29 (psychological): 18 (5.38) to 17 (4.8) vs. 14 (2.2) to 15 (4), p>0.05 MS-29 (physical): 54 (11.5) to 49.4 (12) vs. 48.3 (10.5) to 49.6 (11.6), p=NR
Postural Control Yoga	One-on-one exercise	Balance	1 (N=48) Hogan, 2014	High	Unknown	Imprecise	Undetected	Insufficient	BBS: 30.4 (11.6) to 34.2 (9.8) vs. 22.6 (12.6) to 27.9 (11.5), p<0.05
Postural Control Yoga	One-on-one exercise	Function	1 (N=48) Hogan, 2014	High	Unknown	Imprecise	Undetected	Insufficient	6MWT: 83.9 (39.8) to 100 (55) vs. 70 (30) to 45 (54.5), p>0.05
Postural Control Yoga	Fitness instructor-led exercise	6MWT	1 (N=130) Garrett, 2013a/b	High	Unknown	Imprecise	Undetected	Insufficient	Median Difference (SIQR): 0 (82) vs. 20 (61), NS

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Postural Control Yoga	Fitness instructor-led exercise	MSIS-psychological	1 (N=130) Garrett, 2013a/b	High	Unknown	Imprecise	Undetected	Insufficient	MSIS (psychological): Median Difference (SIQR): -3.7 (22.2) vs. -3.7 (22.2), NS MSIS (physical): MD -4.0, 95% CI -7.5 to -0.5 vs. -5.7, 95% CI -9.1 to -2.4, NS

Abbreviations: 2MWT = 2-Minute Walking Test; 3MinWT = 3-Minute Walking Test; 6MWT = 6-Minute Walking Test; 10MWT = 10-Meter Walking Test; 25-FWT=25-Foot Timed Walking Test; BBS=Berg Balance Scale; CES-D= Center for Epidemiological Studies Depression Scale, CI = confidence interval; ISI =Insomnia Severity Index; RCT=randomized controlled trial; MCS = Mental Component Summary; MD = mean difference; MS = multiple sclerosis; MSIS = Multiple Sclerosis Impact Scale; MSQOL= Multiple Sclerosis Quality of Life; NSR = nonsignificant risk; QENR=quasiexperimental nonrandomized study; QLS=Questionnaire of Life Satisfaction; QOL = Quality of Life; SD = Standard Deviation; SF 36-MCS = Short Form 36 Mental Health Scores; SF 36-PCS = Short Form 36 Physical Component Score; SIQR = Symptom Impact Questionnaire; TUG= Timed Up and Go Test; WT = Walking Time

Table H-6. Strength of evidence for Key Question 2: balance exercise for cerebral palsy

) Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Postural Control Balance Exercises	*Usual care*	Function	1 (28) Curtis, 2018 2 QENR (66) Lorentzen, 2015 Bleyenheuft, 2017	High	Unclear as not all estimates of effect were reported	Imprecise	Undetected	Insufficient	LE GMFM-66: 55 (5.9) to 58 (6.2) to 62 (6.4) vs. 55 (8.7) to 56 (7.6) to 57 (6.6), p<0.001 6MWT: 190 (108.5) to 226 (100.8) to 236 (105.1) vs. 194 (101.1) to 180 (111.1) to 182 (101.1), p=0.026 GMFM–66: 1.1, 95% CI –2.2 to 4.4, p>0.05 (post-intervention); 0.1, 95% CI –3.6 to 3.3, p>0.05 (12 month followup) Sit-to-stand, number of cycles performed: 20.0 (0.9) vs, 15.1 (0.9), p=0.04 Left leg lateral step up, number of steps: 23.5 (1.4) vs 17.8 (2.2), p=0.004 Right leg lateral step up, number of steps: 22.1 (1.4) vs. 18.0 (2.0), p<0.001 SATCo: mean between group difference at end of treatment and at post-treatment followup: p>0.05
Postural Control Balance Exercises	*Usual care*	Balance	1 (28) Curtis, 2018 1 QENR (46) Lorentzen, 2015	High	Consistent	Imprecise	Undetected	Insufficient	PBS: 33 (17.5) to 43 (20.1) to 42 (21.3) vs. 30 (23.9) to 27 (22.2) to 26 (23.2), p=0.002 Romberg Balance Test center of gravity maintenance area (mm2): 462.2 (62.5) vs 314.6 (104.9), p=0.18

) Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Postural Control Balance Exercises	*Usual care*	ADLs	1 (28) Curtis, 2018 1 QENR (20) Bleyenheuft, 2017 1 cohort (23) Kim, 2017	High	Unclear as not all estimates of effect were reported	Imprecise	Undetected	Insufficient	PEDI: 52 (12.4) to 57 (11.5) to 60 (10.7) vs. 51 (14.6) to 51 (15.3) to 51 (15.8), p=0.001 PEDI Self Care, PEDI Mobility, PEDI Mobility Caregiver Assistance: mean between group difference at end of treatment and at post-treatment followup: p>0.05 Modified Barthel Index, mean change from baseline: 2.82 (SD 1.25) vs 1.58 (SD 1.38), p<0.05; MD 1.24, 95% CI 0.09 to 2.34, p=0.04

) Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Postural Control Hippotherapy	*Usual care, previous activity level or attention control*	Function	5 RCTs, 2 QENRs (N=333) Deutz, 2018 Herrero, 2012 Kwon, 2015 Silva e Borges, 2011 Kwon, 2011 Park, 2014 Mutoh, 2019	Moderate	Consistent	Imprecise	Undetected	Low for benefit	GMFM-66: 60.8 (14.9) to 63.5 (15.8) vs. 61.4 (14.8) to 61.8 (15.0), p<0.01 GMFM-88: 72.7 (19.2) to 75.7 (18.3) vs. 73.9 (17.9) to 74.3 (18.1), p<0.01 GMFM-88D: 54.1 (34.2) to 59.7 (32.5) vs. 55.5 (32.2) to 54.9 (33.2), p<0.01 GMFM-88E: 41.0 (34.1) to 45.1 (35.4) vs. 42.0 (33.2) to 43.0 (33.0), p<0.01 GMFM-66 total: 0.52, 95% CI –0.52 to 1.55, p>0.05 GMFM-66D: 0.016, 95% CI -1.09 to 1.12, p>0.05 GMFM-66E: 2.30, 95% CI 0.28 to 4.33, p<0.05 GMFM total: 0.27, 95% CI –0.07 to 0.62, p>0.05 GMFM total: Proportion with improvement from baseline, 10 weeks: (11/19) vs (8/19); OR 1.89 (95% CI 0.5 to 6.9), p>0.05 GMFM-66: 70.4 (7.4) to 73.7 (8.3) vs. 69.8 (8.7) to 70.1 (8.1), p=0.003 GMFM-88: 89.4 (7.3) to 91.1 (6.7) vs. 88.0 (8.3) to 88.3 (8.4), p=0.054 GMFM-88 D: 83.2 (15.5) to 83.3 (10.9) vs. 79.6 (15.5) to 79.3 (16.6), p=0.826 GMFM-88E: 67.2 (17.5) to 74.6 (19.3) vs. 65.3 (20.0) vs. 66.9 (20.1), p=0.042 GMFM-66: 56.6 (9.2) to 62.8 (10.8) vs. 57.4 (7.9) to 57.9 (9.2), p<0.05 GMFM-66E: 45.4 (7.0) to 49.7 (7.6) vs. 46.0 (6.3) to 46.5 (6.6), p<0.05 5MWT (m/min): 31.9 (10.7) to 38.8 (13.5) vs. 31.1 (11.3) to 32.3 (11.6), p<0.05 GMFM-66: 2.93 (3.95) vs. 1.25 (1.99), p<0.05 GMFCS reclassification indicating improved function: 25% (5/20) vs. 10% (2/20), p=0.24

) Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Postural Control Hippotherapy	*Usual care, previous activity level or attention control*	Quality of life	2 RCT (97) Deutz, 2018 Mutoh, 2019	High	Consistent	Imprecise	Undetected	Insufficient	No difference between groups in Child Health Questionnaire-28 psychosocial or physical subscale scores or on KIDSCREEN-27 parental scale scores WHOQOL (positive feelings): 3.1 (1) to 4.1 (1) vs. 3.1 (0.9) to 3.4 (1), p<0.05 WHOQOL (self-esteem): 2.9 (1.2) to 4.0 (0.7) vs. 3.3 (1.1) to 3.7 (0.7), p<0.05 WHOQOL (negative feelings): 2.9 (0.8) to 2.8 (0.7) vs. 2.8 (0.8* to 2.8 (0.8), p>0.05
Postural Control Hippotherapy	*Usual care, previous activity level or attention control*	Spactiicity MAS	1 RCT (N=44) Lucena-Anton, 2018	Moderate	Unknown	Imprecise	Undetected	Insufficient	MAS, left adductors: 2.50 (SD 1.05) vs. 2.54 (SD 1.22), p=0.040 MAS, right adductors: 1.77 (SD 1.26) vs. 2.31 (SD 1.24), p=0.047
Postural Control Hippotherapy	*Usual care, previous activity level or attention control*	Balance PBS	1 RCT, 2 QENRs (N=150) Kwon, 2015 Kwon, 2011 Lee, 2014	Moderate	Consistent	Imprecise	Undetected	Low for benefit	Pooled analysis (3 studies): MD 3.14, 95% CI 0.21 to 6.07, p=0.036
Postural Control Hippotherapy	*Usual care, previous activity level or attention control*	Sitting Balance SAS	2 RCT (N=83) Herrero, 2012 Matusiak-Wieczorek, 2020 1 QENR (N=39) Matusiak-Wieczorek, 2016	HModerate	Consistent	Imprecise	Undetected	Insufficient	SAS: MD: Treatment effect: 0.26 (0.65) vs. -0.21 (0.92), p>0.05 SAS: 14.42 (4.39) to 15.63 (3.65) vs.15.50 (3.14) to 15.75 (3.19), p=0.010 SAS: 10.93 (3.97) to 13.13 (3.46) vs. 14.87 (3.27) to 15.13 (3.36), p<0.001 (but worse disability in control group)

) Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Postural Control Motion gaming	*Neurodeve-lopmental training*	Function (QUEST)	2 (N=61) Acar, 2016 Zoccolillo, 2015	High	Consistent	Imprecise	Undetected	Insufficient	QUEST (dissociated movement): 80.1 (7.73) to 85.6 (8.54) vs. 81.4 (10.70) to 86.4 (8.78), p>0.05 QUEST (grasp): 42.2 (18.76) to 47.1 (16.64) vs. 53.0 (16.45) to 55.7 (15.30), p>0.05 QUEST (weight bearing): 60.2 to 72.7 (19.60) vs. 75.4 (19.97) to 77.3 (15.43), p>0.05 QUEST (extension): 72.9 (14.78) to 77.0 (12.05) vs. 71.0 (23.53) to 74.0 (23.36), p>0.05 QUEST: 76 (21) to 81 (20) vs. 74 (20) to 78 (20), p>0.05
Postural Control Motion gaming (arm exoskeleton)	*Conventional rehabilitation*	Function (QUEST)	1 (N=30) El-Shamy, 2018	Moderate	Unknown	Imprecise	Undetected	Insufficient	QUEST total: 61.9 (2) to 84.6 (2.7) vs. 62.3 (1.8) to 79.1 (2); MD 5.9, 95% CI 3.7 to 7.3, p<0.05
Postural Control Motion gaming	*PC gaming using mouse or traditional balance training*	Function	3 (N=126) Hsieh, 2018 Tarakci, 2016 Hsieh, 2020	Moderate	Inconsistent	Imprecise	Undetected	Insufficient	TUG: 16.43 (2.12) to 17.51 (1.70) vs. 15.60 (1.10) to 15.91 (1.87), p<0.05 TUG: -1.24, 95% CI -4.13 to 1.65, p=0.40 10MWT: -1.4, 95% CI -4.36 to 1.56, p=0.35 Sit to Stand Test: 2.07, 95% CI 0.82 to 3.32, p=0.001, favors conventional balance training 10 Step Climbing Test: -0.99, 95% CI -3.99 to 2.01, p=0.52 2MWT: 103.4 (16.6) to 120.1 (20.2) vs. 101.4 (23.1) to 106.1 (22.8), p=0.002

) Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Postural Control Motion gaming	*PC gaming using mouse or traditional balance training or usual physical activity*	Balance	4 (N=146) Hsieh, 2018 Tarakci, 2016 Hsieh, 2020 Pourazar, 2020	Moderate	Consistent	Imprecise	Undetected	Low for benefit	BBS: 44.74 (2.75) to 48.81 (4.74) vs. 44.39 (2.33) to 45.37 (2.68), p<0.05 Wiibalance: 1.05, 95% CI 0.64 to 1.46, p<0.001 Tilt-table: 11.00, 95% CI 4.74 to 17.26, p=0.001 Tight-rope walking, heading in soccer, and ski slalom: p<0.001 PBS-total: 29.9 (5.3) to 35.8 (5.5) vs. 32.3 (7.5) to 34.4 (5.9), p=0.002 Dynamic balance was improved in the anterior, posterolateral, and posteromedial directions with virtual reality dance game compare with the control group, p=0.001 all comparisons
Postural Control Whole body vibration	*Usual care*	Walking	2 (N=50) Lee, 2013 Ahmadizadeh, 2020	Moderate	Inconsistent	Imprecise	Undetected	Insufficient	Walking speed (meters/second): 0.37 (0.04) to 0.48 (0.06) vs. 0.39 (0.05) to 0.40 (0.05), p=0.001 6MWT: 158.8 (100.24) to 189.45 (115.47) vs. 194 (78.82) to 271.5 (60.81), p=0.04 (favors control)

Abbreviations: 6MWT = 6-minute walk test; BBS=Berg Balance Scale; CHQ=Child Health Questionnaire; CI = confidence interval; CP = cerebral palsy; GMFCS = Gross Motor Function Classification System; GMFM = Gross Motor Function Measure; MAS = Modified Ashworth Scale; MD = mean difference; MWT = Minute Walking Time; NA = not applicable; PBS=Pediatric Balance Scale; QENR=quasiexperimental nonrandomized studies; QUEST = Quality of Upper Extremity Skills Test, SAS=Sitting Assessment Scale; RCT = randomized controlled trial; SD = Standard Deviation; TUG= Timed Up and Go Test; WHOQOL = World Health Organization Quality of Life

Table H-7. Strength of evidence for Key Question 2: balance exercise for spinal cord injury

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Postural Control **Balance training**	*Usual care*	Balance	2 (N=60) Norouzi, 2019 Hota, 2020	Moderate	Consistent	Imprecise	Undetected	Insufficient	BBS pooled 2 studies: MD -4.53, 95% CI -6.46, -2.61 (favors balance exercises)
Postural Control Tai Chi	*Usual care*	Quality of life *Immediately post-treatment*	1 (N=40) Qi, 2018	Moderate	Inconsistent	Imprecise	Undetected	Insufficient	WHOQOL-BREF mean score: 12.23 (1.65) vs. 10.87 (1.08), p=0.04, favors Tai Chi
Postural Control Motion Gaming	*Usual care*	Dynamic balance	1 (26) Tak, 2015	Moderate	Unknown	Imprecise	Undetected	Insufficient	T-shirt test (s): 29.5 (10.95) to 22.60 (8.28) vs. 23.59 (11.35) to 22.15 (12.28), p<0.05
Postural Control Whole body vibration	*Usual care*	Function	1 (N=28) In, 2018	Moderate	Unknown	Imprecise	Undetected	Insufficient	10MWT: 29.3 (9.0) to 25.8 (8.1) vs. 28.8 (7.2) to 27.5 (6.3), p=0.005 TUG: 13.7 (3.1) to 11.4 (2.8) vs. 14.7 (4.5) to 13.7 (4.1), p=0.016

Abbreviations: BBS = Berg Balance Scale; CES-D = Center for Epidemiological Studies Depression Scale, MWT = Minute Walking Time; NA = not applicable; RCT = randomized controlled trial; SCI = spinal cord injury; WHOQOL-BREF = World Health Organization Quality of Life

Table H-8. Strength of evidence for Key Question 2: muscle strength exercise for multiple sclerosis

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Strength Interventions Muscle Strength Exercise	*Usual care, previous activity level or attention control*	Walking *Immediately Post-treatment*	**6MWT** 5 (N=161) Kalron, 2017 Duff, 2018 Dalgas, 2009/2010 Callesen, 2019 Tollar, 2020 **2MWT** 3 (N=153) Kjolhede, 2016 Kalron, 2017 Dodd, 2011 **10MWT** 2 (N= 132) Fox, 2016 Dalgas, 2009/2010 **MSWS-12** 3 (N=165) Kalron, 2017 Fox, 2016 Callesen, 2019 **25FWT** 2 (N=65) Kjolhede, 2016 Callesen, 2019	Moderate	Consistent	Imprecise	Undetected	Low-strength evidence for no clear benefit	**6MWT** p5 trials, MD –12.69 meters, 95% CI –29.45 to 4.07, I^2=0% **2MWT** p3 trials, MD –3.3 meters, 95% CI –11.92 to 2.81, I^2=0% **10MWT** p3 trials, MD –1.04 seconds, 95% CI –2.48 to 0.69, I^2=0% **MSWS-12 (0-100 scale)** –1.36, 95% CI –4.83 to 2.10, I^2=26% **25FWT** p2 trials, MD –0.07 m/s, 95% CI –0.19 to 0.05, I^2=47%
Strength Interventions Muscle Strength Exercise	*Usual care, previous activity level or attention control*	Walking *Short term*	**10MWT** 2 (N= 132) Fox, 2016 Dalgas, 2009/2010	Moderate	Consistent	Imprecise	Undetected	Low-strength evidence for no clear benefit	**10MWT** p2 trials, MD –1.27, 95% CI –2.75 to 0.22, I^2=0%

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Strength Interventions Muscle Strength Exercise	*Usual care, previous activity level or attention control*	Functional capacity *Immediately Post treatment*	**TUG** 3 (N=113) Duff, 2018 Bulguroglu, 2017 Kalron, 2017 **SSST** 2 (N=65) Marandi, 2013a/b Callesen, 2019	Moderate	Consistent	Imprecise	Undetected	Low-strength evidence for no clear benefit	**TUG** MD –1.30 seconds, 95% CI –4.38 to –1.78, I^2=0% **SSST** MD –2.88, 95% CI –7.51 to 1.74, I^2=95%
Strength Interventions Muscle Strength Exercise	*Usual care, previous activity level or attention control*	Quality of Life *Immediately Post-treatment*	**MSQol/SF36 MCS** 3 (N=100) Duff, 2018 Bulguroglu, 2017 Dalgas, 2010	Moderate	Consistent	Imprecise	Undetected	Low-strength evidence for no clear benefit	**MSQol/SF36 MCS (0-100 scale)** MD –3.48, 95% CI –6.61 to -0.27, I^2=0%
Strength Interventions Muscle Strength Exercise	*Usual care, previous activity level or attention control*	Quality of Life *Immediately Post-treatment*	**MSQol/SF36 PCS** 3 (N=100) Duff, 2018 Bulguroglu, 2017 Dalgas, 2010	Moderate	Consistent	Imprecise	Undetected	Low-strength evidence for no clear benefit	**MSQol/SF36 PCS (0-100 scale)** MD –2.77, 95% CI –6.88 to 3.12, I^2= 34%
Strength Interventions Muscle Strength Exercise	*Usual care, previous activity level or attention control*	Quality of Life *Immediately Post-treatment*	**EQ5D total** 1 (N=26) Tollar, 2020	Moderate	Consistent	Imprecise	Undetected	Low-strength evidence for no clear benefit	13.9 (1.44) vs. 13.3 (0.89) (baseline) –0.5 (1.16) vs. 0.0 (1.3) (followup) Difference –0.5, 95% CI –1.5 to 0.5

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Strength Interventions Muscle Strength Exercise	*Usual care, previous activity level or attention control*	Balance	**ABCS** 2 (N=132) Bulguroglu, 2017 Fox, 2016 **FABS** 1 (N=30) Duff, 2018 **BBS** 2 (N=71) Kalron, 2017 Tollar, 2020 **6 (N=319)**	Moderate	Consistent	Imprecise	Undetected	Low-strength evidence for no clear benefit	**ABCS (3 trials):** MD –0.30, 95% CI –1.38 to 0.77, I^2=27% **FABS (1 study):** MD 0.1, 95% CI –5.43 to 5.63 **BBS (2 studies):** –0.93, 95% CI –2.87 to 1.01, I^2=14%MD

Abbreviations: 6MWT = 6-Minute Walk Test; 10MWT = 10-Meter Walk Test; 25FWT = 25-Feet Walk Test; ABCS = Activities-Specific Balance Confidence Scale; BBB Berg Balance Scale; CI = confidence interval; EQ-5D = EuroQOL-5 Dimension Questionnaire; FABS = Fullerton Advanced Balance Scale; MD = mean difference; CI = confidence interval; MS = multiple sclerosis; MSQoL-MCS = Multiple Sclerosis Quality of Life–54 instrument Mental Component Score; MSQoL-PCS = Multiple Sclerosis Quality of Life–54 instrument Physical Component Score; MSWS-12 = Multiple Sclerosis Walking Scale; NA = not applicable; RCT = randomized controlled trial; SF-36 MCS = Short-Form 36 Mental Component Summary; SF-36 PCS = Short-Form 36 Physical Component Score; SSST = Six Spot Step Test; TUG = Timed Up and Go Test

Table H-9. Strength of evidence for Key Question 2: muscle strength exercise for cerebral palsy

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Strength Interventions Muscle Strength Exercise	*Usual care*	Walking *Immediately Post-treatment*	**1MWT** 1 (N=51) Scholtes, 2008, 2010, 2011 **6MWT** 1 (N=49) Taylor, 2013/Bania, 2016 **10MWT** 2 (N=91) Scholtes, 2008, 2010, 2011 Elnaggar, 2019 **Gait Profile Score** 1 (N=49) Taylor, 2013/Bania, 2016	Moderate	Consistent	Imprecise	Undetected	Low-strength evidence for no clear benefit	**1MWT** difference 0.7 m/s, 95% CI −0.23 to 0.9 **6MWT** difference 0.0 meters, 95% CI −41.6 to 41.6 **10MWT** MD –0.26 seconds, 95% CI –0.95 to 0.43, I^2=44% **Gait Profile Score** difference 0.2 degrees, 95% CI –0.86 to 1.26
Strength Interventions Muscle Strength Exercise	*Usual care*	Walking *Short term*	**1MWT** 1 (N=51) Scholtes, 2008, 2010, 2011 **6MWT** 1 (N=49) Taylor, 2013/Bania, 2016 **10MWT** 1 (N=51) Scholtes, 2008, 2010, 2011	Moderate	Consistent	Imprecise	Undetected	Low-strength evidence for no clear benefit	**1MWT** difference 0.0 m/s, 95% CI −0.15 to 0.15 **6MWT** difference 10.7 meters, 95% CI −32.3 to 53.7 **10MWT** difference -0.06 m/s, 95% CI −0.17 to 0.05

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Strength Interventions Muscle Strength Exercise	*Usual care*	Functional Capacity *Immediately Post-treatment*	**GMFM-66** 1 (N=51) Scholtes, 2008, 2010, 2011 **GMFM-66(D)** 1 (N=49) Taylor, 2013/Bania, 2016 **GMFM-66(E)** 1 (N=49) Taylor, 2013/Bania, 2016 GMFM-88 1 (N=25) Cho, 2020 **30SEC LAT STEP-UP** 1 (N=51) Scholtes, 2008, 2010, 2011 **QUEST** 1 (N=34) Kara, 2020 **COPM** 1 (N=34) Kara, 2020	Moderate	Consistent	Imprecise	Undetected	Low-strength evidence for no clear benefit	**GMFM-66 (0-100 scale**) difference 1.3, 95% CI –3.10 to 5.70 **GMFM-66(D) (0-100 scale**) difference 1.9, 95% CI –2.58 to 6.38 **GMFM-66 (E) (0-100 scale**) difference –0.6, 95% CI –8.29 to 7.09 **GMFM-88 (0-100 scale)** 71.78 (21.1) vs. 63.48 (27.5) (postinervention), p=NR **30SEC LAT STEP-UP** difference 0.5 repetitions, 95% CI –1.26 to 2.26 **QUEST total** 8.88 (6.51) vs. 2.22 (4.74), MD 6.65 (95% CI 2.4 to 10.9), p=0.001 **COPM total**: 6.12 (2.33) vs. 0.41 (1.56), MD 5.71 (95% CI 4.2 to 7.2), p<0.001
Strength Interventions Muscle Strength Exercise	*Usual care*	Functional Capacity *Short term*	**30SEC LAT STEP-UP** 1 (N=51) Scholtes, 2008, 2010, 2011	Moderate	Unknown	Imprecise	Undetected	Insufficient	**30SEC LAT STEP-UP** difference 0.4 repetitions, 95% CI –1.53 to 2.33

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Strength Interventions Muscle Strength Exercise	*Neuromus-cular electrical stimulation*	Functional Capacity *Immediately Post-treatment*	**GMFM-66** 1 (N=100) Qi, 2018a	Moderate	Unknown	Imprecise	Undetected	Insufficient	**GMFM-66 (0-100 scale**) difference –13.4, 95% CI –16.90 to –9.90
Strength Interventions Muscle Strength Exercise	*Neuromus-cular electrical stimulation*	Functional Capacity *Short term*	**GMFM-66** 1 (N=100) Qi, 2018a	Moderate	Unknown	Imprecise	Undetected	Insufficient	**GMFM-66 (0-100 scale**) difference and –12.5, 95% CI –16.26 to –8.74
Strength Interventions Muscle Strength Exercise	*Usual care*	Balance	**F-SFRT, S-SFRT** 1 (N=25) Cho 2020 **PBS** 1 (N=62) Tedla 2014	High	Consistent	Imprecise	Undetected	Insufficient	**F-SFRT:** 21.62 (6.87) vs. 28.17 (14.49) (baseline) 26.65 (7.92), p=0.000 vs. 25.37 (10.20), p=0.261 (postintervention) **S-SFRT:** 11.57 (5.72) vs. 15.52 (10.43) (baseline) 16.21 (5.37), p=0.003 vs. 15.95 (8.26), p=0.793 (postintervention) **PBS:** 7.23 (3.350) vs. 1.87 (1.074), p<0.001

Abbreviations: 1MWT = 1-Minute Walk Test; 6MWT = 6-Minute Walk Test; 10MWT = 10-Meter Walk Test**;** 25FWT = 25-Feet Walk Test**;** 30 SEC LAT STEP-UP = 30 second lateral step-up; CI = confidence interval; COPM = Canadian Occupational Performance Measure; CP = cerebral palsy; GMFM-66 = Gross Motor Function Measure 66; GMFM-66(D) = Gross Motor Function Measure 66 dimension D (standing); GMFM-66(E) = Gross Motor Function Measure 66 dimension E (walking, running, jumping); MD = mean difference; NA = not applicable; RCT = randomized controlled trial; QUEST = Quality of Upper Extremity Skills Test

Table H-10. Strength of evidence for Key Question 2: muscle strength exercise for spinal cord injury

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Strength Interventions Muscle Strength Exercise	*Usual care*	Quality of Life *Immediately Post-treatment*	**SF-36** 1 (N=98) Chen, 2016	Moderate	Unknown	Imprecise	Undetected	Insufficient	**SF-36 subscales** **Physical function (0-100)** difference 26.7, 95% CI 24.61 to 28.79 **Social function (0-100)** difference 28.9, 95% CI 26.06 to 31.74 **Role emotional (0-100)** difference 22.0, 95% CI 20.11 to 23.89 **Mental health (0-100)** difference 21.0, 95% CI 19.10 to 22.90 **Body pain (0-100)** difference 0.0, 95% CI –2.74 to 2.74

Abbreviations: CI = confidence interval; NA = not applicable; RCT = randomized controlled trial; SCI = spinal cord injury; SF-36 = Short-Form 36 questionnaire

Table H-11. Strength of evidence for Key Question 2: multimodal exercise that includes strengthening for multiple sclerosis

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Multimodal Exercise Progressive resistance or strength exercise plus aerobic or balance	*Usual care, previous activity level or attention control*	Walking *Immediately Post-treatment*	**6MWT** 35 (N=276) Sandroff, 2017 Sangelaji, 2016 Ebrahimi, 2015 Faramazi, 2020 Ozkul, 2020 **10MWT** 3 (N=93) Sangelaji, 2016 Cakit, 2010 Ebrahimi, 2015 **Other** 1 (N=83) Sandroff, 2017	Moderate	Consistent [a]	Imprecise	Undetected	Low for benefit	**6MWT** 4 trials, MD -64.92, 95% CI -73.5 to -56.2, I^2=0%excluding outlier trial[b] **10MWT** 3 trials MD –1.99 seconds, 95% CI –2.8 to –1.2, I^2=0%: excluding outlier trial[c] Other (no differences) **MSWS-12**: difference –3.30, 95% CI –10.16 to 3.56 (0-100 scale) **25FWT**: difference 0.30 feet/second, 95% CI –0.15 to 0.75
Multimodal Exercise Progressive resistance or strength exercise plus aerobic or balance	*Usual care, previous activity level or attention control*	Walking *Short term*	**6MWT** 1 (N=72) Sangelaji, 2014	High	Unknown	Precise	Undetected	Insufficient	**6MWT** difference 184.3 ± 51.1 meters, p=0.03
Multimodal Exercise Progressive resistance or strength exercise plus aerobic or balance	*Usual care, previous activity level or attention control*	Functional capacity *Immediately Post treatment*	23 (N=142) Cakit, 2010 Ebrahimi 2015 Faramarzi, 2020	High	Inconsistent	Precise	Undetected	Insufficient	**TUG** MD –2.15 seconds, 95% CI –2.72 to –1.58, I^2=0

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Multimodal Exercise Progressive resistance or strength exercise plus aerobic or balance	*Usual care, previous activity level or attention control*	Balance	3 (N=224) Sangelaji, 2014 Sangelaji, 2016 Ebrahimi, 2015 Tarakci, 2013	Moderate	Consistent	Precise	Undetected	Low for benefit	BBS: MD -3.37, 95% CI -3.76 to -3.14, I2=38%
Multimodal Exercise Progressive resistance or strength exercise plus aerobic or balance	*Usual care, previous activity level or attention control*	MSQoL-54 MCS *Immediately Post-treatment*	23 (N=119) Sangelaji, 2014 Ebrahimi, 2105 Ozkul, 2020b	High	Inconsistent	Imprecise	Undetected	Insufficient	**MSQoL-54 MCS (0-100 scale):** 3 trials MD –10.7, 95% CI –22.6 to 1.24, I^2=91%; o
Multimodal Exercise Progressive resistance or strength exercise plus aerobic or balance	*Usual care, previous activity level or attention control*	MSQoL-54 MCS *Long-term (42 weeks)*	1 (N=51) Sangelaji, 2014	High	Unknown	Imprecise	Undetected	Insufficient	**MSQoL-54 MCS (0-100 scale):** 13.54 ± 5.37, p=0.02
Multimodal Exercise Progressive resistance or strength exercise plus aerobic or balance	*Usual care, previous activity level or attention control*	MSQoL-54 PCS *Immediately Post-treatment*	23 (N=119) Sangelaji, 2014 Ebrahimi, 2105 Ozkul. 2020b	High	Consistent [a]	Imprecise	Undetected	Insufficient	**MSQoL-54,PCS (0-100 scale):** MD –13.3, 95% CI –21.6 to -4.9, I^2=75% After excluding outlier MD -12.0, 95% CI -13.8 to 5.0, I^2=75%

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Multimodal Exercise Progressive resistance or strength exercise plus aerobic or balance	*Usual care, previous activity level or attention control*	MSQoL-54 PCS *Long-term (42 weeks)*	1 (N=51) Sangelaji, 2014	High	Unknown	Imprecise	Undetected	Insufficient	**MSQoL-54,PCS (0-100 scale):** difference 10.9 ± 4.55, p=0.02
Multimodal Exercise Progressive resistance or strength exercise plus aerobic or balance	*Multimodal exercise vs. Aerobic exercise*	Quality of Life; SF-36 MCS/PCS *Immediately Post-treatment* *MusiQoL*	1 (N=60) Kerling, 2015 1 (N=110)	Moderate	Unknown	Imprecise	Undetected	Insufficient	**SF36 MCS (0-100 scale)** difference 4.2, 95% CI 0.2 to 8.2 *(favors control*) **SF36 PCS (0-100 scale)** difference –0.7, 95% CI –3.9 to 2.2 **MusiQOL (0-100 scale:)** difference –2.38, 95% CI –4.68 to –0.08
Multimodal Exercise Exercises to improve functional strength, balance, gait speed and endurance plus stretching and core-stability work.	*Group multimodal exercise vs. Home-based multimodal exercise*	Walking Immediatetly Post-treatment 6MWT, 10MWT	1 (N=44), Williams, 2020	Moderate	Unknown	Imprecise	Undetected	Insufficient	**10MWT,** difference 0.01 (95% CI −0.36 to 0.37 m/s) **6MWT,** Difference 18.67 (95% CI −78.22 to 115.56 meters)

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Multimodal Exercise Exercises to improve functional strength, balance, gait speed and endurance plus stretching and core-stability work.	*Group multimodal exercise vs. Home-based multimodal exercise*	Walking Short term (8 weeks) 6MWT, 10MWT	1 (N=44), Williams, 2020	Moderate	Unknown	Imprecise	Undetected	Insufficient	**10MWT,** Difference -0.19 (95% CI -0.41 to 0.03, m/s) **6MWT,** Difference -20.5 (95% CI -60.21 to 19.21 meters)
Multimodal Exercise Exercises to improve functional strength, balance, gait speed and endurance plus stretching and core-stability work.	*Group multimodal exercise vs. Home-based multimodal exercise*	Balance Immediatetly Post-treatment	1 (N=44), Williams, 2020	Moderate	Unknown	Imprecise	Undetected	Insufficient	**BBS** Difference 1.70 (95% CI −8.4 to 11.80)

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Multimodal Exercise Exercises to improve functional strength, balance, gait speed and endurance plus stretching and core-stability work.	*Group multimodal exercise vs. Home-based multimodal exercise*	Balance short term (8 weeks	1 (N=44), Williams, 2020	Moderate	Unknown	Imprecise	Undetected	Insufficient	**BBS** Difference -1.9 (-6.44 to 2.64)

Abbreviations: BBS = Berg Balance Scale; 6MWT = 6-Minute Walk Test; 10MWT = 10-Meter Walk Test; 25FWT = 25-Feet Walk Test; CI = confidence interval; MD = mean difference; MS = multiple sclerosis; MSQoL-MCS = Multiple Sclerosis Quality of Life–54 instrument Mental Component Score; MSQoL-PCS = Multiple Sclerosis Quality of Life–54 instrument Physical Component Score; MSWS-12 = Multiple Sclerosis Walking Scale; NA = not applicable; RCT = randomized controlled trial; SF-36 MCS = Short-Form 36 Mental Component Summary; SF-36 PCS = Short-Form 36 Physical Component Score; TUG = Timed Up and Go Test.

[a] Effect estimates go in the same direction even though magnitude of effect may differ

[b] Outlier excluded, Sangelaji 2014

[c] Outlier excluded, Tarakci 2013

Table H-12. Strength of evidence for Key Question 2: multimodal exercise that includes strengthening for cerebral palsy

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Multimodal Exercise Progressive resistance or strength exercise plus aerobic or balance	*Usual care*	Walking *Immediately Post-treatment*	**6MWT** 1 (N=37) Fosdahl, 2019b **GDI** 1 (N=37) Fosdahl, 2019b	Moderate	Unknown	Imprecise	Undetected	Insufficent	**6MWT (meters)** 1 trial: difference −45.7 (55.4) vs. −55.4 (55.5), adj. MD10.6 (95% CI −29.3 to 50.6), p=0.590 (pre-post change) **GDI** 1 trial: difference −0.4 (4.4) vs. −0.8 (7.14), adj. MD −1.0 (95% CI −5.3 to 3.3), p=0.65
Multimodal Exercise Progressive resistance or strength exercise plus aerobic or balance	*Usual care*	Walking *Intermediate term (16 weeks)*	**6MWT** 1 (N=37) Fosdahl, 2019b **GDI** 1 (N=37) Fosdahl, 2019b 1MWT 2 (N=80) Kaya Kara, 2019 Van Wely, 2014a	Moderate	Inconsistent	Imprecise	Undetected	Insufficient	**6MWT (meters)** 1 trial: difference −differences)vs. −56.6 (59.6), adj. MD 7.2 (−43.3 to 57.7), p=0.772 (16 week change) **GDI** 1 trial: difference −0.7 (6.0) vs. 1.01 (5.9), adj. MD −1.4 (95% CI −5.6 to 2.8), p=0.504 (16 week change) 1MWT:2 pooled trials: MD -5.28, 95% CI -10.24 to -0.33, I^2=45%

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Multimodal Exercise Progressive resistance or strength exercise plus aerobic or balance	*Usual care*	Functional Capacity *Immediately Post-treatment*	**GMFM-66** 2 (N=105) Slaman, 2015a, 2015b, 2014, 2010 Van Wely, 2014a, 2014b, 2010 **GMFM88-D/E** 1 (N=30) Kaya Kara, 2019	Moderate	Inconsistent (GMFM-66) Unknown (GMFM-88 D/E)	Imprecise	Undetected	Low-strength evidence for no clear benefit	**GMFM-66 (0-100 scale)** 2 trials, MD –1.5, 95% CI –6.4 to 4.7, I^2=71%). No difference in one trial (difference 1.6, 95% CI –2.7 to 5.9) in one trial; the other trial favored exercise over usual care (difference –3.1, 95% CI –5.7 to –0.6) **GMFM-88-D** 1 trial: difference –0.2, 95% CI –0.9 to 0.6 **GMFM-88-E** 1 trial: difference 2.7, 95% CI 1.0 to 4.4
Multimodal Exercise Progressive resistance or strength exercise plus aerobic or balance	*Usual care*	Functional Capacity *Intermediate term (16 weeks)*	**TUG** 1 (N=37) Fosdahl, 2019b	Moderate	Unknown	Imprecise	Undetected	Insufficient	**TUG** difference –1.1, 95% CI –1.4 to –0.78
Multimodal Exercise Progressive resistance or strength exercise plus aerobic or balance	*Usual care*	Quality of Life *Immediately Post treatment*	**CP-QOL:** 1 (N=50) Van Wely, 2014a, 2014b, 2010 **SF-36:** 1 (N=57) Slaman, 2015a, 2015b, 2014, 2010	Moderate	Consistent	Unknown	Undetected	Low-strength evidence for no clear benefit	No improvement in any domain of either QOL measure was seen in either study (please see full report).

Abbreviations: 6MWT = 6-Minute Walk Test; CI = confidence interval; CP = cerebral palsy; CP-QOL = cerebral palsy quality of life questionnaire; GDI = Gait Deviation Index; GMFM-66 = Gross Motor Function Measure 66; GMFM-88-D/E = Gross Motor Function Measure 88 dimensions D (standing) and E (walking, running, jumping); MD = mean difference; NA = not applicable; SF-36 = Short-Form 36 questionnaire; QoL = quality of life; RCT = randomized controlled trial; TUG = Timed Up and Go Test

Table H-13. Strength of evidence for Key Question 2: multimodal exercise that includes strengthening for spinal cord injury

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Multimodal Exercise Progressive resistance or strength exercise plus aerobic or balance	*Usual care*	Walking ability *Immediately Post-treatment*	1 (N=48) Jones, 2014a, 2014b	High	Unknown	Imprecise	Undetected	Insufficient	*Change scores* **6MWT** 36.0 ± 48.2 vs. 3.0 ± 25.5 meters, p=0.002 **10MWT** 0.1 ± 0.1 vs. 0.03 ± 0.1 meters per second; p=0.036 **SCI-FAI** (scale not provided) 5.0 ± 8.0 vs. –0.2 ± 2.8, p=0.03
Multimodal Exercise Progressive resistance or strength exercise plus aerobic or balance	*Usual care*	Functional Capacity *Immediately Post - intervention*	1 (N=48) Jones, 2014a, 2014b	High	Unknown	Imprecise	Undetected	Insufficient	**TUG** difference –37.2 ± 81.3 vs. –6.2 ± 18.1 seconds; p=0.267
Multimodal Exercise Progressive resistance or strength exercise plus aerobic or balance (whole body)	*Multimodal Exercise (upper body only)*	Walking ability *Immediately Post-treatment*	1 (N=26) Galea, 2018 (subset of patients who could walk)	Moderate	Unknown	Imprecise	Undetected	Insufficient	**6MWT** difference –12.30, 95% CI –68.01 to 43.41 **10MWT** difference –0.10, 95% CI –0.30 to 0.10
Multimodal Exercise Progressive resistance or strength exercise plus aerobic or balance (whole body)	*Multimodal Exercise (upper body only)*	Walking ability *Short-term Followup (12 weeks)*	1 (N=26) Galea, 2018 (subset of patients who could walk)	Moderate	Unknown	Imprecise	Undetected	Insufficient	**6MWT** difference –88.0, 95% CI –143.71 to –32.29 **10MWT** difference –0.80, 95% CI –2.3 to 0.70

Abbreviations: 6MWT = 6-Minute Walk Test; 10MWT = 10-Meter Walk Test; NA = not applicable; RCT = randomized controlled trial; SCI = spinal cord injury; SCI-FAI = Spinal Cord Injury Function Ambulation Index; TUG = Timed Up and Go Test.

Table H-14. Strength of evidence for Key Question 2a clinical outcomes: mental health

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
All-exercise interventions All physical exercise interventions in MS	*All comparators*	Depression scores	12 RCTs (N=564) Baquet, 2018 Hebert, 2011 Negaresh, 2019 Russo, 2018 Dalgas, 2009 Cakit, 2010 Razazian, 2016 Ahmadi, 2013 Sadeghi Bahmani, 2019 Tollar, 2020 Ozkul, 2020b Sadeghi Bahmani, 2020	Moderate	Consistent	Imprecise	Undetected	Moderate for benefit	(SMD -0.29, 95% CI -0.50 to -0.03, I^2=8%)
All-exercise interventions All physical exercise interventions in SCI	*All comparators*	Depression Scores	3 RCTs (N=171) Yang, 2014 Akkurt, 2017 Galea, 2018	Moderate	Consistent	Imprecise	Undetected	Low-strength evidence for no clear benefit	CES-D: -2.7 vs. -2.4, p>0.05 HADS change scores: 0 vs. 0.5, p>0.05 CES-D change scores: -3 vs. 3, p>0.05 HADS-Depression 10.5 (2) vs. 10.4 (2.1) (baseline) 10 (1.6) vs. 10.2 (1.3) (post-intervention) MD -0.28, 95% CI -0.83 to 0.27, p=0.309 (post-intervention) 10.1 (1.5) vs. 10.2 (1.4) MD -0.23 (95% CI -0.81 to 0.35), p=0.428 (24 weeks—12 weeks post-intervention)

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
All-exercise interventions All physical interventions in MS and SCI	*All comparators*	Anxiety scores	2 RCTs (N=146) Keser, 2011 Galea, 2018	Moderate	Consistent	Imprecise	Undetected	Insufficient	1 MS: HAD Anxiety scores not provided but no difference between calisthenics and neurorehab 1SCI: MD 0.29, 95% CI -0.25 to 0.83, p=0.291, no difference between whole body strength training and upper body strength on depression scores between groups with little change from baseline in both groups

Abbreviations: MS = multiple sclerosis; HAD = Hospital and Depression (Scale); MD = mean difference; NA = not applicable; RCT = randomized controlled trial; SCI = spinal cor injury

Table H-15. Strength of evidence for Key Question 2: general exercise effect across interventions and populations

Intervention Category, Intervention	Comparator	Outcome	Number of RCTs (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
All-exercise interventions (General exercise effect across interventions/ populations)	Usual Care	6MWT	25 (1196) Baguet, 2018 Hebert, 2011 Kargarfard, 2018 Young, 2019 Kim, 2015 Kalron, 2017 Duff, 2018 Dalgas, 2010 Taylor, 2013 Hogan, 2014 Garrett, 2012ab Sandroff, 2017 Sangelaji, 2014 Sangelaji, 2016 Ebrahimi, 2015 Jones, 2014a Bahrami, 2019a Callesen, 2019 Fosdahl, 2019b Tollar, 2020 Yazgan, 2019 Moraes, 2020 Ahmadizadeh 2019	Moderate	Consistent	Precise	Undetected	Moderate for benefit	6MWT: Pooled analysis: MD -32.94, 95% CI -46.07 to -19.81, I^2=78%

Intervention Category, Intervention	Comparator	Outcome	Number of RCTs (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
All exercise	Usual Care	Walking in MS	25 (1529) Baguet, 2018 Hebert, 2011 Kargarfard, 2018 Young, 2019 Kalron, 2017 Duff, 2018 Dalgas, 2010 Hogan, 2014 Garrett, 2012a/b Sandroff, 2017 Sangelaji, 2014 Sangelaji, 2016 Ebrahimi, 2015 Carling, 2017 Cakit, 2010 Tarakci, 2013 Fox, 2016 Forsberg, 2016 Nilsagard, 2012 Callesen, 2019 Ahmadi, 213 Arntzen, 2020 Tollar, 2020 Moraes, 2020 Yazgan, 2019 Faramarzi, 2020 Ozkul, 2020b	Moderate	Consistent	Precise	Not detected	High for benefit	Pooled analysis (19 studies): 6MWT: MD -42.70, 95% CI -57.05 to -28.35, I^2=75% Pooled analysis (9 studies): 10MWT: MD -1.44, 95% CI -2.74 to -0.13, I^2=90% Pooled analysis (9 studies): MS Walking Scale: MD -2.88, 95% CI -4.80 to -0.96, I^2=33%

Intervention Category, Intervention	Comparator	Outcome	Number of RCTs (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
All exercise	Usual Care	10MWT	14 (659) Fox, 2016 Dalgas, 2010 Carling, 2017 In, 2018 Sangelaji, 2016 Cakit, 2010 Ebrahimi, 2015 Tarakci, 2013 Jones, 2014a Bahrami, 2019 Elnaggar, 2019 Scholtes, 2012 Ahmandi, 2013 Arntzen, 2020	Moderate	Consistent	Imprecise	Not detected	Moderate for benefit	MD -1.24, 95% CI -2.04 to -0.44
All exercise	Usual Care	Function: GMFM-66 in CP GMFM-66D in CP GMFM-66E in CP TUG	7 (353) Fowler, 2010 Bryant, 2012 Scholtes, 2010 Deutz, 2017 Herrero, 2012 Slaman, 2015 Van Wely, 2014 2 (78) Wallard, 2018 Taylor, 2013 3 (151) Wallard, 2018 Taylor, 2013 Deutz, 2017 2 (70) Hsieh, 2018 Kaya Kara, 2019	Moderate	Consistent	Imprecise	Not detected	Low-strength evidence for benefit	GMFM-66: MD -0.58, 95% CI -1.62 to 0.45, I2=79% GMFM-66D: MD -0.89, 95% CI -7.33 to 5.55, I2=60% GMFM-66E: MD -3.73, 95% CI -5.78 to -1.67, I2=0% TUG: MD -1.05, 95% CI -1.35 to -0.76)

Intervention Category, Intervention	Comparator	Outcome	Number of RCTs (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
All exercise	Usual Care	Walking in CP	7 (234) Kim, 2015 Taylor, 2013 Bahmani, 2019 Fosdahl, 2019b Ahmadizadeh, 2019 Elnagger, 2019 Scholtes, 2012	Moderate	Consistant	Imprecise	No detected	Low for no clear benefit	Pooled analysis (4 trials) 6MWT: MD 6.85, 95% CI -13.39 to 27.08, I^2=0% Pooled analysis (3 trials) 10MWT: MD -0.46, 95% CI -1.55 to 0.63, I^2=44%
All exercise	Usual Care	BBS	19 (1006) Gervasoni, 2014 Kargarfard, 2018 Afrasiabifar, 2018 Forsberg, 2016 Carling, 2017 Gandolfi, 2015 Hsieh, 2018 Vermohlen, 2018 Sangelaji, 2014 Sangelaji, 2016 Ebrahimi, 2015 Tarakci, 2013 Brichetto, 2015 Tollar, 2020 Ozkul, 2020 Yazgan, 2019 Hota, 2020 Ahmandi, 2013 Kalron, 2017	Moderate	Consistent	Precise	Not detected	Moderate for benefit	MD -3.64, 95% CI -4.23 to -3.04, I^2=68%

Intervention Category, Intervention	Comparator	Outcome	Number of RCTs (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
All exercise	Usual Care	TUG	19 (N=882) Negaresh, 2018 Russo, 2018 Young, 2019 Duff, 2018 Bulguroglu, 2017 Kalron, 2017 Carling, 2017 Forsberg, 2016 Claerbout, 2012 Nilsagard, 2012 Hsieh, 2018 In, 2018 Cakit, 2010 Ebrahimi, 2015 Jones, 2014a Kaya Kara, 2019 Ozkul, 2020 Yazgan, 2019 Faramarzi, 2020	Moderate	Consistent	Imprecise	Undetected	Low-strength evidence for benefit	TUG: MD -0.66, -1.28 to -0.04, I^2=85%
All exercise	Usual Care	TUG in MS	15 (N=743) Negaresh, 2018 Russo, 2018 Young, 2019 Duff, 2018 Bulguroglu, 2017 Kalron, 2017 Carling, 2017 Forsberg, 2016 Claerbout, 2012 Nilsagard, 2012 Cakit, 2010 Ebrahimi, 2015 Ozkul, 2020 Yazgan, 2019	Moderate	Consistent	Precise	Undetected	Moderate-strength evidence for no clear benefit	TUG: MD -0.30, 95% CI -1.18 to 0.59, I^2=89%

Intervention Category, Intervention	Comparator	Outcome	Number of RCTs (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
All exercise	Usual Care	BBS in MS	17 (906) Gervasoni, 2014 Kargarfard, 2018 Afrasiabifar, 2018 Forsberg, 2016 Carling, 2017 Gandolfi, 2015Vermohlen, 2018 Sangelaji, 2014 Sangelaji, 2016 Ebrahimi, 2015 Tarakci, 2013 Ahmadi, 2013 Tollar, 2020 Kalron, 2017 Brichetto, 2015 Ozkul, 2020 Yazgan, 2019	Moderate	Consistent	Precise	Not detected	Moderate for benefit	BBS: MD -3.56, 95% CI -4.58 to -2.54, I^2=77%
All exercise	Usual Care	Function in CP	11 (500) Hsieh, 2018 Kaya Kara, 2019 Fowler, 2010 Bryant, 2012 Schlotes, 2010 Deutz, 2017 Herrero, 2012 Mutoh, 2019 Slaman, 2015 Van Wely, 2014	Moderate	Consistent	Imprecise	Not detected	Low for benefit	BBS: MD -3.09, 95% CI -4.60 to -1.58 Pooled TUG: -1.05, 95% CI -1.35 to -0.76, I^2=0% Pooled GMFM-66: MD -0.58, 95% CI -1.62 to 0.45, I^2=79%
All exercise	Usual Care	Function in SCI	4 (129) Norouzi, 2019 Hota, 2020 Jones, 2014 In, 2018	Moderate	Consistent	Imprecise	Not detected	Low for benefit	Pooled BBS: MD -4.53, 95% CI -6.46 to -2.61, I^2=0% 6MWT: MD -32.97, 95% CI -68.17 to 2.23 Pooled analysis (2 trials) 10MWT: MD -5.06, 95% CI -13.29 to 3.15, I^2=55% Pooled analysis (2 trials) TUG: -10.33, 95% CI -37.10 to 16.45, I^2=61%

Abbreviations: : 6MWT = 6-Minute Walk Test; 10MWT = 10-Meter Walk Test; BBS: Berg Balance Scale; CP = cerebral palsy; GMFM-66 = Gross Motor Function Measure 66; GMFM-66(D) = Gross Motor Function Measure 66 dimension D (standing); GMFM-66(E) = Gross Motor Function Measure 66 dimension E (walking, running, jumping); MD = mean difference; MS = multiple sclerosis; NA = not applicable; RCT = randomized controlled trial; SCI = spinal cord injury; TUG = Timed Up and Go Test

Table H-16. Strength of evidence for Key Question 2b intermediate outcomes: effect of physical activity interventions on VO_2 peak and VO_2 max

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Aerobic Exercise in CP	*Usual care*	VO_2 peak	2 quasiexperimental (54) Nsenga, 2013 Nsenga Leunkeu, 2012	Moderate	Consistent	Imprecise	Undetected	Low for benefit	Both studies show significant increase in VO2 Peak ml/min from baseline with training, not in usual care. (estimates from graphs): VO2 Peak: 32.5 to 39.0 (p<0.05) vs. 32.5 to 32.5 (P>0.05) VO2 Peak (ml/kg/min: 7.00, 95% CI 1.93 to 12.07, p=0.007
Aerobic Exercise in MS	*Usual care*	VO_2 peak	4 (251) Baquet, 2018, Heine, 2017 Negaresh, 2018	Moderate	Inconsistent	Imprecise	Undetected	Insufficient	Mean difference between groups: Study 1: VO2 Peak (ml/min): -51.4, 95% CI -165.2 to 62.5, p=0.37 VO2 Peak (ml/min/kg): -0.9, 95% CI -2.5 to 0.6, p=0.24 Study 2: A vs. B, difference between groups (SD), VO2 Peak (L/min): MD 0.048 (0.082), p=0.561 VO2 Peak (mL/kg/min): MD 0.979 (1.075), p=0.364 Study 3: VO2 Peak (change from baseline, estimated from graph): 2.7 vs. 0 vs. 1.9 vs. 0.6, p=0.001
Aerobic Exercise in SCI	*Usual care*	VO_2 peak	2 (71) van der Scheer 2016 Lavado, 2012 1 cohort study (N=17) Valent, 2010	Moderate	Consistent	Imprecise	Undetected	Low for benefit	Median change RCT 1: VO2 Peak (L/min): 0.05 to -0.07, p=0.01 RCT 2: VO2 Peak (mL/min): 939 to 1154 (p=0.009) vs. 896 to 834, p=0.906; Post-intervention comparison, p<0.001 A vs. B, Mean change Cohort: VO2peak (ml/min): 0.21 vs. 0.13, p=0.356 VO2 Peak (ml/kg/min): 2.9 vs. 1.5, p=0.274

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Aerobic Exercise in SCI	*Head to head comparison of aerobic programs*	VO_2 peak	3 (100) Gorman, 2019 Alexeeva, 2011 Akkurt, 2017	Moderate	Inconsistent	Imprecise	Undetected	Insufficient	Median change: VO2Peak (ml/kg/min): 4.30 vs. 1.35, p=0.02 A vs. B, Mean (SD) VO2Peak (ml/kg/min): 16.48 (5.39) to 16.18 (5.11) vs.13.33 (3.06) to 14.31 (3.88), p=0.063 A vs. B vs. C, Mean (SD) VO2Peak (ml/km/min): 12% nonsignificant increase within groups, but no differences between groups, p>0.05
Multimodal Exercise in CP	*Usual care,*	VO_2 peak	1 (57) Slaman, 2014a, 2014b, 2018	Moderate	Unknown	Imprecise	Undetected	Insufficient	Mean difference between groups: VO2 Peak (mL/min): MD 195.2, 95% CI 57.3 to 333.1, p<0.01
Multimodal Exercise in MS	*Usual care*	VO_2 max/peak	12 (123) Wens, 2015b (high intensity) Banitalebi, 2020	Moderate	UConsistent	Imprecise	Undetected	ILow for benefit	Mean (SD) Study 1: VO2 Max (ml/min): 17.8% (4.6%) vs. 2.5% (4.1%), p<0.01 VO2 Max (ml/min/kg):17.8% (4.6%) vs. 2.5% (4.1%), p<0.01 % Body fat: Study 2: VO2 peak: p=0.004, effect of disability*exercise p=0.097

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Multimodal Exercise in MS	Head-to-head comparison	VO_2 peak/max	2 (96) Wens, 2015b (high intensity); Sandroff, 2017	Moderate	Unknown	Imprecise	Undetected	Insufficient	Mean (SD) VO2 Peak (ml/kg/min): 16.5 (6.5) vs. 15.4 (6.2), p=NR (baseline) 17.1 (5.9) vs. 15.9 (5.5), p=NR (post-intervention) Time X Group interaction p>0.20 Mean (SD) of % change A vs. Control VO2 Max (ml/min): 17.8% (4.6%) vs. 2.5% (4.1%), p<0.01 VO2 Max (ml/min/kg):17.8% (4.6%) vs. 2.5% B vs. Control VO2 Max (ml/min): 7.5% (5.8%) vs. 2.5% (4.1%), p>0.05 VO2 Max (ml/min/kg): 7.5% (5.8%) vs. 2.5% (4.1%), p>0.05

Abbreviations: CI = confidence interval; NA = not applicable; RCT = randomized controlled trial. SD = standard deviation

Table H-17. Strength of evidence for Key Question 2b intermediate outcomes: effect of physical activity interventions on pulmonary function tests

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Aerobic Exercise in SCI	*Usual care*	Pulmonary function	1 cohort study (n=17). Valent, 2010	Moderate	Unknown	Imprecise	Undetected	Insufficient	Mean change scores, p=between groups: FVC%: -9.4 vs. -7.8, p=0.619 PEF%: -12.6 vs. -10.0, p=0.722
Aerobic Exercise in SCI	*Head-to-head comparison of aerobic programs*	Pulmonary function	1 RCT (n=33) Akkurt, 2017	Moderate	Unknown	Imprecise	Undetected	Insufficient	Median change, VO2Peak (ml/kg/min): 4.30 vs. 1.35, p=0.02 FEV1 (ml): -0.14 vs. 0.17, p>0.05 FEV1 %: 1 vs. 5, p>0.05 FVC (ml): -0.31 vs. -0.20, p>0.05 FVC %: 1.5 vs. 1.5, p>0.05 FEV1/FVC, 3.51-0.50, p>0.05
Aerobic Exercise in SCI	*Head-to-head comparison of aerobic programs*	Pulmonary function	1 RCT (n=20) Jung, 2014	Moderate	Unknown	Imprecise	Undetected	Insufficient	Mean change scores, p=between groups: FVC(L): 1.8 (1.3) vs. 0.31 (1.6), p=0.031 FEV1(L): 1.1 (1.2) vs. 0.21 (0.3); p=0.038 FER(L/sec): 10.0 (9.7) vs. 5.4 (7.0), p=0.238 FEV1/FVC: 3.7 (2.3) vs. 2.1 (3.4), p=0.243
Strength Exercise in SCI	*Usual Care*	Pulmonary function	1 RCT (n=98) Chen, 2016	Moderate	Unknown	Imprecise	Undetected	Insufficient	Mean (SD), p=post-intervention: FEV1: 1.17 (0.25) to 2.20 (0.45) vs. 1.17 (0.45) to 1.14 (0.44), p<0.05 FVC: 2.16 (0.36) to 2.98 (0.54) vs. 2.16 (0.42) to 2.17 (0.42), p<0.05 MVV: 50.5 (11.8) to 75.2 (6.8) vs. 50.5 (11.8) to 51.5 (10.6), p<0.05 FEV1/FVC: 0.53 (0.17 to 0.75 (0.08) vs. 0.53 (0.17) to 0.52 (0.15), p<0.05

Abbreviations: FER= Forced Expiratory Flow Rate; FEV1 = forced expiratory volume; FVC = forced vital capacity; MVV = maximal voluntary ventilation; NA = not applicable; RCT = randomized controlled trial; SCI = spinal cord injury

Table H-18. Strength of evidence for Key Question 2c: reduction of harms of immobility

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
---	---	Decubitus Ulcer	No studies	---	---	---	---	---	No studies
Arm cycling + strength + stretching	Usual physical therapy	Asymptomatic bacturia	1 (42) Lavado, 2012	Moderate	Unknown	Imprecise	Not detected	Insufficient	RR 0.20, 95% CI 0.07 to 0.54, p<0.001
RAGT	Treadmill training	Enema dose needed	1 (24) Huang, 2015	Moderate	Unknown	Imprecise	Not detected	Insufficient	-29 ml vs. -11 mL, p<0.05
RAGT	Treadmill training	Defecation time	1 (24) Huang, 2015	Moderate	Unknown	Imprecise	Not detected	Insufficient	-29 min vs. -15 min, p<0.05
---	---	Autonomic dysreflexia	No studies	---	---	---	---	---	No studies

Abbreviations: CI = confidence interval; RAGT = Robot-Assisted Gait Training

Table H-19. Strength of evidence for Key Question 2d, decreased risk of adverse outcomes of mobility devices: effect of physical activity interventions on spasticity

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Aerobic Exercise (Treadmill, Aquatic) in CP	Usual care	Spasticity	1 RCT (N=11) 1 Cohort (N=11) Chrysagis, 2012 Lai, 2015	Moderate	Inconsistent	Imprecise	Undetected	Insufficient	RCT: Mean change, p=value Modified Ashworth Scale: Knee extensors: 0.32 vs. 0.18, p=0.827 Knee flexors: 0.31 vs. 0.22, p=0.632 Foot plantar flexors: 0.32 vs. 0.17, p=0.460 Cohort: A vs B (ANCOVA p-values) Modified Ashworth Scale: Ankle: 0.614 Knee: 1.000 Wrist: 1.000 Elbow: 1.000
Aerobic Exercise (Treadmill) in CP	RAGT vs Treadmill	Spasticity	1 RCT (N=21) Wu, 2017a (pilot study)	Moderate	Unknown	Imprecise	Undetected	Insufficient	Modified Ashworth Scale (Baseline vs 6 weeks vs 8 weeks f/u) 0.62 (0.46) to 0.67 (0.60) to 0.41 (0.38), p=0.18, vs. 0.65 (0.36) to 0.48 (0.47) to 0.58 (0.44), p=0.19
Aerobic Exercise in CP	Partial body-weight supported treadmill vs individualized strength training	Spasticity	1 RCT (N= 26) Johnston, 2011	Moderate	Unknown	Imprecise	Undetected	Insufficient	Mean difference between groups, p=between groups KinCom computerized dynamometer: Plantar Flexor Spasticity ($J/^{O}/s$): -0.0003, p=0.75 Knee flexor spasticity ($J/^{O}/s$): -0.0026, p=0.59

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Aerobic Exercise in CP	*Aquatic vs land-based exercise*	Spasticity	1 RCT (N=32) Adar, 2017	Moderate	Unknown	Imprecise	Undetected	Insufficient	Median pre-post p-values on MAS <u>Location Aquatics Land</u> RKneeFlexors 0.039 0.008 LKneeFlexors 0.003 0.003 RAnkleFlexors 0.005 0.001 LAnkleFlexors 0.046 0.046 RHipAdductors 0.025 0.083 LHipAdductors 0.003 0.013
Aerobic Exercise in MS	*Neuromuscular electrical stimulation+ Strength exercises vs NMS alone*	Spasticity	1 RCT (N=100) Qi, 2018a	Moderate	Unknown	Imprecise	Undetected	Insufficient	Mean difference between groups: <u>Comprehensive Spasticity Scale (CSS):</u> 1.6, 95% CI 0.33 to 2.87, p=0.01
Aerobic Exercise in MS	*Lokomat-Pros (RAGT+VIRTUAL REALITY) VS Lokomat-Nanos (RAGT alone)*	Spasticity	1 RCT (N=40) Calabro, 2017	Low	Unknown	Imprecise	Undetected	Insufficient	Effect size, p-value is between groups: <u>MAS</u>: -0.01, 95% CI -0.539 to 0.539, p=0.40
Aerobic Exercise in MS	*RAGT vs Conventional walking training*	Spasticity	1 RCT (N=23) Pompa, 2017	Moderate	Unknown	Imprecise	Undetected	Insufficient	Mean SD, p=between groups: <u>Spasticity VAS 100mm ranged from "no problem" to "very bad":</u> 5.05 to 3.40 vs. 5.31 to 5.23, p=0.048
Aerobic Exercise in MS	*Aquatics vs. land-based relaxation exercises*	Spasticity	1 RCT (N=73)	Low	Unknown	Imprecise	Undetected	Low for benefit	<u>Spasm VAS</u>: 5 (2.8) to 2 (4.3) vs. 6 (3.1) to 4 (4.5), 91% improvement vs. 10% improvement, p<0.05

Intervention Category, Intervention	Comparator	Outcome	Number of Studies (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Aerobic Exercise in SCI	*Body weight support treadmill with FES vs Aerobic and resistance training*	Spasticity	1 RCT (N=34) Kapadia, 2014	Moderate	Unknown	Imprecise	Undetected	Insufficient	MAS: No between group differences in MAS involving the hip, knee, and ankle joints.(data/results not reported)
Aerobic Exercise in SCI	*RAGT+rTMS vs RAGT+sham rTMS*	Spasticity	1 RCT (N=31) Kumru, 2016	Moderate	Unknown	Imprecise	Undetected	Insufficient	Mean Difference between groups: MAS: -0.20, 95% CI -0.94 to 0.54, p=0.59
Strength Exercise (progressive resistance) in CP	*Usual care*	Spasticity	1 (N= 49) Scholtes, 2010	Moderate	Unknown	Imprecise	Undetected	Insufficient	Effect Size: 0.46, 95% CI −0.34 to 1.26, p=0.26
Strength Exercise (progressive resistance) in MS	*Attention control (social program)*	Spasticity	1 (N= 71) Dodd, 2011	Low	Unknown	Imprecise	Undetected	Low for no clear benefit	Mean Difference between groups: MSIS-88 stiffness: -2.4, 95% CI -0.52 to 0.5 MSIS-88 muscle spasms: -2.8, 95% CI -5.6 to 0.03
Balance Exercise Hippotherapy in CP	*Usual care (physical therapy)*	Spasticity	1 (N=44) Lucena-Anton, 2018	Moderate	Unknown	Imprecise	Undetected	Insufficient	Mean (baseline to post-treatment), p=between groups Modified Ashworth Scale: Left Abductors: 2.77 to 2.50 vs. 2.59 to 2.54, p=0.040 Right Abductors: 2.22 to 1.77 vs. 2.40 to 2.31, p=0.047
Balance Exercise Hippotherapy in MS	*Usual care (physical therapy)*	Spasticity	1 (N= 70) Vermohlen, 2018	Moderate	Unknown	Imprecise	Undetected	Insufficient	Mean Difference between groups: Spasticity NRS: −0.9 (95% CI −1.9 to −0.1), p=0.031

Abbreviations: CI = confidence interval; CSS = Comprehensive Spasticity Scale; MAS = Modified Ashworth Scale; NA = not applicable; NRS = Numeric Rating Scale; RAGT = Robot-Assisted Gait Training; SD = standard deviation; RCT = randomized controlled trial.

Table H-20. Strength of evidence for Key Question 2e: harms of physical activity

Intervention	Comparator	Outcome	Number of RCTs (Participants) Author Year (See Appendix B for Full Citation)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Intensive whole body exercises	Intensive upper body exercises	Autonomic dysreflexia	1 (116) Galea, 2018	Moderate	Unknown	Unknown as number of events rather than number of persons with event	Not detected	Moderate-strength evidence that AD can occur with exercise in SCI; Low-strength evidence that risk is increased with whole body vs. upper body exercise in SCI	26 episodes of AD (3 serious) with intensive exercise along with 5 episodes of dizziness/ nausea vs. 7 episodes in upper body exercise along with 15 episodes of headache (n=60 whole body exercises vs. n=56 in upper body exercises group)
Hippotherapy Pilates Balance exercises Usual physio-therapy	Usual care, no treatment	Falls	6 (456) Kwon, 2015 Deutz, 2017 Vermohlen, 2018 Fox, 2016 Carling, 2017 Gandolfi, 2015	Moderate	Consistent	Imprecise	Not detected	Insufficient	RR 3.74, 95% CI 0.80 to 17.45, p=0.093 Gandolfi p<0.005 Kwon 2 falls, groups not specified
Multiple interventions	Usual care, no treatment, other interventions	Most frequently reported AEs: Joint pain, joint swelling, muscle soreness, muscle cramps, sprain, strains, arm pain, leg pain	Multiple studies	Moderate	Unknown	Unknown	Potential reporting bias as many trials did not address harms	Insufficient	Not possible to determine among outcomes which are due specifically to an overuse; no intervention was more likely to lead to muscle and joint pains than another based on current evidence; pains were also frequent in control groups All population subgroups also had insufficient evidence for AEs due to inadequate reporting All intervention subgroups also had insuffient evidence for AEs due to inadequate reporting

Abbreviations: AE = adverse event; RR = risk ratio; SCI = spinal cord injury