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REVIEW ARTICLE (META-ANALYSIS)

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

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Abstract

Objective: To understand the benefits and harms of physical activity in people who may require a wheelchair with a focus on people with multiple sclerosis (MS), cerebral palsy (CP), and spinal cord injury (SCI).

Data Sources: Searches were conducted in MEDLINE, Cumulative Index to Nursing and Allied Health, PsycINFO, Cochrane CENTRAL, and Embase (January 2008 through November 2020).

Study Selection: Randomized controlled trials, nonrandomized trials, and cohort studies of observed physical activity (at least 10 sessions on 10 days) in participants with MS, CP, and SCI.

Data Extraction: We conducted dual data abstraction, quality assessment, and strength of evidence. Measures of physical functioning are reported individually where sufficient data exist and grouped as “function” where data are scant.

Data Synthesis: No studies provided evidence for prevention of cardiovascular conditions, development of diabetes, or obesity. Among 168 included studies, 44% enrolled participants with MS (38% CP, 18% SCI). Studies in MS found walking ability may be improved with treadmill training and multimodal exercises; function may be improved with treadmill, balance exercises, and motion gaming; balance is likely improved with balance exercises and may be improved with aquatic exercises, robot-assisted gait training (RAGT), motion gaming, and multimodal exercises; activities of daily living (ADL), female sexual function, and spasticity may be improved with aquatic therapy; sleep may be improved with aerobic exercises and aerobic fitness with multimodal exercises. In CP, balance may be improved with hippotherapy and motion gaming; function may be improved with cycling, treadmill, and hippotherapy. In SCI, ADL may be improved with RAGT.

Conclusions: Depending on population and type of exercise, physical activity was associated with improvements in walking, function, balance, depression, sleep, ADL, spasticity, female sexual function, and aerobic capacity. Few harms of physical activity were reported in studies. Future studies are needed to address evidence gaps and to confirm findings.

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Disclaimer: 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 of the US Department of Health and Human Services.

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The benefits of regular physical activity for the general population include reduced risk of heart disease, stroke, type 2 diabetes, dementia, depression, and various cancers (eg, breast, colon, 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 because of their physical disabilities is broad and poorly captured in the literature on physical activity; thus, we expanded our criteria for study inclusion beyond "wheelchair users." This review includes 3 diverse conditions commonly associated with wheelchair use: multiple sclerosis (MS), cerebral palsy (CP), and spinal cord injury (SCI). One survey estimated that 45% of patients with MS have difficulties with mobility shortly after diagnosis and almost all have mobility issues after 10 years.[3] One study found 29% of children aged 3-18 years used a wheelchair indoors and 41% used a wheelchair outdoors.[4] Depending on the level and extent of spinal cord injury, many persons with SCI require a wheelchair for all mobility.

These 3 conditions not only represent different etiologies and pathophysiologies but different populations as well. Studies enrolling a population with MS are often in adult women, studies enrolling people with SCI are largely in adult men, and studies enrolling participants with CP are often in children and adolescents.

The review was conducted to inform a National Institutes of Health Pathways to Prevention Workshop and guideline development on "Can Physical Activity Improve the Health of Wheelchair Users?" to evaluate evidence on the benefits and risks of physical activity for potential and current wheelchair users (https://prevention.nih.gov/research-priorities/research-needs-and-gaps/pathways-prevention/can-physical-activity-improve-health-wheelchair-users) and was nominated to the Agency for Healthcare Research and Quality (AHRQ), who funded this review (AHRQ contract no. HHSA290201500009I). AHRQ did not participate in the literature search, determination of study eligibility criteria, data analysis, or interpretation of findings.

Methods

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, along with other federal partners for a Pathways to Prevention 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. Prior to conducting this review, the Evidence-based Practice Center refined the preliminary Key Questions and PICOTS (Populations, Interventions, Comparators, Outcomes, Timing, Studies, Settings) with the AHRQ Task Order Officer and representatives from National Institutes of Health (tables 1 and 2). In considering studies related to physical activity among 3 representative populations, we prioritized certain outcomes. These include long-term health outcomes, function, activities of daily living, and quality of life, among others. We considered walking, balance, activities of daily living (ADL), and other outcomes individually when data permitted. When data were sparse, we grouped different outcomes under the umbrella term "function" to determine whether an intervention was beneficial or not overall. Individual study findings can be found in the supplemental tables S1-4 (available online only at http://www.archives-pmr.org/). We also specify the type of function involve in the summary of evidence table 3 (eg, mobility includes standing, stepping, walking, running, and jumping). Specific outcomes included in each function domain are found in supplemental table S5 (available online only at http://www.archives-pmr.org/). We evaluated outcomes of diverse physical activity interventions, inclusion/exclusion criteria, and research methodologies to identify future research needs. The protocol was published on the AHRQ 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). Comprehensive methods including the search strategies, evidence tables, and study quality ratings are in the full report (*in press to be available* at https://effectivehealthcare.ahrq.gov/).

The key questions for this report include the following:

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 MS, CP, or spinal cord injury?
2. What are the benefits and harms of physical activity interventions for people with MS, CP, or spinal cord injury?
3. What are the patient factors that may affect the benefits and harms of physical activity in patients with MS, CP, or spinal cord injury?
4. What are methodological weaknesses or gaps that exist in the evidence to determine benefits and harms of physical activity in patients with MS, CP, or spinal cord injury?

For the search strategy a research librarian searched MEDLINE, Cumulative Index to Nursing and Allied Health, PsycINFO, Cochrane CENTRAL, Embase, Rehabilitation and Sports Medicine Source, and ClinicalTrials.gov. We limited the search to studies published since 2008, when the first United States Department of Health and Human Services physical activity guidelines were published,[1] and systematic reviews since 2014. An updated literature search was conducted in November 2020. The full search strategies are in appendix 1 of the full report (*in press to be available* at https://effectivehealthcare.ahrq.gov/).

We reviewed reference lists of systematic reviews for includable literature, Technical Expert Panel members were asked to

List of abbreviations:

ADL	**activities of daily living**
AHRQ	**Agency for Healthcare Research and Quality**
CP	**cerebral palsy**
MS	**multiple sclerosis**
RCT	**randomized controlled trial**
RAGT	**robot-assisted gait training**
SCI	**spinal cord injury**
Vo_2peak	**peak oxygen consumption**

Table 1 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 because of 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 d 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 (eg, tai chi) • Hippotherapy (equine-assisted therapy) Physical/aerobic exercise • Arm ergometry • Cycling (stationary, recumbent, arm) • Weight lifting/strength training • Functional electronic stimulation • Robot-assisted gait training • Swimming • Aquatic therapy • 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 d • Unobserved physical activity • Family- or caregiver-observed physical activity • Patient-recalled physical activity • Postoperative physical activity • Intervention focused on improving reaching • Interventions without whole body effect (eg, targeting one joint) • Intervention reported in only one study
Comparators	Comparisons with 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, $\dot{V}o_2$max/Vo_2peak, spirometry Endocrine • Development of diabetes, Hb A_{1c}, 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 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 Neurologic • Autonomic dysreflexia, spasticity, thermodysregulation, carpal tunnel syndrome	• Outcomes not used to make clinical decisions (eg, estradiol) • Other outcomes (eg, 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

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Table 1 (*Continued*)

PICOTS	Inclusion	Exclusion
Timing	At least 10 d with at least 1 session of physical activity per day.	• Acute SCI, undergoing stabilization • Immediate postoperative period
Setting	Any setting, including, clinic, home, or community setting (eg, gym or athletic class). Physical activity occurring in the home must still be observed by medical, research, or athletic staff.	• Non-US 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 (eg, case series, case reports) • Studies published before 2008 • Systematic reviews published before 2015

Abbreviations: BMI, body mass index; Hb A_{1c}, glycosylated hemoglobin; US, United States; $\dot{V}o_2$max, maximum oxygen consumption.

Table 2 Overview of included studies by intervention category and population*

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[5-7] 2 quasi-experimental studies[8-10]	2 RCTs[11,12]	No studies	n=8 6 RCTs 2 quasi-experimental studies
Aerobic exercise	Aquatics	6 RCTs[13-19]	1 RCT[20] 1 cohort study[21]	2 RCTs[22,23]	n=10 9 RCTs 1 cohort study
Aerobic exercise	Cycling	7 RCTs[24-31] 1 quasi-experimental study[32]	2 RCTs[33-35] 1 quasi-experimental study[36]	1 RCT[37] 1 cohort study[38] 1 quasi-experimental study[39]	n=14 10 RCTs 3 quasi-experimental studies 1 cohort study
Aerobic exercise	Hand cycling	No studies	No studies	2 RCTs[37,40] 1 cohort study[41]	n=3 studies 2 RCTs 1 cohort study
Aerobic exercise	Robot-assisted gait training	5 RCTs[42-46]	5 RCTs[47-52] 1 quasi-experimental study[53] 1 cohort study[54]	8 RCTs[55-64]	n=20 studies 18 RCTs 1 quasi-experimental study 1 cohort study
Aerobic exercise	Treadmill	4 RCTs[65-68]	10 RCTs[69-78] 2 quasi-experimental studies[79,80]	6 RCTs[62,81-88]	n=22 20 RCTs 2 quasi-experimental studies
Postural control	Balance exercises	12 RCTs[8,28,89-99]	1 RCT[100] 2 quasi-experimental studies[101,102] 1 cohort study[103]	2 RCT[104,105]	n=18 15 RCTs 2 quasi-experimental studies 1 cohort study
Postural control	Hippotherapy	2 RCTs[106-108]	8 RCTs[109-116] 2 quasi-experimental studies[117,118] 1 cohort study[119]	No studies	n=13 studies 10 RCTs 2 quasi-experimental studies 1 cohort study
Postural control	Tai chi	1 RCT[120] 1 quasi-experimental study[121]	No studies	1 RCT[122]	n=3 studies 2 RCTs 1 quasi-experimental study
Postural control	Motion gaming	6 RCTs[27,97,123-126]	7 RCTs[127-133]	1 RCT[134]	n=14 studies 14 RCTs
Postural control	Whole body vibration	2 RCTs[135,136]	2 RCTs[137,138]	1 RCT[139] 5 RCTs[66,140-147]	n=5 studies 5 RCTs
Postural control	Yoga	6 RCTs[5,66,140-147]	No studies	No studies	n=6 studies 6 RCTs
Strength exercise	Muscle strength exercises			1 RCT[169,170]	

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Table 2 (*Continued*)

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)
		11 RCTs[16,17,28,93,148-157] 1 quasi-experimental study[9]	7 RCTs[158-167] 1 quasi-experimental study[168]		n=21 studies 19 RCTs 2 quasi-experimental study
Multimodal exercise	PRE or strength exercise plus aerobic or balance	12 RCTs[171-183] 1 quasi-experimental study[184]	5 RCTs[185-194]	3 RCTs[195-200] 1 cohort study[201]	n=21 studies 19 RCTs 1 cohort study 1 quasi-experimental study

Abbreviations: PRE, progressive resistance exercise.
* Studies with multiple interventions appear more than once on the table. Studies with only intermediate outcome(s) appear in full report tables.

provide suggestions about unpublished literature, and authors of studies were contacted for information (no additional information was provided).[5,24,124,128,148]

Methods were consistent with those outlined in the AHRQ Evidence-based Practice Center Program Methods Guidance (https://effectivehealthcare.ahrq.gov/topics/cer-methods-guide/overview) and are detailed in the full report (*in press to be available* at https://effectivehealthcare.ahrq.gov/).

The criteria for selection of studies to be included in the review were preestablished and used to determine eligibility for inclusion and exclusion of abstracts according to the Evidence-based Practice Center Methods Guide (see table 1).[202] We included studies from countries with a very high or high score on the Human Development Index because results from these studies are more likely similar to studies conducted in the United States. Using these predefined eligibly criteria, 2 independent investigators reviewed abstract and full-text articles. Systematic reviews were used to identify additional studies.

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 (fig 1). Observed sessions were required to ensure the physical activity intervention took place. Unobserved sessions were allowed as long as 10 sessions were observed. We required studies to have analyzed a minimum of 30 participants in MS and 20 participants in CP and SCI (differences in required sample sizes was because of fewer participants in CP and SCI studies and a desire not to exclude a bulk of the evidence).

The findings are summarized in evidence tables indicating study characteristics and outcome results and study quality ratings and are included in summary tables of the key findings (see tables 2 and 3, detailed in the full report)**.** Findings are organized by the intervention categories: aerobic exercise (eg, aquatics, cycling, robot-assisted gait training [RAGT]), postural control (eg, balance exercises, hippotherapy, motion gaming, yoga), and strength exercises and multimodal exercise with strength as a major component. Results for each of these categories are reported by etiology of disability (ie, MS, CP, SCI). Study quality was independently assessed by 2 investigators and rated as good, fair, or poor using predefined criteria; disagreements were resolved by consensus.

We conducted quantitative synthesis involving pooling of study findings in meta-analyses when studies were homogeneous enough to provide meaningful combined estimates to summarize data from multiple studies and to obtain more precise and accurate estimates of effects.

Meta-analyses were conducted using STATA 14.0/14.2[a] and RevMan v5.3.[b]

Because of the large number of potential outcomes, quantitative synthesis focused on outcomes previously prioritized for strength of evidence rating (table 4) with the addition of the Berg Balance Scale, which was not a prioritized outcome but was the outcome with the most evidence.

Results

The literature search and selection resulted in 19,247 potentially relevant articles. After dual review of abstracts and full text, we included 168 studies (N=7511), of which 146 were randomized controlled trials (RCTs), 15 were quasi-experimental studies, and 7 were cohort studies. Figure 2 indicates the literature flow, and included studies with primary outcomes are listed in table 2 and supplemental figure 1 (available online only at http://www.archives-pmr.org/).

Seventy-four studies enrolled participants with MS (44%), 63 studies enrolled participants with CP (38%), and 31 studies enrolled participants with SCI (18%). The average number of participants per study was 45 (range, 20-242), with only 3 studies having a sample size of 100 or more. In MS, the mean number of physical activity sessions was 25 over a mean of 9 weeks, with a mean of 28 sessions over 10 weeks in CP and 68 sessions over 17 weeks in SCI. Studies compared one physical activity intervention with another physical activity intervention, usual care and/or standard physical therapy, attention control, waitlist control, or no intervention. Some studies had more than 1 comparator arm. Age and sex of study participants varied by population enrolled (ie, MS, CP, SCI). Reporting of baseline disability also varied by population. Fifty-five MS studies reported baseline scores on the Expanded Disability Status Scale (average study mean 3.6±1.77, representing moderate disability); most studies in CP (63%) reported scores on the Gross Motor Function Classification System, with disability levels I to III most frequently studied (average Gross Motor Function Classification System study mean 2.40±0.87, representing mild to moderate disability). Reporting of baseline impairment status in SCI studies varied, with studies reporting specific spinal injury levels, proportion with paraplegia vs tetraplegia, proportion with complete vs incomplete injury, and proportion with each American Spinal Injury Association Impairment Scale score. Studies were conducted most often in Iran (26 studies), Turkey (19 studies), and the United States (15 studies). Most studies were conducted in an outpatient setting (51%) or an inpatient hospital or rehabilitation center (14%); the study location was not specified in 20% of studies. Eight percent (n=13) of the studies were considered good quality, two-thirds of the studies were rated fair quality (n=113), and one-fourth were poor quality (n=42).

Table 3 Summary of evidence

Category	Intervention	No. of Studies; Study Design; Participants (n)	Key Points	Strength of Evidence
KQ 1. Prevention of cardiovascular conditions, diabetes, and obesity				
No studies	NA	NA	NA	NA
KQ 2. Benefits and harms of physical activity vs usual care, attention control, waitlist control, no intervention				
Aerobic exercise	Aerobics	MS: 2 RCTs (77)	Improved sleep scores	Low
		MS/CP: 2 RCTs (81)	Improved function (mobility)*	Low
	Aquatics	MS: 2 RCTs (62)	Improved balance	Low
		MS: 1 RCT (73)	Improved ADL	Low
		MS: 1 RCT (60)	Improved female sexual function	Low
		MS: 1 RCT (73)	Improved spasticity	Low
	Cycling	MS: 6 RCTs (277)	No clear benefit on function (multifactorial)†	Low
		CP: 2 RCTs (85)	Improved function (multifactorial)†	Low
	Robot-assisted gait training	MS: 2 RCTs (97)	No clear benefit on function (mobility)*	Low
		MS: 2 RCTs (97)	Improved balance	Low
		SCI: 2 RCTs (176)	Improved ADL	Low
		SCI: 3 RCTs (170)	No clear benefit on function (multifactorial)†	Low
	Treadmill	MS: 2 RCTs (50)	Improved walking	Low
		CP: 2 RCTs (53)	Improved function (multifactorial)†	Low
Postural control interventions	Balance exercises	MS: 7 RCTs (369)	Improved function (multifactorial)†	Low
		MS: 10 RCTs (553)	Improved balance	Moderate
		MS: 2 RCTs (128)	Improved fall risk	Low
	Hippotherapy	CP: 5 RCTs, 2 QENRS (333)	Improved function (multifactorial)†	Low
		CP: 1 RCT, 2 QENRS (150)	Improved balance	Low
	Tai chi	MS, CP, SCI	Any included outcome	Insufficient
	Motion gaming	MS: 4 RCTs (177)	Improved function (mobility)*	Low
		MS: 3 RCTs (94)	Improved balance	Low
	Whole body vibration	MS, CP, SCI	Any included outcome	Insufficient
	Yoga	MS: 4 RCTs (215)	No clear benefit on function (mobility)*	Low
Strength interventions	Muscle strength exercises	MS: 8 RCTs (332)	Improved walking	Low
		MS: 5 RCTs (178)	No clear benefit on function (mobility)*	Low
		MS: 3 RCTs (100)	No clear benefit on quality of life	Low
		MS: 6 RCTs (319)	No clear benefit on balance	Low
		MS: 1 RCT (71)	No clear benefit on spasticity	Low
		CP: 3 RCTs (140)	No clear benefit on walking	Low
		CP: 3 RCTs (134)	No clear benefit on function (multifactorial)†	Low
Multimodal interventions	PRE or strength exercise plus aerobic or balance	MS: 4 RCTs (176)	Improved walking	Low
		MS: 4 RCTs (224)	Improved balance	Low
		MS: 2 RCTs (123)	Improved cardiovascular fitness	Low
		CP: 3 RCTs (135)	No clear benefit on function (motor)‡	Low
		CP: 2 RCTs (107)	No clear benefit on quality of life	Low
All Exercise		MS: 10 RCTs (448)	Improved depression scores	Moderate
		MS: 25 RCTs (1436)	Improved walking	High
		MS: 17 RCTs (906)	Improved balance	Moderate
		MS: 15 RCTs (743)	No clear benefit on function (mobility)*	Moderate
		CP: 11 RCTs (500)	Improved function (multifactorial)†	Low
		CP: 2 QENRS (54)	Improved cardiovascular fitness	Low
		SCI: 3 RCTs (171)	No clear benefit on depression scores	Low
		SCI: 4 RCTs (129)	Improved function (multifactorial)†	Low
		SCI: 2 RCTs/1 Cohort study (88)	Improved cardiovascular fitness	Low
Benefits and harms of physical activity vs another physical activity				
Aerobic exercise	Robot-assisted gait training vs overground walking	MS: 1 RCT (72)	No clear benefit on function (mobility)*	Low
		MS: 1 RCT (72)	No clear benefit on quality of life	Low
		MS: 1 RCT (72)	No clear benefit on balance	Low
	Treadmill training vs overground walking	CP: 5 RCTs (130)	No clear benefit on walking	Low
		CP: 4 RCTs (109)	No clear benefit on function (multifactorial)†	Low
KQ 3. Patient factors affect the benefits and harms of physical activity				
		MS: 1 RCT (69)	Greatest strength improvement in women who were least strong at baseline	NA
		MS: 1 RCT (89)		NA
		CP: 1 RCT (39)	Improvements in walking, function, and Vo_2 peak with multimodal exercise compared with a waitlist control, but these differences were not	NA
		SCI: 2 RCTs (58)		NA

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Table 3 (*Continued*)

Category	Intervention	No. of Studies; Study Design; Participants (n)	Key Points	Strength of Evidence
			statistically significant after adjustment for baseline disability 6-7 year olds had improved sitting scores with hippotherapy compared with no hippotherapy, whereas children aged 8-12 years had similar scores, but there was no difference in the effect of the intervention based on disability level at baseline Better baseline function and more recent injury were associated with greater improvements in walking	
KQ 4. Methodological weaknesses or gaps				
No studies	NA	NA	NA	NA

NOTE. Specific instruments/measures that comprised function outcomes can be found in supplemental table S5.
Abbreviations: KQ, key question; NA, not applicable; PRE, PRE, progressive resistance exercise; QENRS, quasi-experimental nonrandomized studies.
* Mobility outcomes involve standing, stepping, walking, running, jumping.
† Multifactorial outcomes include outcomes from multiple domains or scales that assess multiple domains (activities of daily living, balance, participation, motor skills, mobility).
‡ Motor outcomes measure gross motor or upper extremity function (Gross Motor Function Measure-66, Gross Motor Function Measure-88, Quality of Upper Extremity Skills Test).

Studies were downgraded because of unclear randomization methods, lack of blinding of outcome assessors, and high attrition.

Key question 1. Prevention of cardiovascular conditions, diabetes, and obesity

No studies on the effects of physical activity in participants with MS, CP, or SCI assessed the prevention of cardiovascular conditions (eg, myocardial infarction, stroke, development of hypertension) or the development of diabetes or obesity.

Key question 2. Benefits and harms of physical activity

Aerobic exercise interventions

Aerobic interventions included aerobic exercises, aquatics, cycling, RAGT, and treadmill training. Individual study findings can be found in the supplemental tables S1-4 (available online only at http://www.archives-pmr.org/).

In studies that enrolled participants with MS, compared with usual care or attention control, we found evidence that aerobic

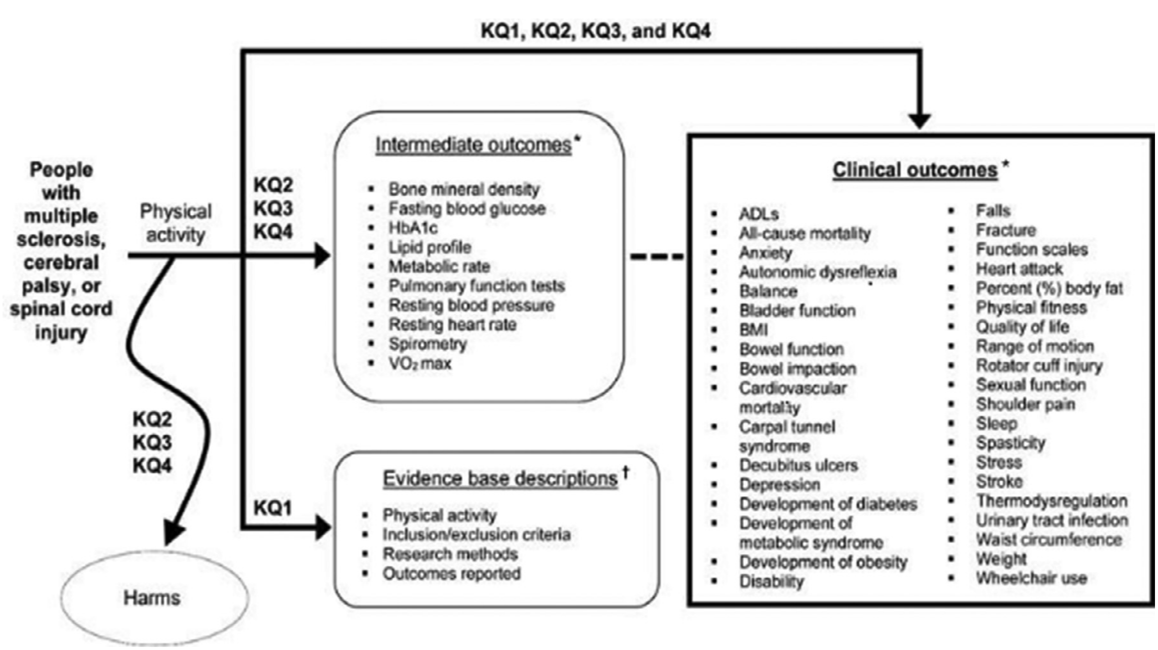

Fig 1 Analytic framework diagram. The analytic framework for physical activity and the health of wheelchair users with multiple sclerosis, cerebral palsy, and spinal cord injury concepts are illustrated based on key questions and clinical outcomes as well intermediate outcomes and are described in detail in the full report. Evidence base descriptions are of studies that evaluate prevention of obesity, diabetes, cardiovascular conditions, and harms. Abbreviations: BMI, body mass index; Hb A_{1c}, glycosylated hemoglobin; KQ, key question; $\dot{V}o_2$max, maximum oxygen consumption. *Outcomes are specified in the Methods section †Studies that evaluate prevention of obesity, diabetes, cardiovascular conditions, and harms.

Table 4 Effects of physical activity interventions compared with usual care

Intervention Category Intervention	Multiple Sclerosis Studies Strength of Evidence (Direction of Finding)	Cerebral Palsy Studies Strength of Evidence (Direction of Finding)	Spinal Cord Injury Studies Strength of Evidence (Direction of Finding)
Aerobic exercise dance (1 RCT in MS and 1 RCT in CP)*	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 Robot-assisted gait training	Low (balance improvement) Low (no clear benefit in function)	Insufficient	Low (ADL improvement) Low (no clear benefit on function)
Aerobic exercise Treadmill	Low (walking, function, 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, $\dot{V}O_2$ improvement)	Low (no clear benefit on function, quality of life)	Insufficient
All types of exercise	High (walking improvement) Moderate (balance, depression improvement, no clear benefit on function)	Low (function) Low ($\dot{V}O_2$ improvement)	Low (function) Low ($\dot{V}O_2$ improvement, increased episodes of autonomic dysreflexia,[†] no clear benefit on depression)

Abbreviation: $\dot{V}O_2$, peak/max (studies reported either peak or max which are slightly different).
* Strength of evidence based on combining the 2 populations, multiple sclerosis and cerebral palsy.
† Whole body exercise versus exercise limited to upper body.

exercise may improve sleep.[6,8] Aquatic exercises may improve ADL,[13] female sexual function,[14] balance,[15,16] and spasticity.[13] RAGT may improve balance[42,43] compared with usual care but with no clear benefit in function (mobility).[42,43] There was also no clear benefit on function (mobility), balance, or quality of life when RAGT was compared with overground walking.[44] Two studies in MS found evidence that walking may improve with treadmill training compared with usual care or waitlist control.[65,66] Six studies found no clear benefit of cycling on walking in participants with MS compared with usual care, attention control, or waitlist control.[24-29] One study in MS[5] and 1 in CP[11] together provided evidence that dance may improve function (mobility) compared with usual care.

In study participants with CP, function (multifactorial) may be improved with stationary cycling compared with a no intervention

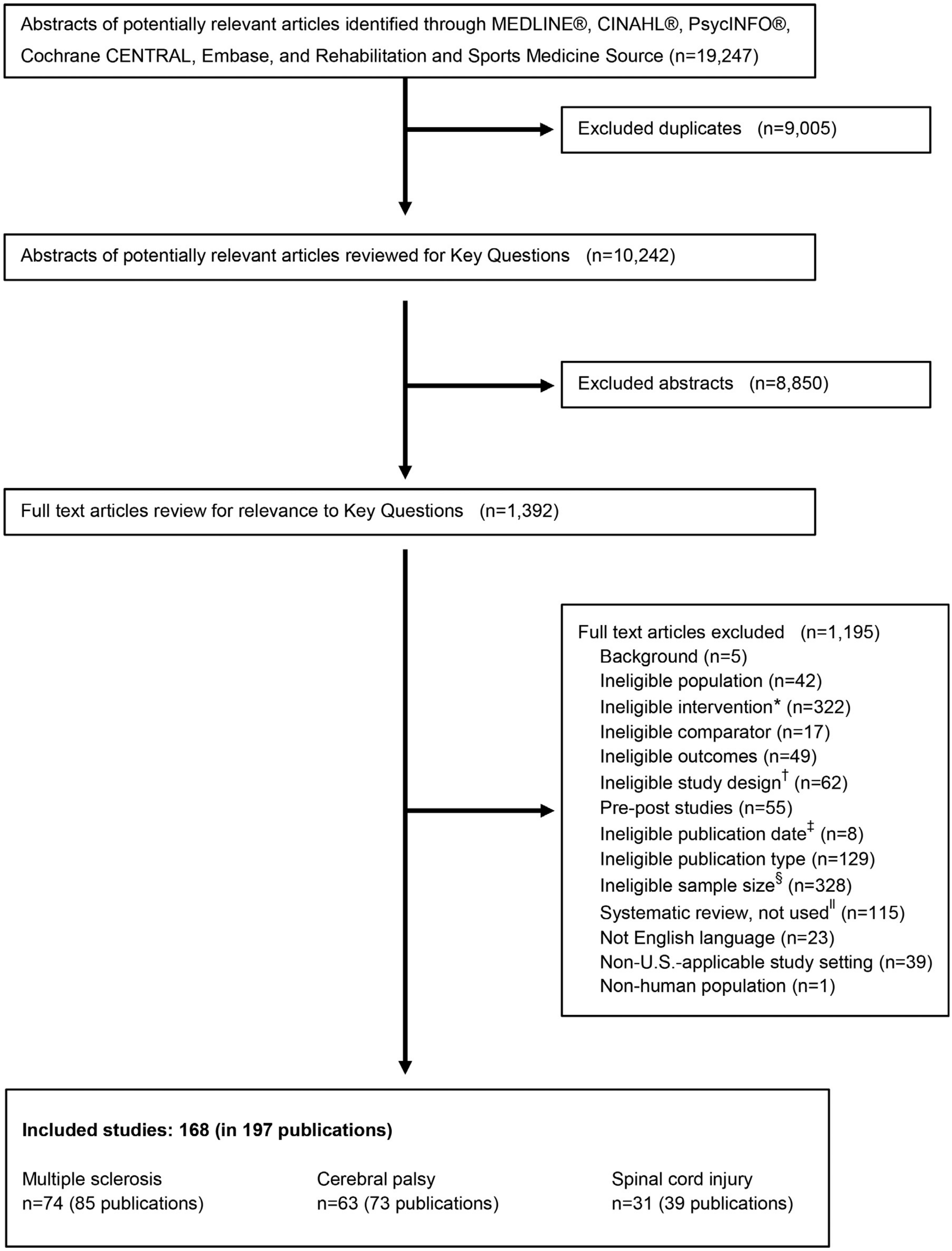

Fig 2 Literature flow diagram. The diagram indicates the number of abstracts and full-text articles reviewed for inclusion and subsequently included or excluded and the final studies included for each population. *Interventions with <10 sessions/<10 d, or only family/caregiver observed. †Case reports and case series are not included because of methodological limitations. ‡Studies before January 2008 and systematic reviews from 2014 or older are outside of the search dates. §Studies with sample sizes <30 for multiple sclerosis and cerebral palsy and <20 for spinal cord injury. ‖Systematic reviews not used because they did not meet all inclusion criteria but checked for includable studies.

control.[33-35] Function (multifactorial) may also be improved with treadmill training compared with usual care,[69,70] but evidence was inconsistent and demonstrated no clear benefit of treadmill training on walking or function (multifactorial) compared with overground walking.[71-74]

In study participants with SCI, ADL may be improved with RAGT compared with usual care or walking overground without robot-assistance[55,56] (see supplemental table S1 [available online only at http://www.archives-pmr.org/]. Benefits and harms of physical activity—aerobic exercise intervention studies).

Postural control interventions

Postural control or balance interventions included balance exercises, hippotherapy, tai chi, motion gaming, whole body vibration, and yoga. Hippotherapy involved riding a horse or horse simulator. Motion gaming used body movement rather than a mouse or game controller to play a game using a computer or television screen (eg, Xbox, Wii).

In participants with MS, studies found that balance exercises likely improve balance[28,89-97] including decreased risk for falls,[91,92] and may improve function (multifactorial)[28,92-97] compared with usual care, waitlist control, attention control, or no intervention. Balance[28,97,124] and function (mobility)[28,97,124,125] may also be improved with motion gaming vs usual care or waitlist control. There was no clear benefit on function (mobility) with yoga vs usual care or waitlist control.[5,66,140-142]

In CP studies, balance[110,117] and function (multifactorial)[109,111-114,117,119] may be improved with hippotherapy compared with usual care or waitlist control. Motion gaming may also improve balance in participants with CP compared with usual care or motion gaming using a mouse.[127-130]

There was insufficient evidence to draw conclusions regarding the effect of postural control interventions in participants with SCI (see supplemental table S2 [available online only at http://www.archives-pmr.org/]). Benefits and harms of physical activity—postural control intervention studies)

Strength interventions

Strength interventions included progressive resistance exercises and body weight resistance exercises (eg, abdominal crunches, Pilates).

In MS studies, there was limited evidence for no clear benefit on balance,[9,28,148-151] function (mobility),[16,17,93,148-150] walking,[28,93,148,150-155] quality of life,[149,150,153] and spasticity[155] with strength exercises compared with usual care, attention control, or waitlist control.

In studies that enrolled participants with CP, there was no clear benefit of strength exercises on walking[158-163] or function (multifactorial).[158-162,164]

Evidence for the effects of strength exercises in SCI was too sparse to draw conclusions

(see supplemental table S3 [available online only at http://www.archives-pmr.org/]. Benefits and harms of physical activity—muscle strength exercise intervention studies).

Multimodal interventions

Multimodal interventions included strength exercises plus aerobic exercise and/or balance training and may also include stretching or other interventions.

Balance,[170-174] walking,[172,173,175,176] and cardiovascular fitness (peak oxygen consumption [Vo_2peak])[177-179] may be improved with multimodal exercises in participants with MS vs usual care, waitlist control, or no intervention.

In CP, there was no clear benefit on function (motor)[185-192] or quality of life with multimodal interventions[185-191] compared with usual care.

Evidence on the effect of multimodal interventions in SCI was insufficient to draw conclusions (see supplemental table S4. [available online only at http://www.archives-pmr.org/]. Benefits and harms of physical activity—multimodal intervention studies).

All-exercise interventions

To determine if physical activity, regardless of type of activity, resulted in improved outcomes, we pooled RCTs that had a usual care, attention control, waitlist control, or no intervention arm and reported the same outcome.

When all exercises types (ie, aerobic, postural control, strength, multimodal exercises) were pooled, physical activity improved walking in MS[5,15,26-28,66,92,93,124,125,140-142,148,150,151,153,171-176] and likely improved balance[15,28,65,66,89-92,95,97,106,124,148,171-174] and depression scores,[8,18,24,26-28,42,66,152,176] with no clear benefit on function (mobility assessed with the timed Up and Go test)[5,24,42,92,95,97,124,125,135,148-150,173,176] compared with usual care, attention or waitlist control, or no intervention.

When all exercise types were combined in CP, function (multifactorial)[33-35,111,112,114,127,158-160,185-192] and cardiovascular fitness as measured with Vo_2peak[36,79] may be improved vs usual care, attention control, or no intervention.

In SCI, function (multifactorial)[104,105,139,195,196] and cardiovascular fitness (Vo_2peak)[40,41,81] may be improved when all exercise types were combined, but there was no clear benefit on depression scores[37,82,197] (supplemental figs 2-4 [available online only at http://www.archives-pmr.org/]).

Harms of physical activity

Harms of physical activity were infrequently reported. One trial reported an increased risk of autonomic dysreflexia in SCI with whole body exercises compared with upper body exercises.[197,198] Although fractures, falls, and other adverse events were reported by a few studies, they were not always reported by study group and were not always study related, making it impossible to determine if a particular exercise was associated with increased risk of harms or adverse events compared with usual care or no treatment.

Key question 3. Effects of patient factors on the benefits and harms of physical activity

Limited evidence in MS found greatest improvements in core strength in those who were least strong compared with those with less disability.[96] One MS study found improvements in walking, function, and Vo_2peak with multimodal exercise compared with a waitlist control, but these differences were not statistically significant after adjustment for baseline disability.[177,178]

One CP study analyzed the effects of the exercise intervention according to demographic characteristics and found that younger children aged 6 and 7 years had improved sitting scores with hippotherapy compared with no hippotherapy, whereas children aged 8 through 12 years had similar scores, but there was no difference in the effect of the intervention based on disability level at baseline.[115]

Limited evidence in participants with incomplete SCI found having better function and more recent injury at baseline associated with better response to aerobic interventions than those with worse function and longer time since injury.[82,195,196]

Key question 4. Methodological weaknesses and gaps in the evidence

This is covered in the discussion section and more thoroughly in the report (*in press to be available* at https://effectivehealthcare.ahrq.gov/).

Discussion

The average study sample size was 45 (range, 20-242), including 3 studies with samples sizes of 100 or more. Most studies were rated fair quality or as having moderate risk of bias. The bulk of the evidence was in participants with MS. In participants with MS, walking ability may be improved with treadmill training and multimodal exercise regimens; function may be improved with treadmill training, balance exercises, and motion gaming; balance is likely improved with balance exercises (which may also reduce risk of falls) and may be improved with aquatic exercises, RAGT, motion gaming, and multimodal exercises; ADL, spasticity, and female sexual function may be improved with aquatic therapy; sleep may be improved with aerobic exercises; and cardiovascular fitness may be improved with multimodal exercises. In participants with CP, balance may be improved with hippotherapy and motion gaming and function may be improved with cycling, hippotherapy, and treadmill training. In participants with 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, were 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. Evidence was also lacking on the role sex, age, race and ethnicity, socioeconomic status, patient comorbidities, and other patient characteristics may play on the effects of physical activity. There was inadequate reporting of control group activities and adverse events in many trials. However, more intense physical activity was associated with increased autonomic dysreflexia episodes in SCI compared with less intense activity.

Implications for primary care providers with patients with MS, CP, and SCI

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 so as to avoid serious episodes of autonomic dysreflexia, which could be life threatening. We found benefits in all 3 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[203] found improved function (gross motor function measure 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[199] that enrolled people with chronic SCI reported improved balance with a combination of aerobic, strength, and core stability training.

Physical activity guidelines from the National Multiple Sclerosis Society recommend at least 150 minutes per week of exercise and/or lifestyle physical activity based on abilities, preferences, and safety.[204] The American Academy for Cerebral Palsy and Developmental Medicine recommends at least 150 minutes of moderate physical activity weekly and muscle strengthening at least 2 days per week.[205] For adults with SCI, the Spinal Cord Injury Research Evidence Community recommends at least 30 minutes of moderate to vigorous intensity aerobic activity twice per week for cardiorespiratory fitness (3 times per week for cardiometabolic health benefits) and strength exercises twice per week.[206] Although we do not specify a recommended "dose" of any particular exercise, both aerobic activity and strength training are important elements of any exercise program, including programs for people with MS, CP, and SCI, and should be encouraged by primary care providers.

Implications for primary care providers with patients with other disabilities

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 disease or Lyme disease may have similar issues and challenges as patients with MS. Patients with intellectual disability and motor impairment owing to other neurologic disease or inborn errors of metabolism may face similar challenges as patients with CP. Patients with stroke, patients with arthritis, or wheelchair-using elderly persons 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[207] found gait performance improved with gait and strength training in people with lower limb amputation using a prosthesis. A 2019 systematic review[208] found that home-based exercise improved balance and gait speed in people with Parkinson disease and that the improvement was similar to that seen in center-based exercise. A 2019 systematic review[209] in patients with stroke reported improved walking speed and endurance with a combination of aerobic and strength exercises. A 2015 systematic review[210] of elderly patients reported a large effect of Pilates in improving muscle strength, walking, ADL, and quality of life. A 2015 systematic review[211] found improved depression scores with exercise in adult patients with arthritis.

Applicability and generalizability

This review included patients with 1 of 3 conditions to represent the diversity of wheelchair users and potential users. Most studies enrolled participants with less disability (including ambulatory participants), although there was a wide range of ability levels across studies. This report also 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. Challenges facing people with MS, CP, and SCI may be similar to people with other conditions such as Parkinson disease, stroke, and arthritis. Elderly persons often face mobility challenges and may eventually require a use of a wheelchair. Although study participants were required to engage in 10 observed physical activity sessions over a minimum of 10 days, a wide variety of exercise modalities and outcomes were included.

Study limitations

The majority of evidence is low strength because of small sample sizes and heterogeneity of interventions and outcomes studied. No evidence for the prevention of cardiovascular events, development of diabetes, or obesity was identified. Studies rarely provided data on intensity of physical activity or reported the proportion of wheelchair users enrolled, and those that did failed to stratify results by wheelchair use. Reporting of control group activities and adverse events was inadequate.

Larger, well-conducted RCTs are needed in MS, CP, and SCI to address evidence gaps and to confirm current findings. Large, controlled cohort studies (which are often longer in duration than RCTs) could provide data on long-term outcomes and on potential harms of the intervention. Larger sample sizes would enable subgroup analyses based on patient characteristics and comorbidities.

Conclusions

Physical activity was associated with improvements in walking ability, general function, balance (including fall risk), depression, aerobic capacity, ADL, female sexual function, spasticity, and sleep, depending on population and type of physical activity. No studies reported long-term cardiovascular or metabolic disease health outcomes.

Suppliers

a Stata 14.0/14.2; StataCorp.
b RevMan v5.3; Cochrane.

Keywords

Activities of daily living; Cerebral palsy; Exercise; Mental health; Multiple sclerosis; Physical fitness; Rehabilitation; Spinal cord injuries; Wheelchairs

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Supplemental Appendix Figures and Tables

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Supplemental Table 1 Studies of the Benefits and Harms of Physical Activity—Aerobic Exercise Interventions

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Aerobics—Multiple Sclerosis			
Al-Sharman, 2019[6] 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[7] 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[9] 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
Keser, 2011[10] 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[8] 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[5] 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 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
Aerobics—Cerebral Palsy			
Gibson, 2018[12] 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[11] 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

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Supplemental Table 1 (*Continued*)

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Aerobics—Spinal Cord Injury			
No studies identified	—	—	—
Aquatics—Multiple Sclerosis			
Castro-Sanchez, 2012[13] 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[15] 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[19] 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[16,17] 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
Aquatics—Cerebral Palsy			
Adar, 2017[20] 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[21] 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
Aquatics—Spinal Cord Injury			
No studies identified	—	—	—
Cycling—Multiple Sclerosis			
Baquet, 2018[26] 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[31] 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[29] 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

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Supplemental Table 1 (*Continued*)

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Hebert, 2011[27] 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[25] 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
Negaresh, 2019[24] 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[32] Aerobic exercise Quasiexperimental Fair	A. Cycle ergometry, 60 sessions over 4 weeks plus 480 min of rehab exercises over 4 weeks (n=21) B. 480 min 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[28] 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
Cycling—Cerebral Palsy			
Bryant, 2013[33] 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[34] Fowler, 2010[35] 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
Cycling—Spinal Cord Injury			
Akkurt, 2017[37] 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[38] Aerobic exercise Cohort study Poor	A. 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

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Supplemental Table 1 (*Continued*)

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Robot-assisted gait training—Multiple Sclerosis			
Calabro, 2017[46] 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[45] 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[42] 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[43] 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
Straudi, 2019[44] 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
Robot-assisted gait training—Cerebral Palsy			
Aras, 2019[51] 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[52] 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[53] 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	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%	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

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Supplemental Table 1 (*Continued*)

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
	4 weeks (n=12) C. TOP 40 sessions over 10 weeks (n=10) D. RAGT 40 sessions over 10 weeks (n=12)	Spastic bilateral CP: 100% Ambulatory: 100% with or without aid	(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
Yazici, 2019[54] 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[49] Wallard, 2018[50] 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[47] (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[48] 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
Robot-assisted gait training—Spinal Cord Injury			
Duffell, 2014[63] 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[55] 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[57] Kressler, 2013[59] 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	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%	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

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Supplemental Table 1 (*Continued*)

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
	(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)	Hispanic: 29.4% vs. 38.9% vs. 40% vs. 35.7% African American: 11.8% vs. 16.7% vs. 20% vs. 21.4%	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
Kumru, 2016[60] 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[64] 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[61] 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[56] 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
Treadmill—Multiple Sclerosis			
Ahmadi, 2013[66] 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[65] 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[67] 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[68] 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

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Supplemental Table 1 (*Continued*)

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Treadmill—Cerebral Palsy			
Aviram, 2017 [80] 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 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 GMFM-66: 1.98 (0.40) vs. 3.10 (0.44), p=0.001 GMFM-66-D: 5.53 (1.61) vs. 8.36 (1.24), p=0.013 GMFM-66-E: 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
Bahrami, 2019 [69] 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 10MWT: 22.46% change vs. 1.28% change, p<0.05 6MWT: 23.68% change vs. 16.54% change, p>0.05 WHOQOL-Brief: % change 3.83% change vs. 8.94% change, p>0.05
Chrysagis, 2012 [70] 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 [78] Aerobic exercise RCT Fair May share participants with Grecco, 2014 [75]	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 [73] 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 [75] Aerobic exercise RCT Fair May share participants with Duarte Nde, 2014 [78]	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 [74] 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 [76] 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
Kim, 2015 [77] 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: 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

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Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Nsenga Leunkeu, 2012[79] 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) 6MWT: 480 to 601 vs. 450 to 450, no difference in baseline values, significant difference in postintervention values favoring treatment
Swe, 2015[72] 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: 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-88-D: −2.94, 95% CI −16.42 to 10.64, p=0.67 GMFM-88-E: −2.8, 95% CI −20.02 to 14.42, p=0.75
Willoughby, 2010[71] 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: 10MWT: 244.33 (115.41) to 219.38 (123.71) vs. 118.36 (89.89) to 135.82 (95.65), p=0.097
Treadmill—Spinal Cord Injury			
Alexeeva, 2011[83] 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
Giangregorio, 2012[84] Hitzig, 2013[85] Kapadia, 2014[86] Craven, 2017[87] 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[82] 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 $\geq$ 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: 2MWT = 2-Minute Walk Test; 6MWT = 6-Minute Walk Test; 10MWT= 10-Meter Walk Test; 25FWT = 25-Foot Walk Test; AIS = Asia Impairment Scale; BMI = body mass index; BBS = Berg Balance Scale; BWS = body weight supported; CHART = Craig Handicap and Assessment Reporting Technique; CI = confidence interval; CP = cerebral palsy; CPQoL = Cerebral Palsy Quality of Life scale; DGI = Dynamic Gait Index; EDSS = Expanded Disability Status Scale; FAC = functional ambulation category; FAP = Functional Ambulation Profile; FES = functional electrical stimulation; FIM = Functional Independence Measure; 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; HAQUAMS = Hamburg Quality of Life Questionnaire in Multiple Sclerosis questionnaire; HiMAT = High-level Mobility Assessment Tool; ICF = International Classification of Functioning; IPA = Impact on Participation and Autonomy; ISI = Insomnia Severity Index; LEMS = Lower Extremity Motor Score; LMN = lower motor neuron; MD = mean difference; MQLIM = Multicultural Quality of Life Index; MS = multiple sclerosis; MSFC = multiple sclerosis functional composite; MSIS-29 = Multiple Sclerosis Impact Scale-29; MSIS= Multiple Sclerosis Impact Scale; MSWS-12 = Multiple Sclerosis Walking Scale-12; MusiQoL = Multiple Sclerosis International Quality of Life questionnaire; NR = not reported; NS = not significant; PBS = Pediatric Balance Scale; PEDI = Pediatric Evaluation Disability Inventory; PODCI = Pediatric Outcomes Data Collection Instrument; PPMS = primary progressive multiple sclerosis; PSQI = Pittsburg Sleep Quality Index; PT = physical therapy; 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; SCI = spinal cord injury; SCIM = Spinal Cord Independence Measure; SD = standard deviation; SE = standard error; SF-12 = Short Form (12) Health Survey; SF- 36 = Short Form (36) Health Survey; SPMS = secondary progressive multiple sclerosis; TBS = Tinetti Balance Scale; TUG = Timed Up and Go Test; UEMS = Upper Extremity Motor Score; UMN = upper motor neuron; WeeFIM = Wee-Functional Independence Measure for children; WHOQOL = World Health Organization Quality of Life; WISCI = Walking Index for Spinal Cord Injury.

Supplemental Table 2 Studies of the Benefits and Harms of Physical Activity—Postural Control Interventions

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Balance Exercise—Multiple Sclerosis			
Afrasiabifar, 2018[89] 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): BBS: 8.9 (SD 1.8) vs. 2.3 (SD 0.9) vs. −1.2 (SD 1.05) BBS: 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[96] 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)
Arntzen, 2019[94] Arntzen, 2020[99] 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[90] 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[93] 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[92] Postural control RCT Fair	A. Group balance training (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[95] Postural control RCT Fair	A. Group Core Stability Dual Tasking Sensory Strategies (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
Gandolfi, 2015[91] Postural control RCT Fair	A. Balance training (sensory integration), 15 sessions over 5 weeks (n=39) B. Conventional rehabilitation, 15	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: MSQOL-54 PHC: 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) MSQOL-54 MHC: 61.05 (20.15) to 65.32 (18.29) vs. 60.50 (16.6) to 63.09 (12.19), p>0.05 (postintervention);

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Supplemental Table 2 (*Continued*)

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
	sessions over 5 weeks (n=41)		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) BBS: 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) Number of Falls: 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[97] 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): BBS: 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[8] 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: EDSS: 3.38 (1.87) to 3.10 (1.86) vs. 2.02 (1.84) to 1.98 (1.70), p>0.05 ISI: 13.46 (5.81) to 10.13 (4.92) vs. 1.71 (5.43) to 11.14 (5.39), p>0.05
Salci, 2017[98] 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: 2MWT: 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 BBS: 3.57 (SD 2.20) vs. 5.78 (SD 3.40) vs. 5.57 (SD 3.73); p=>0.05 for all comparisons
Tollar, 2020[28] 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
Balance Exercise—Cerebral Palsy			
Bleyenheuft, 2017[101] Postural control Quasiexperimental Poor	A. Hand-arm bimanual intensive therapy including lower extremity, MSFC 6.4-hour sessions 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): 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 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
Curtis, 2018[100] 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

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Supplemental Table 2 (*Continued*)

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Kim, 2017[103] 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[102] 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
Balance Exercise—Spinal Cord Injury			
Hota, 2020[104] 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[105] 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
Hippotherapy—Multiple Sclerosis			
Moraes, 2020[108] 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[106] 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
Hippotherapy—Cerebral Palsy			
Deutz, 2018[111] 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[112] 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[117] Postural control	A. Hippotherapy, 16 sessions over 8 weeks	A vs. B Age: 6.4 vs. 6.1	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

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Supplemental Table 2 (*Continued*)

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Quasiexperimental Fair	plus usual PT, 16 sessions over 8 weeks (n=16) B. Usual PT, 16 sessions over 8 weeks (n=16)	Female: 31% vs. 38% Ambulatory: 100% GMFCS I: 25% vs. 25% GMFCS II: 75% vs. 75%	(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[109] 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
Lee, 2014[110] 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[118] 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[115] 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[114] 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[119] 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%	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

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Supplemental Table 2 (*Continued*)

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
		GMFCS II: 32% vs. 19% GMFCS III: 15% vs. 29% GMFCS IV: 29% vs. 24%	
Silva e Borges, 2011[113] 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: GMFCS reclassification indicating improved function: 25% (5/20) vs. 10% (2/20), p=0.24
Hippotherapy—Spinal Cord Injury			
No studies identified	—	—	—
Tai Chi—Multiple Sclerosis			
Azimzadeh, 2015[120] 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[121] 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
Tai Chi—Cerebral Palsy			
No studies identified	—	—	—
Tai Chi—Spinal Cord Injury			
Qi, 2018b[122] 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
Motion Gaming—Multiple Sclerosis			
Kalron, 2016[123] 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: Berg Balance Scale: 46.8 (9.6) to 47.9 (6.4) vs. 43.3 (7.1) to 44.6 (4.9), p=0.56 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 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
Khalil, 2018[126] 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	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: 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 3MWT: −7.11, 95% CI −34.18 to 19.95, p=0.59 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

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Supplemental Table 2 (*Continued*)

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
	home, 18 sessions over 6 weeks (n=16)		FES-I: 3.86, 95% CI −0.062 to 8.34, p=0.08 BBS: −4.52, 95% CI −7.90 to −1.09, p=0.01
Nilsagard, 2013[125] 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: TUG: −0.8 (2.4) vs. 0.1 (2.1), p=0.10 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
Ozkul, 2020[97] 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): 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
Tollar, 2020[28] 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: 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
Yazgan, 2020[124] 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
Motion Gaming—Cerebral Palsy			
Acar 2016[131] 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[133] 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[127] Postural control RCT Fair	A. PC gaming using arm and trunk, 60 sessions over 12 (n=20) B. PC gaming using mouse,	A vs. B Age: 7.3 vs. 7.4 Female: 30% vs. 25% Quadriplegia: 55% vs. 60% Diplegia: 20% 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

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Supplemental Table 2 (*Continued*)

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
	60 sessions over 12 weeks (n=20)	Athetoid: 10% vs. 10% Ataxic: 15% vs. 15%	(2.68), p<0.05
Hsieh, 2020[128] 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[130] 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
Tarakci, 2016[129] 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[132] 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
Motion Gaming—Spinal Cord Injury			
Tak, 2015[134] 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
Whole Body Vibration—Multiple Sclerosis			
Abbasi, 2019[136] 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[135] Postural control RCT Fair	A. WBV, 10 sessions over 3 weeks plus conventional therapy (n=16) B. Whole body light vibration, 10 sessions	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

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Supplemental Table 2 (*Continued*)

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
	over 3 weeks plus conventional therapy (n=14) C. Conventional therapy (n=17)		comparisons BBS: 3.9 (4.4) vs. 4.2 (6.1) vs. 0.2 (7.5), p>0.05 for all comparisons
Whole Body Vibration—Cerebral Palsy			
Ahmadizadeh, 2020[138] 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[137] 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
In, 2018[139] 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
Yoga—Multiple Sclerosis			
Ahmadi, 2013[66] 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[143] Najafidoulatabad, 2014[144] 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[140] Garrett, 2013b[141] Postural control RCT Poor	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 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[147] Hasanpour-Dehkordi, 2016[146] Hasanpour-Dehkordi, 2016 (2)[145] Postural control	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

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Supplemental Table 2 (*Continued*)

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
RCT Poor			
Hogan, 2014[142] 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[5] 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
Yoga—Cerebral Palsy			
No studies identified	—	—	—
Yoga—Spinal Cord Injury			
No studies identified	—	—	—

Abbreviations: 2MWT = 2-Minute Walk Test; 6MWT = 6-Minute Walk Test; 10MWT= 10-Meter Walk Test; 25FWT = 25-Foot Walk Test; ASIA = American Spinal Injury Association Impairment Scale; BBS = Berg Balance Scale; CI = confidence interval; CIS = Clinically Isolated Syndrome; CoDuSe = core stability, dual tasking, sensory strategies; CP = cerebral palsy; DGI = Dynamic Gait Index; EDSS = Expanded Disability Status Scale; EQ-5D = EuroQOL-5 Dimension Questionnaire; FES = functional electrical stimulation; FIM = Functional Independence Measure; 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); IPA = Impact on Participation and Autonomy; IQR = interquartile range; ISI = Insomnia Severity Index; MD = mean difference; MiniBEST = Mini Balance Evaluation System Test; MS = multiple sclerosis; MSFC = multiple sclerosis functional composite; MSIS-29 = Multiple Sclerosis Impact Scale-29; MSIS= Multiple Sclerosis Impact Scale; MSQOL= Multiple Sclerosis Quality of Life; MSWS-12 = Multiple Sclerosis Walking Scale-12; MusiQoL = Multiple Sclerosis International Quality of Life questionnaire; NR = not reported; PBS = Pediatric Balance Scale; PEDI = Pediatric Evaluation Disability Inventory; PPMS = primary progressive multiple sclerosis; PT = physical therapy; QLS = Questionnaire of Life Satisfaction; QOL = quality of life; RCT = randomized controlled trial; RRMS = relapsing-remitting multiple sclerosis; SD = standard deviation; SE = standard error; SF- 36 = Short Form (36) Health Survey; SPMS = secondary progressive multiple sclerosis; TUG = Timed Up and Go Test; VR = virtual reality; WBV = whole body vibration; WeeFIM = Wee-Functional Independence Measure for children; WHO-QOL = World Health Organization Quality of Life.

Supplemental Table 3 Studies of the Benefits and Harms of Physical Activity—Strength Exercise Interventions

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Muscle Strength Exercise—Multiple Sclerosis			
Bulguroglu, 2017[149] 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)
Callesen, 2019[93] 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** 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-12: −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 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 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-12: −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 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 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
Dalgas, 2009[152] Dalgas, 2010[153] 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: 6MWT: 15.3% (9.8% to 20.9%) vs. 3.9% (−1.2% to 8.9%), p<0.05 10MWT: −12.3% (−16.8% to −7.9%) vs. 6.7% (−0.7% to 14.1%), p<0.05 SF-36 MCS: 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 SF-36 PCS: 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 EDSS: 3.9% (−3.4% to 11.2%) vs. −0.7% (−9.3% to 7.9%), p>0.05

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Supplemental Table 3 (*Continued*)

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Dodd, 2011[155] 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[150] 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[151] Freeman, 2012[156] 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)
Kalron, 2017[148] 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[9] 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[154] 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[16,17] 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** Right leg Six Spot Step Test: −5.96 (1.4), p=0.000 Left leg Six Spot Step Test: −6.23 (1.2), p=0.000 **A vs. B** Right leg Six Spot Step Test: −0.08 (1.4), p=0.955 Left leg Six Spot Step Test: 0.00 (1.2), p=0.997

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Supplemental Table 3 (*Continued*)

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Ortiz-Rubio, 2016[157] 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: ARAT most affected upper limb: 2.21 (−2.95 to −1.46) vs. 0.16 (−0.29 to 0.62), p=<0.001 ARAT least affected upper limb: 0.68 (−1.28 to −0.08) vs. 0.16 (−0.08 to 0.42), p<0.001
Tollar, 2020[28] **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) 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) EQ-5D 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: 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)
Muscle Strength Exercise—Cerebral Palsy			
Cho, 2020[167] Strength RCT Poor	A. Functional progressive resistance exercise (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[163] 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) 10MWT (m/s): 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[164] 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 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) COPM 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)
Scholtes, 2010[159] Scholtes, 2012[160] Scholtes, 2008[158] Strength	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%	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);

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Supplemental Table 3 (*Continued*)

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
RCT Fair		GMFM II: 33% vs. 36% GMFM III: 13% vs. 16%	−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[161] Bania, 2016[162] 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[168] 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[165] 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
Tedla, 2014[166] Strength RCT Poor	A. Strength training 18 sessions over 6 weeks + conventional PT (n=31) B. Conventional PT 3-5 sessionsweek 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
Muscle Strength Exercise—Spinal Cord Injury			
Chen, 2016[169] 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): SF-36 Subscale - physical function: 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) SF-36 Subscale - social function: 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) SF-36 Subscale - role emotional: 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) SF-36 Subscale - mental health: 54.1 (7.7) vs. 54.2 (7.8), p>0.05 (baseline)

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Supplemental Table 3 (*Continued*)

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
			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: 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, ASIA = American Spinal Injury Association Impairment Scale; BBS = Berg Balance Scale; BDI = Beck Depression Inventory; CI = confidence interval; CP = cerebral palsy; EDSS = Expanded Disability Status Scale; EQ-5D = EuroQOL-5 Dimension Questionnaire; FABS = Fullerton Advanced Balance Scale; FPRE = functional progressive resistance exercise; 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); MACS = manual ability classification system; MD = mean difference; MiniBEST = Mini Balance Evaluation System Test; MS = multiple sclerosis; MSIS-29 = Multiple Sclerosis Impact Scale-29; MSQOL= Multiple Sclerosis Quality of Life; MSWS-12 = Multiple Sclerosis Walking Scale-12; NR = not reported; NS = not significant; PBS = Pediatric Balance Scale; PPMS = primary progressive multiple sclerosis; PRE = progressive resistance exercise; PT = physical therapy; QOL = quality of life; RCT = randomized controlled trial; RRMS = relapsing-remitting multiple sclerosis; SCIM = Spinal Cord Independence Measure; 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; SPMS = secondary progressive multiple sclerosis; SSST; Six Spot Step Test; TUG = Timed Up and Go Test.

Supplemental Table 4 Studies of the Benefits and Harms of Physical Activity—Multimodal Interventions (Progressive Resistance or Strengthening Combination Exercises) Muscle Strength Exercise—Multiple Sclerosis

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Multimodal Exercises—Multiple Sclerosis			
Cakit, 2010[176] 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
Ebrahimi, 2015[173] 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[177] Has companion: Banitalebi, 2020[178] 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

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Supplemental Table 4 (*Continued*)

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Kerling, 2015[180] 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[183] 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 BDI: 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
Roppolo, 2013[184] Multimodal exercise Quasiexperimental Fair	A. Combination therapy (aerobic + strength training), 24 sessons 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) BDI: 8.8 (5.80) vs. 9.2 (3.70) (baseline) 3.4 (2.90) vs. 17 (7.00) (postintervention)
Sandroff, 2017[175] 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
Sangelaji, 2014[171] 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[172]	A. 1 aerobic + 3 resistance training, 32 sessions over 8	A vs. B vs. C vs. D Age: 36 vs. 31 vs. 34 vs. 34	Mean difference (SE), p=vs. control group: A vs. D

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Supplemental Table 4 (*Continued*)

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Multimodal exercise RCT Fair	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)	Female: 60% vs. 60% vs. 60 vs. 60% Baseline EDSS: 1.33 vs. 2.06 vs. 1.95 vs. 1.81	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[174] 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
Wens, 2015b[179] 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: WBV 2.3 vs. 2.7 vs. 2.5	A vs. B, mean (SD): VO_2 max (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 Mean (SD) of % change 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% 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
Williams, 2020[182] 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)

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Supplemental Table 4 (*Continued*)

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
			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) 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) 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)
Multimodal Exercises—Cerebral Palsy			
Fosdahl, 2019b[193] 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) 6MWT (meters): −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) GDI: −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)

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Supplemental Table 4 (*Continued*)

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
Kaya Kara, 2019[192] 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) 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 1MWT: 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
Slaman, 2015[188] Slaman, 2015[185] Slaman, 2014[186] Slaman, 2010[187] 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: GMFM-66: −1.94 (−4.69 to 0.82), p>0.05 (postintervention); −0.08 (−1.99 to 1.83), p>0.05 (1-year followup) SF-36 Physical functioning: 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) SF-36 Role physical: 4.15 (−15.10 to 23.40), p>0.05 (postintervention); 16.27 (−8.65 to 41.20), p>0.05 (1-year followup) SF-36 General health: 7.41 (−3.81 to 18.62), p>0.05 (postintervention); 10.28 (−1.42 to 21.98), p>0.05 (1 year followup) SF-36 Vitality: 1.64 (−4.96 to 8.23), p>0.05 (postintervention); −0.40 (−6.92 to 7.71), p>0.05 (1-year followup) SF-36 Social functioning: 1.76 (−5.88 to 9.41), p>0.05 (postintervention); −3.08 (−12.64 to 6.49), p>0.05 (1-year followup) SF-36 Role emotional: 5.94 (−5.01 to 16.90), p>0.05 (postintervention); 11.09 (−1.22 to 23.39), p>0.05 (1 year followup) SF-36 Mental health: 8.00 (0.96 to 15.05), p<0.05 (postintervention); 8.80 (0.99 to 16.61), p<0.05 (1-year followup)
Van Wely, 2014a[189] Van Wely, 2014b[190] Van Wely, 2010[191] Multimodal exercise RCT Fair	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)
Multimodal Exercises—Spinal Cord Injury			
Galea, 2018[197] Multimodal exercise RCT Fair	A. Whole body strength + aerobics, 36 sessions over 12 weeks (n=60) B. Upper body strength +	A vs. B Age: 40.1 vs. 42.8 Female: 15% vs.16% ASIA A: 48% vs. 50% ASIA B: 15% vs. 14%	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)

(*continued on next page*)

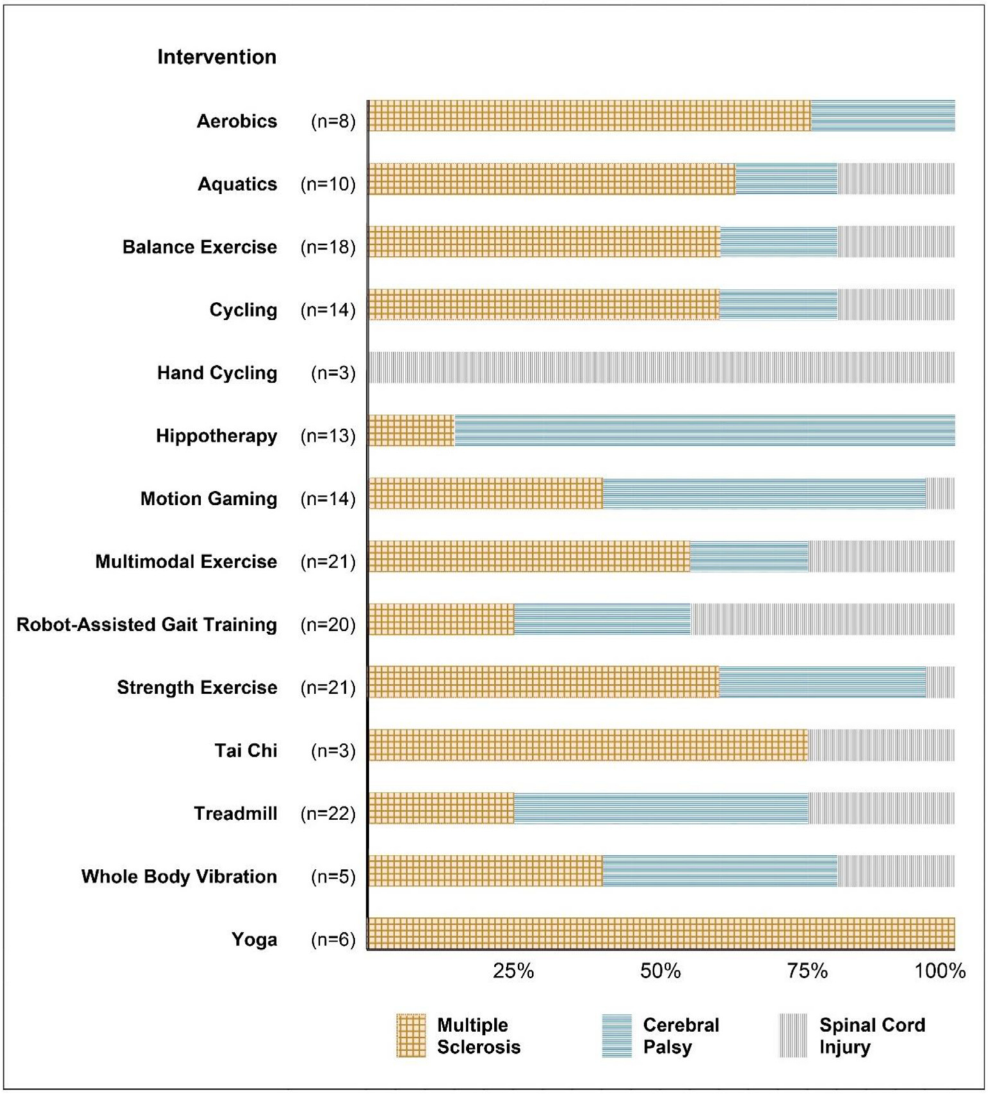
Supplemental Table 4 (*Continued*)

Author, Year Intervention Study Design Study Quality	Intervention and Comparison	Population	Results
	aerobics, 36 sessions over 12 weeks (n=56)	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%	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[201] 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[196] 2014b[104] 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[199] 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: 1MWT = 1-Minute Walk Test; 6MWT = 6-Minute Walk Test; 10MWT= 10-Meter Walk Test; AIS = Asia Impairment Scale; 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; CHART = Craig Handicap and Assessment Reporting Technique; CI = confidence interval; CP = cerebral palsy; CPQoL = Cerebral Palsy Quality of Life scale; DGI = Dynamic Gait Index; EDSS = Expanded Disability Status Scale; EPC = Evidence-based Practice Center; EQ-5D = EuroQOL-5 Dimension Questionnaire; FIM = Functional Independence Measure; 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); LEMS = Lower Extremity Motor Score; MD = mean difference; MS = multiple sclerosis; MSFC = multiple sclerosis functional composite; MSIS-29 = Multiple Sclerosis Impact Scale-29; MSIS-88 = Multiple Sclerosis Impact Scale-88; MSQOL= Multiple Sclerosis Quality of Life; MSWS-12 = Multiple Sclerosis Walking Scale-12; MusiQoL = Multiple Sclerosis International Quality of Life questionnaire; NR = not reported; PPMS = primary progressive multiple sclerosis; PT = physical therapy; QOL = quality of life; RCT = randomized controlled trial; RRMS = relapsing-remitting multiple sclerosis; SCI = spinal cord injury; SCIM = Spinal Cord Independence Measure; 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; SPMS = secondary progressive multiple sclerosis TUG = Timed Up and Go Test; UEMS = Upper Extremity Motor Score; VO2 max = maximal oxygen uptake; VO2 peak = highest value of VO2 attained upon an incremental or other high-intensity

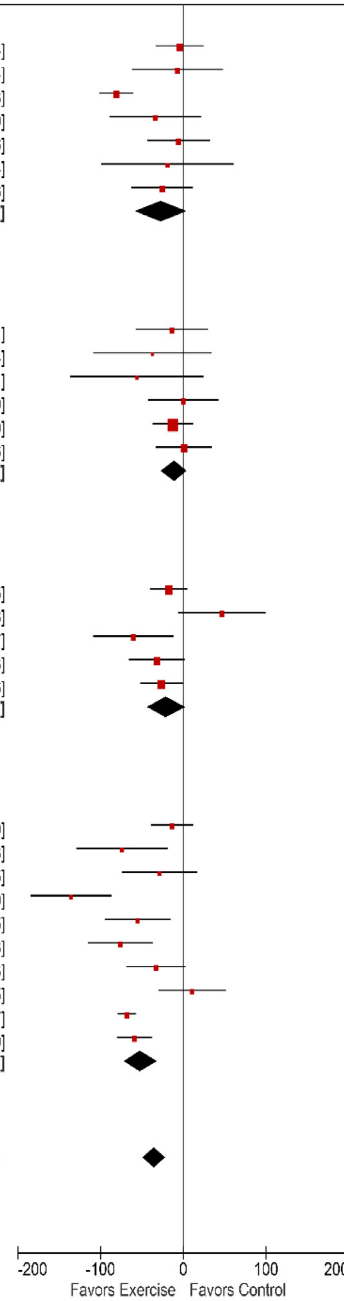
Supplemental Table 5 Measures of Function

Measure	Function Category
Spinal Cord Independence Measure	ADL
Berg Balance Scale	Balance
5-meter walk test	Mobility
6-minute walk test	Mobility
10-meter walk test	Mobility
25-foot walk test	Mobility
30-Second Lateral Step Up	Mobility
600-yard walk-run test	Mobility
Dynamic Gait Index	Mobility
Four Square Step Test	Mobility
Functional Ambulation Profile	Mobility
Gross Motor Function Classification System	Mobility
Multiple Sclerosis Walking Scale	Mobility
Self-selected walking speed	Mobility
Sit-to-Stand	Mobility
Time Up and Go	Mobility
Walking Index for Spinal Cord Injury	Mobility
Gross Motor Function Measure	Motor
Quality of Upper Extremity Skills Test	Motor
Canadian Occupational Performance Measure	Multiple domains
Multiple Sclerosis Impact Scale	Multiple domains
Impact of Participation and Autonomy Questionnaire	Participation

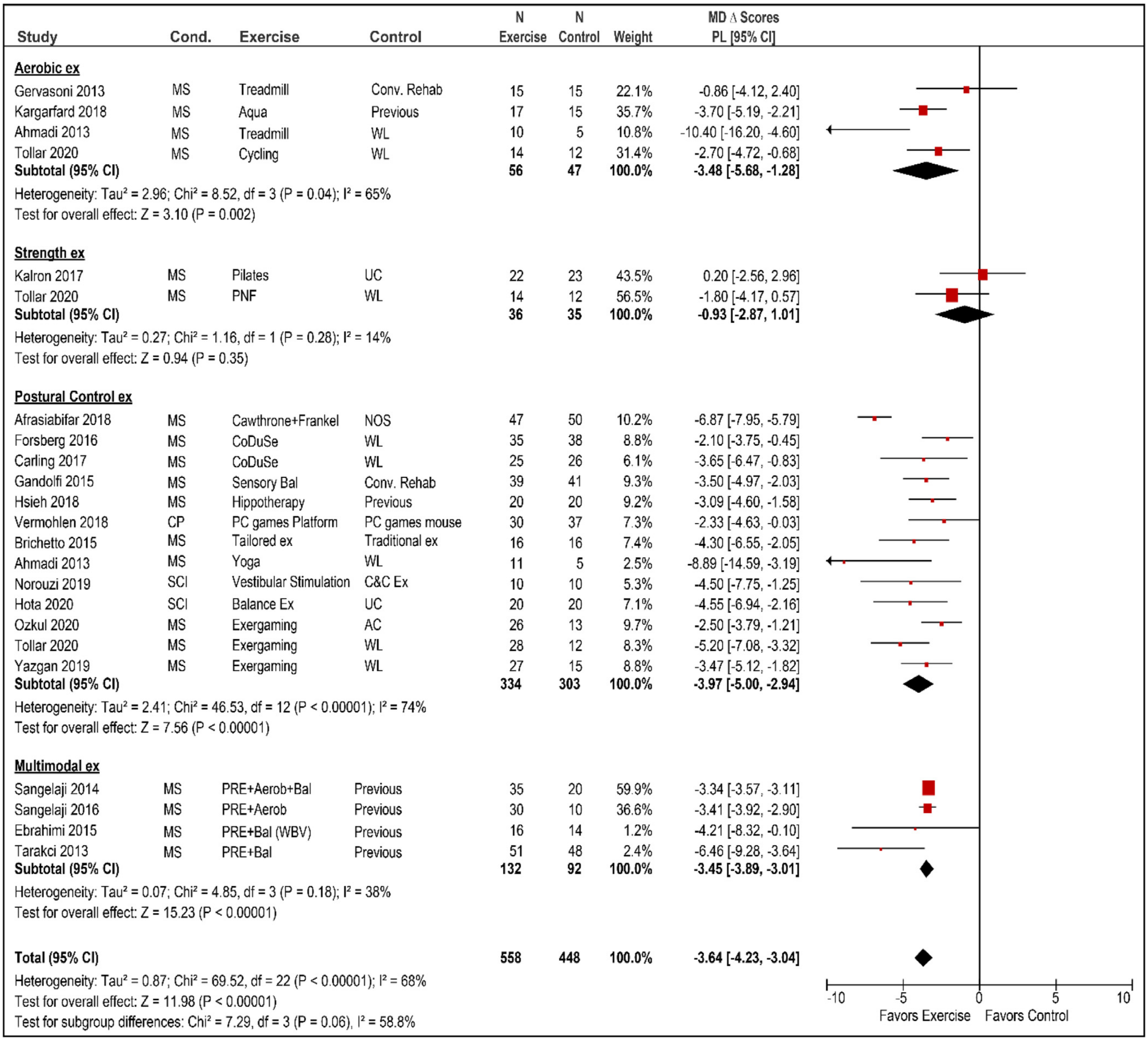


Supplemental Figure 1 Overview of included studies by population and intervention A stacked bar chart illustrating the proportion of included studies by intervention for each population: multiple sclerosis or MS, cerebral palsy or CP, spinal cord injury or SCI. Footnote: *Studies with multiple interventions appear more than once.

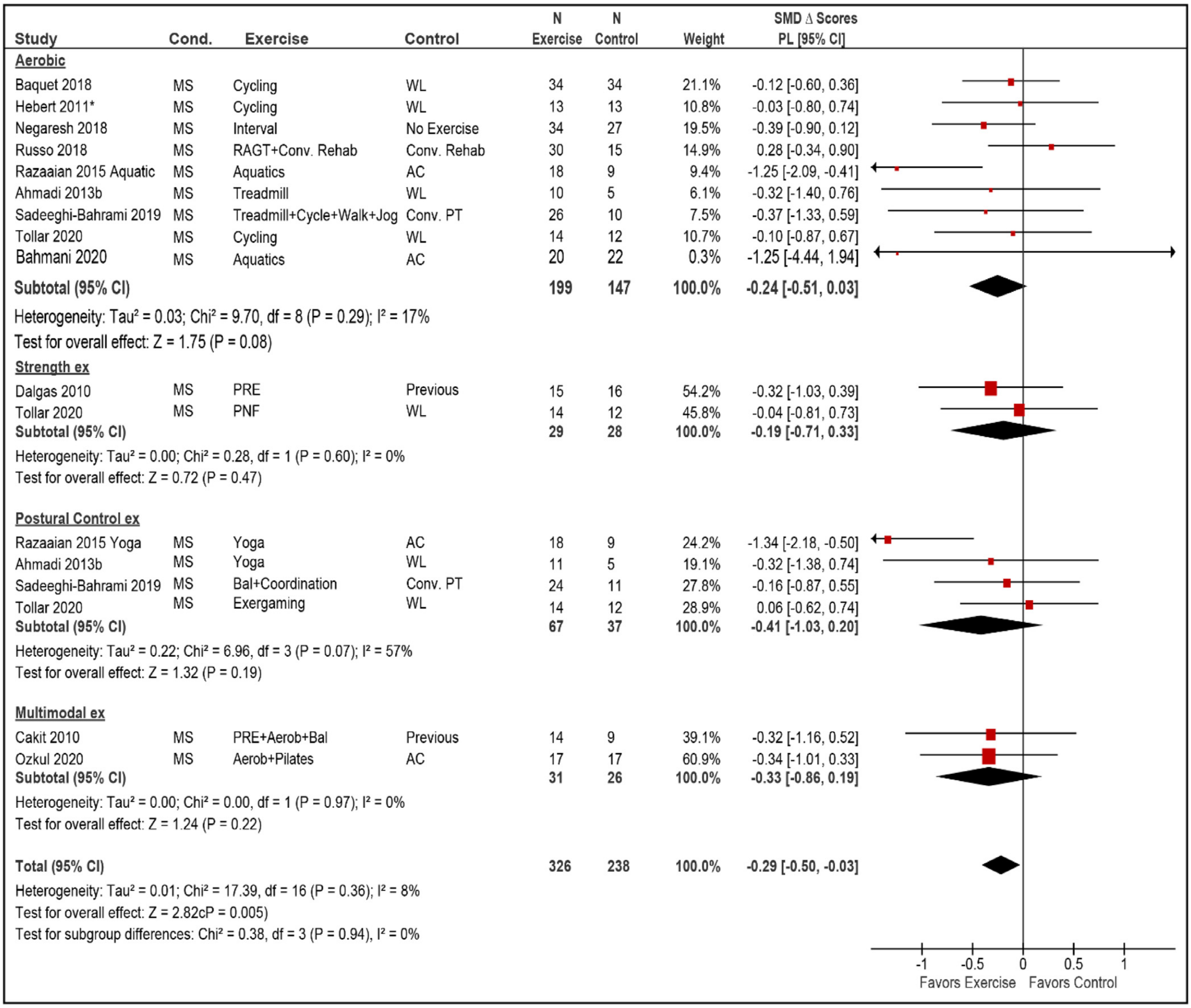
Study	Cond.	Exercise	Control	N Exercise	N Control	Weight	MD Δ Scores PL [95% CI]
Aerobic ex							
Baquet 2018	MS	Cycling	WL	34	34	17.1%	-4.40 [-32.74, 23.94]
Hebert 2011*	MS	Cycling	WL	13	13	12.4%	-7.19 [-61.42, 47.04]
Kargarfard 2018	MS	Aqua	WL	17	15	18.4%	-81.00 [-100.72, -61.28]
Young 2018	MS	Movement 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%							



Supplemental Figure 2 6MWT meta-analysis of all randomized controlled trials versus no treatment/usual care Forest plot examining the 6 minute walk test scores for all randomized controlled trials comparing exercise with no treatment or usual care. 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



Supplemental Figure 3 BBS meta-analysis of all randomized controlled trials versus no intervention/usual care Forest plot examining BBS scores comparing exercise with no intervention or usual care. 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; PRE = progressive resistance exercise; Previous = continuation of previous activities; Rehab = rehabilitation; SCI = spinal cord injury; WL = waitlist



Supplemental Figure 4 Effect of exercise versus usual care on depression scores in multiple sclerosis Forest plot examining depression scale scores for all randomized controlled trials comparing exercise with no treatment or usual care 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; PRE = progressive resistance exercise; Previous = continuation of previous activities; PT = physical therapy; RAGT = robotic assisted gait training; SMD = standardized mean difference; WL = waitlist