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Review article

The effect of exercise training in adults with multiple sclerosis with severe mobility disability: A systematic review and future research directions

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ARTICLE INFO

Abbreveations:
2 MWT2-min walk test
6 MWT6-min walk test
ABCactivities-specific balance confidence scale
BBSBerg Balance Scale
BWSTTbody-weight support treadmill training
DGIDynamic Gait Index
EDSSExpanded Disability Status Scale
ESACelectrical stimulation assisted cycling
FWSfast walking speed test
HRQOLhealth-related quality of life
MFISmodified fatigue impact scale
MMTmanual muscle test
MSmultiple sclerosis
MSIS-29Multiple Sclerosis Impact Scale
NNewtons
PEDrophysiotherapy evidence database
RCTrandomized control trial
SSWSself-selected walking speed test
TBRSTtotal body recumbent stepper training
T25FWTtimed 25-foot walk
TUGTimed Up-and-Go
VO_2volume of oxygen consumption

Keywords:
Multiple sclerosis
Exercise training
Disability
Mobility impairment

ABSTRACT

Introduction: There is evidence for the benefits of exercise training in persons with multiple sclerosis (MS). However, these benefits have primarily been established in individuals with mild-to-moderate disability (i.e., Expanded Disability Status Scale [EDSS] scores 1.0–5.5), rather than among those with significant mobility impairment. Further, the approaches to exercise training that have been effective in persons with mild-to-moderate MS disability may not be physically accessible for individuals with mobility limitations. Therefore, there is a demand for an evidence-base on the benefits of physically accessible exercise training approaches for managing disability in people with MS with mobility impairment.
Objective: To conduct a systematic review of the current literature pertaining to exercise training in individuals with multiple sclerosis (MS) with severe mobility disability.
Methods: Four electronic databases (PubMed, EMBASE, OvidMEDLINE, and PsychINFO) were searched for relevant articles published up until October 2016. The review focused on English-language studies that examined the effect of exercise training in people with MS with severe mobility disability, characterized as the need for assistance in ambulation or EDSS score ≥ 6.0. The inclusion criteria involved full-text articles that: (i) included participants with a diagnosis of MS; (ii) included primarily participants with a reported EDSS score ≥ 6.0 and/or definitively described disability consistent with this level of neurological impairment; and (iii) implemented a prospective, structured exercise intervention. Data were analyzed using a descriptive approach and summarized by exercise training modality (conventional or adapted exercise training), and by outcome (disability, physical fitness, physical function, and symptoms and participation).
Results: Initially, 1164 articles were identified and after removal of duplicates, 530 articles remained. In total, 512 articles did not meet the inclusion criteria. 19 articles were included in the final review. Five studies examined conventional exercise training (aerobic and resistance training), and thirteen studies examined adapted exercise modalities including body-weight support treadmill training (BWSTT), total-body recumbent stepper training (TBRST), and electrical stimulation cycling (ESAC). Outcomes related to mobility, fatigue, and quality of life (QOL) were most frequently reported. Two of five studies examining conventional resistance exercise training reported significant improvements in physical fitness, physical function, and/or symptomatic and participatory outcomes. Nine of 13 studies examining adapted exercise training reported significant improvements in disability, physical fitness, physical function, and/or symptomatic and participatory outcomes.
Conclusions: There is limited, but promising evidence for the benefits of exercise training in persons with MS with severe mobility disability. Considering the lack of effective therapeutic strategies for managing long-term disability accumulation, exercise training could be considered as an alternative approach. Further research is necessary to optimize the prescription and efficacy of exercise training for adults with MS with severe mobility disability.

1. Introduction

Multiple sclerosis (MS) is a chronic, neurological disease that affects 1 in 1000 people in the United States making it the most common non-traumatic cause of neurological disability in young adults (Freeman, 2001). The disease is characterized by inflammation, demyelination and neurodegeneration within the central nervous system (CNS), and this damage results in functional impairments and symptomatic

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experiences. Unfortunately, these impairments and symptoms worsen as neurological disability increases (Motl and Learmonth, 2014).

An EDSS score of 6.0 (i.e., use of assistive device for ambulation) (Kurtzke, 1983) is a commonly reported benchmark of disease progression and disability (Confavreux et al., 2000, 2003). It is well documented that individuals with MS with an EDSS score of ≥ 6.0 have greater impairments in muscular fitness, aerobic fitness, mobility, and balance compared to individuals with lower disability scores (Motl and Learmonth, 2014; Pilutti et al., 2015; Sandroff et al., 2013; Motl et al., 2010; Sosnoff and Sung, 2015; Bakshi et al., 2000). Additionally, symptoms of fatigue, spasticity, depression and cognitive impairment become more severe with increasing disability (Amato et al., 2001; Bakshi et al., 2000; Benito-León et al., 2003; Flachenecker et al., 2014; Motl and McAuley, 2010; Sandroff et al., 2015). Physiological deconditioning induced by lower levels of physical activity likely contributes to these impairments with disability progression (Motl, 2010). Indeed, lower levels of physical activity have also been reported in individuals with MS with higher disability scores (Klaren et al., 2013).

Current disease-modifying agents have limited efficacy in preventing the accumulation of long-term disability in MS (Confavreux et al., 2003). Consequently, alternative strategies for disease management in persons with MS with severe mobility disability should be considered. One potential strategy is exercise training. There is evidence for the benefits of exercise training for improving walking performance, fitness, cognition, fatigue, anxiety, and depressive symptoms in persons with MS (Ensari et al., 2014; Pilutti et al., 2013; Platta et al., 2016; Sandroff et al., 2015; Snook and Motl, 2009). Despite these benefits, much of the current literature pertaining to exercise training in people with MS has focused on individuals with mild-to-moderate disability (i.e., EDSS scores 1.0–5.5) (Latimer-Cheung et al., 2013). This is problematic as individuals with MS with severe mobility disability are often excluded from studies of exercise training, limiting the evidence to those with mild-to-moderate MS disability. Furthermore, the exercise approaches that have been effective in persons with mild-to-moderate disability may not be physically accessible for individuals with MS with severe mobility limitations. Therefore, there is a demand for a comprehensive review of exercise training strategies that have been implemented for managing disability for people with MS with severe mobility disability.

Herein, we conducted a systematic review of exercise training interventions in persons with MS with severe mobility disability (EDSS ≥ 6.0) to: (i) evaluate and summarize the current evidence for the effects of exercise training on disability, physical fitness, physical function, symptoms, and participatory outcomes; (ii) evaluate the exercise training modalities and approaches applied; and (iii) identify current limitations and future research directions for exercise training in persons with MS with severe mobility disability. This review will provide a summary of the potential benefits of exercise training in persons with MS with severe mobility disability, and a future research agenda for developing effective strategies for managing disability through exercise training.

2. Methods

2.1. Article inclusion criteria and search strategy

This review focused on English-language studies that examined the effect of exercise training on disability, physical fitness, physical function, symptoms, and participatory outcomes in individuals with MS with severe mobility disability. Exercise training is defined as “planned, structured and repetitive bodily movement done to improve or maintain one or more components of physical fitness” (Bouchard et al., 1994). We conducted a search of four electronic databases (PubMed, EMBASE, OvidMEDLINE, and PsychINFO) using the search terms “multiple sclerosis” AND “exercise” OR “physical activity” OR “fitness” AND “advanced disability” OR “severe mobility disability” OR “progressive” OR “robot”. This search was supplemented by an additional hand-search of the authors’ personal databases and relevant reviews and meta-analyses involving exercise training in persons with MS.

The inclusion criteria involved full-text articles that: (i) included participants with a diagnosis of MS; (ii) included primarily participants with a reported EDSS score ≥ 6.0 and/or definitively described disability consistent with this level of neurological impairment (e.g., use of an assistive device for ambulation); and (iii) implemented a prospective, structured exercise intervention per the definition of exercise previously described. For the purpose of this review, we selected an EDSS score of ≥ 6.0 as this is considered a robust disability landmark characterized by the need for assistance in ambulation (e.g., cane, walker) (Confavreux et al., 2000, 2003; Kurtzke, 1983). We included randomized and nonrandomized controlled trials, and pre-post intervention designs.

2.2. Article quality assessment

The quality of each article was determined using the Physiotherapy Evidence Database (PEDro)(Verhagen et al., 1998) scale for randomized control trials (RCTs) and the Downs and Black scale for non-RCTs (Downs and Black, 1998). The PEDro scale has a maximum possible score of 11 points, while the Downs and Black scale has a maximum possible score of 28 points. For both scales, a higher score is indicative of better methodological quality. Articles were independently evaluated by each of the authors. Scoring discrepancies between the authors were resolved by re-examining the articles and through discussion. The level of evidence of each article was categorized using the Spinal Cord Injury Rehabilitation Evidence (SCIRE) system (Eng et al., n.d.), a 5-level system that distinguishes between studies of differing quality and incorporates the types of research designs commonly used in rehabilitation research (Table 1). These scales have been used in several published systematic reviews and meta-analyses of exercise training in persons with MS (Ensari et al., 2014; Platta et al., 2016; Pilutti et al., 2013; Latimer-Cheung et al., 2013).

2.3. Descriptive approach and data summary

Considering the limited number of studies that were retrieved and the variability in the outcomes included across studies, we did not attempt a meta-analytic approach. After review of the articles for inclusion, relevant data was extracted from each manuscript. Data were extracted by one member of the research team (TAE), and verified by a

Table 1
Level of evidence and criteria applied to studies included in the review based on the Spinal Cord Injury Rehabilitation Evidence (SCIRE) system.

Level of evidence	Criteria
Level 1 ($n = 5$)	• **RCT:** PEDro Score > 6. Includes cross over design with randomized experimental conditions and within-subjects comparison.
Level 2 ($n = 0$)	• **RCT:** PEDro Score ≤ 6. • **Prospective controlled trial:** non-randomized. • **Cohort:** longitudinal study using two (minimally) similar groups with one group being exposed to a condition.
Level 3 ($n = 0$)	• **Case-control studies:** retrospective study comparing controls conditions.
Level 4 ($n = 13$)	• **Pre-post:** trial with a baseline measure, intervention and a post-test using a single group of subjects. • **Post-test**: post-test with 2 or more groups using a single group (intervention followed by a post-test with no retest or baseline assessment).
Level 5 ($n = 0$)	• **Observational**: study using cross sectional analysis to interpret relations.

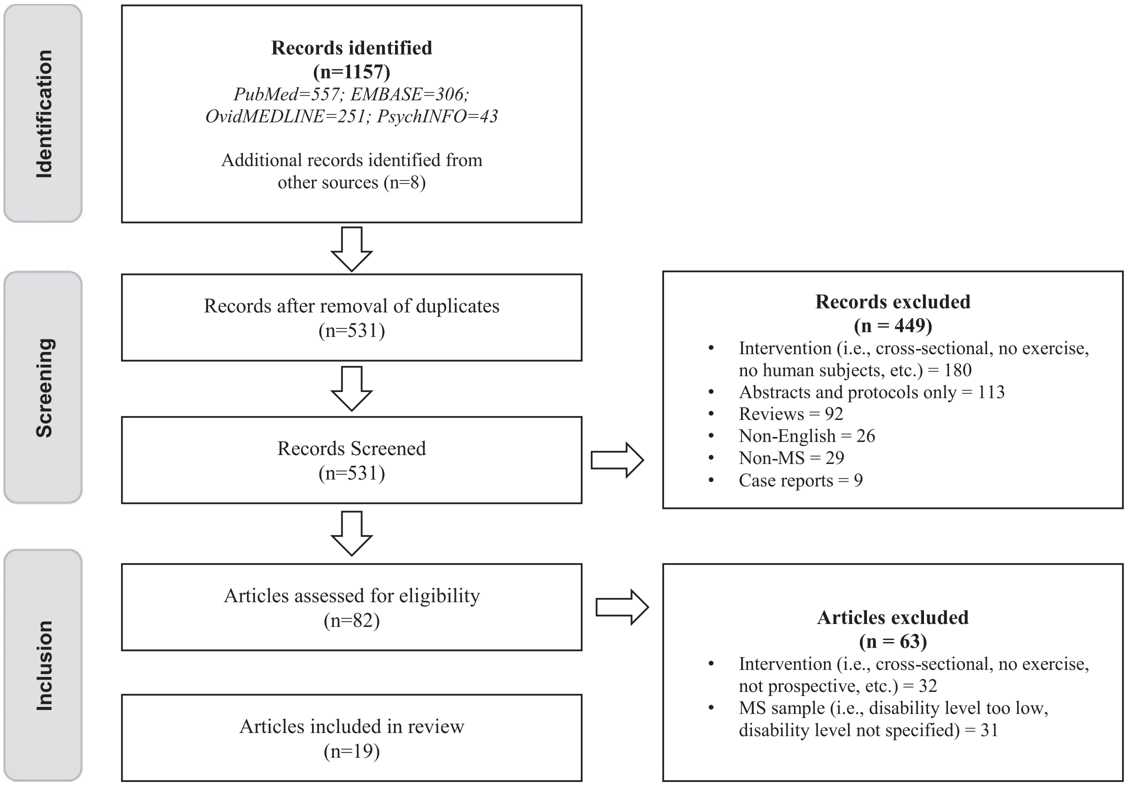

Fig. 1. PRISMA (the preferred reporting items for systematic reviews and meta-analyses) flow diagram of the literature review process.

second researcher (LAP). Data were first extracted relative to study (e.g., number of participants), participant (e.g., disability status), and exercise training (e.g., duration) characteristics. Information was then extracted relative to the efficacy of the intervention on study outcomes including the magnitude and significance of reported changes. Data were categorized and summarized by the type of exercise training modality, as either conventional or adapted exercise training, and the type of outcome measure grouped as disability, physical fitness, physical function, and symptoms and participation outcomes. We tabulated the number of studies that included each exercise training modality, and the number of studies reporting on each type of outcome to provide a summary of the literature. We then tabulated the number of studies per training modality showing statistically significant changes in reported outcomes. Nonsignificant improvements in outcomes that may have clinical importance were also noted based on the limited number of studies and small samples.

3. Results

Fig. 1 illustrates the literature search and screening process. The electronic database search retrieved 1157 articles and eight additional articles were retrieved from other sources. After removal of duplicate articles, 531 articles remained. In total, 512 articles did not meet the specific inclusion criteria, leaving 19 articles from 18 studies in the review. Specific reasons for article exclusion are presented in Fig. 1.

Table 2 summarizes the study, participant, and exercise training characteristics for each of the 18 studies reviewed, grouped by exercise training modality. Five articles examined conventional exercise training (aerobic and resistance exercise), eight articles from seven studies examined body-weight support treadmill training (BWSTT), one article examined total-body recumbent stepper training (TBRST), and five articles examined electrical stimulation assisted cycling (ESAC). Table 3 summarizes the effect of exercise training for each study grouped by type of outcome. Overall, there was considerable variability in the number and type of outcomes reported in the studies. Six studies reported disability assessed using the EDSS or the MSFC. Ten studies reported physical fitness using a variety of aerobic and muscular fitness outcomes. There were 16 studies that included measures of physical function captured by tests of walking, gait, agility, balance, spasticity, and upper extremity function. Finally, 12 studies reported symptoms and participatory outcomes assessed most commonly as fatigue and QOL.

3.1. Conventional exercise training

The characteristics and results from the five studies involving conventional exercise training are presented in Tables 2 and 3, respectively. Three studies involved conventional aerobic exercise training, one was an RCT with level 1 evidence and the other two were level four evidence (Jackson et al., 2012a, 2012b; Skjerbæk et al., 2014). There were no statistically significant improvements in any of the outcomes. Nonsignificant improvements were reported for cardiorespiratory fitness (VO_{2peak}), some physical function tasks (balance, gait, agility, walking speed, and upper extremity function), depression, and QOL.

Two level four evidence studies examined conventional resistance exercise training (Coote et al., 2015; Filipi et al., 2011). Significant improvements in muscular strength were reported in both studies. One of the studies also reported significant improvements in muscle endurance, balance, fatigue symptoms, and QOL in response to progressive resistance training combined with neuromuscular electrical stimulation (Coote et al., 2015).

3.2. Adapted exercise training

For this review, we considered adapted exercise training as the use of specialized exercise training equipment that is designed to accommodate individuals with mobility disability. The adapted exercise modalities reviewed were BWSTT, TBRST, and ESAC. A detailed summary of these adapted exercise modalities has been published elsewhere (Pilutti and Hicks, 2013).

Table 2
Study, participant and exercise training characteristics of the 19 articles reviewed, grouped by modality as conventional or adapted exercise training.

Study characteristics			Participant characteristics			Exercise training characteristics			
Ref. (quality)	n	Exercise modality	EDSS range	Disease Duration (y) Mean ± SD	Age (y) Mean ± SD	Duration (weeks)	Frequency (x/week)	Time (min)	Intensity
CONVENTIONAL EXERCISE TRAINING									
Aerobic exercise training (n = 3)									
Jackson et al. (2012a)	2	KICK	6.0–6.5	NR	58 ± 4.2	8	2	30–40	≤ 75% HRR or ≤ 5 RPE
D & B = 16									
Jackson et al. (2012b)	5	KICK	6.0–6.5	10.6 ± 4.9	55.6 ± 5.4	5	3	60	≤ 75% HRR or ≤ 5 RPE
D & B = 17									
Skjerbæk et al. (2014)	6	ARM/LEG CON	6.5–8.0	NR	62.0 ± 5.9	4	10 sessions	23	65–75% VO_{2peak}
PEDro = 7	5		6.5–8.0	NR	55.2 ± 8.2				
Resistance exercise training (n = 2)									
Coote et al. (2015)	10	PRT	NR[a]	12.2 ± 4.0	51.8 ± 12.1	12	2–3	NR	1–3 sets of 12 repetitions
D & B = 20	15	PRT + NMES	NR[a]	11.8 ± 5.5	51.8 ± 12.6	12	2–3	NR	1–3 sets of 12 repetitions
Filipi et al. (2011)	23	PRT	5.0–7.0	NR	NR	24	2	50	2–3 sets of 10 repetitions
D & B = 17	17	PRT	7.0–8.0	NR	NR	24	2	50	2–3 sets of 10 repetitions
ADAPTED EXERCISE TRAINING									
Body Weight Support Treadmill Training (BWSTT) (n = 8)									
Beer et al. (2008)	19	RBWS	6.0–7.5	15.0 ± 8.0	49.7 ± 11.0	3	5	30	1–2.8 km/h
PEDro = 8	16	CON	6.0–7.5	15.0 ± 9.0	51.0 ± 15.5				
Giesser et al. (2007)	4	TBWS	7.0–7.5	NR	47.0 ± 5.3	~ 20	2	60	.85–1.03 m/s
D & B = 14									
Lo and Triche (2008)/Wier et al. (2011)	6	RBWS	3.5–7.0	NR	50.2 ± 11.4	3	2	40	30–40% BWS
D & B = 16/15	7	TBWS	3.5–7.0	NR	49.6 ± 11.8				2.2–2.5 km/h
Pilutti et al. (2011)	6	TBWS	6.0–8.0	11.5 ± 6.6	48.2 ± 9.3	12	3	30	1.1–1.6 km/h
D & B = 19									77.9–51.7% BWS
Schwartz et al. (2012)	15	RBWS	5.0–7.0	11.3 ± 6.7	46.8 ± 11.5	4	2–3	30	40–20% BWS
PEDro = 8	17	CON	5.5–7.0	14.9 ± 8.1	50.5 ± 11.5				
Straudi et al. (2013)	8	RBWS	4.5–6.5	17.1 ± 12.0	49.6 ± 12.0	6	2	30	3 km/h, 100–0% BWS
PEDro = 7	8	CON	4.5–6.5	18.6 ± 10.8	61.0 ± 8.8				
Vaney et al. (2012)	26	RBWS	3.0–6.5	NR	58.2 ± 9.4	3	NR	30	50% BWS (gradually decreased)
PEDro = 7	23	CON	3.0–6.5	NR	54.2 ± 11.3				
Total Body Recumbent Stepper Training (TBRST) (n = 1)									
Pilutti et al. (2016)	5	TBRST	7.0(mdn)	15.2 ± 8.9	58.8 ± 3.0	12	3	30	3.8–4.6 RPE
D & B = 18	5	BWSTT	7.0(mdn)	12.7 ± 11.2	48.2 ± 4.3	12	3	30	2.8–4.5 RPE
Electrical Stimulation Assisted Cycling (ESAC) (n = 5)									
Backus et al. (2016)	14	FES	NR[b]	15.3 ± 7.4	55.4 ± 11.0	4	2–3	30	35–50 rpm
D & B = 20									
Fornusek and Hoang (2014)	7	NMES	6.5–8.5	NR	48.0 ± 9.0	10	~1.8	40	35–50 rpm
D & B = 18									
Ratchford et al. (2010)	5	FES	6.0–6.5	13	50 (mdn)	24	3	60	NR
D & B = 18									
Reynolds et al. (2015)	8	FES	> 6.0	16.8 ± 6.9	54.5 ± 13.9	4	3	30	50 rpm
D & B = 20									
Szecsi et al. (2009)	8	FES	4.0–8.0	13.3 ± 8.0	52.1 ± 7.5	2	3	20–30	NR
D & B = 20									

Abbreviations: PEDro, physiotherapy evidence database scale; D & B, Downs and Black scale; KICK, kickboxing training; ARM, arm ergometry; LEG, leg ergometry; CON, control group; BWS, body weight support; RBWS, Robot-assisted body weight support; TBWS; therapist-assisted body weight support; FES, functional electrical stimulation; NMES, neuromuscular electrical stimulation; NR, Not reported; AT, aerobic threshold; rpm, revolution per minute.
NR[a] = EDSS score not-reported. Participants used assistive devices for ambulation.
NR[b] = EDSS score not-reported. Participants were described as non-ambulatory; unable to ambulate outside the home without assistance.

Table 3
Summary of the outcomes and results reported in the 19 articles reviewed involving exercise training in severe MS.

Ref.	Outcomes: Disability	Physical fitness	Physical function	Symptoms & participation
CONVENTIONAL EXERCISE TRAINING				
Aerobic exercise training (n = 3)				
Jackson et al. (2012a)	–	–	↓ABC, ↑BBS, ↑DGI, ↓TUG, ↔Walking speed	–
Jackson et al. (2012b)	–	–	↑ABC, ↑Mini-BESTest	–
Skjerbæk et al. (2014)	–	↑VO_{2peak}, ↔HR_{peak}↔Grip strength	↓9HPT, ↔Box and Block, ↔6-min wheelchair test	↔Fatigue, ↓MDI, ↑QOL
Resistance exercise training (n = 2)				
Coote et al. (2015)	–	PRT: ↔Muscular endurance (KE), ↑Strength* (hip extensors), ↑Strength (KE) PRT + NMES: ↑Muscular endurance* (KE), ↑ Strength* (hip extensors), ↑Strength (KE)	PRT: ↑BBS, ↓MSWS-12, ↔Spasticity, ↔TUG PRT + NMES: ↑BBS**, ↓MSWS-12, ↓ Spasticity, ↔TUG	PRT: ↔Fatigue, ↔QOL PRT + NMES: ↓Fatigue*, ↑QOL*(physical), ↔QOL(psychological)
Filipi et al. (2011)	–	↑1-RM*(leg extension, shoulder press, back row, lat pulldown, chest press)	–	–
ADAPTED EXERCISE TRAINING				
Body Weight Support Treadmill Training (BWSTT) (n = 8)				
Beer et al. (2008)	–	↑Strength** (KE)	↑6 MW**, ↔Stride length ↑Walking speed**	–
Giesser et al. (2007)	↔EDSS	↑Strength (combined MMT of hip abductors/flexors/ extensors, KE/KF, and dorsiflexors/plantarflexors)	↑6 MW, ↑BBS, ↓Spasticity, ↑Walking speed	↑QOL
Lo and Triche (2008)/ Wier et al. (2011)	↓EDSS**	–	↑6 MW**, ↓Double support time**, ↔Step length ratio, ↑T25FW**	↔Bladder/bowel control ↓Fatigue*, ↓Fatigue, ↑Life satisfaction*, ↑MHI, ↓Pain*, ↓ Perceived deficits*, ↑QOL*, ↑QOL, ↔Sexual satisfaction, ↔Social support, ↔Visual impairment impact
Pilutti et al. (2011)	↔EDSS, ↓ MSFC	–	↔9HPT, ↑Walking speed	↓Fatigue, ↑QOL*
Schwartz et al. (2012)	↓EDSS*	–	↑6 MW, ↑BBS*, ↓TUG* ↔Walking speed	↑FIM**, ↑QOL
Straudi et al. (2013)	–	–	↑6 MW*, ↑Gait kinematics*/**, ↓TUG, ↑ Walking speed*	↓Fatigue
Vaney et al. (2012)	–	–	↑BBS, ↔RMI, ↔Spasticity ↔Walking speed	↓Fatigue, ↔PA, ↔Pain, ↑QOL
Total Body Recumbent Stepper Training (TBRST) (n = 1)				
Pilutti et al. (2016)	↔MSFC	–	↔9HPT, ↔Walking speed	↓Fatigue*, ↑QOL
Electrical Stimulation Assisted Cycling (ESAC) (n = 5)				
Backus et al. (2016)	–	↔Strength (combined MMT of hip flexors, KE/KF, dorsiflexors)	↔Spasticity	↔Bladder/bowel control ↓Fatigue*, ↓Fatigue, ↔MHI, ↓Pain*, ↔Perceived deficits, ↔ QOL, ↔Sexual satisfaction, ↔Social support, ↔Visual impairment impact
Fornusek and Hoang (2014)	–	↑Thigh circumference**	↓Spasticity (self-reported)	↑Circulation, ↑Transfer ability (self-reported)
Ratchford et al. (2010)	↔EDSS	↑ Strength (hip extensors, KE/KF) ↓Strength (hip flexors, dorsiflexors)	↑2 MW, ↓9HPT (dominant), ↑T25FW, ↑Gait kinematics, ↓TUG, ↑Walking speed ↔ Spasticity	↑QOL, ↔SCL-90
Reynolds et al. (2015)	–	↑mVO_2*	–	–
Szecsi et al. (2009)	–	↔Strength (KE/KF)	↓Spasticity (acute), ↔Spasticity (long-term), ↔Walking speed	–

↑Indicates increase in outcome measure; ↓ Indicates decrease in outcome measure, ↔ Indicates no increase or decrease in outcome.
* Indicates statistically significant difference, $p < .05$; ** Indicates statistically significant difference, $p < .001$.
Abbreviations: 1-RM, 1-repetition maximum; 2 MW, 2-min walk test; 6 MW, 6-min walk test; 9HPT, 9-hole peg test; ABC, activities-specific balance confidence scale; BBS, Berg Balance Scale; DGI, Dynamic Gait Index; EDSS, Expanded Disability Status Scale; FIM, functional independence measure; KE, knee extensors; KF, knee flexors; MDI, Major Depression Inventory; MHI, Mental Health Inventory; Mini-BESTest, Mini-Balance Evaluation Systems Test; MMT, Manual Muscle Test; MSFC, Multiple Sclerosis Functional Composite; MSWS-12, 12-item Multiple Sclerosis Walking Scale; mVO_2, muscle oxygen consumption; PA, physical activity; QOL, quality of life; RMI, Rivermead Mobility Index; SCL-90, Symptom Checklist-90; T25FW, timed 25-foot walk test; TUG, Timed Up-and-Go test; VO_{2peak}, peak oxygen consumption. Outcome variables are presented in alphabetical order within each category.

3.2.1. Bodyweight support treadmill training (BWSTT)

The characteristics and results from the eight studies involving BWSTT are summarized in Tables 2 and 3, respectively. Four of the studies were level one evidence RCTs and four were level four evidence. Two studies reported a significant decrease (i.e., improvement) in EDSS score; however, two other studies reported no change in disability status. A significant improvement in knee extensor strength was reported in one study. Several studies reported significant improvements in physical function including walking endurance (n = 3), walking speed (n = 3), gait kinematics (n = 2), balance (n = 1), and agility (n = 1), although nonsignificant improvements and no change in the same outcomes were also noted in other trials. Several studies reported significant improvements in fatigue (n = 1), QOL (n = 2), and independence in daily activities (n = 1); non-significant improvements in symptomatic and participatory outcomes were also noted.

3.2.2. Total body recumbent stepper training

We retrieved one level four study involving TBRST in persons with MS with severe mobility disability (Pilutti et al., 2016). There was no change in disability or physical function reported. Symptoms of fatigue were significantly reduced after the intervention, and non-significant, small-to-moderate effects of exercise training on QOL were reported. The characteristics and results of this study is summarized in Tables 2 and 3, respectively.

3.2.3. Electrical stimulation assisted cycling

The characteristics and results of the five studies involving ESAC are summarized in Tables 2 and 3, respectively. Two forms of ESAC were used in the studies reviewed: functional electrical stimulation (FES) and neuromuscular electrical stimulation (NMES) cycling. All five studies involving ESAC included level four evidence. Only one study reported disability status and did not observe a change in response to ESAC. Two studies reported significant improvements in physical fitness assessed as thigh circumference and muscle oxygen consumption (mVO_2). None of the studies reported significant improvements in physical function. One study reported a significant reduction in fatigue and pain symptoms following ESAC. There was mixed evidence for the effects of ESAC on spasticity, walking speed, and other participatory outcomes.

4. Discussion

The purpose of this review was to evaluate and summarize the current body of literature involving exercise training in persons with MS with severe mobility disability. Eighteen studies with 290 participants were retrieved and reviewed. Overall, there may be benefits of conventional resistance exercise training on muscular fitness, balance, fatigue and QOL. There are potential benefits of adapted exercise training on disability, physical fitness, physical function, fatigue, and QOL, and the evidence was most consistent for BWSTT. Herein, we evaluate each method of exercise training and provide specific direction to advance the body of literature pertaining to exercise training in individuals with MS with severe mobility disability.

4.1. Conventional exercise training

4.1.1. Aerobic exercise training

Considering the limited number of studies and lack of significant findings, we unable to make definitive conclusions on the potential benefits of conventional aerobic exercise training at this time. There may be benefits of aerobic exercise training on aerobic fitness, physical function, depression, and QOL, although these preliminary findings require confirmation. Importantly, these studies reported that aerobic exercise training was feasible and safe for individuals with MS with severe mobility disability based on low dropout rates, few adverse events, and high exercise compliance, and this is promising for future work in this area (Jackson et al., 2012a, 2012b; Skjerbæk et al., 2014). There is evidence for the benefits of aerobic exercise training for improving physical fitness, physical function, symptoms and participatory outcomes in persons with mild-moderate MS which supports the need for additional research (Briken et al., 2013; Latimer-Cheung et al., 2013; Platta et al., 2016). There are several advantages of conventional aerobic exercise modalities such as ease of use and availability. Conventional aerobic exercise modalities are also inexpensive compared to adapted exercise equipment, and in many cases, can be used in the home-setting. There are limitations, however, in the physical accessibility of some types of conventional aerobic exercise (e.g., treadmill walking).

4.1.2. Resistance exercise training

Conventional resistance exercise training might have benefits for muscular fitness, balance, fatigue, and QOL in people with MS with severe mobility disability (Coote et al., 2015; Filipi et al., 2011). This is consistent with current literature involving progressive resistance exercise training in persons with mild-moderate MS, as improvements in strength, fatigue, balance, and mood have all been reported (Kjølhede et al., 2012; Platta et al., 2016). Improvements in physical fitness would be particularly beneficial for those with severe mobility disability as these individuals have particularly low fitness levels (Pilutti et al., 2015), and improvements in physical fitness might further translate into improvements in physical function (e.g., walking performance). There are several advantages of conventional resistance training. Resistance training can be performed with free-weights, weight-machines, resistance bands or an individual's body weight. This allows for variation in exercise prescription and adaptability for all individuals. Resistance exercises can be performed in a seated position, reducing the risk for falls and increasing accessibility for those who are wheelchair-dependent. Despite these advantages, instruction in appropriate exercise techniques and adaptations may be required and may not be readily available in all settings.

4.2. Adapted exercise training

4.2.1. Bodyweight support treadmill training

The effects of exercise training were most consistent for BWSTT, likely due to the number of studies involving this modality. Significant improvements were noted for disability scores, muscular strength, several mobility tests, fatigue, independence in daily activities, and QOL. Similar improvements have been reported in other clinical populations after BWSTT (e.g., stroke, spinal cord injury) (Adams et al., 2006; Giangregorio et al., 2005; Hassid et al., 1997; Hesse et al., 2001; Mao et al., 2015). The main advantage of BWSTT is the task-specific nature of this training modality as a tool for walking and gait rehabilitation (Pilutti and Hicks, 2013). The potential to improve walking performance is particularly relevant for individuals with MS, as impaired walking is one of the most prevalent and debilitating symptom experienced (Confavreux et al., 2000; Freeman, 2001; Kornblith et al., 1986). BWSTT is also safe for individuals of all disability levels as the harness minimizes risk of falling and is accessible for all individuals regardless of disability level. Despite the benefits of BWSTT, there are still important drawbacks such as high costs, and subsequently low availability of this equipment, limiting use to specialized rehabilitation centers. Further, it has been suggested that restricting gait kinematics (via therapist or robotic assistance) may limit opportunities to self-correct gait, which may hinder walking and gait recovery (Dobkin and Duncan, 2012). The contribution from therapists or robotic assistance may result in less active contribution from the individual, further limiting potential adaptations in physical fitness (Pilutti and Hicks, 2013).

4.2.2. Total body recumbent stepper training

One study evaluated TBRST and reported a reduction in symptoms of fatigue and improved QOL (Pilutti et al., 2016). Improvements in VO_{2peak} and walking performance has been observed in individuals with stroke after TBRST (Billinger et al., 2012). One distinct advantage of TBRST is the full-body training stimulus involving both upper and lower extremity exercise. This full-body exercise can result in improvements in aerobic and muscular fitness, and this could translate into improvements in physical function (Dobkin and Duncan, 2012; Hassid et al., 1997; Pilutti and Hicks, 2013). Furthermore, the self-driven nature of TBRST allows for all work to be done by the exerciser, rather than assistance from therapists or a robotic orthosis. TBRST does not require extensive setup or preparation and it is a viable modality for community and/or home setting. Unfortunately, the efficacy of TBRST is currently unknown as only one study has examined this modality in those with MS.

4.2.3. Electrical stimulation assisted cycling

The evidence supporting ESAC was mixed, likely owing to the low quality of the studies reviewed (i.e., no RCTs, all level 4). There was some evidence for the benefits of ESAC on physical fitness, fatigue, and pain, although there was mixed evidence for the effect of ESAC on physical function. There are potential advantages of combined electrical stimulation and volitional exercise such that the added stimulation allows for greater recruitment and activation of weakened muscles, increasing the potential for adaptations in physical fitness. This is particularly advantageous for those with MS with severe mobility disability due to physiological deconditioning of the lower extremity musculature (Kent-Braun et al., 1997; Pilutti et al., 2015). ESAC is an easily accessible modality as many protocols allow individuals to exercise while remaining seated in their own personal wheelchair. There are inherent limitations of ESAC. First, the set-up may be challenging (e.g., electrode placement, tablet interface) for individuals with motor and/or cognitive impairment. Further, the electrical stimulation excites both motor and sensory nerves which may cause pain for individuals with spared sensation, potentially discouraging individuals from using this modality.

5. Limitations

5.1. Limitations of the literature

When reviewing the literature, it became apparent that there were many limitations. First, many of the studies had small samples, with the largest sample including 49 participants. Many of the studies included did not involve appropriate control conditions. Furthermore, the studies included heterogeneous MS samples with respect to demographic and other clinical characteristics. Another limitation of the literature is the lack of a consistent cut-point or grouping for participants with MS with severe mobility disability. This makes it difficult to apply the findings to all people with MS with severe mobility impairment. Another limitation is inconsistency in exercise prescriptions as there was considerable variability in frequency, duration, intensity, and/or modality of exercise training. Another important limitation is the lack of clearly defined primary outcomes; only six of the 19 articles stated the primary outcome(s) of the trial. This is important as most participants were likely not recruited based on a specific primary outcome. Additionally, there was variability in the types of measures used to assess similar outcomes, making it difficult to draw meaningful conclusions considering the limited evidence. Lastly, outcomes were measured and reported immediately after exercise training, and few studies reported follow-up assessments; therefore, the long-term or lasting effect of exercise training is unknown.

5.2. Limitations of the review

In addition to the limitations of the literature, there are also limitations of the review itself. We used a descriptive systematic approach for study selection and review. Due to the limited evidence and diverse outcomes included in the studies reviewed, we chose not to perform a meta-analysis, but rather summarized the potential benefits of each exercise approach. We were further unable to report changes with exercise training relative to primary and secondary outcomes, as few studies identified these outcomes. The studies reviewed were selected by two members of the research team and were therefore subject to selection bias. Additionally, we only included articles that were published in English academic journals, subjecting our review to publication bias. We chose to only include studies that implemented a structured exercise training program and excluded studies that involved various types of rehabilitation (e.g., physiotherapy, occupational therapy, etc.). Lastly, our classification of severe mobility disability (EDSS score $\geq$ 6.0 and/or disability consistent with this level of impairment) may have resulted in the exclusion of studies with other pertinent information.

6. Future research directions

Considering the limitations of the current literature, we provide direction for future researchers regarding exercise training interventions in people with MS with severe mobility disability. We recommend comprehensive and systematic investigations to determine the most efficacious prescription of exercise training with respect to duration, intensity, frequency, and modality on important outcomes such those summarized within this review (i.e., disability, physical fitness, physical function, symptoms and participation). This should be accomplishing using high-quality, randomized controlled trial designs, with appropriate control conditions. Specifically, different exercise modalities that have received minimal attention (e.g., recumbent stepper) or have not been evaluated at all in persons with MS with mobility disability (e.g., combined arm and leg ergometer) should be examined in future trials. Future research should also consider developing and evaluating different prescriptions of exercise training based on ambulatory ability (e.g., unilateral and bilateral support vs. wheelchair-dependent). In particular, exercise training approaches for persons with MS who are non-ambulatory are needed to improve the health of all individuals living with MS. Another consideration should be to determine the optimal mechanisms of delivery of exercise training, particularly given limitations in transportation and accessibility for those with severe mobility disability. The efficacy of home-based or telerehabilitation approaches (e.g., Internet-delivered) should be evaluated and compared with supervised exercise training in future investigations. Finally, the section, refinement, and evaluation of appropriate and comprehensive outcomes of exercise training interventions in persons with MS with severe mobility disability should be considered and reported, including detailed metrics of safety, feasibility, and patient-reported experiences of exercise training.

7. Conclusions

There is limited evidence on the role of exercise training in persons with MS with severe mobility disability, and we summarize this literature based on conventional and adapted exercise training approaches. Preliminary data suggest that conventional resistance exercise training might improve physical fitness, physical function, and/or symptomatic and participatory outcomes. Adapted exercise training may have benefits on disability, physical fitness, physical function, and/or symptomatic and participatory outcomes. There are potential advantages of adapted exercise training modalities in physical accessibility and task-specificity. However, adapted exercise modalities are often expensive and only available in specialized settings. Considering the limited evidence, further research is necessary to determine the most efficacious and effective exercise approaches for individuals with MS with severe mobility disability.

Disclosure statement

We certify that no party having a direct interest in the results of the research supporting this article has or will confer a benefit on us or on any organization with which we are associated and we certify that all financial and material support for this research and work are clearly identified in the title page of the manuscript.

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References

Adams, M.M., Ditor, D.S., Tarnopolsky, M.A., Phillips, S.M., McCartney, N., Hicks, A.L., 2006. The effect of body weight-supported treadmill training on muscle morphology in an individual with chronic, motor-complete spinal cord injury: a case study. J. Spinal Cord. Med. 29, 167–171.

Amato, M.P., Ponziani, G., Rossi, F., Liedl, C.L., Stefanile, C., Rossi, L., 2001. Quality of life in multiple sclerosis: the impact of depression, fatigue and disability. Mult. Scler. 7, 340–344.

Backus, D., Burdett, B., Hawkins, L., Manella, C., McCully, K., Sweatman, M., 2016. Pilot study of outcomes after functional electrical stimulation cycle training in individuals with multiple sclerosis who are nonambulatory. Int. J. MS Care. http://dx.doi.org/10.7224/1537-2073.2015-036.

Bakshi, R., Shaikh, Z.A., Miletich, R.S., Czarnecki, D., Dmochowski, J., Henschel, K., Janardhan, V., Dubey, N., Kinkel, P.R., 2000. Fatigue in multiple sclerosis and its relationship to depression and neurologic disability. Mult. Scler. 6, 181–185.

Beer, S., Aschbacher, B., Manoglou, D., Gamper, E., Kool, J., Kesselring, J., 2008. Robot-assisted gait training in multiple sclerosis: a pilot randomized trial. Mult. Scler. 14, 231–236.

Benito-León, J., Morales, J.M., Rivera-Navarro, J., Mitchell, A., 2003. A review about the impact of multiple sclerosis on health-related quality of life. Disabil. Rehabil. 25, 1291–1303.

Billinger, S.A., Mattlage, A.E., Ashenden, A.L., Lentz, A.A., Harter, G., Rippee, M.A., 2012. Aerobic exercise in subacute stroke improves cardiovascular health and physical performance. J. Neurol. Phys. Ther. 36, 159–165.

Bouchard, C., Shephard, R.J., Stephens, T., 1994. Physical Activity, Fitness, and Health: International Proceedings and Consensus Statement. Human Kinetics Publishers, Champaign, IL, England.

Briken, S., Gold, S.M., Patra, S., Vettorazzi, E., Harbs, D., Tallner, A., Ketels, G., Schulz, K.H., Heesen, C., 2013. Effects of exercise on fitness and cognition in progressive MS: a randomized, controlled pilot trial. Mult. Scler. J (1352458513507358).

Confavreux, C., Vukusic, S., Adeleine, P., 2003. Early clinical predictors and progression of irreversible disability in multiple sclerosis: an amnesic process. Brain J. Neurol. 126, 770–782.

Confavreux, C., Vukusic, S., Moreau, T., Adeleine, P., 2000. Relapses and progression of disability in multiple sclerosis. N. Engl. J. Med. 343, 1430–1438.

Coote, S., Hughes, L., Rainsford, G., Minogue, C., Donnelly, A., 2015. Pilot randomized trial of progressive resistance exercise augmented by neuromuscular electrical stimulation for people with multiple sclerosis who use walking aids. Arch. Phys. Med. Rehabil. 96, 197–204.

Dobkin, B.H., Duncan, P.W., 2012. Should body weight-supported treadmill training and robotic-assistive steppers for locomotor training trot back to the starting gate? Neurorehabil. Neural Repair 26, 308–317.

Downs, S.H., Black, N., 1998. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J. Epidemiol. Community Health 52, 377–384.

Eng, J., Teasell, R., Miller, W., Wolfe, D., Townson, A., Hsieh, J., Connolly, S., Mehta, S., Sakakibara, B., n.d. The Spinal Cord Injury Rehabilitation Evidence (SCIRE). URL 〈https://www.scireproject.com/〉. (Accessed 18 April 2016).

Ensari, I., Motl, R.W., Pilutti, L.A., 2014. Exercise training improves depressive symptoms in people with multiple sclerosis: results of a meta-analysis. J. Psychosom. Res. 76, 465–471.

Filipi, M.L., Kucera, D.L., Filipi, E.O., Ridpath, A.C., Leuschen, M.P., 2011. Improvement in strength following resistance training in MS patients despite varied disability levels. NeuroRehabilitation 28, 373–382.

Flachenecker, P., Henze, T., Zettl, U.K., 2014. Spasticity in patients with multiple sclerosis–clinical characteristics, treatment and quality of life. Acta Neurol. Scand. 129, 154–162.

Fornusek, C., Hoang, P., 2014. Neuromuscular electrical stimulation cycling exercise for persons with advanced multiple sclerosis. J. Rehabil. Med. 46, 698–702.

Freeman, J.A., 2001. Improving mobility and functional independence in persons with multiple sclerosis. J. Neurol. 248, 255–259.

Giangregorio, L.M., Hicks, A.L., Webber, C.E., Phillips, S.M., Craven, B.C., Bugaresti, J.M., McCartney, N., 2005. Body weight supported treadmill training in acute spinal cord injury: impact on muscle and bone. Spinal Cord. 43, 649–657.

Giesser, B., Beres-Jones, J., Budovitch, A., Herlihy, E., Harkema, S., 2007. Locomotor training using body weight support on a treadmill improves mobility in persons with multiple sclerosis: a pilot study. Mult. Scler. 13, 224–231.

Hassid, E., Rose, D., Commisarow, J., Guttry, M., Dobkin, B.H., 1997. Improved gait symmetry in hemiparetic stroke patients induced during body weight-supported treadmill stepping. Neurorehabil. Neural Repair 11, 21–26.

Hesse, S., Werner, C., Bardeleben, A., Barbeau, H., 2001. Body weight-supported treadmill training after stroke. Curr. Atheroscler. Rep. 3, 287–294.

Jackson, K., Edginton-Bigelow, K., Bowsheir, C., Weston, M., Grant, E., 2012a. Feasibility and effects of a group kickboxing program for individuals with multiple sclerosis: a pilot report. J. Bodyw. Mov. Ther. 16, 7–13.

Jackson, K., Edginton-Bigelow, K., Cooper, C., Merriman, H., 2012b. A group kickboxing program for balance, mobility, and quality of life in individuals with multiple sclerosis: a pilot study. J. Neurol. Phys. Ther. 36, 131–137.

Kent-Braun, J.A., Ng, A.V., Castro, M., Weiner, M.W., Gelinas, D., Dudley, G.A., Miller, R.G., 1997. Strength, skeletal muscle composition, and enzyme activity in multiple sclerosis. J. Appl. Physiol. 83, 1998–2004.

Kjølhede, T., Vissing, K., Dalgas, U., 2012. Multiple sclerosis and progressive resistance training: a systematic review. Mult. Scler. J (1352458512437418).

Klaren, R.E., Motl, R.W., Dlugonski, D., Sandroff, B.M., Pilutti, L.A., 2013. Objectively quantified physical activity in persons with multiple sclerosis. Arch. Phys. Med. Rehabil. 94, 2342–2348.

Kornblith, A.B., La Rocca, N.G., Baum, H.M., 1986. Employment in individuals with multiple sclerosis. Int. J. Rehabil. Res. 9, 155–165.

Kurtzke, J.F., 1983. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 33, 1444–1452.

Latimer-Cheung, A.E., Pilutti, L.A., Hicks, A.L., Martin Ginis, K.A., Fenuta, A.M., MacKibbon, K.A., Motl, R.W., 2013. Effects of exercise training on fitness, mobility, fatigue, and health-related quality of life among adults with multiple sclerosis: a systematic review to inform guideline development. Arch. Phys. Med. Rehabil. 94, 1800–1828.

Lo, A.C., Triche, E.W., 2008. Improving gait in multiple sclerosis using robot-assisted, body weight supported treadmill training. Neurorehabil. Neural Repair 22, 661–671.

Mao, Y.-R., Lo, W.L., Lin, Q., Li, L., Xiao, X., Raghavan, P., Huang, D.-F., 2015. The effect of body weight support treadmill training on gait recovery, proximal lower limb motor pattern, and balance in patients with subacute stroke. BioMed Res. Int. 2015, e175719.

Motl, R., Goldman, Benedict, B., 2010. Walking impairment in patients with multiple sclerosis: exercise training as a treatment option. Neuropsychiatr. Dis. Treat. 767.

Motl, R.W., 2010. Physical activity and irreversible disability in multiple sclerosis. Exerc. Sport Sci. Rev. 38, 186–191.

Motl, R.W., Learmonth, Y.C., 2014. Neurological disability and its association with walking impairment in multiple sclerosis: brief review. Neurodegener. Dis. Manag. 4, 491–500.

Motl, R.W., McAuley, E., 2010. Symptom cluster and quality of life: preliminary evidence in multiple sclerosis. J. Neurosci. Nurs. J. Am. Assoc. Neurosci. Nurses 42, 212–216.

Pilutti, L.A., Greenlee, T.A., Motl, R.W., Nickrent, M.S., Petruzzello, S.J., 2013. Effects of exercise training on fatigue in multiple sclerosis: a meta-analysis. Psychosom. Med. 75, 575–580.

Pilutti, L.A., Hicks, A.L., 2013. Rehabilitation of ambulatory limitations. Phys. Med. Rehabil. Clin. N. Am. 24, 277–290 (Ambulation in Adults with Central Neurologic Disorders).

Pilutti, L.A., Lelli, D.A., Paulseth, J.E., Crome, M., Jiang, S., Rathbone, M.P., Hicks, A.L., 2011. Effects of 12 weeks of supported treadmill training on functional ability and quality of life in progressive multiple sclerosis: a pilot study. Arch. Phys. Med. Rehabil. 92, 31–36.

Pilutti, L.A., Paulseth, J.E., Dove, C., Jiang, S., Rathbone, M.P., Hicks, A.L., 2016. Exercise training in progressive multiple sclerosis: a comparison of recumbent stepping and body weight–supported treadmill training. Int. J. MS Care. http://dx.doi.org/10.7224/1537-2073.2015-067.

Pilutti, L.A., Sandroff, B.M., Klaren, R.E., Learmonth, Y.C., Platta, M.E., Hubbard, E.M., Stratton, M.B., Motl, R.W., 2015. Physical fitness assessment across the disability spectrum in persons with multiple sclerosis: a comparison of testing modalities. J. Neurol. Phys. Ther. 39, 1–9.

Platta, M.E., Ensari, I., Motl, R.W., Pilutti, L.A., 2016. The effect of exercise training on fitness in multiple sclerosis: a meta-analysis. Arch. Phys. Med. Rehabil. 97, 1564–1572.

Ratchford, J.N., Shore, W., Hammond, E.R., Rose, J.G., Rifkin, R., Nie, P., Tan, K., Quigg, M.E., de Lateur, B.J., Kerr, D.A., 2010. A pilot study of functional electrical stimulation cycling in progressive multiple sclerosis. NeuroRehabilitation 27, 121–128.

Reynolds, M.A., McCully, K., Burdett, B., Manella, C., Hawkins, L., Backus, D., 2015. Pilot study: evaluation of the effect of functional electrical stimulation cycling on muscle metabolism in nonambulatory people with multiple sclerosis. Arch. Phys. Med. Rehabil. 96, 627–632.

Sandroff, B.M., Pilutti, L.A., Benedict, R.H.B., Motl, R.W., 2015. Association between physical fitness and cognitive function in multiple sclerosis: does disability status matter? Neurorehabil. Neural Repair 29, 214–223.

Sandroff, B.M., Sosnoff, J.J., Motl, R.W., 2013. Physical fitness, walking performance, and gait in multiple sclerosis. J. Neurol. Sci. 328, 70–76.

Schwartz, I., Sajin, A., Moreh, E., Fisher, I., Neeb, M., Forest, A., Vaknin-Dembinsky, A., Karusis, D., Meiner, Z., 2012. Robot-assisted gait training in multiple sclerosis patients: a randomized trial. Mult. Scler. J. 18, 881–890.

Skjerbæk, A.G., Næsby, M., Lützen, K., Møller, A.B., Jensen, E., Lamers, I., Stenager, E., Dalgas, U., 2014. Endurance training is feasible in severely disabled patients with progressive multiple sclerosis. Mult. Scler. J. 20, 627–630.

Snook, E.M., Motl, R.W., 2009. Effect of exercise training on walking mobility in multiple sclerosis: a meta-analysis. Neurorehabil. Neural Repair 23, 108–116 (d).

Sosnoff, J.J., Sung, J., 2015. Reducing falls and improving mobility in multiple sclerosis. Expert Rev. Neurother. 15, 655–666.

Straudi, S., Benedetti, M.G., Venturini, E., Manca, M., Foti, C., Basaglia, N., 2013. Does

robot-assisted gait training ameliorate gait abnormalities in multiple sclerosis? A pilot randomized-control trial. NeuroRehabilitation 33, 555–563.
Szecsi, J., Schlick, C., Schiller, M., Pöllmann, W., Koenig, N., Straube, A., 2009. Functional electrical stimulation-assisted cycling of patients with multiple sclerosis: biomechanical and functional outcome–a pilot study. J. Rehabil. Med. 41, 674–680.
Vaney, C., Gattlen, B., Lugon-Moulin, V., Meichtry, A., Hausammann, R., Foinant, D., Anchisi-Bellwald, A.-M., Palaci, C., Hilfiker, R., 2012. Robotic-assisted step training (lokomat) not superior to equal intensity of over-ground rehabilitation in patients with multiple sclerosis. Neurorehabil. Neural Repair 26, 212–221.
Verhagen, A.P., de Vet, H.C.W., de Bie, R.A., Kessels, A.G.H., Boers, M., Bouter, L.M., Knipschild, P.G., 1998. The Delphi list: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by delphi consensus. J. Clin. Epidemiol. 51, 1235–1241.
Wier, L.M., Hatcher, M.S., Triche, E.W., Lo, A.C., 2011. Effect of robot-assisted versus conventional body-weight-supported treadmill training on quality of life for people with multiple sclerosis. J. Rehabil. Res. Dev. 48, 483–492.