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REVIEW ARTICLE (META-ANALYSIS)

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

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Abstract

Objective: To conduct a systematic review of evidence surrounding the effects of exercise training on physical fitness, mobility, fatigue, and health-related quality of life in adults with multiple sclerosis (MS).

Data Sources: The databases included EMBASE, 1980 to 2011 (wk 12); Ovid MEDLINE and Ovid OLDMEDLINE, 1947 to March (wk 3) 2011; PsycINFO, 1967 to March (wk 4) 2011; CINAHL all-inclusive; SPORTDiscus all-inclusive; Cochrane Library all-inclusive; and Physiotherapy Evidence Database all-inclusive.

Study Selection: The review was limited to English-language studies (published before December 2011) of people with MS that evaluated the effects of exercise training on outcomes of physical fitness, mobility, fatigue, and/or health-related quality of life.

Data Extraction: One research assistant extracted data and rated study quality. A second research assistant verified the extraction and quality assessment.

Data Synthesis: From the 4362 studies identified, 54 studies were included in the review. The extracted data were analyzed using a descriptive approach. There was strong evidence that exercise performed 2 times per week at a moderate intensity increases aerobic capacity and muscular strength. The evidence was not consistent regarding the effects of exercise training on other outcomes.

Conclusions: Among those with mild to moderate disability from MS, there is sufficient evidence that exercise training is effective for improving both aerobic capacity and muscular strength. Exercise may improve mobility, fatigue, and health-related quality of life.

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Multiple sclerosis (MS) is an immune-mediated, neurodegenerative disease that affects an estimated 2.5 million adults worldwide.[1] This disease manifests in a wide range of symptoms including muscle weakness, extreme fatigue, imbalance, impaired speech, double vision, cognitive dysfunction, and paralysis. Such symptoms often lead to poor health-related quality of life (HRQOL),[2-4] neurologic disability, and high health care costs (approximately $1.7 billion annually in Canada, for example).[5]

Exercise training has been proposed to counteract many of the consequences of MS.[6-8] Indeed, evidence indicates that engaging in exercise has the potential to improve and/or maintain functional ability, aerobic fitness, strength, fatigue, HRQOL, depression, cognition, and chronic disease risk profiles among people with MS.[9-13] Unfortunately, despite the benefits of exercise training, most people with MS are physically inactive. The studies directly comparing physical activity patterns of people with MS, people without MS, and people with other chronic diseases indicate that

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people with MS may be at the lowest end of the physical activity participation spectrum.[11,14]

A systematic effort to promote physical activity in the MS population is needed, but it is very difficult to design effective physical activity programs and resources for people with MS in the absence of population-specific physical activity guidelines. To date, 2 groups have put forth MS-specific recommendations for physical activity in MS.[15,16] These guidelines conflict with each other and have methodological limitations. The first set of guidelines is not evidence based.[16] The second set is evidence based[15] but is not underpinned by a robust, standardized consensus guideline development process—a process that has become the accepted norm for guideline development worldwide.[17] Furthermore, the 2 guidelines are based on descriptive reviews of fitness outcomes only; the reviews did not concurrently examine other key outcomes (eg, physical functioning, fatigue, HRQOL) for persons with MS that might be impacted by physical activity, and did not systematically evaluate the quality of the evidence reviewed. A focus on only 1 set of outcomes and a failure to evaluate evidence quality could be considered as limitations of the published reviews in this area.

According to international standards for the development of evidence-based clinical practice guidelines and evidence-based physical activity guidelines,[17,18] having a systematically developed and evaluated evidence base is a critical first step in establishing guidelines. Thus, the present systematic review was undertaken as part of a larger project to develop physical activity guidelines for adults with MS. The purpose of this review was to examine the evidence of the minimum dose of exercise training needed to elicit benefits in physical fitness, mobility, fatigue, and HRQOL in persons with MS. This information served as the evidence base for subsequent deliberation and recommendations in the guideline development process.

Methods

Scope of the review/study inclusion criteria

The review focused on English-language studies examining the fitness, mobility, fatigue, or HRQOL benefits of exercise training in persons with diagnosed MS. We ascribed to the following definition of exercise by Bouchard et al: "a form of leisure-time physical activity that is usually performed repeatedly over an extended period of time with a specific external objective such as the improvement of fitness, physical performance, or health."[19(p12)] Other outcomes including balance, body composition, disease progression, and adverse events resulting from exercise participation were also considered. However, because of inconsistency in measurement, poor measurement quality, and lack of reporting, these outcomes were not included in the review. Thus, the studies reviewed had to include at least 1 of the following measures in the analyses: fitness, mobility, fatigue, or HRQOL. Both randomized and nonrandomized controlled designs were included.

List of abbreviations:

EDSS	**Expanded Disability Status Scale**
FES	**functional electrical stimulation**
HRQOL	**health-related quality of life**
MS	**multiple sclerosis**
PEDro	**Physiotherapy Evidence Database**
RCT	**randomized controlled trial**
RM	**repetition maximum**
$\dot{V}O_2max$	**maximal oxygen consumption**

Literature search strategy

A master's level research assistant developed the search strategy in consultation with the project director (A.E.L.-C.) and a research methodologist (K.A.M.). A list of keywords was generated from the key search terms included in existing literature reviews and meta-analyses.[11,20-22] The search terms included "exercise" OR "physical activity" OR "exercise prescription" OR "exercise therapy" OR "training" OR "fitness" OR "aerobic" OR "strength" OR "resist" OR "ambulatory activity" OR "walk" AND "multiple sclerosis."

A preliminary search of 6 electronic databases (MEDLINE, PsycInfo, EMBASE, Physiotherapy Evidence Database [PEDro], CINAHL, SPORTDiscus) was conducted to ensure that most of the articles included in existing reviews[11,20-22] were captured using these keywords; 92.8% of articles cited in extant reviews were captured. This search strategy was used in a comprehensive search of 7 electronic bibliographic databases conducted in April 2011. The databases included EMBASE, 1980 to 2011 (wk 12); Ovid MEDLINE and Ovid OLDMEDLINE, 1947 to March (wk 3) 2011; PsycINFO, 1967 to March (wk 4) 2011; CINAHL all-inclusive; SPORTDiscus all-inclusive; Cochrane Library all-inclusive; and PEDro all-inclusive. The database search was further supplemented with a hand search of relevant reviews, meta-analyses, and the authors' personal libraries.

Screening

Article screening was conducted by 2 independent research assistants. One research assistant was a master's level student and Canadian Society for Exercise Physiology certified exercise physiologist with expertise in disability and exercise. The second research assistant held a Master's degree in kinesiology and had extensive experience conducting systematic reviews on topics related to disability and health. After removing duplicate citations, the 2 research assistants independently scanned the title and abstract of each citation to determine its suitability for inclusion (fig 1). In the initial scan, articles were excluded if they were clearly outside the scope of the review, did not report results of a trial (eg, reviews, commentaries), and/or used qualitative research methods only. Next, using the inclusion criteria to determine eligibility, the research assistants reviewed the full text of potentially relevant articles and articles where suitability could not be determined from the title and abstract scan alone. The same 2-step process was applied in conducting the hand search of reference lists and personal libraries. The research assistants' decisions to include/exclude each article were compared. Discrepancies were discussed and when necessary, reviewed by the authorship team.

Data extraction and analysis

The same research assistants who conducted the article screening also conducted the data extraction. One research assistant extracted data related to study design, participant characteristics, methodology, outcomes related to the defined scope, and conclusions for each of the 54 articles. The second research assistant verified the extraction. The research assistants were not blinded to the journal or the authors.

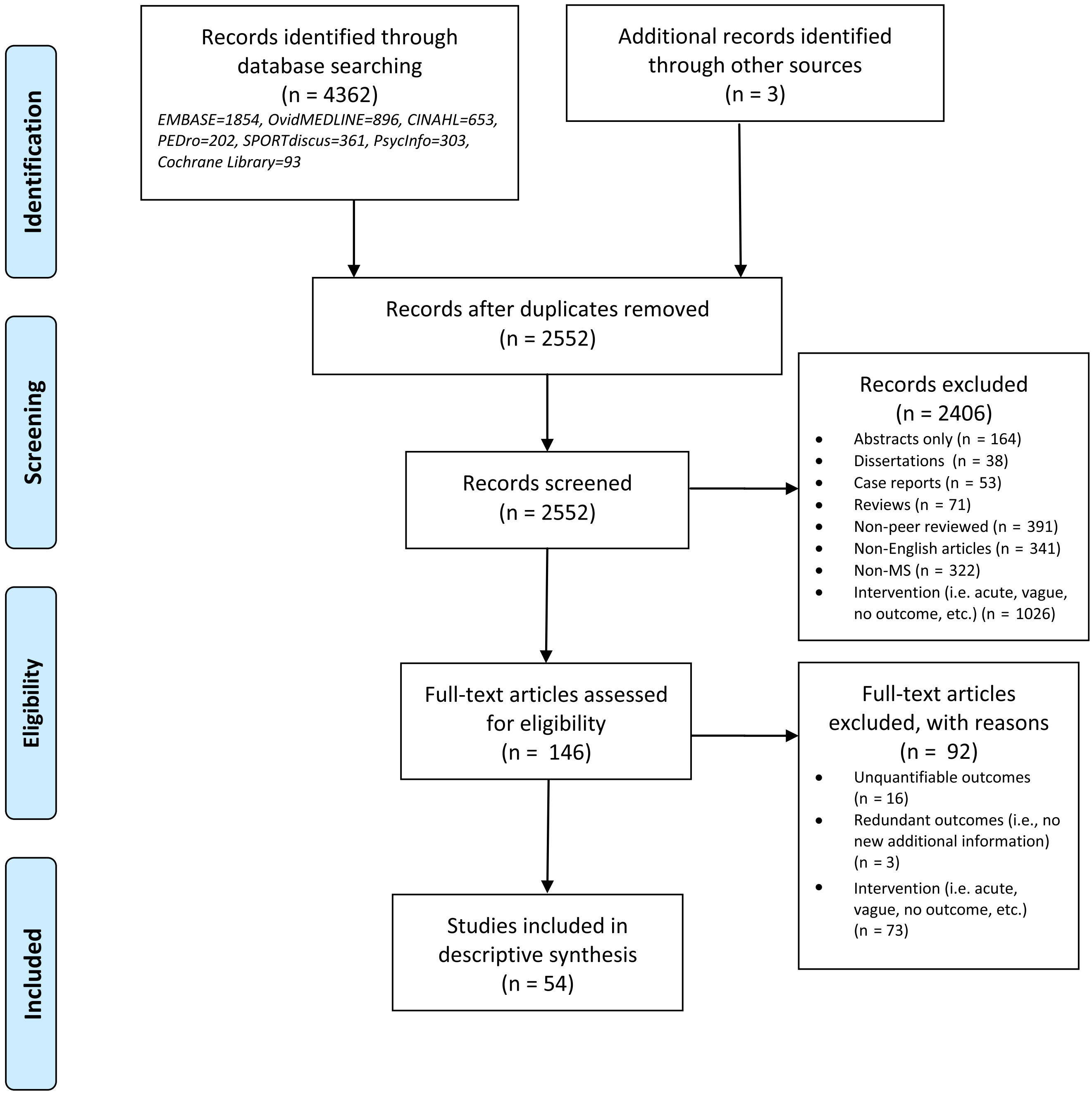

Fig 1 PRISMA (preferred reporting items for systematic reviews and meta-analyses) flow diagram of literature review process.

The findings for each outcome were considered separately for distinct types of exercise training interventions including: aerobic training interventions, resistance training interventions, combined aerobic and resistance training interventions, and alternative training interventions (ie, nontraditional forms of exercise such as yoga, aquatics, supported treadmill walking, etc). Because of the limited evidence base, studies and results were not divided according to the clinical course of MS, stage of disease remission, or severity of disability. In accordance with recommendations within the Cochrane Handbook for Systematic Reviews of Interventions regarding when not to submit data to a meta-analysis, the data were analyzed using a descriptive synthesis approach given the variability in the participant characteristics, intervention characteristics (eg, frequency, intensity, type, and duration of exercise), and outcome assessment strategies. For consistency across studies, the postintervention measures were considered those assessed immediately after the conclusion of the trial.

Assessment of evidence quality

The quality of each study was determined using the PEDro score for randomized controlled trials (RCTs) and the modified Downs and Black scale for non-RCTs. On the PEDro scale,[23] the maximum possible score was 10. Consistent with the quality assessment approach used in the review by Valent et al,[24] 2 PEDro items—“blinding of all therapists” and “blinding of all

Table 1 Levels of evidence scaling criteria applied to the articles

Levels of Evidence	Criteria
Level 1 (n=29)	• RCT: PEDro score >6. Includes within-subjects comparison with randomized conditions and crossover designs.
Level 2 (n=1)	• RCT: PEDro score ≤6
	• Prospective controlled trial: not randomized
	• Cohort: prospective longitudinal study using at least 2 similar groups with 1 exposed to a particular condition
Level 3 (n=0)	• Case-control studies: retrospective study comparing conditions, including historical controls
Level 4 (n=24)	• Pre-post: prospective trial with a baseline measure, intervention, and a posttest using a single group of subjects
	• Posttest: prospective posttest with 2 or more groups (intervention followed by posttest and no retest or baseline measurement) using a single group of subjects
	• Case series: retrospective study usually collecting variables from a chart review
Level 5 (n=0)	• Case report: pre-post or case series involving 1 subject
	• Observational: study using cross-sectional analysis to interpret relations
	• Clinical consensus: expert opinion without explicit critical appraisal, or based on physiology, biomechanics, or "first principles"

subjects"—were considered irrelevant when comparing a training group with a no-exercise control group; such studies were credited the 2 points for these items. The Downs and Black scale[25] had a maximum possible score of 28. On both scales, higher scores indicate better methodological quality. Articles were independently evaluated by 2 raters. Any scoring discrepancies were resolved through discussion with the research team. The level of evidence associated with each study was then coded using the Spinal Cord Injury Rehabilitation Evidence system,[26] which is 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).

Results

Figure 1 shows the flow of articles through the search and screening process. In total, the electronic search yielded 4362 titles. The hand search yielded 3 additional citations. After removing duplicate citations, 2552 citations remained. In total, 2498 articles did not meet inclusion criteria and were excluded after review, leaving 54 articles for review in the final evidence base. The reasons for exclusion are included in figure 1.

The extracted data for trials included in the review are reported in tables 2 and 3. The findings for each outcome are summarized in tables 4 through 8. A comprehensive review of the findings for fitness outcomes is described below. Because of the intricacies of the findings for mobility, fatigue, and HRQOL outcomes, we provide a brief description of the findings below, with a more comprehensive description provided as supplemental material (available online only at the *Archives* website, http://www.archives-pmr.org/).

Fitness: physical capacity

Indicators of physical capacity included (1) aerobic capacity, most commonly defined as maximal oxygen consumption ($\dot{V}O_2$max), but also included $\dot{V}O_2$ at aerobic threshold; and (2) power output (ie, the mechanical power generated during exercise[27]), most often defined as peak power output, but also included power output at aerobic threshold. These fitness outcomes are relevant to mobility, performance of activities of daily living, fatigue, and HRQOL among individuals with MS.[20,28] Aerobic capacity is pertinent for cardiovascular health, functional independence, fatigue resistance, brain health,[29] and overall HRQOL.[30,31] Power output can impact the ability to effectively perform everyday functions in activities of daily living, such as walking and climbing stairs.[32] Eleven studies that met systematic review criteria investigated the effects of exercise training on aerobic capacity, power output, or both. These protocols included aerobic training (leg/arm cycling) alone or in combination with resistance training (weight machines and plyometrics). Although the magnitude of improvements varies across studies, there is compelling evidence of the beneficial effects of exercise for improving these fitness outcomes in people with MS. This evidence is summarized in table 4 and described below.

Aerobic capacity

Nine studies[31,33-40] reported changes in aerobic capacity, 5[31,33,36,37,39] of which provided level 1 evidence supporting the efficacy of aerobic training in improving aerobic capacity. Across these studies, aerobic exercise[31,36,37,39] training programs at a minimum frequency of 2 to 3 times per week for 30 to 60 minutes at moderate intensities (60%−80% maximum work rate or 60% $\dot{V}O_2$max) are effective at improving aerobic capacity. These effects were supported by 3 studies[34,38,40] with level 4 evidence. There was mixed evidence[33,35] regarding the effectiveness of combined aerobic and resistance training for improving aerobic capacity in persons with MS. However, 1 study[31] with level 1 evidence did report a significant increase in VO_2peak after 5 weeks of training 3 times per week, for 60 minutes, at an intensity of 33% to 55% $\dot{V}O_2$max.

Power output

Six studies[31,36,37,39,41,42] reported changes in power output, 5[31,36,37,39,41] of which provided level 1 evidence. Power output increased after cycle ergometry (leg or combined leg/arm) on 2 or more days per week for 30 to 50 minutes, at a moderate intensity (60% $\dot{V}O_2$max or anaerobic threshold).[31,36,37,39] Further, studies with both level 1[41] and 4[42] evidence indicate that combination training (eg, cycle ergometry and plyometrics) performed for 60 minutes at a moderate intensity 2 times per week may also lead to improved power output.

Fitness: muscular strength

Muscular strength is an important fitness outcome for adults with MS. Improvements in strength can impact mobility, balance, performance of activities of daily living, and fatigue.[43] If strength

Table 2 Data extracted for all RCTs

	Participant Characteristics					Training Program Characteristics					Outcomes	
Reference	n	EDSS Mean ± SD	Type of MS (n)	Age (y) Mean ± SD	Time Since Diagnosis (y) Mean ± SD	Type	Intensity	Time (min)	Frequency (times/wk)	Duration (wk)	Fitness	Other
Bjarnadottir et al[33] Iceland (PEDro=7) *Level 1*	E:6 C:10	2.1	RR	38.7	8.7	Monark Cycle Ergometer; 13 RT exercise using major groups (upper and lower extremity, back, abdomen)	33%–35% VO_2peak; 15–20 repetitions	60	3	5	↑ VO_2peak (mL·kg^{-1}·min^{-1})* ↑ Anaerobic threshold (L/min)*; ↑ Peak workload (W/kg)*	*HRQOL**: ↑ SF-36-Vitality*
Broekmans et al[46] Belgium (PEDro=8) *Level 1*	E1:11	4.5±1.3	RR (5) SP (3) PP (3)	44.9±11.6		Leg RT (press, EXT, curl) on Technogym equipment	Light-moderate intensity unilateral leg RT; 1–2 sets of 10–15 reps 50%–60% of 1RM, 10–15RM with 2min rest between	60	5 training sessions/2-wk cycle	20	↑ 1RM (kg)—leg press + EXT + curl* ↑ Isometric (Nm) EXT −45+90°*/† ↑ Isometric (Nm) FLEX −45°+90°/† ↑ Isometric (Nm) FLEX severely impaired leg −45°+90°* ↑ Isokinetic (Nm) EXT severely impaired leg −60°/s*/† ↑ Muscle strength	
	E2:11	4.4±0.9	RR (2) SP (4) PP (4)	48.7±8.6		Leg RT (same as above) with simultaneous electrostimulation	100Hz, biphasic symmetric wave, 400μs, 3s hold, 4s rest				↑ 1RM (kg) – leg press + EXT + curl* ↑ Isometric (Nm) FLEX severely impaired leg −45°+90°* ↑ Isokinetic (Nm) EXT 60°/s* ↑ Isokinetic (Nm) EXT severely impaired leg −60°/s* ↑ Muscle strength	
	C:14											
Cakt et al[41] Turkey (PEDro=8) *Level 1*	E1:14	≤6	RR SP	36.4±10.5	9.2 (5)	RT on static bicycle ergometer; balance + lower body plyometric exercises	15 sets of reps/session (2min high-resistance pedaling [40% TMW]+2min low resistance	60	2	8	↑ Tolerated maximum workload (W)‡ ↑ Power output	*Mobility*: ↓ TUG (s)‡; ↓ 10-m walk Test (s)‡ *Fatigue*: ↓ FSS* *HRQOL*: SF-36 (2/8

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Table 2 (*continued*)

	Participant Characteristics					Training Program Characteristics					Outcomes	
		EDSS		Age (y)	Time Since Diagnosis (y)							
Reference	n	Mean ± SD	Type of MS (n)	Mean ± SD	Mean ± SD	Type	Intensity	Time (min)	Frequency (times/wk)	Duration (wk)	Fitness	Other
							[30–40W] or rest)					scale significant); ↑ Physical Function‡; ↑ Role Physical*
	E2:10 C:9			43±10.2	6.2±2.2	Balance + lower body plyometric exercises					↑ Tolerated maximum workload (W)*	*HRQOL*: SF-36 (1/8 scale significant); ↑ Physical Function*
Conklyn et al[73] USA (PEDro=6) *Level 1*	E:5 C:5		RR (4) PP (1)	47±10.51	16.6±10.43	Walk to the music	8 songs on MP3 replicated in 15 cadences (50–120BPM in increments of 5BPM); Each week appropriate song based on spontaneous baseline cadence +10% for the visit	20	7	4		*Mobility*: ↔ T25FW (s)§
Dalgas et al[47] Denmark (PEDro=8) *Level 1*	E:15 C:16	3.7±0.9	RR	47.7±10.4	6.6±5.9	Lower extremity resistance training (5 exercises)	3–4 sets of 8–12 reps at 8–15RM; 2–3min rests between sets and exercises		2	12	↑ KE MVC (Nm) −180 */†; ↑ KF MVC (Nm) −90+180*/† ↑ Muscle strength	
Dalgas et al[48] Denmark (PEDro=8) *Level 1*	E:15 C:16	3.7±0.9	RR	47.7±10.4	6.6±5.9	Lower extremity resistance training (5 exercises)	3–4 sets of 8–12 reps at 8–15RM; 2–3min rests between sets and exercises		2	12	↑ KE MVC (Nm)† ↑ Muscle strength	*Fatigue*: ↓ FSS†; MFI-20 (2/6 scale significant); ↓ General fatigue† *HRQOL*: SF-36 (1/2 scale significant); ↑ Physical

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Table 2 (*continued*)

	Participant Characteristics					Training Program Characteristics					Outcomes	
		EDSS		Age (y)	Time Since Diagnosis (y)							
Reference	n	Mean ± SD	Type of MS (n)	Mean ± SD	Mean ± SD	Type	Intensity	Time (min)	Frequency (times/wk)	Duration (wk)	Fitness	Other
												component†
Dalgas et al[96] Denmark (PEDro=9) *Level 1*	E:15 C:16	3.7	RR	47.7	6.6	Lower extremity resistance training (5 exercises)	3–4 sets of 8–12 reps at 8–15RM; 2–3min rests between sets and exercises		2	12	↑ KE MVC (Nm)*/†; ↑ KF MVC (Nm)*/†; ↑ 1RM leg press*	*Mobility*: ↑ 6MWT (m)*/† ↓ 10MWT (s)*/†
DeBolt et al[32] USA (PEDro=8) *Level 1*	E:19 C:17	1–6.5	PP RR	40–67	1–40	Instructional sessions before treatment (6min video + equipment provided); lower extremity RT (lunge, step-up, etc)	2–3 sets of 8–12 reps; Initial weight vest resistance: 0.5% BW		3 (alternate day) 3	2 8	↑ Leg extensor power (W/kg)‡/† ↑ Leg extensor power (W)‡/† ↑ Muscle strength	*Mobility*: ↔ TUG (s)
Dettmers et al[65] Germany (PEDro=7) *Level 1*	E:15 C:15	2.6±1.2	RR (13) SP (2) PP (0)	45.8±0.9	8±5.9	Interval endurance exercise		45	3	3		*Mobility*: ↑ Max walking distance (m)†; ↑ Walking time (min)† *Fatigue*: ↔ MFIS
Geddes et al[66] USA (PEDro=7) *Level 1*	E:8 C:4	≤4.7	RR (2) PP (1) Not classified (5)	51.3	>1	Walking	15–30min within THR range	30	3	12		*Mobility*: ↔ 6MWT (m) *Fatigue*: ↔ FSS
Golzari et al[35] Iran (PEDro=5) *Level 1*	E:10 C:10	2.14±1.06	RR	32.15±7.57		Combined exercises: aerobic, endurance, resistance		60	3	8	↑ Muscle strength (kg)* ↔ $\dot{V}O_2$max (mL·kg^{-1}·min^{-1}) ↑ Aerobic capacity	
Harvey et al[49] UK (PEDro=7) *Level 1*	E1:6		RR	49	5	Exercise program prescribed by physiotherapist (ie, balance, stretching, swim, bike, etc)				8	↔ Quadriceps MVC (kg) ↑ Muscle strength	*Mobility*: ↔ Walking Speed (m/s)
	E2:6			40–48	5	Daily leg-raising exercises aimed at strengthening	0.5 or 1kg ankle weight; 5 sets of 10 reps (both legs)		2×/d			

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Table 2 (*continued*)

	Participant Characteristics					Training Program Characteristics					Outcomes	
		EDSS		Age (y)	Time Since Diagnosis (y)							
Reference	n	Mean ± SD	Type of MS (n)	Mean ± SD	Mean ± SD	Type	Intensity	Time (min)	Frequency (times/wk)	Duration (wk)	Fitness	Other
	C:5						through 45					
McCullagh et al[83] Ireland (PEDro = 7) *Level 1*	E:12 C:12		RR (9) SP (3)	40.5±12.68	5.4±4.35	4 exercise stations (ie, treadmill, cycling, arm-strengthening exercises, volleyball, etc)	11–13 RPE "fairly light" – "somewhat hard"	40–60	2	12		*Fatigue*: ↓ MFIS* *HRQOL*: ↔ MSIS-29 *Other*: ↓ FAMS
Mostert et al[36] Switzerland (PEDro = 7) *Level 1*	E:13 C:13	2.5–2.6	RR (30.8%) CP (23.1%) RP (46.2%)	45.23±8.66	11.2±8.5	Bicycle exercise training at aerobic threshold (Cardiotrainer bicycle ergometers)	Individualized	30	5	4	↑ Work rate*; ↑ Mean $\dot{V}O_2$ at aerobic threshold ($mL \cdot kg^{-1} \cdot min^{-1}$)*; ↑ Work rate at aerobic threshold (W)‡; ↑ O_2 consumption at zero-load pedaling ($mL \cdot kg^{-1} \cdot min^{-1}$)*; ↑ O_2 consumption between 20 and 60W*; ↑ Aerobic capacity ($mL \cdot kg^{-1} \cdot min^{-1}$)§; ↑ PO	
Mutluay et al[75] Turkey (PEDro = 6) *Level 1*	E:22 C:21	5.34±1.36	PP (5) SP (12) RR (5)	42.7±7.7	11.6±7.6	General conditioning + calisthenic exercises (13 movements)	Each exercise repeated 10× at comfortable pace with 1min rest between sequences	60	1	6	↑ Muscle strength (0–130)†	*Mobility*: ↓ 10-m walking time (s)†; ↓ 20-m walking time (s)† *HRQOL*: MSQOL (1/4 scale significant); ↑ Physical health†
Oken et al[81] USA (PEDro = 8) *Level 1*	E1:15	2.9±1.7		48.8±10.4		Stationary bicycle exercise class (periodic option of exercise with Swiss ball)	Borg Scale: 2–3 (very light to moderate intensity)	Until fatigue	1 (+ home practice)	24		*Fatigue*: ↓ MFI–General fatigue‡; ↑ SF-36: Energy and fatigue‖
	E2:22 C:20	3.2±1.7		49.8±7.4		Iyengar yoga class	Pose held ∼10–30s with 30–60s rest	90	1 (+ daily home practice encouraged)			*Fatigue*: ↓ MFI–General fatigue‡; ↑ SF-36: Energy and

(*continued on next page*)

Table 2 (*continued*)

	Participant Characteristics					Training Program Characteristics					Outcomes	
		EDSS		Age (y)	Time Since Diagnosis (y)							
Reference	n	Mean ± SD	Type of MS (n)	Mean ± SD	Mean ± SD	Type	Intensity	Time (min)	Frequency (times/wk)	Duration (wk)	Fitness	Other
												fatigue[‖] *HRQOL*: SF-36 (1/8 scale significant); ↓ SF-36: Health transition[‖]
Petajan et al[31] USA (PEDro = 8) *Level 1*	E:21 C:26	3.8±0.3		41.1±2	9.3±1.6	Arm + leg ergometry	~73% HRmax; ~60% $\dot{V}O_2max$	40–50	3	15	↑ $\dot{V}O_2max$ ($mL \cdot kg^{-1} \cdot min^{-1}$)[‡/†]; ↑ Physical work capacity (W/min)[‡/†]; ↑ Total strength (upper + lower extremity)[†]; ↑ KE strength[†]; ↑ Elbow flexion strength[†]; ↑ Shoulder strength (extension + flexion)[†]; ↑ PO	*Fatigue*: ↓ POMS: Fatigue[*] *HRQOL*: POM (2/5 scale significant); ↓ POMS: Depression[*]; ↓ POMS: Anger[*]
Rampello et al[37] Italy (PEDro = 7) *Level 1*	11	3.5		41±8	8±5	Leg ergometry	60%–80% maximum work rate	60	3	8	↑ VO_2peak ($mL \cdot kg^{-1} \cdot min^{-1}$)[‡/†]; ↑ Max work rate (W)[‡/†]; ↑ PO	*Mobility*: ↑ 6MWT: Walking speed (m/min)[*]; ↑ 6MWT: Walking distance (m)[*]; ↑ T25FW (s)[‡†] *Fatigue*: ↔ MFIS *HRQOL*: MSQOL (1/16 scale significant); ↑ Emotional well-being[*]
Romberg et al[92] Finland (PEDro = 9) *Level 1*	E:45 C:46	2.00		43.8±6.3	6±6.5	Resistance therabands: Wk 1–3: Inpatient rehab (5 sessions aerobic; 5 sessions resistance); Wk 4–26: Resistance			5	26	↑ Muscle strength	*HRQOL*: ↔ MSQOL

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Table 2 (*continued*)

	Participant Characteristics					Training Program Characteristics					Outcomes	
Reference	n	EDSS Mean ± SD	Type of MS (n)	Age (y) Mean ± SD	Time Since Diagnosis (y) Mean ± SD	Type	Intensity	Time (min)	Frequency (times/wk)	Duration (wk)	Fitness	Other
						training program (3–4 sessions resistance; 1 session aerobic)						
Romberg et al[50] Finland (PEDro = 9) *Level 1*	E:47 C:48	1–5.5		43.8±6.3	6±6.5	Resistance therabands: Wk 1–3: Inpatient rehab (5 sessions aerobic; 5 sessions resistance); Wk 4–26: Resistance training program (3–4 sessions resistance; 1 session aerobic)	10 exercises with 10–15 reps in 2 sets of circuit		5	26	↑ Max isometric knee torque: Knee flexion (Nm)[‖]; ↑ Upper extremity endurance (maximum no. of reps)[†]	*Mobility*: ↓ 7.62 MWT (s)[‖/†]; ↓ 500 MWT (min)[‖/†]
Schulz et al[39] Germany (PEDro = 9) *Level 1*	E:38 C:29	2.0±1.4 2.5±1.4	RR PP SP	39±9 42±9.5	11.4±1.6	Aerobic bicycle program	60% $\dot{V}O_2$max	30	2	8	↑ Stepwise ergometry test: Max performance (W)[‖]; ↑ Stepwise ergometry test: $\dot{V}O_2$max[‖]; ↑ 30-min endurance test: Workload (W)[‖]; ↑ Aerobic capacity; ↑ PO	*Fatigue*: ↔ MFIS *HRQOL*: Hamburg QOL (3/6 scale significant); ↓ Total[†]; ↓ Social function[†]; ↓Mood[†]
Surakka et al[95] Finland (PEDro = 7) *Level 1*	E:47 C:48	M: 2.9±1.2 F: 2.0±0.8	RR (38) PP (4) SP (5)	M: 45±6 F: 43±6	M: 6±7 F: 6±6	Resistance therabands: Wk 1–3: Inpatient rehab (5 sessions aerobic; 5 sessions resistance); Wk 4–26: Resistance training program (3–4 sessions)	65%–70% HRmax; 10 exercises of 10–15 reps in 2 sets of circuit		5	26	↓F: Fatigue Index (%): Knee extension*; ↑ Muscle strength	
Sutherland et al[84] Australia (PEDro = 5)	E:11 C:11	0–5		47.18±4.75	7±5.59	Wk 1–4: Water aerobics Wk 5–6: Land-based weight training		45	Wk 1–4: 6 Wk 5–6: 5 Wk 7–10: 3	10		*Fatigue*: ↓ POMS-SF: Fatigue[†]; ↑ MSQOL: Energy[†] *HRQOL*: MSQOL (3/

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Table 2 (*continued*)

Reference	n	EDSS Mean ± SD	Type of MS (n)	Age (y) Mean ± SD	Time Since Diagnosis (y) Mean ± SD	Type	Intensity	Time (min)	Frequency (times/wk)	Duration (wk)	Fitness	Other
	Participant Characteristics					Training Program Characteristics					Outcomes	
Level 2						Wk 7–10: Water aerobics						10 scale significant); ↑ Pain†; ↑ Social function†; ↑ Sexual function‡; POMS-SF (2/5 scale significant); ↓ Tension†; ↑ Vigor†
Van Den Berg et al[67] UK (PEDro = 7) *Level 1*	16			30–65		Treadmill training	55%–85% HRmax	30	3	4		*Mobility*: ↓ Immediate group: 10-m timed walk*; ↔ 2-min walk (m) *Fatigue*: ↔ FSS

Abbreviations: BPM, beats/min; BW, body weight; C, control group; CP, chronic progressive; E, experimental group; E1, exercise intervention group 1; E2, exercise intervention group 2; EXT, extension; F, female; FAMS, Functional Assessment of Multiple Sclerosis; FLEX, flexion; FSS, Fatigue Severity Scale; HR, heart rate; KE, knee extension; KF, knee flexion; M, male; MFI, Multidimensional Fatigue Inventory; MFIS, Modified Fatigue Impact Scale; MSIS, Multiple Sclerosis Impact Scale; MSQOL, Multiple Sclerosis Quality of Life; MVC, maximum voluntary contraction; MWT, meter walk test; PO, power output; POMS, Profile of Mood States; PP, primary progressive; QOL, quality of life; reps, repetitions; RPE, rate of perceived exertion; RR, relapsing remitting; RT, resistance training; SF, short form; SF-36, Short-Form Health Survey-36; 6MWT, 6-minute walk test; SP, secondary progressive; 10MWT, 10-meter walk test; THR, target heart rate; TMW, tolerated maximum workload; T25FW, timed 25-foot walk; TUG, Timed Up & Go; $\dot{V}O_2$, aerobic capacity.

* Significant difference pre-post, $P<.05$.

† Significant difference between groups (ie, E vs C).

‡ Significant difference pre-post, $P<.01$.

§ Significance not indicated.

|| Significant difference pre-post, $P<.001$.

Table 3 Data extracted for all nonrandomized trials

Reference	n	Participant Characteristics: EDSS Mean ± SD	Type of MS (n)	Age (y) Mean ± SD	Time Since Diagnosis (y) Mean ± SD	Training Program Characteristics: Type	Intensity	Time (min)	Frequency (times/wk)	Duration (wk)	Outcomes: Fitness	Other
Beer et al[57] Switzerland (D+B=18) *Level 1*	E1:14	6–7.5	RR (2) SP (8) PP (9)	49.7±11	15±8	Robot-assisted gait training		30	5	3	↑ Knee extensor strength (kp)[†/§] ↑ Muscle strength	*Mobility*: ↑ 20-m walking velocity (m/s)[†]; ↑ 6-min walking distance (m)[†]
	E2:15		RR (1) SP (10) PP (5)	51±15.5	15±9	Conventional walking training		30	5	3	↑ Knee extensor strength (kp)[†] ↑ Muscle strength	*Mobility*: ↑ 20-m walking velocity (m/s)*; ↔ 6-min walking distance (m)
Castellano et al[34] USA (D+B=14) *Level 4*	E:8 C:9	0–5.5	RR	40±10		Cycle ergometer	60% V_{O_2}peak	30	3	8	↑ V_{O_2}peak (L/min)*	
Chang et al[59] Taiwan (D+B=13) *Level 4*	7			42.86±13.47		Quadriceps surface FES training while seated (knee at 90° flexion)	25Hz, 200μs, 500ms on/1s off	30	3	8	↔ MVC (kg) ↔ Twitch force (kg)	*Other*: ↑ FI (%)[†]; ↑ CFI (%)* *Fatigue*: ↓ MFIS (score)*
Collett et al[68] UK (D+B=20) *Level 1*	E1:20		RR (8) SP (10) PP (2)	52±8	15±8	Continuous cycling	45% Peak power	20	2	12	↑ Leg power (W) – wk 6+12+24[†] ↑ Peak power on exercise test (W) – wk 24*	*Mobility*: ↑ 2-min walk (m) – wk 6[†]; ↓ TUG (s) – wk 6+24* *HRQOL*: ↑ SF-36 – wk 6–12*
	E2:18		RR (7) SP (8) Unidentified (1)	50±10	11±7	Intermittent cycling	30s ON 30s OFF at 90% peak power					
	E3:17		RR (7)	55±10	12±11	Combined (continuous	10min intermittent					

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Table 3 (*continued*)

Reference	n	EDSS Mean ± SD	Type of MS (n)	Age (y) Mean ± SD	Time Since Diagnosis (y) Mean ± SD	Type	Intensity	Time (min)	Frequency (times/wk)	Duration (wk)	Fitness	Other
			Participant Characteristics			Training Program Characteristics					Outcomes	
			SP (7) PP (3)			+ intermittent) cycling	at 90% peak power, then 10min continuous at 45% peak					
de Souza-Teixeira et al[51] Spain (D+B=16) *Level 4*	13	3.4±1.7	Mild-moderate	43±8		Leg extension machine	3× 10–15 reps at 40%–70% MVC; 2:1 ECC:CON speed; 3min between sets; Minimum 48h between sessions		2	8	↑ MVC (N)†; ↑ Torque (Nm)‡; ↑ Muscular endurance (reps)‡; ↑ Maximal power (W)† ↑ Muscle strength	↓ TUG (s)‡
Fimland et al[52] Norway (D+B=14) *Level 4*	E:7 C:7	4.6±0.4	Mild-moderate	53±4	8±1	Unilateral horizontal leg press and seated calf raises	4 sets, 4 reps; 85%–90% of 1RM; 1–2min between sets; control lower, short pause, maximum CON		5	3	↑ MVC* ↑ Muscle strength	↑ V wave (μV)*
Fragoso et al[82] Brazil (D+B=17) *Level 4*	9	1.89	RR (8) SP (1)	35.44		Stretching (cervical region, limbs, trunk); Repetitive series with light weight; Conditioning with walks and short run periods	1kg/arm 2kg/leg	60–90	3	20		*Fatigue*: ↓ Chalder's score†
Freeman et al[71] UK (D+B=16) *Level 4*	10	5		50±11.9	16±11.5	Standing and floor exercises; Stretches with core stability focus		60	1	10		*Mobility*: ↑ 6-min walk test (m)*; ↑ 6-min walk test (m/min)*; *Fatigue*: FIS (1/3 scale significant); ↓ Physical component*

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Table 3 (*continued*)

Reference	n	EDSS Mean ± SD	Type of MS (n)	Age (y) Mean ± SD	Time Since Diagnosis (y) Mean ± SD	Type	Intensity	Time (min)	Frequency (times/wk)	Duration (wk)	Fitness	Other
												HRQOL: MSIS (1/2 scale significant); ↓ Motor component†
Freeman et al[79] UK (D+B=13) *Level 4*	8		PP (5) RR (3)	47.88	7.38	Core stability training sessions; Home core stability exercise program	Each exercise had 2–3 levels of difficulty (individualized)	30 15	2 7	8		↓ 10-m timed walk (s)*; ↓TUG (s)*
Gehlsen et al[58] USA (D+B=12) *Level 4*	10		Remissive	40.2		Freestyle swimming; Shallow water calisthenics	60%–75% MHR	60	3	10	↑Peak torque (Nm): EXT-pre-mid trial*; ↑ Upper extremity force (N)*; ↑ Upper extremity work (Nm)*; ↑ Upper extremity power (Nm/s)*; ↑ Cybex II: Total work (Nm)*; ↓ Cybex II: Fatigue (% decline force)*; ↑Swim bench: Total work (Nm)*	
Hayes et al[56] USA (D+B=19) *Level 4*	E:9 C:10	5.33±1		48±11.9	149.9± 113.8mo	High-intensity lower extremity eccentric ergometric (Eccentron) resistance exercise	"Very, very light" (7/10) "Somewhat hard" (13/20)	45–60	3	12	↑ Knee flexion strength left Leg (kg)*; ↑ Knee extension strength left Leg†; ↔ Hip strength (kg); ↔ Ankle strength (kg); ↔ SUM strength (kg); ↑ Muscle strength	*Mobility*: ↔ TUG (s); ↔ TMWSS (m/s); ↔ TMWMP (m/s); ↔ 6 MWT (m) *Fatigue*: ↔ FSS

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Table 3 (*continued*)

	Participant Characteristics					Training Program Characteristics					Outcomes	
Reference	n	EDSS Mean ± SD	Type of MS (n)	Age (y) Mean ± SD	Time Since Diagnosis (y) Mean ± SD	Type	Intensity	Time (min)	Frequency (times/wk)	Duration (wk)	Fitness	Other
Kent-Braun et al[60] USA (D+B=16) *Level 4*	6	2.5–8		46.2±5.2		Electrically stimulated endurance dorsiflexion (electrode on tibialis anterior)	50-Hz tetanic contractions, 25% duty cycle; pulse width 300μs; Stimulator force: 65%–85% maximum tetanic force; Duty cycle: 2s contract: 6–8s relax	60 (2× 30)	6	8	↔ Tetanic force; ↔ Preexercise tetanic tension; ↔ Postexercise tetanic tension (% initial), ↔ CMAP (mV, % initial)	
Kileff et al[69] UK (D+B=15) *Level 4*	6	4–6		45		Cycling on static bike	Maximum level of exertion (60%–80% working HR)	30	2	12		*Mobility*: ↑ 6-min walk (m)*; ↔ 10-m walk (steps/m) *Fatigue*: ↔ Fatigue
Konecny et al[42] Czech Republic (D+B=18) *Level 4*	15	2.8±0.7	PP (1) SP (5) RR (9)	50.7±13.1	15.4±14.4	Aerobic phase; Resistance training (bench press, pulldown, leg EXT)	30%–60% of 1RM with weekly increase of 10%; 3–5 sets of 10	60–90	2	8	W_{sl} (W)*; W_{sl}/kg (W/kg)*; $\dot{V}O_{2SL}$ (mL O_2)*; 1RM: Bench/pulldown/ leg extension (kg)‡; ↑ Muscles strength; ↑ Power output	*Fatigue*: ↓ MFIS*; ↓ MFIS: Physical*
Lo et al[72] USA (D+B=15) *Level 1*	E1:6	5±1.6	RR (3) PP (3)	50.2±11.4		BWSTT alone followed by BWSTT with robot-driven gait orthotic	30%–40% body weight supported + initial treadmill speed 1.5km/h	40	2	3+6 washout +3 crossover		*Mobility*: ↓ T25FW (s)*; ↔ 6 MWT (m)* *Mobility*: ↓ T25FW (s)*; ↑ 6 MWT (m)*
	E2:7	4.9±0.9	RR (5) PP (2)	49.6±11.8		BWSTT with robot-driven gait orthotic followed by BWSTT alone						
McAuley et al[91] Illinois (D+B=15) *Level 4*	E:9 C:6		RR (24) SP (1) PP (1)	43.46±7.6	106.73± 77.05mo	Aerobic exercise (ie, treadmills/stationary cycles/elliptical trainers)	50% of age-predicted maximum HR	60	3	12		*HRQOL*: ↓ Mental health status§; ↑ Satisfaction with life§

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Table 3 (*continued*)

Reference	n	EDSS (Mean ± SD)	Type of MS (n)	Age (y) (Mean ± SD)	Time Since Diagnosis (y) (Mean ± SD)	Type	Intensity	Time (min)	Frequency (times/wk)	Duration (wk)	Fitness	Other
	Participant Characteristics					Training Program Characteristics					Outcomes	
Perez et al[53] Spain (D+B=14) *Level 4*	24	1.5	SP	44.4±9.5	8.17±8.3	Resistance training (calisthenic/body weight exercises)	Based on participant's performance (1–2 sets/session)	60	3	6	↑ Abdominal repetitions‡; ↑ Back muscle repetitions‡; ↑ Leg lift repetitions*; ↑ Medicine ball over head (cm)‡; ↔ Vertical jump (cm); ↑ Muscle strength	
Pilutti et al[76] Canada (D+B=16) *Level 4*	6	6.9±1.07	PP (5) SP (1)	48.2±9.3	11.5±6.6	BWSTT	Individualized and changed based on progress	30 (2× 15) 2–5min rest	3	12		*Mobility*: ↑ Walking speed (km/h)‡; ↔ T25FW (s) *Fatigue*: ↔ MFIS *HRQOL*: MSQOL (5/12 scale significant); ↑ Emotional well-being*; ↑ Energy†; ↑ Health distress*; ↑ Physical health composite*; ↑ Mental health composite†
Ponichtera-Mulcare et al[40] USA (D+B=11) *Level 2*	E1:11	1.91±0.63	Ambulatory	41±5		Leg and arm ergometer	55%–60% $\dot{V}O_2$max; 65%–75% age-predicted MHR	30	3	24	↑ Ambulatory group: $\dot{V}O_2$max (L/min)§	
	E2:8	5.81±0.75	Semiambulatory	46±14			55%–60% $\dot{V}O_2$max; 65%–75% age-predicted MHR					

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Table 3 (*continued*)

	Participant Characteristics					Training Program Characteristics					Outcomes	
		EDSS		Age (y)	Time Since Diagnosis (y)							
Reference	n	Mean ± SD	Type of MS (n)	Mean ± SD	Mean ± SD	Type	Intensity	Time (min)	Fre-quency (times/ wk)	Duration (wk)	Fitness	Other
	C:4											
Rodgers et al[38] USA (D+B=14) *Level 4*	18	3.6±2.1		43.2±10.8		Arm/leg ergometer	65%–70% MHR	30	3	24	↑ $\dot{V}O_2max$*	
Roehrs et al[85] USA (D+B=14) *Level 4*	19	M: 52.7±9.1 F: 50.4±10.8	PP SP	M: 40–65 F: 39–71		Aquatic exercise (pool at 83°–85°F)		60	2	12		*HRQOL*: MSQLI (2/9 scale significant) ↑ MFIS*; ↑ Modified Social Support Survey*; SF-36 (1/1 scale significant); ↑ Social function*
Sabapathy et al[70] Australia (D+B=17) *Level 4*	16		RR (10) SP (3) PP (3)	55±7	10±10	Resistance intervention: 3 upper + 3 lower body + 1 core + 1 stability exercise Aerobic intervention: 8 exercise stations (arm crank, step-ups, upright cycle, recumbent cycle, cross-trainer, treadmill walk)	2–3 sets of 6–10 reps/ex/set; Borg Category Ratio Scale of 3–5 (moderate-hard) 5min ex/station with 2min rest after 2 stations; Borg Category Scale of 3–5 (moderate-hard)		2	8	↔ Grip strength (kg)	*Mobility*: ↓ Get Up and Go (s)†; ↑ 6-min walk test (m) *Fatigue*: MFIS (2/3 scale significant); ↓ MFIS: Physical scale*; ↓ MFIS: Psychological scale† *HRQOL*: ↔ SF-36; MSIS (1/2 scale significant); ↓ MSIS: Physical score*
Salem et al[77] USA (D+B=15) *Level 4*	10			55.9±9.12	13.7±8.64	Aquatic exercise program: Aerobics, strengthening, balance, walking, etc		60	2	5	↑ Grip strength	*Mobility*: ↑ 10-m walking test (cm/s)*; ↓TUG (s)‡

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Table 3 (*continued*)

		Participant Characteristics				Training Program Characteristics					Outcomes	
		EDSS		Age (y)	Time Since Diagnosis (y)							
Reference	n	Mean ± SD	Type of MS (n)	Mean ± SD	Mean ± SD	Type	Intensity	Time (min)	Fre-quency (times/wk)	Duration (wk)	Fitness	Other
Salem et al[78] USA (D+B=13) *Level 4*	10			55.4±11.04	16.2±14.49	Aquatic exercise program: Aerobics, strengthening, balance, walking, etc.		60	8	8	↑ Grip strength	*Mobility*: ↑ 10m Walking Test (cm/s)‡; ↓ Get Up and Go Test (s)* *Fatigue*: ↓ MFIS*
Szecsi et al[61] Germany (D+B= 17) *Level 4*	8	6.45±1.12		50.92±6.91	15.25±8.18	FES cycling	Maximum resistance that a participant could perform 12–18min without exhaustion	~25	3	2	↑ Power output prestimulation*; ↔ Knee muscle strength	*Mobility*: ↔ 10-m walk test
Taylor et al[54] Australia (D+B=17) *Level 4*	8		Mild-moderate	45.6±10.7	6±4.1	Progressive resistance program using weight machines: Latissimus dorsi pulldown, seated arm press, seated row, seated leg press, knee extension, calf raises	60%–80% of 1RM; 2 sets of 10–12 reps/exercise with 2min rest between sets	60	2	14	↑ Training load (12RM)*; ↑ 1RM-leg/arm press (kg)†; ↑ Leg press endurance (reps)†; ↔ Arm press endurance (reps); ↑ Muscle strength	*Mobility*: ↑ Fastest walking speed (m/s)*; ↔ Self-selected walking speed (m/s); ↔ 2-min walk (m) *HRQOL*: MSIS-29 (1/2 scale significant); ↓ Physical impact*
Velikonja et al[86] Slovenia (D+B=14) *Level 4*	20	4	RR PP SP	Median: 42		Sport climbing	90° incline		1	10		*Fatigue*: MFIS (3/4 scale significant); ↓ Total*; ↓ Cognitive*; ↓ Psychological*
		4.2	RR PP SP	Median: 41		Hatha yoga			1	10		*Fatigue*: MFIS (0/4 scale significant); ↔ Total; ↔ Cognitive; ↔ Psychological

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Table 3 (*continued*)

	Participant Characteristics					Training Program Characteristics					Outcomes	
		EDSS	Type of	Age (y)	Time Since Diagnosis (y)				Fre-quency			
Reference	n	Mean ± SD	MS (n)	Mean ± SD	Mean ± SD	Type	Intensity	Time (min)	(times/ wk)	Duration (wk)	Fitness	Other
White et al[74] USA (D+B=16) *Level 4*	8	3.7±0.8		46±12		Lower body resistance (knee flexion/ extension, plantar flexor, spinal flexion/ extension)	1 set, 8–15 reps at 50%–70% MVC; 48h rest between sessions	30	2	8	↑ Isometric strength: Knee extension*; ↑ Isometric strength: Plantar flexion*;	*Mobility*: ↔ Walking speed 25ft (s) *Fatigue*: ↓ MFIS*
White et al[55] USA (D+B=15) Level 4	12	4±1.37		47.3±4.7		Lower body resistance (knee flexion/ extension, plantar flexor, spinal flexion/ extension)	1 set, 8–15 reps at 50%–70% MVC; 48h rest between sessions	30	2	8	↑ Static strength: Knee extension*; ↑ Static strength: Ankle flexion*;	*Fatigue*: ↓ MFIS*
Wier et al[87] USA (D+B=13) *Level 4*	E:6 C:7	5.3±1.3	RRSP (8) PP (5)	50.2±11.4		BWSTT with robotic assistance followed by BWSTT alone (R-T)		40	2	2 blocks of 6 biweekly sessions; 6-wk washout between blocks		*Fatigue*: ↔ FSS, ↔ MFIS *HRQOL*: (3/10 scale significant); ↑ Physical component*/§; ↑ Perceived Deficits Questionnaire*; ↑ Life satisfaction* *Other*: ↑ Pain Effects Scale*

Abbreviations: BWSTT, body weight–supported treadmill training; C, control group; CFI, Central Fatigue Index; CMAP, compound muscle action potential; CON, concentric; D+B, Downs and Black; E, experimental group; ECC, eccentric; EXT, extension; FI, General Fatigue Index; FIS, Fatigue Impact Scale; HR, heart rate; kp, kilopounds; FSS, Fatigue Severity Scale; MFIS, Modified Fatigue Impact Scale; MHR, maximum heart rate; MSIS, Multiple Sclerosis Impact Scale; MSQLI, Multiple Sclerosis Quality of Life Inventory; MSQOL, Multiple Sclerosis Quality of Life; MVC, maximum voluntary contraction; MWT, meter walk test; PP, primary progressive; reps, repetitions; RR, relapsing remitting; RRSP, relapsing remitting/secondary progressive; SF-36, Short-Form Health Survey-36; SP, secondary progressive; TMWMP, 10-meter walk maximal pace; TMWSS, 10-meter walk self-selected; T25FW, timed-25-foot walk; TUG, Timed Up & Go; $\dot{V}O_2$, aerobic capacity; W_{sl}, watts-symptom limited.

* Significant difference pre-post, $P<.05$.

† Significant difference pre-post, $P<.01$.

‡ Significant difference pre-post, $P<.001$.

§ Significant difference between groups (ie, E vs C).

Table 4 Summary of studies and evidence for aerobic fitness outcomes

Fitness Component	Outcome	No. of Studies	Description of Studies	Summary of Evidence
Physical Capacity		11		
	Aerobic capacity		Aerobic Exercise Training Programs: These 7 studies (4 RCTs,[31,36,37,39] median PEDro = 7.5; 3 non-RCTs,[34,38,40] median D&B = 14) included 200 participants from Europe and the U.S. Studies involved leg cycling ergometry alone or in combination with arm cycling ergometry for the duration of 4–24wk.	There is level 1 evidence[31,36,37,39] that training 2–3 times/wk, 30–60min at intensities that ranged from 60%–80% maximum work rate or 60% $\dot{V}O_2$max increases VO_2peak. VO_2peak also increased significantly in all 3 studies with level 4 evidence.[34,38,40]
			Other Exercise Programs: These 2 RCTs[33,35] (median PEDro = 6) included 36 participants from Iceland and Iran. Both studies involved combined aerobic and resistance training, and one further included stretching and relaxation.	A significant increase in VO_2peak was seen in 1 of the level 1 studies[33] with training 3 times/wk, 60min, at an intensity of 33%–55% $\dot{V}O_2$max for 5wk. No significant change in aerobic capacity was reported in the other level 2 study.[35]
	Power output		Aerobic Exercise Training Programs: These 4 RCTs[31,36,37,39] (median PEDro = 7.5) involved 166 participants from Europe and the U.S. Exercise programs involved leg cycling ergometry alone or in combination with arm cycling ergometry for 5–15wk.	There is level 1 evidence[31,36,37,39] indicating significant increases in PO after 2–5 times/wk of training, 30–50min, at an intensity of 60% $\dot{V}O_2$max or anaerobic threshold.
			Other Exercise Programs: Two studies[41,42] (RCT, PEDro = 8; non-RCT, D&B = 18) involved 48 participants from Turkey and the Czech Republic in combined exercise programs for the duration of 8wk.	Level 1 evidence[41] indicated a significant improvement in PO with twice-weekly (60min) resistance training cycling combined with lower extremity plyometric and balance exercises. Level 4 evidence[42] revealed a significant increase in PO with 60min, 2 times/wk of combined aerobic training (at aerobic threshold) and resistance training (30%–60% of 1RM) in combination with relaxation.

NOTE. D&B score, out of a possible 28 points.
Abbreviations: D&B, Downs and Black; PO, power output.

improvements are associated with gains in lean mass, such changes can have benefits for bone health and metabolism.[44,45] Twenty reports of 18 studies that met systematic review criteria examined the efficacy of various exercise-training protocols for improving muscular strength. These protocols included resistance training of various types (weight machines, free weights, resistance bands) and other, less traditional forms of strength training (specialized locomotor training, cycling with or without electrical stimulations, aquatics). Overall, there is consistent evidence for beneficial effects of exercise training for improving muscular strength. The results are summarized in table 5 and described below.

Five reports[32,46-49] of 4 RCTs provide level 1 evidence that 8 to 20 weeks of supervised resistance training performed 2 to 3 times per week at an intensity of 10 to 12 repetitions maximum (RM) (~70%–80% of 1RM) increased muscle strength. A home-based resistance training RCT (level 1)[50] indicated that resistance bands are effective for increasing upper but not lower extremity strength, as well as increasing lower extremity fatigue resistance. Supporting evidence from other studies[51-55] with level 4 evidence suggests training frequencies from 2 to 3 times per week at intensities ranging from 10 to 15RM (60%–80% of 1RM) may result in significant strength increases.

In terms of less traditional forms of strength training, there is 1 RCT[31] with level 1 evidence that demonstrates that combined arm/leg cycling (3 times/wk for 15wk at 30% to 60% $\dot{V}O_2$max) is effective for increasing muscle strength. There is supporting evidence (level 4)[42,56-58] that alternative forms of training such as leg cycling, robotic-assisted treadmill training, combined aerobic and resistance training, or swimming/water calisthenics performed 2 to 3 times per week for 8 to 12 weeks at moderate intensities might be effective in increasing muscle strength. Three studies[59-61] with level 4 evidence used functional electrical stimulation (FES)-assisted cycling as a training intervention, but the efficacy for increasing strength is not as clear for this training modality.

Mobility

Walking impairment is one of the most common and life-altering features in MS[62] and is often used to track disease progression over time.[63] Walking impairment is most commonly assessed with performance measures such as the 6-minute walk, the Timed 25-Foot Walk, and the Timed Up & Go tests. These measures reflect walking endurance, speed, and agility, respectively. Exercise-induced increases in aerobic capacity and muscular

Table 5 Summary of studies and evidence for muscle strength outcomes

Fitness Component	No. of Studies	Description of Studies	Summary of Evidence
Muscle Strength	20 reports of 18 studies	Traditional Resistance Training: Twelve reports (5 RCTs,[32,46,47,49,50,95,96] median PEDro=8; 5 non-RCTs,[51-55] median D&B=16) included 406 participants from 10 countries and 3 continents. Resistance training was performed using weight machines, free weights, or resistance bands.	Five reports of 4 RCTs[32,46,47,49,96] with level 1 evidence indicated that 8–20wk of supervised resistance training performed 2–3 times/wk at moderate intensity significantly increases muscle strength. Evidence from level 4 studies[51-55] support these findings. Two reports of 1 RCT[50-95] with level 1 evidence indicate that home-based training using resistance bands significantly increases upper extremity strength and lower extremity fatigue resistance.
		Other Forms of Resistance Training: Eight studies, (1 RCT,[31] PEDro=8; 8 non-RCTs,[42,56-61] median D&B=16.5) from Europe and the U.S. included 195 participants who engaged in a variety of activities including aerobic training, combined aerobic and resistance training, and other forms of physical activity (eg, robotic-assisted treadmill training, swimming).	Level 1 evidence from 1 RCT[31] indicates that arm/leg cycling (3 times/wk, 60% maximum, 15wk) increases muscle strength. Level 4 evidence suggests that leg cycling,[56] robotic-assisted treadmill training,[57] combined aerobic and resistance training,[42] or swimming/water calisthenics[58] performed 2–3 times/wk for 8–12wk at moderate intensities may increase muscle strength. There is no evidence that electrical stimulation-assisted cycling is effective for increasing strength.

NOTE. D&B score, out of a possible 28 points.
Abbreviation: D&B, Downs and Black.

strength may be expected to translate into improved walking performance in people with MS.[64] Twenty-five studies[32,37,41,47,50,51,54,56,57,61,65-79] that met systematic review criteria evaluated the effects of exercise training on outcomes of mobility. These protocols included aerobic exercise (arm/leg cycling, treadmill walking, home-based walking, recumbent stepping), resistance training (weight machines, free weights, resistance bands, plyometrics), combined aerobic and resistance training, and a variety of other forms of physical activity (body weight–supported treadmill training, aquatic exercise, FES cycling, balance and stability training). The evidence from these trials is summarized in table 6, and a comprehensive description is provided as supplemental material (available online only at the Archives website, http://www.archives-pmr.org/). Briefly, there is promising evidence that some types of exercise training (aerobic training, resistance training, or a combination of both) may improve walking endurance and speed. Although this evidence suggests promise, it is insufficient to definitively determine minimal dose. The evidence is less clear, however, regarding the benefits of exercise training for walking agility.

Fatigue

Fatigue is the most common and debilitating symptom of MS and has a significant impact on virtually all aspects of an individual's daily functioning. It typically is measured through self-report questionnaires.[80] Measures included in this review are the Fatigue Severity Scale, Fatigue Impact Scale, Modified Fatigue Index Scale, Short-Form Health Survey-36 vitality subscale, Profile of Mood States energy and fatigue subscales, and Multiple Sclerosis Quality of Life-54 energy subscale. Thirty studies[31,33,36,37,39,41,42,48,55,56,59,65-71,74-78,81-87] that met the systematic review criteria used at least 1 of these measures to evaluate the impact of various forms of exercise training on fatigue. These protocols included aerobic exercise (arm/leg cycling), resistance training (weight machines, free weights, resistance bands), combined aerobic and resistance training, and a variety of other forms of physical activity (sport, yoga, body weight–supported treadmill training, aquatic exercise, FES cycling, Pilates). The evidence from these studies is summarized in table 7. A comprehensive description is provided as supplemental material (available online only at the Archives website, http://www.archives-pmr.org/). Overall, the evidence regarding exercise training on symptomatic fatigue was inconsistent; although some types of exercise training are promising, there are insufficient data for determining an optimal dose. Interventions including a resistance-training component, in particular, may be most effective for fatigue reduction.

Health-related quality of life

There is consistent evidence that HRQOL is compromised among persons with MS compared with the general population and with persons with other chronic disease conditions.[3,88,89] This reduction in HRQOL is associated with many aspects of MS, including a diagnosis in the most productive years of one's life, the unpredictable and unstable nature of the disease course, and the absence of a convincing disease-modifying therapy.[3] Importantly, physical activity might be associated with improved HRQOL in persons with MS by improving fatigue, depression, self-efficacy, social support, and disability status.[90] In the MS population, HRQOL is generally measured using self-report measures. Twenty-one studies[31,33,36,37,39,41,48,54,65,68,70,71,75,76,81,83-85,87,91,92] met the systematic review criteria and included at least 1 measure that evaluated the impact of various forms of exercise training on HRQOL. Many studies included multiple indicators of HRQOL from the

Table 6 Summary of studies and evidence for mobility outcomes

Outcome	No. of Studies	Description of Studies	Summary of Evidence
Walking	25		
Walking endurance		Aerobic Exercise Training Programs: These 8 studies (4 RCTs,[37,65-67] median PEDro=7; 4 non-RCTs,[56,68-70] median D&B=18) included 156 participants from Australia, Europe, the UK, and the U.S. in aerobic exercise programs.	There is level 1 evidence from 2 RCTs[37,65] that 45—60min of aerobic exercise 3 times/wk for 3—8wk significantly improves walking endurance. The other 2 RCTs[66,67] (level 1 evidence) did not report an improvement in walking endurance after a home-based walking program (3 times/wk, 30min, 12wk). Three studies[68-70] with level 4 evidence observed a significant improvement in walking endurance after aerobic exercise (2 times/wk, 8—12wk).
		Resistance Exercise Training Programs: These 3 studies (1 RCT,[47] PEDro=9; 2 non-RCTs,[54,70] mean D&B=17) involved 55 individuals from Australia and Denmark in resistance exercise.	There is level 1 evidence[47] that progressive resistance training (2 times/wk, 12wk) improves walking endurance. Level 4 evidence is conflicting; 1 study[70] showed an improvement in walking endurance after full-body resistance training (2 times/wk, 8wk, RPE=3—5), and the other study[54] showed no significant change after progressive lower extremity resistance training (2 times/wk, 10wk, 60%—80% of 1RM).
		Other Exercise Programs: Five studies (1 RCT,[50] PEDro=9; 4 non-RCTs,[56,57,71,72] D&B=17) involved 142 participants from Europe, the UK, and the U.S. in combined aerobic and resistance training, supported treadmill walking, and group exercise programs.	The single study[50] with level 1 evidence reported a significant improvement in walking endurance after twice-weekly combined aerobic and resistance training (26wk, 10—15 repetitions). Level 4 evidence from 3 of 4[56,57,72] studies supports the benefit of alternative modes of exercise (BWSTT, RAGT, group exercise classes) to improve walking endurance, but optimal exercise prescription is unclear.
Walking speed		Aerobic Exercise Training Programs: These 4 studies (2 RCTs,[67,73] mean PEDro=6.5; 2 non-RCTs,[56,69] mean D&B=15) included 42 participants from the UK and the U.S. in aerobic exercise programs.	One of the 2 RCTs (level 1)[67] reported a significant improvement in walking speed after treadmill walking (30min, 3 times/wk, 4wk, 55%—85% HRmax). The other RCT[73] reported no significant change in walking speed after home-based walking (20min, 7 times/wk, 4wk). Level 4 evidence[56,69] does not support a beneficial effect of aerobic training on walking speed.
		Resistance Exercise Training Programs: These 3 studies (1 RCT,[47] PEDro=9; 2 non-RCTs,[54,74] mean D&B=16.5) involved 72 individuals from Australia, Europe, and the U.S. in resistance exercise.	There is level 1 evidence from 1 RCT[47] that 12wk of progressive resistance training (2 times/wk) significantly increases walking speed. Level 4 evidence from 1 study[54] (2 times/wk, 10wk) supports these results. The other study[74] with level 4 evidence does not support the effects of progressive lower extremity resistance training (2 times/wk, 8wk) on walking speed.
		Other Exercise Programs: Eleven studies (3 RCTs,[41,50,75] median PEDro=8; 8 non-RCTs,[56,57,61,71,72,76-78] median D&B=16) involved 250 participants from Canada, Europe, the UK, and the U.S. in combined aerobic and resistance training, BWSTT, FES cycling, stability training, and group exercise programs.	Level 1 evidence from 3 RCTs[41,50,75] reported a significant improvement in walking speed after combined exercise interventions using various modalities and prescriptions. There is supporting level 4 evidence from 5[57,71,72,77,78] of 8 studies for the effect of alternative exercise interventions on walking speed.
Timed Up & Go		Aerobic Exercise Training Programs: Three non-RCTs[56,68,70] (median D&B=19) included 81 participants from Australia, the UK, and the U.S. in aerobic exercise programs.	There is level 4 evidence from 2 of 3[60,68] studies that TUG performance improves after moderate-intensity cycling or aerobic circuit training (2 times/wk, 8—12wk).

(*continued on next page*)

Table 6 (*continued*)

Outcome	No. of Studies	Description of Studies	Summary of Evidence
		Resistance Exercise Training Programs: These 3 studies (1 RCT,[32] PEDro = 8; 2 non-RCTs,[51,70] mean D&B = 16.5) included 65 participants from Australia, Europe, and the U.S. in resistance training exercise for 8–12wk in duration.	There is no level 1 evidence to support the benefit of resistance training on TUG performance; however, there is level 4 evidence from 2 non-RCTs[51,70] that resistance training (2 times/wk, 8wk) improves TUG performance.
		Other Exercise Programs: These 5 studies (1 RCT,[41] PEDro = 8; 4 non-RCTs,[56,77-79] median D&B = 14) included 70 participants from Turkey, the UK, and the U.S. in combined aerobic and resistance exercise, stability and aquatic exercise programs.	Level 1 evidence from 1 RCT[41] supported combined aerobic, lower extremity exercise and balance training to improve TUG performance (2 times/wk, 8wk). Three[77-79] of the 4 studies with level 4 evidence also supported improved TUG performance after twice-weekly group exercise classes (stability and aquatic, 5–8wk).

NOTE. Walking speed measures included timed 25-foot walk (T25FW), timed 10-m walk (T10MW), timed 20-m walk (T20MW), and walking velocity over a 14-m distance. Walking endurance measures included 2-minute walk test (2MWT), 6-minute walk test (6MWT), 500-m walk (500MW), and maximum walking distance.
Abbreviations: BWSTT, body weight–supported treadmill training; D&B, Downs and Black; HRmax, maximum heart rate; RAGT, robot-assisted gait training; RPE, rate of perceived exertion; TUG, Timed Up & Go.

following scales: the Short-Form Health Survey-36, the Multiple Sclerosis Quality of Life-54, the Multiple Sclerosis Impact Scale, the Hamburg Quality of Life Questionnaire in Multiple Sclerosis, and the Multiple Sclerosis Quality of Life Inventory. These protocols included aerobic exercise (arm/leg cycling), resistance training (weight machines, free weights, resistance bands), combined aerobic and resistance training, and a variety of other forms of physical activity (sport, yoga, body weight–supported treadmill training, aquatic exercise). The evidence from these studies is summarized in table 8. A comprehensive description is provided as supplemental material (available online only at the Archives website, http://www.archives-pmr.org/). Overall, the current evidence is insufficient to generate conclusions regarding the effects of exercise training on HRQOL outcomes in persons with MS.

Discussion

The purpose of this review was to examine the evidence regarding exercise training for improving fitness, mobility, fatigue, and HRQOL outcomes as a basis for developing evidence-informed physical activity guidelines for adults with MS. Approximately half of the studies identified were RCTs of good quality (ie, level 1); the remaining trials were of low quality (ie, level 4). There was consistent and strong evidence that aerobic and resistance exercise performed 2 times per week at a moderate intensity increases physical capacity and muscular strength, respectively. While the evidence supporting the benefits of exercise on mobility and fatigue is promising, there is insufficient evidence to definitively establish the prescriptive amounts, intensities, or types of exercise to improve these outcomes. There is not enough good-quality evidence to date supporting the benefits of exercise for improving HRQOL outcomes. Below we consider the evidence for each of these outcomes and highlight directions to further expand and improve the quality of research in this area. A companion article included in this issue provides a comprehensive discussion of the implication of the systematic review findings for the development of physical activity guidelines for adults with MS.[93]

Fitness outcomes

Based on findings from several studies with level 1 evidence and supporting research with level 4 evidence, we conclude that 30 to 60 minutes of moderate-intensity aerobic training performed at least 2 to 3 times per week improves physical capacity and that resistance training performed 2 to 3 times per week at a moderate intensity increases muscular strength. These findings are entirely consistent with the results of an earlier review by Dalgas et al[22] that included fewer studies (n = 23) but similar fitness outcomes as in the current, broader systematic review of 54 studies.

Most of the studies reviewed used traditional forms of exercise training. Studies examining alternative forms of exercise (eg, aquatics) provide some evidence that these forms of training might be effective for increasing physical capacity and muscular strength. However, this evidence is generally low quality. This highlights the need for high-quality RCTs that investigate more diverse types of exercise training. Indeed, the scope of exercise modalities investigated overall was quite limited. The only mode of aerobic exercise used in the high-quality RCTs was leg cycling ergometry alone or in combination with arm cycling ergometry. There was a general lack of studies using treadmill walking, for example, as a modality for increasing physical capacity. Because

Table 7 Summary of studies and evidence for fatigue outcomes (only those studies that used the SF-36 vitality, POMS energy and fatigue, MSQOL energy, FSS, MFIS)

Outcome	No. of Studies	Description of Studies	Summary of Evidence
Fatigue	30		
		Aerobic Exercise Training Programs: Thirteen studies (9 RCTs,[31,36,37,39,65-67,75,81] PEDro=7; 4 non-RCTs,[56,68-70] D&B=18) included 431 participants, from Europe, Switzerland, the U.S., Australia, and Turkey who participated in aerobic exercise programs.	Three RCTs[31,37,81] with level 1 evidence reported significant improvements in some general fatigue symptoms but not specific symptoms after 2–6mo of light to moderate cycling for 40–60min 3 times/wk or until fatigue. One non-RCT with level 4 evidence[70] reported significant decreases in general, physical, and psychological fatigue symptoms after 8wk of moderate-intensity aerobic activities 2 times/wk. The remaining studies with level 1[36,39,65-67,75] and level 4[56,68,69] evidence did not indicate significant change (positive or negative).
		Traditional Resistance Training: Four studies (1 RCT,[48] PEDro=8; 3 non-RCT,[55,70,74] PEDro=16) included 67 participants from Denmark, the U.S., and Australia engaged in resistance training using weight machines, free weights, or resistance bands.	One RCT[48] with level 1 evidence reported significant improvements in general symptomatic fatigue after a 12-wk, 2 times/wk resistance training program (8–15RM). Three level 4 studies[55,70,74] reported decreased fatigue overall or specifically physical and psychological fatigue after 8wk of moderate-intensity resistance training 2 times/wk (6–15RM).
		Combined Training Programs: These 5 studies (2 RCTs,[33,41] PEDro=7.5; 3 non-RCTs,[42,56,82] D&B=17) involved 92 participants from the U.S., Iceland, Turkey, Brazil, and the Czech Republic who participated in both aerobic and resistance training exercise programs.	Two RCTs[33,41] with level 1 evidence reported a significant increase in vitality or decrease in fatigue severity after 5–8wk of supervised aerobic and resistance training performed at moderate to high intensity. Three non-RCTs[42,56,82] with level 4 evidence reported significant improvements in fatigue symptoms or severity after 8–10wk of 2–3 times/wk combined training.
		Other Types of Exercise: Eleven studies (3 RCTs,[81,83,84] PEDro=7; 8 non-RCTs,[59,71,76-78,85-87] D&B=14) involving 178 participants from Canada, the U.S., Europe, Australia, and Taiwan used a variety of exercise modalities including sport, yoga, body weight support treadmill training, aquatic exercise, FES cycling, and Pilates.	Ten of 11 studies (level 1, n=2[81,83]; level 2, n=1[84]; level 4, n=7[59,71,76,77,85-87]) reported a significant decrease on at least 1 indicator of fatigue (general or specific symptoms). RCTs with level 1 evidence included a mixed activity program (volleyball and other aerobic activities[83]) or a yoga program 2–3 times/wk for 40–90min at light to moderate intensity for 12–24wk.[81] One RCT with level 2 evidence included 10wk of aquatic exercise 45min/session 3–5 times/wk.[84] Seven non-RCTs[59,71,76,77,85-87] with level 4 evidence included a range of activities 1–3 times/wk for 5–12wk often performed at individualized intensities.

NOTE. D&B score, out of a possible 28 points.
Abbreviations: D&B, Downs and Black; FSS, Fatigue Severity Scale; MFIS, Modified Fatigue Impact Scale; MSQOL, Multiple Sclerosis Quality of Life; POMS, Profile of Mood States; SF-36, Short-Form Health Survey-36.

walking has been reported as the most common type of physical activity self-selected by persons with MS,[94] future research should focus on evaluating the effects of this training modality.

Our review further underscores the importance of 2 fundamental training principles for optimizing fitness: training progression and training volume. The importance of progression becomes clear when comparing the results of trials that used supervised versus unsupervised strength-training protocols. Whereas 2 reports of a single home-based resistance training RCT[50,95] with level 1 evidence indicated that this modality of exercise did elicit some improvements in strength, the benefits were not comparable to those reported in RCTs of supervised training.[32,46,47,49,96] Perhaps in an unsupervised environment such as the home, individuals are less likely to modify training programs to ensure adequate workload progression, which is essential for adaptation. Training volume is an important consideration as well. Studies with a short training period (<8wk) were effective if the volume of training increased beyond 3 sessions per week.[36,52,57,73] Evidently several bouts of training per week can be tolerated by adults with MS; however, for training effects to be maintained, ongoing participation must be emphasized.

Mobility, fatigue, and HRQOL outcomes

We considered outcomes beyond standard indicators of physical fitness including measures of mobility, fatigue, and HRQOL. Whereas other reviews have examined the impact of exercise on each of these outcomes separately, only 1 published review[97] of 11 RCTs has examined fitness, mobility, fatigue, and HRQOL outcomes simultaneously. Given that the current review was

Table 8 Summary of studies and evidence for HRQOL outcomes

Outcome	No. of Studies	Description of Studies	Summary of Evidence
HRQOL	21		
		Aerobic Exercise Training Programs: Ten studies (7 RCTs,[31,36,37,39,65,75,81] median PEDro=7.5; 3 non-RCTs,[68,70,91] median D&B=17) included 403 participants from Europe, the U.S., Australia, and Turkey. Most studies involved walking, leg cycling, and arm cycling, alone or in combination for the duration of 3–15wk.	Four of 7[31,36,39,75] RCTs with level 1 evidence found improvements in physical composite, mental composite, physical function, mood, or social function measures after training 1–5 times/wk, for 30–60min, at intensities ranging from light to moderate. Three RCTs[37,65,81] with level 1 evidence reported no change in HRQOL. One study[91] with level 4 evidence reported a significant improvement in mental composite scores, whereas the other studies[68,70] with level 4 evidence reported no changes or decrement in HRQOL.
		Resistance Training Programs: Four studies (2 RCTs,[48,92] PEDro=8.5; 2 non-RCTs,[54,70] D&B=17) included 137 participants from Europe and Australia. All the studies involved traditional resistance-training exercise for 8–26wk.	One RCT with level 1 evidence[48] found significant improvements in physical function, physical role, and physical composite measures of HRQOL with training 2 times/wk for 12wk, but 1 RCT with level 1 evidence reported no change.[92] One study with level 4 evidence[54] showed improvements in the mental composite score, and 1 study showed no changes in HRQOL.[70]
		Aerobic + Strength Training Programs: Two RCTs[33,41] (PEDro=7.7) with 56 participants from Iceland and Turkey examined a combination of aerobic and strength training.	One RCT[41] with level 1 evidence reported improvements in physical function and physical role of HRQOL with training 2 times/wk for 12wk, whereas the other RCT with level 1 evidence[33] reported no changes in HRQOL with training 3 times/wk.
		Other Types of Exercise: Seven studies (3 RCTs,[81,83,84] median PEDro=7; 4 non-RCTs,[71,76,85,87] median D&B=15) included 163 participants from Canada, Europe, and the U.S. The studies used aquatic exercises, yoga, standing and floor exercises, core exercises, BWSTT, and a combination of exercise and sport as training modalities for 10–24wk.	Two RCTs with level 1 evidence[81,83] reported no changes after a twice-weekly yoga or a sport/exercise regimen. The level 2 evidence from 1 RCT[84] and level 4 evidence from 4 non-RCTs[71,76,85,87] reported significant improvements in pain, social function, physical composite, and mental composite measures of HRQOL after BWSTT, pool, standing, or floor exercises.

NOTE. D&B score, out of a possible 28 points.
Abbreviations: BWSTT, body weight–supported treadmill training; D&B, Downs and Black.

undertaken to inform the development of physical activity guidelines, we considered the impact of exercise on multiple outcomes in a single review in an effort to develop a guideline with robust implications for fitness, functioning, and well-being. Although our review included more studies than the extant review by Asano et al,[97] our conclusions were similar and point to a lack of consistent and high-quality evidence in this area. Whereas there is adequate evidence to begin to develop physical activity recommendations for physical fitness benefits, the evidence is lacking to provide the minimal prescription of physical activity to enhance mobility, fatigue, and HRQOL. Our review, however, does highlight areas with considerable promise worthy of further investigation.

There is some evidence that aerobic training, resistance training, or a combination of both may improve walking speed and endurance in persons with MS. Snook and Motl[21] reported a similar pattern of findings in a meta-analysis examining the impact of exercise on mobility in general (ie, collapsing across all mobility outcomes). Moreover, our review provides some indication that for people with significant mobility impairment, consistent with more advanced disease status, assisted technologies such as body weight–supported treadmill training have shown considerable promise for improving walking outcomes. The small number of high-quality RCTs in this area is a primary limitation hindering the clear delineation of an appropriate dose of exercise for impacting mobility outcomes.

The evidence that resistance training or a combination of resistance and aerobic training reduces fatigue is promising. However, with only 1 RCT[48] examining the effects of resistance training alone, and 2 RCTs[33,41] examining combination training, it is premature to draw definitive conclusions. From the current evidence, aerobic training alone does not consistently reduce fatigue, and the evidence is not strong enough to produce a prescriptive recommendation for improving HRQOL. These findings are somewhat contradictory to the conclusion Motl and Gosney[20] drew from a meta-analysis examining the impact of exercise training on HRQOL and fatigue which suggested that aerobic activity is associated with small improvements in both outcomes. The difference in conclusions is likely due to the limited scope of evidence available for review at the time of Motl and Gosney's[20] meta-analysis.

In addition to being restricted by insufficient evidence, research related to mobility, fatigue, and HRQOL is hindered by considerable measurement limitations. Inconsistent test administration, reporting, and measurement protocols are common among trials assessing mobility. For example, variability in the use and reporting of mobility aids during mobility testing may confound study outcomes. For outcomes such as walking agility, inconsistencies in testing protocols cloud comparisons between studies, hindering the inclusion of this outcome in a systematic review.

Research evaluating the impact of exercise training on fatigue and HRQOL is challenged with the use of a mix of disease-specific versus generic measures, and the reporting of composite versus individual subscale scores. These measurement inconsistencies make it difficult to draw meaningful conclusions and make comparisons across studies. Going forward, researchers should be more strategic in selecting measures that will reveal meaningful exercise-induced change. The current practice of measuring multiple indicators, demonstrating change in some outcomes and not others, risks diluting or masking a significant change in meaningful outcomes. Focusing on measures that assess the physical dimensions of HRQOL and fatigue will likely be beneficial; these dimensions of HRQOL seem to improve more consistently than other dimensions, such as social functioning. There may be value in distinguishing different indicators of these outcomes, such as physiological fatigue threshold (ie, fatigability) versus symptomatic fatigue. The nature of meaningful change in these outcomes must further be established. This research might consider evaluating the effect of exercise training in individuals with MS who are preselected with compromised fatigue or HRQOL.

Limitations of the research

In addition to the considerable measurement constraints, the reviewed research had further limitations. The studies are subject to a self-selection bias wherein participants are motivated to engage in exercise. Indeed, the participants in these trials generally have a mild to moderate level of disability. The benefits of exercise for populations with more severe disability and the development of adapted exercise strategies for this group require further investigation. Moreover, the extant studies generally include heterogeneous participant samples with varying clinical courses of MS, thus precluding any distinctions that can be made in exercise prescription for individuals with different types of MS (ie, relapsing-remitting vs progressive) and in different stages of disease remission. Additionally, most studies do not include prescreening for existing impairments in variables of interest. Finally, outcomes are reported for periods immediately after intervention, thus precluding the potential to determine the long-term or lasting effects of exercise training.

Limitations of the review

Our review was limited in several ways. We only included research published in English peer-reviewed journals, thus subjecting our review to a publication bias. We used a descriptive synthesis approach. Because of the variation in outcomes used, intervention characteristics, and participant characteristics, we did not examine effect sizes or factors moderating the effects of exercise on the outcomes of interest as would be determined through meta-analytic procedures. However, the systematic approach used allowed us to provide a detailed assessment of the effects of exercise training with respect to specific training prescriptions and outcomes measures, providing the necessary information to develop physical activity guidelines. Largely because of measurement limitations and small samples, several meaningful outcomes were not captured in our review. For example, we were unable to systematically examine change in disability status as an outcome. Of the studies included in the current review, only 15 reported change in disability status. None reported worsening of MS symptoms. However, this outcome is problematic because (1) the accepted standard scale of disability, the Expanded Disability Status Scale (EDSS),[98,99] has a low sensitivity to intervention-induced change; (2) the EDSS reporting method is inconsistent across studies (ie, some studies report sample means, whereas others report median scores); and (3) the method of measurement is variable (ie, some studies use a self-reported EDSS, while others conduct a clinical assessment of EDSS). Balance and body composition were not considered as outcomes because the studies reviewed were not designed as interventions to improve balance or body composition. Moreover, when balance and body composition were measured, a variety of measures were used, none of which are considered criterion standard assessment tools (ie, balance: force platform, posturography; body composition: dual-energy x-ray absorptiometry). Adverse events associated with exercise participation were not reported because this information could not be adequately extracted from the studies reviewed (ie, relapse rates and reasons for dropout were not consistently reported). There is emerging evidence establishing a relationship between exercise participation and cognitive functioning[100]; however, this outcome was not considered in our review because of the limited, poor-quality evidence.[81,92] Since the review was conducted, additional studies[101-110] have been published. A cursory review of these studies suggests a pattern of findings from these additional studies consistent with those reported in the current review.

Conclusions

Moderate-intensity exercise performed 2 times per week is effective for increasing aerobic and muscular fitness among adults with mild to moderate disability resulting from MS. Exercise training may be effective in improving mobility and symptoms of fatigue. There is currently insufficient evidence to conclude that exercise training can improve HRQOL in this population. The conclusions from this systematic review and the accompanying prescriptive exercise information provide the necessary evidence base for the development of much-needed physical activity guidelines for people with MS. Such guidelines will be critical to encourage the MS community to engage in physical activity and to accumulate primary and secondary health benefits.

Keywords

Exercise; Guideline; Multiple sclerosis; Physical fitness; Rehabilitation

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Supplemental Appendix S1

Mobility

Walking impairment is one of the most common and life-altering features in MS[62] and is often used to track disease progression over time.[63] Walking impairment is most commonly assessed with performance measures such as the 6-minute walk, the Timed 25-Foot Walk, and the Timed Up & Go (TUG) tests. These measures reflect walking endurance, speed, and agility, respectively. Exercise-induced increases in aerobic capacity and muscular strength may be expected to translate into improved walking performance in people with MS.[64] Twenty-five studies[32,37,41,47,50,51,54,56,57,61,65-79] that met systematic review criteria evaluated the effects of exercise training on outcomes of mobility. The exercise protocols included aerobic exercise (arm/leg cycling, treadmill walking, home-based walking, recumbent stepping), resistance training (weight machines, free weights, resistance bands, plyometrics), combined aerobic and resistance training, and a variety of other forms of physical activity (body weight−supported treadmill training [BWSTT], aquatic exercise, FES cycling, balance and stability training). The evidence from these trials is summarized in table 6. From this review there is promising evidence that some types of exercise training may improve walking endurance and speed. The evidence is less clear, however, regarding the benefits of exercise training for walking agility.

Walking endurance

There is supportive but not consistent evidence that aerobic training can improve walking endurance in people with MS. With respect to resistance training, the evidence is promising yet insufficient. One RCT[47] with level 1 evidence observed a significant improvement in walking endurance after 12 weeks of twice-weekly progressive resistance exercise (10−12RM). This is supported by another study[70] with level 4 evidence reporting a significant improvement in walking endurance after 2 weekly sessions of mild-moderate full-body resistance training for 8 weeks. One small study (n=8)[54] with level 4 evidence did not observe a significant change in walking endurance with progressive resistance training (2 times/wk, 10wk, 60%−80% of 1RM).

Studies incorporating combination or alternative exercise modalities demonstrate promise with respect to improving walking endurance. A large RCT (n=91)[50] with level 1 evidence reported a significant improvement in walking endurance after 26 weeks of combined home-based aerobic (aquatic or other) and resistance training (2 times/wk, 10−15 repetitions). The program progressed from inpatient to home-based training environments, but the intensity of training was unclear. Among studies[56,57,71,72] with level 4 evidence, other exercise modalities, such as BWSTT (with or without robotic assistance),[57,72] recumbent stepping combined with resistance exercises, and group exercise classes, may also be effective in improving walking endurance.

Walking speed

There are conflicting results from the 2 RCTs with level 1 evidence[67,73] regarding the effect of aerobic exercise on walking speed. One study[67] reported a significant improvement in walking speed after 3 weekly sessions (30min) of treadmill walking at an intensity of 55% to 85% of maximum heart rate for 4 weeks, whereas there was no significant change in walking speed after home-based walking (20−30min, 2−7 times/wk) for 4 to 12 weeks.[73] Two studies[56,69] with level 4 evidence reported no significant change in walking speed after aerobic training (30−60min, 2−3 times/wk, 12wk, cycling or recumbent stepping).

Regarding the effects of resistance training, 1 RCT[47] with level 1 evidence reported a significant improvement in walking speed after 12 weeks (2 times/wk) of progressive resistance training. This is supported by 1 study[54] with level 4 evidence that reported a significant improvement in fast, but not self-selected walking speed, after a 10-week (2 times/wk) progressive resistance training program (60%−80% of 1RM). Only 1 small study[74] (n=8) with level 4 evidence did not observe a significant improvement in walking speed with progressive lower extremity resistance training (2 times/wk, 8wk, 30−60min).

Two RCTs[41,50] with level 1 evidence reported a significant improvement in walking speed after either 8 weeks of cycling/balance/plyometric training or 26 weeks of inpatient and home-based aerobic (aquatic or other) and resistance training (2 times/wk, 10−15 repetitions). Improvements in walking speed have been reported with other exercise modalities. For example, 1 RCT[75] provided level 1 evidence that 6 weeks of group-based calisthenics can significantly improve walking speed. Similarly, evidence from 5[57,71,72,77,78] of 8[56,61,76] studies (level 4) suggests that BWSTT (with or without robotic assistance, 2−5 times/wk, 30−40min, 3−6wk) or group exercise classes (aquatic, stability training, 1−2 times/wk, 30−60min, 5−10wk) might also be effective in improving walking speed.

Timed Up & Go

Regarding the effects of aerobic exercise, there were only 3 low-quality studies (level 4 evidence) that evaluated this outcome. Two[68,70] of the 3[56] studies report improvements in TUG performance after moderate-intensity cycling or multimodal aerobic exercise (2 times/wk, 8−12wk, 20−40min).

Similarly, with respect to resistance training, 2 non-RCT[51,70] provide level 4 evidence that twice-weekly sessions of resistance training at a mild-moderate intensity (2 times/wk, 8wk) improves TUG performance. Although the 1 RCT[32] with level 1 evidence did not determine a significant change in TUG performance with 2 weekly sessions (35−50min, 8wk) of home-based resistance training using a weighted vest, TUG performance improved by 12.7% in the training group compared with 1.0% in the control group.

One RCT[41] with level 1 evidence observed that twice-weekly (60min, 8wk) combined exercise training (leg cycling/balance/plyometrics) improves TUG performance, although this was not supported by another combined training study[56] with level 4 evidence (3 times/wk, 12wk of recumbent stepping/resistance training). Regarding other exercise modalities, group exercise classes (aquatic[77,78] and stability training[79]) all demonstrated improved TUG performance after 2 weekly (8−12wk) training sessions (level 4 evidence).

Fatigue

Fatigue is the most common and debilitating symptom of MS and has a significant impact on virtually all aspects of an individual's daily functioning. It typically is measured through self-report questionnaires.[80] Measures included in this review are the Fatigue

Severity Scale, Fatigue Impact Scale, Modified Fatigue Index Scale, Short-Form Health Survey-36 (SF-36) vitality, Profile of Mood States energy and fatigue subscales, and Multiple Sclerosis Quality of Life-54 (MSQOL-54) energy subscale. Thirty studies[31,33,36,37,39,41,42,48,55,56,59,65-71,74-78,81-87] that met the systematic review criteria used at least 1 of these measures to evaluate the impact of various forms of exercise on fatigue. These protocols included aerobic exercise (arm/leg cycling), resistance training (weight machines, free weights, resistance bands), combined aerobic and resistance training, and a variety of other forms of physical activity (sport, yoga, BWSTT, aquatic exercise, FES cycling, and Pilates). The evidence from these studies is summarized in table 7. Overall, the evidence regarding exercise training on symptomatic fatigue was inconsistent, although some types of exercise training are promising yet insufficient for determining an optimal dose. Interventions including a resistance-training component, in particular, may be most effective for fatigue reduction.

The quality of evidence examining the effects of aerobic exercise on symptomatic fatigue is high; however, the pattern of findings is not convincing. Only 3[36,37,81] of 9[36,39,65-67,75] RCTs with level 1 evidence report significant improvements in symptomatic fatigue-related outcomes after moderate-intensity aerobic exercise 2 to 3 times per week for at least 40 minutes per session. The other 6 studies[36,39,65-67,75] report nonsignificant changes in symptomatic fatigue, suggesting that these protocols neither worsened nor improved fatigue symptoms. The findings from the 4 studies[56,68-70] with level 4 evidence are not definitive. One study[70] demonstrated some improvement in general, physical, and psychological fatigue symptoms, whereas the 3 others reported no change in fatigue symptoms.

Fewer studies have examined the effects of resistance training on symptomatic fatigue, but the evidence supporting the benefits of resistance training for reducing general fatigue symptoms is consistently more favorable than for aerobic training alone. The 1 RCT[48] with level 1 evidence reported significant decreases in general measures of symptomatic fatigue, but not in specific measure of fatigue symptoms (eg, physical, psychological) after twice-weekly resistance training performed at a moderate intensity. Consistent with this finding, 3 studies[55,70,74] with level 4 evidence, and similar training parameters as the level 1 RCT,[48] reported decreases in overall symptomatic fatigue or specifically physical and psychological fatigue.

The effects of a combined program of aerobic and resistance training seem promising for fatigue reduction. Level 1 evidence from 2 RCTs[33,41] indicates that a combination of moderate-intensity aerobic activity and light-moderate intensity strength training performed at least 2 times per week can lead to an improvement in indicators of symptomatic fatigue. Using similar combined aerobic and resistance-training parameters, all 3 studies[42,56,82] with level 4 evidence reported significant decreases in general and/or physical symptomatic fatigue. Considering the pattern of results for aerobic and resistance training alone, the beneficial effects of these combined programs may be due in large part to the resistance training component of these programs.

Eleven studies[59,71,76-78,81,83-87] of varying quality incorporating a range of physical activities (eg, sport, yoga) generally suggest that engaging in physical activity can potentially improve some, but not all, indicators of symptomatic fatigue. For example, an RCT[83] with level 1 evidence reported decreased symptomatic fatigue after a mixed activity program including volleyball and other aerobic activities performed at a light to moderate intensity (40–60min, 3 times/wk). Another RCT[81] with level 1 evidence reported decreased general symptomatic fatigue and increased vitality after 24 weeks of a 90-minute yoga class plus home practice. This intervention did not impact specific fatigue symptoms (eg, physical fatigue, mental fatigue). A study[84] with level 2 evidence reported increased energy and vigor and decreased feelings of fatigue after 10 weeks of aquatic exercise (45min/session, 3–5 times/wk).

With regards to studies with level 4 evidence, 7 of 8[59,71,76,77,85-87] non-RCTs reported a positive impact on at least 1 indicator of fatigue symptoms. These changes were reported for general or physical measures of symptomatic fatigue, but not for specific, nonphysical fatigue symptoms. Training protocols included 12 weeks of BWSTT, 2 to 3 times per week[76,87]; 8 weeks of FES cycling, 3 times per week for 30 minutes per session[59]; 10 weeks of Pilates-type activity, once a week for 60 minutes[71]; 10 weeks of sport climbing, once a week[86]; and 5 to 12 weeks of aquatic exercise, 2 times per week for 60 minutes per session.[77,85] Although the evidence is promising, it is not adequate to determine the optimal dose (ie, frequency, intensity) of these varying types of physical activity for reducing general symptomatic fatigue.

Health-related quality of life

There is consistent evidence that HRQOL is compromised among persons with MS compared with the general population and with persons with other chronic disease conditions.[3,88,89] This reduction in HRQOL is associated with many aspects of MS, including a diagnosis in the most productive years of one's life, the unpredictable and unstable nature of the disease course, and the absence of a convincing disease-modifying therapy.[3] Importantly, physical activity might be associated with improved HRQOL in persons with MS by improving fatigue and depression, self-efficacy, social support, and disability status.[90] In the MS population, HRQOL is generally measured using self-report measures. Twenty-one studies[31,33,36,37,39,41,48,54,65,68,70,71,75,76,81,83-85,87,91,92] that met the systematic review criteria included at least 1 measure that evaluated the impact of various forms of exercise on HRQOL. Many studies included multiple indicators of HRQOL from the following scales: the SF-36, the Multiple Sclerosis Quality of Life-54, the Multiple Sclerosis Impact Scale, the Hamburg Quality of Life Questionnaire in Multiple Sclerosis, and the Multiple Sclerosis Quality of Life Inventory. The exercise protocols included aerobic exercise (arm/leg cycling), resistance training (weight machines, free weights, resistance bands), combined aerobic and resistance training, and a variety of other forms of physical activity (sport, yoga, BWSTT, aquatic exercise). The evidence from these studies is summarized in table 8. Overall, the current evidence is insufficient to generate conclusions regarding the effects of exercise training on HRQOL outcomes in persons with MS.

There is mixed evidence for the impact of aerobic training on HRQOL. Four RCTs[31,36,39,75] with level 1 evidence found improvements in some indicators of HRQOL including physical composite, mental composite, physical function, mood, or social function measures. Training included leg cycling or combined leg/arm cycling 1 to 5 times per week, for 30 to 60 minutes, at light to moderate intensities. Three additional RCTs[37,65,81] with level 1 evidence found no effects. Of the studies with level 4 evidence, 1 study[91] of thrice-weekly moderate-intensity aerobic exercise (treadmill walking, elliptical training, cycling) led to a significant improvement in mental health composite scores. However, the other 2 studies[68,70] with level 4 evidence found no changes in HRQOL or decrements in HRQOL. Of note, the study[68] reporting a decrement in HRQOL included a training regimen that required participants to perform high-intensity aerobic activity (90% peak power).

The evidence for the impact of resistance training on HRQOL is inconclusive. One RCT[48] with level 1 evidence found significant improvements in physical function, physical role, and physical composite measures of HRQOL with resistance training twice a week. Conversely, 1 RCT[92] with level 1 evidence reported no significant changes in any of the multiple HRQOL measures assessed. Participants in this study engaged in home-based resistance training using resistance bands. The evidence from the lesser-quality studies is mixed. One study[54] with level 4 evidence showed change in only 1 of the several HRQOL dimensions assessed (physical HRQOL) after twice-weekly supervised resistance training performed at a moderate to hard intensity (3−5 on Borg Scale). Another study with level 4 evidence showed no change in HRQOL.[70]

The results of 2 RCTs[33,41] with level 1 evidence that examined the impact of combined aerobic and resistance training on HRQOL were mixed. One RCT[41] reported improvements in physical function and physical role of HRQOL with aerobic and resistance training 2 times per week for 8 weeks. However, the other RCT[33] reported no changes in HRQOL after 60 minutes of thrice-weekly cycling and resistance training of major muscle groups for 5 weeks. This discrepancy may be related to the duration of training or other prescriptive differences between the training regimens.

The studies[81,83] included in the review provide no level 1 evidence to support changes in HRQOL after alternative types of physical activity including yoga or a sport/exercise regimen. The evidence from 1 RCT[84] (level 2) and 4 non-RCTs[71,84,85,87] (level 4) indicates significant improvements in some of the measured HRQOL outcomes including pain, social function, physical composite, and mental composite measures after BWSTT, aquatic, standing, or floor exercises. Many of these studies included additional measures of HRQOL that did not significantly change.