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# Is aerobic or resistance training the most effective exercise modality for improving lower extremity physical function and perceived fatigue in people with multiple sclerosis? A systematic review and meta-analysis

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1 **Objective:** The purpose of this systematic review was to investigate whether aerobic training  
2 (AT) or resistance training (RT) is most effective in terms of improving lower limb physical  
3 function and perceived fatigue in persons with multiple sclerosis (pwMS).

4 **Data sources:** Nine databases (MEDLINE, EMBASE, CINAHL, AMED, PEDro, SPORTdiscus,  
5 PsycINFO, Web of Science and SCOPUS) were electronically searched in April 2020.

6 **Study Selection:** Included studies were randomized controlled trials (RCTs) involving pwMS  
7 attending one of two exercise interventions; AT or RT. Studies had to include at least one  
8 objective or self-reported outcome of lower extremity physical function and/or perceived  
9 fatigue.

10 **Data Extraction:** Data was extracted using a customized spreadsheet, which included detailed  
11 information on patient characteristics, interventions and outcomes. The methodological quality  
12 of the included studies was independently assessed by two reviewers using the TESTEX rating  
13 scale.

14 **Data synthesis:** Twenty-seven papers reporting data from 22 RCTS (AT=14, RT=8) including 966  
15 pwMS. The two modalities were found to be equally effective in terms of improving short walk  
16 test (AT: ES=0.33 [-1.49: 2.06]; RT: ES=0.27 [0.07: 0.47]) and long walk test performance (AT:  
17 ES=0.37 [-0.04: 0.78]; RT: ES=0.36 [-0.35: 1.08]), as well as in reducing perceived fatigue (AT:  
18 ES=-0.61 [-1.10:-0.11]; RT: ES=-0.41 [-0.80: -0.02]). Findings on other functional mobility tests  
19 along with self-reported walking performance were sparse and inconclusive.

20 **Conclusions:** AT and RT appear equally highly effective in terms of improving lower extremity  
21 physical function and perceived fatigue in pwMS. Clinicians can thus use either modality to

1 target impairments in these outcomes. In a future perspective, head-to-head exercise modality  
2 studies are warranted. Future MS exercise studies are further encouraged to adapt a consensus  
3 'core battery' of physical function tests to facilitate a detailed comparison of results across  
4 modalities.

5

6 **Keywords:**

7 Rehabilitation; Exercise; Multiple Sclerosis; Systematic Review.

8

9

10 **Abbreviations:**

11 MS: Multiple Sclerosis

12 pwMS: Person with multiple sclerosis

13 RCT: Randomized controlled trial

14 AT: Aerobic training

15 RT: Resistance training

16 RM: Repetition maximum

17 HR: Heart rate

18 Testex: Tool for assessment of study quality for reporting on exercise

19 RPE: ratings of perceived exertion

20 ES: Effect size

21 CI: Confidence interval

22 EDSS: Expanded disability status scale

23 6MWT: Six minute walk test

1 MSWS: 12-item multiple sclerosis walking scale

2 SSST: Six spot step test

3 FSS: Fatigue severity scale

#### 4 **Introduction**

5 Multiple sclerosis (MS) is a chronic, autoimmune, and inflammatory disease of the central  
6 nervous system, exemplified through demyelination and axonal loss<sup>1</sup>. As a consequence,  
7 multiple symptoms can appear<sup>1-3</sup>, with fatigue and walking limitations reported to be among  
8 the most debilitating<sup>4-7</sup>. Moreover, an estimated 50% of persons with MS (pwMS) will require a  
9 walking aid within 15-25 years after disease onset<sup>8,9</sup>. Since physical function is associated with  
10 lowered quality of life at the individual level along with a greater economic burden at a health  
11 service and societal level<sup>10,11</sup>, it is crucial to diminish progression of disability<sup>12</sup>.

12 While pharmacological treatments appear to have limited beneficial effect on fatigue and  
13 walking limitations<sup>13</sup>, exercise has proven to be a potent non-pharmacological treatment  
14 option, being both safe and eliciting numerous beneficial effects in pwMS<sup>14,15</sup>. Specifically,  
15 exercise is an effective way of reducing fatigue<sup>16,17</sup> and improving walking performance<sup>18,19</sup>,  
16 with the latter often considered to be clinically meaningful<sup>20,21</sup>.

17

18 Exercise constitutes a number of different modalities known to elicit different physiological  
19 adaptations (such as neuromuscular function or cardiovascular function) that in most cases are  
20 paralleled by (and perhaps even translated into) improved physical function<sup>22</sup>. A recent review  
21 investigating randomized controlled trials (RCTs) of exercise interventions in pwMS reported

1 that the two most applied exercise modalities were aerobic training (AT) and resistance training  
2 (RT)<sup>23</sup>. Several studies have reported positive effects of both AT<sup>24-26</sup> and RT<sup>27,28</sup> on parameters  
3 directly related to lower extremity physical function (e.g. walking performance, chair rise, stair  
4 negotiation) as well as on parameters indirectly related to lower extremity physical function,  
5 such as perceived fatigue. However, based on the existing literature it currently remains  
6 unknown which of these two common exercise modalities is the most effective in terms of  
7 improving physical function and perceived fatigue in pwMS. Despite the somewhat impossible  
8 task of matching AT and RT on traditional exercise parameters such as duration, frequency, and  
9 intensity, understanding the specific effectiveness of the two different exercise modalities is an  
10 important factor for consideration in optimizing exercise prescription in pwMS.

11

12 Therefore, the objectives of this systematic review were to investigate which of the two  
13 exercise modalities (AT or RT) are the most effective in terms of improving lower extremity  
14 physical function and reducing perceived fatigue in pwMS.

15

## 16 **Methods:**

17 The present systematic review follows the Preferred Reporting Items for Systematic Reviews  
18 and Meta Analyses (PRISMA) guidelines on systematic reviews of RCTs<sup>29</sup>. Search strategy, study  
19 selection, eligibility criteria, methodology assessment, data extraction and analysis were  
20 performed in accordance with a protocol pre-registered in PROSPERO (CRD42020189855).

## 21 **Definitions:**

1 In this review the following definitions were applied:

2 Exercise: A form of physical activity that is planned, structured and repetitive, and is  
3 undertaken with the objective of improving or maintaining at least one aspect of physical  
4 fitness, comprising strength, flexibility or aerobic endurance<sup>30</sup>.

5  
6 Physical activity: Any bodily movement produced by skeletal muscles that requires energy  
7 expenditure above resting levels<sup>30</sup>.

8 Physical function: The ability of an individual to perform physical activities of daily living. For the  
9 purposes of this systematic review, this particularly relates to lower extremity tasks (e.g.  
10 simple/complex/endurance walking, chair rise, stair negotiation) <sup>31</sup>.

11 Perceived fatigue: Subjective sensations of weariness, increasing sense of effort, mismatch  
12 between effort expended and actual performance or exhaustion<sup>32</sup>.

13 Resistance training: Performed with external resistance of varying degrees relative to maximal  
14 strength provided by either free weights, machines, bodyweight, or some other implements  
15 (e.g., resistance bands), either with single or multiple sets of repetitions which may or may not  
16 be performed to momentary failure (but are often performed to a relatively high effort)<sup>33</sup>.

17 Aerobic training: Performed using locomotor or ergometer tasks (e.g., walking, jogging, running,  
18 cycling, rowing, etc.) in a continuous or intermittent fashion with respect to duration at  
19 submaximal intensities of effort, commonly determined relative to either maximal heart rate,  
20 heart rate reserve,  $VO_{2max}$ , or sometimes using ratings of perceived effort scales<sup>33</sup>.

1 Exercise intensity: For AT, exercise  $\leq$  63% of Heartrate max (HRmax) was defined as low  
2 intensity, 64-76% of HRmax as moderate intensity, and  $\geq$  77 % of HRmax as high intensity<sup>34</sup>. For  
3 RT, exercise  $\geq$  16 Repetition Maximum (RM) was defined as low intensity ( $\leq$  64% of 1RM), 9-15  
4 RM as moderate intensity (65-79% of 1RM) and  $\leq$  8 RM as high intensity ( $\geq$  80% of 1RM)<sup>35,36</sup>

## 5 **Searches**

6 An original search was carried out as part of another review by the same authors in 2018,  
7 having the aim to summarize reported adherence and drop-out data from RCT studies of  
8 exercise interventions in pwMS.<sup>23</sup>

9  
10 This search was updated in April 2020. Furthermore, in March 2020, The World Health  
11 Organization's International Clinical Trials Registry Platform (ICTRP)  
12 <http://apps.who.int/trialsearch/>, which comprise the 16 primary registries of the WHO registry  
13 network and ClinicalTrials.gov, was searched for relevant ongoing trials investigating a head-to-  
14 head comparison of AT and RT in pwMS.

## 15 **Data sources and search strategy**

16 In brief, the search strategy was based on the key terms "multiple sclerosis" OR MS AND  
17 exercise OR "physical activity". For full search strategy please see Dennett et al. 2020<sup>23</sup>.

18 The original search was carried out in October 2018 and updated in April 2020.

19 Two reviewers (LM and RD) conducted the original search in the electronic databases MEDLINE,  
20 EMBASE, CINAHL, AMED, PEDro, SPORTdiscus, PsycINFO, Web of Science and SCOPUS limited to  
21 scientific research papers being published between January 1993 and October 2018. The same

1 databases were searched from September 2018 to March 2020 by two reviewers (LM and LC) in  
2 April 2020. All searches were supplemented by hand searches of reference lists.

3

#### 4 ***Study selection***

5 The following PICO (population, intervention, comparison, outcome) question guided the  
6 search and inclusion strategy. “Which exercise modality, AT or RT, is most effective in improving  
7 physical function (specifically lower extremity tasks such as simple/complex/endurance  
8 walking, chair rise, stair negotiation) and perceived fatigue in pwMS?”

#### 9 *Eligibility criteria*

10 RCT studies involving adults over the age of 18 with a definite diagnosis of MS, regardless of  
11 gender, disease duration, MS phenotype or level of disability were considered eligible for  
12 inclusion. While all identified studies could be included regardless of location, group/ individual  
13 structure, level of supervision, intervention duration, session duration, intensity, progression,  
14 frequency, the content had to be either AT or RT; with or without a follow-up period.

15

16 Control interventions had to include non-training controls only or active control conditions  
17 having no expected effects on the cardiovascular system or the musculoskeletal system, for  
18 example stretching were accepted.

19 Studies had to include at least one objective or self-reported measure of lower extremity  
20 physical function (such as simple/complex/endurance walking, chair rise, stair negotiation)  
21 and/or perceived fatigue. If reported, measures of cardiovascular function (i.e. maximal oxygen

1 uptake) and neuromuscular function (i.e. maximal muscle strength or muscle power) were also  
2 extracted, as these outcomes could, (1) help verify the effectiveness of interventions, and (2)  
3 are likely mediators of adaptations in lower extremity physical function.

4

#### 5 **Data management and selection process**

6 The original search resulted in 93 papers included in the previous review, all of which were  
7 considered for inclusion in the present review (see figure 1).

8 Results from the updated search were exported to EndNote, where duplicates were removed.

9 The remaining papers were imported into Rayyan data management system ([rayyan.qcri.org](http://rayyan.qcri.org))  
10 where titles and abstracts were independently screened for eligibility by two reviewers (LC and  
11 LTM). If papers were included at this stage, a full-text reading by the same two reviewers was  
12 performed, and any discrepancies were discussed with a third party (LGH). Reasons for  
13 excluding full text RCTs were recorded.

14

#### 15 **Data extraction**

16 Data was extracted using the same spreadsheet as the previous review<sup>23</sup>, which included  
17 detailed information on participant characteristics (age, gender, disease duration, MS  
18 phenotype, disability level, and fatigue as a symptom); modality of the intervention (setting,  
19 group/individual structure, level of supervision, intervention duration, session duration,  
20 intensity, frequency); content of the intervention (aerobic or resistance); report of adverse

1 events, % drop-out, and adherence during the intervention period and at any follow up.  
2 Furthermore, an additional customized spreadsheet was made to extract information on all  
3 outcomes of lower extremity physical function, perceived fatigue and measures of  
4 cardiovascular and neuromuscular function. Data extraction was completed by two reviewers  
5 (LC and LTM).

6

### 7 **Quality assessment**

8 The methodological quality of the included studies was independently assessed by two  
9 reviewers (LTM and LC) using the 'Tool for assessment of study quality for reporting on  
10 exercise' (TESTEX) rating scale<sup>37</sup>. Any discrepancies were discussed and resolved between the  
11 two reviewers.

12

### 13 **Synthesis of results**

14 In addition to the qualitative analysis (summary of identified studies and their data), we also  
15 performed quantitative analysis by calculating sample-size weighted averages across selected  
16 studies. A minimum of two studies was required in order to conduct a meta-analysis. Random  
17 effects meta-analyses comprising data on physiological adaptations, short walking tests, long  
18 walking tests and perceptions of fatigue were conducted by using *Meta-Essentials version 1.5*  
19 designed for Excel.<sup>38</sup> Intervention effect sizes (ES) (between-group differences) for different  
20 outcomes at post-treatment, were calculated using Hedges' g statistic, along with 95%

1 confidence intervals (CIs) around the estimated effect-size. Also, if data was available and  
2 adequate, we performed a weighted regression of all study ES as a function of intervention  
3 duration and frequency (weeks and number of sessions) as well as intervention intensity, as  
4 these factors were hypothesized to impact the outcomes<sup>39</sup>. Of note, this approach was done to  
5 establish specific within-modality information only. ES were interpreted as follows: small = 0.14,  
6 moderate = 0.31, large = 0.61 based on empirical data from 99 meta-analyses examining the  
7 effects of rehabilitation/exercise<sup>41</sup>. Statistical heterogeneity was quantified using Higgins'  $I^2$   
8 statistic, and was interpreted as follows: heterogeneity: > 50%, no or limited heterogeneity: <  
9 50%<sup>42</sup>.

10 If studies reported on more than one outcome in each domain (e.g. physiological adaptations  
11 such as knee extensor and knee flexor muscle strength as well as perceptions of fatigue using  
12 different questionnaires), an average was calculated and used for the meta-analyses.

13

14

15 [INSERT FIGURE 1]

16

## 17 Results

### 18 Study characteristics

19 As depicted in figure 1, the search yielded 2117 hits. After removal of duplicates, 1538 papers  
20 remained for the screening process, with 12 of these assessed for full-text reading. Five papers  
21 were included, which with the addition of 22 papers from the previous review, resulted in a

1 total of 27 papers being included in the qualitative and quantitative synthesis.  
2 The 27 papers reported 22 RCTs (AT (n=14), RT (n=8)) which involved a total of 966 pwMS. As  
3 seen in table 1, Expanded disability status scale (EDSS) ranged from 1.5-7 while disease duration  
4 ranged from 2.7-18.6 years. The duration of AT interventions ranged from 3-26 weeks  
5 (involving 9-48 sessions) with the intensity being deemed moderate (n=5)<sup>43-47</sup>, high (n=4)<sup>26,48-50</sup>,  
6 or unknown (no information, n=5)<sup>25,51-54</sup>. The duration of RT interventions ranged from 8-24  
7 weeks (involving 15-48 sessions) with the intensity being deemed moderate (n=1)<sup>55</sup>, high  
8 (n=4)<sup>28,56-58</sup>, or unknown (no information, n=3)<sup>40,59,60</sup>. Due to the missing information and the  
9 use of divergent scales of exercise intensity for both AT (e.g. % of HR<sub>max</sub>, RPE, % of VO<sub>2max</sub>, % of  
10 Peak Power) and RT (% of 1RM, % of bodyweight, absolute weights), we were unable to  
11 perform weighted (moderator) analysis using this parameter. Two<sup>25,60</sup> of the 22 identified RCTs  
12 reported a primary outcome that was not based on a sample size calculation. Ten  
13 papers<sup>26,28,44,48-50,52,54,55,57</sup> of the 22 identified RCTs reported a primary outcome based on a  
14 sample size calculation, with five of these having a primary outcome aligned with the purpose  
15 of the present systematic review.

16 The median TESTEX score of the included studies was nine out of 15. Detailed information on  
17 the scores can be found in Table 2.

18

19 [INSERT TABLE 1]

20 [INSERT TABLE 2]

21 [INSERT TABLE 3]

22

1 ***Physiological adaptations***

2 Seven of the 14 AT studies<sup>26,45-48,50,52</sup> reported a between-group change in aerobic capacity,  
3 with four of these<sup>45,46,48,52</sup> reporting a statistically significant improvement (Table 3). The meta-  
4 analysis showed an overall large effect on aerobic capacity, ES=0.88 [0.25: 1.50], p=0.001,  
5 I<sup>2</sup>=78% (Figure 2). Aerobic capacity ES was not positively associated with AT intervention  
6 duration (weeks: slope -0.03, r<sup>2</sup>=0.06, p=0.563; number of sessions: slope 0.00, r<sup>2</sup>=0.00, p=0.97.  
7 In regard to RT studies, seven out of nine studies<sup>28,40,55-59</sup> reported a between-group change in  
8 one or more strength measurements, with five of these changes being reported as statistically  
9 significant. The meta-analysis showed an overall large effect of RT on muscle strength, ES=0.86  
10 [0.02: 1.70], p=0.013, I<sup>2</sup>=75% (Figure 2). Strength ES appeared to be positively associated with  
11 RT intervention duration (weeks: slope 0.08, r<sup>2</sup>=0.25, p=0.104; number of sessions slope 0.06,  
12 r<sup>2</sup>=0.44, p=0.019).

13 [INSERT FIGURE 2]

14

15 ***Performance on short walking tests***

16 Three out of the 14 AT studies<sup>43,50,52</sup> reported a between-group change in short walking tests,  
17 with one of these changes<sup>43</sup> being reported as statistically significant (Table 3). An overall  
18 moderate effect was observed in the meta-analysis, ES=0.33 [-1.49: 2.06], p=0.20, I<sup>2</sup>=69%  
19 (Figure 3). Short walk ES was not positively associated with AT intervention duration (weeks:  
20 slope -0.32, r<sup>2</sup>=1.00, p=0.011; number of sessions: slope -0.10, r<sup>2</sup>=0.68, p=0.15).

1 Six RT studies<sup>28,40,56-59</sup> reported a between-group change in any short walking test, with one of  
2 these reporting a significant change (Table 3). The meta-analysis showed a moderate effect of  
3 RT on short walking performance, ES=0.27 [0.07: 0.47], p=0.006, I<sup>2</sup>=0% (Figure 3). Short walk ES  
4 was not positively associated with RT intervention duration (weeks: slope -0.02, r<sup>2</sup>=0.64,  
5 p=0.51; number of sessions slope -0.01, r<sup>2</sup>=0.42, p=0.59).

6 [INSERT FIGURE 3]

7

### 8 ***Performance on long walking tests***

9 Of the long walking tests, the Six minute walk test (6MWT) was the most used in AT studies.  
10 Five<sup>44,48-50,52</sup> out of the seven<sup>25,43,44,48-50,52</sup> studies investigating performance on a long walking  
11 test used this test. The meta-analysis showed an overall moderate effect of AT on the  
12 performance during long walking tests, ES=0.37 [-0.04: 0.78], p=0.026, I<sup>2</sup>=43% (Figure 4). Long  
13 walk ES was not positively associated with AT intervention duration (weeks: slope 0.01, r<sup>2</sup>=0.03,  
14 p=0.70; number of sessions: slope 0.01, r<sup>2</sup>=0.14, p=0.36).

15 Four RT studies<sup>28,55,57,58</sup> reported a between-group change in any long term walking test, with  
16 one of these reporting a statistically significant finding and the meta-analysis showing a  
17 moderate effect of RT on long walking test performance, ES=0.36 [-0.35: 1.08], p=0.11, I<sup>2</sup>=48%  
18 (Figure 4). Long walk ES was positively associated with RT intervention duration (weeks: slope  
19 0.07, r<sup>2</sup>=0.87, p=0.025; number of sessions slope 0.07, r<sup>2</sup>=0.87, p=0.025).

20 [INSERT FIGURE 4]

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**Performance on functional mobility tests**

Only one<sup>52</sup> of the AT studies investigated effects on the performance of a functional mobility test, and reported a statistically significant change between groups.

Five<sup>28,56-58,60</sup> of the RT studies investigated the performance on a functional mobility test between groups, with two<sup>56,58</sup> of these changes being reported as statistically significant.

As the aim of this present review was to evaluate differences between modalities, we were not able to conduct a meta-analysis on this outcome.

**Self-reported walking performance**

Two of the AT<sup>50,52</sup> studies reported a between group change in self-reported walking performance (both 12-item Multiple Sclerosis Walking Scale (MSWS)), with one of these<sup>52</sup> being reported as statistically significant. The meta-analysis of AT on self-reported walking performance showed a negligible effect, ES= -0.04 [-2.34; 2.26], p=0.82, I<sup>2</sup>=0% (Figure 5).

Of the RT studies, two<sup>57,58</sup> reported a between group change in self-reported walking performance (both MSWS), with one of these<sup>58</sup> being reported as statistically significant. The meta-analysis of RT on self-reported walking performance showed a negligible effect, ES= 0.07 [-5.20; 5.33], p=0.88, I<sup>2</sup>=66% (Figure 5).

[INSERT FIGURE 5]

1 **Perceptions of fatigue**

2 Nine of the 14 AT studies<sup>26,43-45,47,51-54</sup> reported a between-group change in any measure of  
3 perceived fatigue, with four<sup>26,43-45</sup> being reported as statistically significant. The meta-analysis  
4 showed a large effect of AT on perceptions of fatigue, ES=-0.61 [-1.10:-0.11], p=0.005, I<sup>2</sup>=58%  
5 (Figure 6). Improvements in perceived fatigue ES was not positively associated with AT  
6 intervention duration (weeks: slope -0.05, r<sup>2</sup>=0.00, p=0.85; number of sessions: slope 0.03,  
7 r<sup>2</sup>=0.31, p=0.052).

8 Of the RT studies, three<sup>55,57,61</sup> reported a between-group change in any measurement of  
9 perceived fatigue, with all of these changes being reported as statistically significant. The meta-  
10 analysis of RT on perceived fatigue showed a moderate effect, ES=-0.41 [-0.80: -0.02], p=0.00,  
11 I<sup>2</sup>=0% (Figure 6). Improvements in perceived fatigue ES was not positively associated with RT  
12 intervention duration (weeks: slope 0.10, r<sup>2</sup>=0.38, p=0.63; number of sessions slope 0.05,  
13 r<sup>2</sup>=0.38, p=0.63).

14 [INSERT FIGURE 6]

15

16 **Comparison between modalities**

17 While both interventions were shown to elicit adaptations in favor of exercise, we were not  
18 able to detect differences in any outcomes between the two different exercise modalities as  
19 evidenced by the comparable effect sizes and overlapping confidence intervals.

20

## 1 Discussion

2 Based on our findings, AT and RT present themselves as broadly equivalent modalities in terms  
3 of improving lower extremity physical function (walking performance) and reducing perceived  
4 fatigue, with meta-analyses revealing moderate-large effect sizes. Of note, only 14 out of 23  
5 studies reported physiological adaptations thereby limiting the in-depth understanding of the  
6 potential mechanistic effect(s) leading to an improvement in physical function (i.e. the  
7 translational potential).

8

### 9 ***Physiological adaptations***

10 Although only seven out of 14<sup>26,45-48,50,52</sup> AT studies reported a between-group change in  
11 aerobic capacity, the observed large effect size (ES=0.88 [0.25; 1.50]) of AT on aerobic capacity  
12 corroborate findings of a previous review<sup>62</sup> (ES=0.63 [0.00; 1.26]) using broader inclusion  
13 criteria (e.g. by including small pilot studies). Altogether, these provide clear evidence  
14 underlining AT as a highly effective intervention targeting the cardiovascular system in pwMS.

15 The observed large effect size of RT studies on lower extremity muscle strength (ES=0.86 [0.02;  
16 1.70]) corroborate findings previously reported by Jørgensen et al.<sup>63</sup>, who in a systematic  
17 review and meta-analysis including isokinetic dynamometry determined muscle strength,  
18 reported an ES of 0.45 [0.18; 0.72] following RT.

19 Overall, the physiological adaptations observed by the present systematic review verify that AT  
20 and RT interventions overall work as intended, thereby establishing the potential for a

1 translation into improvements in mobility aspects of lower extremity physical function along  
2 with reduction in perceived fatigue.

3

#### 4 ***Physical function - walking tests***

5 The identified AT studies predominantly focused on the longer walk tests, with only three  
6 studies<sup>43,50,52</sup> investigating the effect on the short walk tests. Despite the moderate ES on the  
7 short walk test (ES=0.33 [-1.49; 2.06]; data presented as walking speed) observed in the present  
8 systematic review, CIs indicate a high degree of uncertainty. This corroborates the findings of  
9 Pearson et al.<sup>19</sup>, who reported an ES=-1.96 [-2.67; -1.25] (data presented as walking time). Of  
10 note, both findings are based on very few studies (three in the present systematic review and  
11 two in the study by Pearson and colleagues), and should therefore be interpreted cautiously.  
12 Participants in two of the three identified studies in the present review were relatively high  
13 functioning at baseline, based on their short walk test performance and low EDSS<sup>50,52</sup>,  
14 potentially leaving little room for improvement (due to a ceiling effect). More studies are  
15 needed to establish a robust insight into the effects of AT on short walk tests, ideally by  
16 involving pwMS who are ambulatory across a wider range of disability levels, especially in  
17 severely disabled pwMS having substantial walking limitations.

18 Of the seven studies<sup>25,43,44,48-50,52</sup> investigating the effect of AT on the long walk tests, three of  
19 these<sup>25,43,49</sup> had a large ES. Yet, the meta-analysis showed an overall moderate ES of AT on this  
20 outcome (ES=0.37, [-0.04; 0.78]), that appeared quite certain based on CIs. As for the two  
21 aforementioned studies involving relatively high functioning participants at baseline<sup>50,52</sup>, their

1 long walk test performance was also quite high (6MWT >575m), again potentially leaving little  
2 room for improvement. Following 12 weeks of AT, an ES=-0.14 [-0.62; 0.34] was observed on  
3 the 6MWT in Baquet et al.<sup>50</sup> whereas an ES=0.33 [-0.34; 1.01] was observed in the study of  
4 Feys et al.<sup>52</sup> Interestingly, participants in the study by Feys et al.<sup>52</sup> performed specific  
5 walking/running exercises that may have been more beneficial for performance on the long  
6 walk test (moderate ES=0.33) compared to short walk test (negligible ES=0.00). Another study  
7 whose intervention involved specific walking exercises, was Dettmers et al.<sup>25</sup> who on maximal  
8 walking distance observed a moderate ES=0.47 [-0.25; 1.22].

9 Of the five studies<sup>28,56-59</sup> investigating the effect of RT on short walk test performance, three  
10 studies<sup>28,56,59</sup> detected a moderate ES corresponding to the ES of the meta-analysis (ES=0.27  
11 [0.07; 0.47]).

12 Previously, the effect of RT on the performance on a short walk test has been summarized in a  
13 review<sup>64</sup> and in a meta-analysis based on only one study<sup>19</sup>. However, to our knowledge, this is  
14 the first systematic review to perform a meta-analysis on RT studies alone, examining the  
15 effects on short walk tests (and walking performance in general).

16 On the long walk test, four RT studies<sup>28,55,57,58</sup> were included in the meta-analysis which showed  
17 a moderate ES (ES=0.36 [-0.35; 1.08]), with CIs displaying some degree of uncertainty. These  
18 variable results are in line with previous reports<sup>64</sup>. Of note, Kjølhede et al.<sup>58</sup> was the only study  
19 showing a large beneficial effect of RT on long walk test performance, ES=1.07 [0.34; 1.86].  
20 Potentially, this is because of the length of the intervention (24 weeks), compared to the  
21 shorter interventions in the other studies (10 weeks<sup>55,57</sup> and 12 weeks<sup>28</sup>). This was supported by

1 our weighted (moderator) regression analysis, showing a positive association between  
2 intervention duration (weeks and number of sessions) and ES.

3 Only a few studies investigated the effect of AT<sup>50,52</sup> or RT<sup>57,58</sup> on self-reported walking  
4 performance. Based on the two identified studies in each modality, meta-analyses showed a  
5 negligible effect on MSWS (AT, ES=-0.04 and RT, ES=0.07), despite both modalities being  
6 effective on all objective walking outcomes. As these results are sparse and somewhat  
7 inconclusive, they should be interpreted cautiously. Speculatively, they may indicate that  
8 adaptations in objectively measured outcomes precede self-reported outcomes, which is  
9 somehow contradictory to what has been shown previously<sup>65</sup>, and/or that adaptations in self-  
10 reported outcomes are limited due to a potential ceiling effect.

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### 12 ***Physical function - functional measurements***

13 While walking performance is an essential aspect of lower extremity physical function, our  
14 sparse and inconclusive findings reveal an existing knowledge gap in terms of how the two  
15 exercise modalities (AT in particular) might impact other measures such as chair rise, six spot  
16 step test (SSST) and stair negotiation. This is problematic, since complex walking tests such as  
17 the SSST<sup>66</sup> along with highly physically demanding walking tests such as stair negotiation<sup>67</sup>, have  
18 the potential to give a more in depth picture of patients walking ability. Such tests incorporate  
19 not only acceleration and endurance, but also other components such as coordination and  
20 balance which are recognized as being important for general physical function. Hence, future  
21 AT as well as RT studies should incorporate such complex functional tests in their test battery.

1

## 2 ***Fatigue measurements***

3 Nine studies<sup>26,43-45,47,51-54</sup> investigated the effect of AT on perceived fatigue. In the majority of  
4 these a moderate-large ES<sup>26,43,45,47,54</sup> was observed, with an overall large ES as determined by  
5 our meta-analysis (ES=-0.61, [-1.10; -0.11]). This adds further weight to findings of previous  
6 systematic reviews (including a Cochrane review) in this area<sup>17,68</sup>, with the combined evidence  
7 indicating that AT is effective in reducing perceived fatigue.

8 In this present systematic review and meta-analysis, only three studies<sup>55,57,61</sup> investigated the  
9 effect of RT on perceived fatigue. Hence, whilst remaining cautious in our interpretation, data  
10 indicate a moderate and beneficial effect of RT on perceptions of fatigue, ES=-0.41, [-0.80; -  
11 0.02]. This provides further evidence for already existing guidelines<sup>16</sup>.

12

## 13 ***Comparison between modalities***

14 We did not detect any apparent differences in the magnitude of effect on physiological  
15 adaptations in the two exercise modalities. Many components such as duration, frequency and  
16 intensity should be taken into account when comparing the two modalities. The average  
17 frequency and duration was somewhat comparable between the two exercise modalities (AT: 3  
18 days/week\*11 weeks (range 3-26 weeks), 28 sessions (range 9-48 sessions); RT: 2  
19 days/week\*11 weeks (range 8-24 weeks), 25 sessions (range 15-48 sessions)), along with the  
20 intensity being moderate-to-high in both AT and RT. A plausible explanation for the lack of

1 association between intervention duration (weeks and number of sessions) and meta-analysis  
2 ES is that the majority of interventions had durations of 8-12 weeks involving 16-24 sessions.  
3 The only exceptions showing positive associations were for RT on muscle strength and long  
4 walk test, respectively, although likely driven by one study only<sup>58</sup> having a much longer  
5 intervention duration (24 weeks, 48 sessions) compared to the remaining RT studies.  
6 Unfortunately the quantity and quality of the reported exercise intensity data (missing  
7 information, use of divergent scales of exercise intensity) did not allow us to examine the  
8 associations between exercise intensity and meta-analysis ES within each modality. Since  
9 factors such as duration, frequency and intensity are crucial for the extent of adaptations<sup>39</sup>,  
10 further studies seem warranted to help advance our understanding of any potential dose-  
11 response association between general exercise parameters (e.g. duration, frequency and  
12 intensity) and physiological as well as functional adaptations in pwMS.

13 To our knowledge, only one pilot study<sup>69</sup> has previously performed a head-to-head comparison  
14 of the two modalities, finding no difference in either lower extremity physical function as  
15 measured by the six minute walk test and the timed up and go, or in perceived fatigue  
16 measured by the Modified Fatigue Index Scale. However, only n=19 participants finished this  
17 cross-over study having an eight week wash-out period. Adaptations from exercise  
18 interventions may last as long as 12<sup>24</sup> or 24<sup>58</sup> weeks, hence, one must be cautious when  
19 interpreting results from this pilot study<sup>69</sup>.

20 Resembling the observations in physiological adaptations, no difference was observed in the  
21 magnitude of change on short or long walking tests with AT or RT. All meta-analyses on the  
22 walking tests had comparable moderate ES, although data – based on CIs – appeared most

1 robust for short walk with RT and for long walk with AT, respectively. While this is likely  
2 influenced by the number of studies for each meta-analyses, it may also be due to physiological  
3 adaptations that are intuitively associated with certain aspects of walking (AT: increment in  
4 aerobic capacity associated with walking endurance; RT: increment in muscle strength  
5 associated with walking acceleration)<sup>70</sup>. While the present findings are aligned with previously  
6 reported findings in systematic reviews and meta-analyses<sup>18,19</sup>, these were based on a limited  
7 number of RCT studies (as the search was performed March 2014)<sup>19</sup> or a combination of RCT  
8 and non-RCT studies, different exercise modalities, and different measures of walking  
9 performance (self-reported as well as clinician-rated short and long walking performance)<sup>18</sup>.

10 The novel approach of the present systematic review, apart from updating existing evidence,  
11 was to include RCTs only, clearly separate study findings across the two most common exercise  
12 modalities, and uphold a clear distinction between the selected walking performance outcome  
13 measures.

14 Both modalities were found to be effective in terms of reducing perceived fatigue, with a large  
15 ES observed for AT and a moderate ES for RT. While Andreasen et al.<sup>71</sup> in their systematic  
16 review previously reported RT to be slightly more effective than AT in terms of reducing  
17 perceived fatigue, Heine et al.<sup>17</sup> in their Cochrane systematic review and meta-analysis  
18 reported the opposite (applying a broader definition of exercise modalities). In context of the  
19 two exercise modalities and their effect on perceived fatigue, Rooney et al.<sup>72</sup> performed a  
20 systematic review and meta-analysis and found a strong association between aerobic capacity  
21 and perceived fatigue ( $r=-0.47$  [-0.64;-0.25]), but only a moderate association between muscle  
22 strength and perceived fatigue ( $r=-0.22$  [-0.40;-0.03]).

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***Translational or parallel improvements?***

Assessment of physiological adaptations are important due to two aspects. First, it is a simple way of validating exercise efficacy as effects on these basic primary (sensitive) physiological targets are expected (i.e. AT expectedly improve aerobic capacity while RT expectedly improve muscle strength). Second, physiological adaptations may be a prerequisite for improvements in physical function, thereby having a translational effect. Interestingly, the findings from the present systematic review and meta-analyses suggest that improvements in lower extremity physical function can be achieved via different physiological pathways (i.e. cardiovascular system or neuromuscular system). At least, we observed parallel improvements in physiological adaptations and in physical function. However, since only a limited number of studies reported parallel data of both physiological parameters and physical function of the same outcome (see Table 3) and since even fewer studies report associations between changes in these outcomes, we were unable to perform any analysis of association. A small number of studies have reported data supporting an exercise-induced translational link, i.e. between improvements in muscle strength and Fatigue Severity Scale (FSS)<sup>61</sup>, aerobic capacity and FSS<sup>46</sup>, as well as muscle strength and Timed 25-Foot Walk, two minute walk test, five repetition sit-to-stand and stair climb<sup>58</sup>. This is nevertheless challenged by the fact that lower extremity physical function relies on different physiological systems, and adaptations in just one system may elicit little translational response. Also, in high-functioning pwMS the ceiling effect of many commonly used walking measures may mean that changes in performance are not detectable. Nevertheless, physiological adaptations can still be achieved, building physiological reserve

1 capacity as well as improving general health thereby potentially postponing the onset of future  
2 physical functional limitations. In order to advance our understanding of any translational link,  
3 more studies examining the association between exercise-induced physiological adaptations  
4 and measures of physical function are required in pwMS across the entire disability span. This  
5 could also help elucidate why some pwMS have a positive effect of an exercise intervention  
6 whereas others do not (i.e. responders vs. non-responders).

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### 8 ***Clinical and research implications***

9 The present study findings emphasize the importance of providing structured intensive AT  
10 and/or RT when aiming to improve lower extremity physical function (along with physiological  
11 adaptations). While many different exercise modalities exist, AT and RT have consistently been  
12 shown to be among the most effective in terms of positively affecting numerous different  
13 domains<sup>22</sup>. As the two modalities proved somewhat comparable (based on magnitude of ESs), it  
14 implies that clinicians could use either modality to target impairments in lower extremity  
15 physical function - we suggest patient preference be central to this decision to optimize the  
16 likelihood of them sustaining exercise over long term. The inconsistency in reporting across  
17 studies, emphasize the need for using a “core battery” of physical function tests, as previously  
18 proposed<sup>73</sup>. This would enable comparability of findings across studies and facilitate generation  
19 of more robust evidence, which is essential for clinicians’ decision-making. Moreover, exercise  
20 studies should report data for the physiological outcomes they are targeting. This would  
21 advance our understanding of potential translational links between physiology and function.

1 Finally, future studies should compare the modalities directly by performing a head-to-head  
2 study to establish whether differences in outcomes exist.

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#### 4 ***Study limitations***

5 The present systematic review and meta-analyses, provides a detailed and comprehensive  
6 overview of the RCTs investigating the effect of AT and RT on lower extremity physical function  
7 and perceived fatigue. However, some methodological considerations deserve mentioning.  
8 First, the majority of identified studies included patients with mild-moderate disease severity,  
9 making the results applicable for this subgroup of patients only. Second, more studies are  
10 needed to elucidate effects of AT and RT in pwMS with higher levels of disability, including  
11 those who are non-ambulatory (EDSS  $\geq$  7.0), which is a problem that has been exposed  
12 previously<sup>74</sup>. Third, this systematic review provides an overview of existing studies evaluating  
13 the two modalities, and hence is not able to provide a direct comparison. To provide such  
14 information, a well-considered head-to-head study of the two modalities, designed to diminish  
15 the difference in intensity and volume, is needed. Finally, our review focused on either solely  
16 AT or RT. As such, we cannot comment on the effectiveness of interventions which combine  
17 these two exercise modalities or use other exercise modalities (for example pilates, yoga,  
18 balance).

#### 19 ***Conclusions***

20 Based on knowledge from existing RCTs, aerobic training (AT) and resistance training (RT)  
21 appear comparable in improving lower extremity physical function (walking performance in

1 particular) and perceived fatigue. Although substantial physiological adaptations were  
2 observed, conclusions about the underlying mechanisms for the improvement are yet to be  
3 determined. Future studies should adapt a 'core battery' of physical function tests to facilitate a  
4 detailed comparison of results across exercise modalities. This will enable evidence-based  
5 treatment selection according to the defined purpose of training.

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**Figure 1: PRISMA flow diagram on the search result and study selection process.**

**Figure 2: Meta-analysis of the effect of aerobic training and resistance training on physiological adaptations.**

*Abbreviations: RT: Resistance training; AT: Aerobic training;  $VO_{2max}$ : Maximal oxygen consumption  
a: Strength measured in knee extensor; b: Strength measured in knee extensor and flexor (average); c: Strength measured in legpress*

**Figure 3: Meta-analysis of the effect of aerobic training and resistance training on the performance of a short walking test.**

*Abbreviations: RT: Resistance training; AT: Aerobic training*

**Figure 4: Meta-analysis of the effect of aerobic training and resistance training on the performance of a long walking test.**

*Abbreviations: RT: Resistance training; AT: Aerobic training  
a: 6 minute walk test, b: 2 minute walk test, c: Maximum walking distance*

**Figure 5: Meta-analysis of the effect of aerobic training and resistance training on self-reported walking ability.**

*Abbreviations: RT: Resistance training; AT: Aerobic training*

**Figure 6: Meta-analysis of the effect of aerobic training and resistance training on the perceptions of fatigue.**

*Abbreviations: RT: Resistance training; AT: Aerobic training  
a: Effect size as an average of the Fatigue Severity Scale, Modified Fatigue Impact Scale and the CIS20r: Checklist Individual Strength*