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Is fatigue associated with aerobic capacity and muscle strength in people with Multiple Sclerosis: a systematic review and meta-analysis

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Abstract

Objective: Determine the relationship between self-reported fatigue and aerobic capacity and muscle strength in people with Multiple Sclerosis (MS).

Data sources: Four databases (CINAHL, MEDLINE, ProQuest, and Web of Science Core Collections) were searched up to October 2018.

Study selection: Cross-sectional or longitudinal studies that reported the association between self-reported fatigue and aerobic capacity or objectively measured muscle strength in people with MS were included.

Data extraction: Study details, participant demographics, outcome measurement protocols, and the correlation coefficient derived from the association between fatigue and aerobic capacity or muscle strength at baseline was extracted, and methodological quality of included studies was assessed using the Joanna Briggs Institute Appraisal Checklist for Analytical Cross-sectional Studies.

Data synthesis: Ten studies were identified, of which five examined the association between fatigue and aerobic capacity and seven examined the association between fatigue and muscle strength. Meta-analysis of the extracted correlation coefficients was performed using the Hedges-Olkin method, and pooled correlation coefficients demonstrated a moderate, negative association between fatigue and aerobic capacity ($r = -0.471$; 95% CI = -0.644, -0.251; $p<0.001$), and a weak, negative association between fatigue and muscle strength ($r = -0.224$; 95% CI = -0.399, -0.032; $p = 0.022$).

Conclusions: The results of this meta-analysis suggest that higher levels of aerobic capacity are associated with lower fatigue. Therefore, this finding highlights the potential role of aerobic exercise interventions in managing fatigue. Conversely, the relationship between fatigue and muscle strength was weak and inconsistent, and further studies are required to examine the association between these variables.

Key words: Multiple Sclerosis; Fatigue; Fitness; Aerobic capacity; Muscle strength

Abbreviations: CPET, Cardiopulmonary exercise testing; EDSS, Expanded Disability Status Scale; FSS, Fatigue Severity Scale; MFI, Multidimensional Fatigue Inventory; MFIS, Modified Fatigue Impact Scale; MS, Multiple Sclerosis; MVIC, Maximum voluntary isometric contraction; RCT, Randomised controlled trial; VO_{2max}, Maximum oxygen consumption; VO_{2peak}, Peak oxygen consumption

1 Introduction

Fatigue is a common symptom of Multiple Sclerosis (MS) reported in around 70% of those with the condition (1-3), which can be defined as "a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities"(4). MS-related fatigue is often considered one of the most debilitating symptoms of MS, and is associated with impaired physical and cognitive functioning, reduced quality of life, and unemployment (5-7). While the exact pathophysiological mechanisms of fatigue are not fully understood, it is thought that inflammation and altered function of demyelinated neural pathways may lead to the development of fatigue alongside secondary factors such as depression and sleep quality (8).

Exercise – defined as "planned, structured and repetitive bodily movement with a purpose of improving or maintaining one or more components of physical fitness" (9) – has been recommended to manage MS-related fatigue (10), and several systematic reviews have demonstrated that exercise can reduce fatigue symptoms in both progressive and non-progressive forms of MS (11-13). Although the mechanisms underlying the positive effects of exercise on fatigue are not fully known, several factors have been proposed including exercise inducing an anti-inflammatory and neuroprotective effect in addition to improving other symptoms (e.g. depression) that are commonly associated with fatigue (14). Furthermore, constructs of physical fitness (9), specifically aerobic capacity and muscle strength, have been shown to improve in response to exercise in people with MS (15,16). However, the relationship between fatigue and these outcomes is unclear; therefore, it is unknown whether higher levels of aerobic capacity or muscle strength are associated with lower levels of fatigue in people with MS.

Measures of physical fitness are important markers of health and function in people with MS, as higher aerobic capacity is associated with lower cardiovascular risk, lower levels of disability, and greater physical function (17), while lower-limb muscle strength is a strong predictor of walking performance and physical function (18,19). Furthermore, aerobic capacity and muscle strength may contribute to the development of fatigue, as a lower level of aerobic capacity and muscle strength are associated with increased oxygen consumption when walking (20). Consequently, as both aerobic capacity and muscle strength are reduced in people with MS in comparison to healthy controls (16,17), it has been proposed that the reduced capacity to carry-out physical work will subsequently lead to fatigue due to increased energy expenditure during everyday tasks (21). Therefore, improving aerobic capacity and muscle strength through exercise may decrease the impact and severity of fatigue in people with MS.

Although this pathway is speculative, no systematic review has yet synthesised the evidence to determine whether a relationship exists between fatigue and aerobic capacity or muscle strength. If fatigue is found to be associated with these constructs of physical fitness, then these outcomes may be a key target of exercise interventions which aim to reduce fatigue, and may inform the design of exercise interventions by guiding the choice of exercise mode and dosage relevant to the target fitness outcome. Accordingly, the aim of this systematic review and meta-analysis was to determine the relationship between self-reported fatigue and aerobic capacity and muscle strength in people with MS.

2 Methods

A review protocol was registered with the PROSPERO database in November 2018 (number: CRD42018117209)

2.1 Eligibility criteria

The following criteria were used to screen studies for eligibility: 1) observational studies with either a cross-sectional or prospective design, or a randomised controlled trial (RCT) if the association between aerobic capacity/muscle strength and fatigue was reported at baseline; 2) inclusion of adult participants with a definite diagnosis of MS; 3) the subjective perception of fatigue was assessed using a patient reported outcome measure; 4) aerobic capacity (defined as either maximum (VO_{2max}) or peak (VO_{2peak}) oxygen consumption (22)) was directly measured through graded cardiopulmonary exercise testing or muscle strength (defined as the maximum voluntary contractile force of a muscle group (22)) was assessed using an objective measurement scale; 5) the association between fatigue and aerobic capacity or muscle strength was reported. In addition, only full-text articles published in English were included in this review. Where the results of the same study were reported in multiple articles, only the original article was included.

2.2 Search strategy

Searches of the following databases were conducted from inception to October 2018: CINAHL (via EBSCOhost), MEDLINE (via Ovid), ProQuest (Health & Medical Collection, Nursing & Allied Health Database, PsychInfo) and Web of Science Core Collections. Search strategies were comprised of keywords related to MS, fatigue, aerobic capacity, and muscle strength (Supplementary table 1). Reference lists of included articles were also hand searched to identify additional articles.

2.3 Study selection

The results of each database search were exported to Covidence systematic review software (2017, Veritas Health Innovation, Melbourne, Australia) and, after removing duplicates, the title and abstracts of all articles were screened against the eligibility criteria by one reviewer (SR). Subsequently, two reviewers (SR, LP) independently screened full texts of the remaining articles for eligibility. Disagreements were resolved through consensus in consultation with a third reviewer if required. Authors were contacted for results when studies included measures of self-reported fatigue and aerobic capacity/muscle strength but did not report the association between the variables at baseline.

2.4 Quality assessment

Methodological quality of included studies was assessed using the Joanna Briggs Institute Appraisal Checklist for Analytical Cross-sectional Studies (23), which contains eight questions related to the internal and external validity of studies that can be answered as “yes”, “no” or “unclear”. Quality assessment of included articles was completed independently by two reviewers (SR, LP), and discrepancies were resolved through consensus in consultation with a third reviewer if required. Prior to completing the quality assessment, a pilot assessment was conducted where each reviewer read and independently scored an article to ensure consistency in assessment. There were no exclusion criteria based on the quality assessment in order to allow the identification of any limitations within the current evidence.

2.5 Data extraction

Data extraction was completed independently by one reviewer (SR) using a standardised data extraction form. The data extracted from each study included: study details (author, year of publication, study design), participant demographics (total number, age, gender, disability, MS-type), the outcome measures and protocol used to assess fatigue and aerobic capacity or muscle strength. In addition, the correlation coefficient derived from the association between fatigue and aerobic capacity or muscle strength was extracted when the result was reported at baseline. If correlation coefficients were reported for fatigue outcome measure subscales in addition to the overall outcome measure, then only the overall outcome correlation was extracted.

2.6 Data synthesis

2.6.1 Narrative synthesis

Firstly, the results of all included studies were analysed by narrative synthesis, and the association between fatigue and aerobic capacity/muscle strength was classified by direction and strength – correlation coefficients <0.3 were interpreted as weak association, ≥0.3 to <0.7 as moderate association, and ≥0.7 as strong association (24). Studies were categorised according to the construct of physical fitness that was assessed, and the association between each outcome and fatigue was compared between studies that used the same outcome.

2.6.2 Meta-analysis

Meta-analysis of correlation coefficients was performed using MedCalc software v18.10.2. Correlation coefficients were transformed to z scores using Fisher's z transformation (25), and meta-analysis of the transformed values was conducted using the Hedges-Olkin method (26). Results of the meta-analysis were then back-transformed from z scores to correlation coefficients for interpretation (25). Heterogeneity in results across studies was assessed using

I^2, and when $I^2 > 40\%$ a random effects model was used due to evidence of significant heterogeneity (27). When correlation coefficients were reported for multiple fatigue outcome measures within the same study, these results were averaged to generate a single value as including multiple correlations from one study would increase the weight of this study in the meta-analysis leading to a misrepresentation of the overall association. However, to account for possible variance in fatigue outcome measures used between studies, a sensitivity analysis was performed by pooling the results of studies that used the same fatigue outcome measures. In addition, a further sensitivity analysis was performed depending on whether an upper-limb or lower limb modality was used for cardiopulmonary exercise testing (CPET). For all tests, a significance level of $p<0.05$ was used.

3 Results

3.1 Results of the search

After removing duplicates, the titles and abstracts of 403 articles were screened against the eligibility criteria and 362 records were excluded (Figure 1). Of the remaining 41 articles, 33 were initially excluded as: the association between fatigue and aerobic capacity/muscle strength was not reported (n=20); the association between fatigue and aerobic capacity/muscle strength was reported for post-intervention changes values only (n=8); studies did not include a subjective measure of fatigue (n=2), studies did not measure aerobic capacity or muscle strength (n=1); results were reported in an earlier article (n=1); results were reported in a conference abstract (n=1). The authors of the 28 articles that included measures of both fatigue and aerobic capacity or muscle strength but had not reported the association between the variables at baseline were contacted for these results. Two authors responded and provided this data; therefore, 10 articles were included in this review and meta-analysis (Table 1). Of the included articles, nine reported the results of cross-sectional studies (28-36), whereas one reported the results of a RCT (37). Five studies examined the association between fatigue and aerobic capacity (29-31,35,36), and seven examined the association between fatigue and muscle strength (28,32-37).

Figure 1 near here

Table 1 near here

3.2 Participants

A total of 445 people with MS were included in the studies in this review, and sample sizes ranged from 18-112. Participants were mostly female (61.8%) and had a relapsing-remitting form of MS (77.1%); however, one study did not report the sex of study participants (33), and another did not report participant MS type (30). All studies used the Expanded Disability Status Scale (EDSS) to measure disability, with mean and median scores ranging from 3.1-4.4 and 2.5-4.3 respectively, indicating that most participants were mild-moderately disabled.

3.3 Outcome measures

3.3.1 Fatigue

Four different self-reported outcome measures were used to assess fatigue: six studies used the Fatigue Severity Scale (FSS) (28,30,32-34,36,37), three studies used the Modified Fatigue Impact Scale (MFIS) (29,31,35), two studies used the Multidimensional Fatigue Inventory (MFI) (32,37), and one study used a Visual Analogue Scale (VAS) (28).

3.3.2 Aerobic capacity

The most commonly used modality for CPET was a lower limb bicycle ergometer (29,31,36), although one study used an upper limb ergometer only (30), and one study used both an upper limb ergometer and recumbent stepper over two tests separated by one week (35). All studies measured aerobic capacity as peak oxygen uptake (VO_{2peak}), and four studies reported $VO2_{peak}$ values normalised to body weight (mL/kg/min) (30,31,35,36); however, one study reported VO_{2peak} as VO_2/kilogram without stating the measurement units (29). Of the studies that used lower limb CPET and normalised VO_{2peak} to body weight, the mean baseline values of 20.6 ± 5.9 mL/kg/min (31) and 19.87 (95% CI = 16.95, 22.79) mL/kg/min (36) were within 1-2 standard deviations of the population estimate of 25.5 ± 5.2 mL/kg/min (17). VO_{2peak} was lower when an upper limb cardiopulmonary exercise testing modality was used, as Koseoglu et al. (30) reported a mean value of 10.06 ± 4.7 mL/kg/min.

3.3.3 Muscle strength

The most commonly used technique for assessing muscle strength was recording maximal voluntary isometric contraction (MVIC) through dynamometry (28,33-37). Of the studies that recorded MVIC, five assessed lower limb muscle groups (knee extensors (33,35-37); knee flexors (35,37); ankle dorsiflexors (28)), and one assessed an upper limb muscle group - 2nd metacarpal-phalangeal joint flexors (34). MVIC values were reported for the right limb (28,33,34), an average of both limbs (35,36) or the least affected limb (37). Only one study used manual muscle testing where strength was measured on an ordinal scale and a composite score (derived from bilateral upper and lower limb muscle strength) was reported (32).

3.4 Study quality

The total number of items on the Joanna Briggs Institute Appraisal Checklist that were adequately addressed by studies ranged from 3-8 (Table 2). Most studies used valid and reliable outcomes to measure fatigue and aerobic capacity/muscle strength, clearly defined inclusion criteria, and appropriate statistical tests. However, few studies accounted for confounding variables as only two studies adjusted for gender (28,37), one study adjusted for depression (34), and one study adjusted for disability (35). In addition, only five studies adequately reported the demographics of the study participants and study setting (29,31,35-37).

Table 2 near here

3.5 Association between fatigue and aerobic capacity

Across the five studies that investigated the association between fatigue and aerobic capacity, all found a negative association with four studies reporting a moderate negative association (30,31,35,36), and one study reporting a weak negative association (29). When the correlation coefficients were pooled in a meta-analysis (Figure 2), fatigue was found to have a moderate, negative association with aerobic capacity (r = -0.471; 95% CI = -0.644, -0.251;

$p<0.001$); however, there was evidence of significant heterogeneity across studies (I^2 = 70.18%; p = 0.009). Sensitivity analysis indicated that the strength of association was consistent across studies that used the FSS (r = -0.655; 95% CI = -0.800, -0.438; df = 1; $p<0.001$) and MFIS (r = -0.362; 95% CI = -0.471, -0.242; df = 3; $p<0.001$), and lower limb (r = -0.446; 95% CI = -0.661, -0.163; df = 3; p=0.003) and upper limb CPET modalities (r = -0.560; 95% CI = -0.690, -0.395; df = 1; $p<0.001$).

Figure 2 near here

3.6 Association between fatigue and muscle strength

Inconsistent findings were reported across the six studies investigating the association between fatigue and muscle strength, as three studies reported a moderate negative association (28,34,35), two studies reported a weak negative association (33,36), and two studies reported a weak positive association (32,37). The pooled correlation coefficient across all studies was -0.224 (95% CI = -0.399, -0.032; p = 0.022), indicating that fatigue has a weak negative association with muscle strength (Figure 3). However, there was evidence of heterogeneity between studies (I^2 = 55.84%; p = 0.03) and the upper CI limit was greater than 0 in five studies (28,32,34,36,37) suggesting variability in the presence and direction of association between these variables.

Figure 3 near here

As the study by Trojan et al. (32) was the only study that did not use dynamometry to assess muscle strength a sensitivity analysis was conducted with this study excluded, and, although greater consistency across studies was found (I^2 = 50.85%; p = 0.133), the association between fatigue and strength remained weak (r = -0.282; 95% CI = -0.446, -0.100; df = 5; p = 0.003). In addition, further sensitivity analysis indicated that the strength of association was inconsistent across studies that used different fatigue outcome measures, as studies that used the MFIS demonstrated a stronger association with strength (r = -0.436;

95% CI = -0.598, -0.211; df = 1; p<0.001) in comparison to studies that used the FSS (r = -0.122; 95% CI = -0.258, 0.019; df = 5; p = 0.090).

4 Discussion

The evidence from the 10 studies included in this systematic review and meta-analysis demonstrate that fatigue has a moderate, negative association with aerobic capacity in people with MS. Therefore, these results suggest that higher aerobic capacity is associated with lower fatigue. Conversely, the association between fatigue and muscle strength was weak and inconsistent and varied depending on the outcome measure used; thus, it is unclear whether higher levels muscle strength is associated with lower fatigue.

While people with MS generally have reduced levels of cardiorespiratory fitness (17), aerobic exercise interventions have been demonstrated to be effective in improving aerobic capacity (15). Therefore, as lower fatigue is associated with higher aerobic capacity, the results of this review highlight the potential role of aerobic exercise interventions in improving fatigue in people with MS. Previous systematic reviews have reported that aerobic exercise interventions have a homogenous moderate positive effect on fatigue in MS (13), and the potential benefits of aerobic exercise in managing fatigue have been demonstrated in people with progressive MS (38) – a population with a higher prevalence and severity of fatigue (1,3,39). While there is insufficient evidence from intervention studies to determine the optimal dose of exercise to improve fatigue, the results of this current review suggest that, in order to have a beneficial effect on fatigue, exercise prescription must be sufficient to increase aerobic capacity. However, due to the cross-sectional nature of these results, the direction of causality between fatigue and aerobic capacity cannot be inferred from this analysis and longitudinal studies are required to confirm this association.

Although the mechanisms underlying the beneficial effects of aerobic exercise on fatigue remain unclear, one possible mechanism is that changes in aerobic capacity following exercise may account for improvements in fatigue (14). While previous articles have suggested that cardiorespiratory fitness and deconditioning may contribute to MS-related fatigue (8,14), this is the first systematic review and meta-analysis to confirm the association between these variables. A possible pathway to explain this relationship is the association between aerobic capacity and energy expenditure. In a cross-sectional sample of 44 people with MS, aerobic capacity (measured as VO_{2peak}) was negatively associated with estimated energy cost of walking during a 6-minute walk test at the participant's self-selected speed (20). In addition, estimated energy cost of walking has been shown to be positively associated with fatigue in people with MS, highlighting that greater energy expenditure may lead to increased fatigue (21,40). Therefore, increasing aerobic capacity may reduce energy expenditure during every day physical activities and subsequently attenuate fatigue.

However, fatigue is a complex and multidimensional symptom and several clinical features such as depression, sleep quality, and cognition are associated with fatigue in people with MS (3,41-43). Furthermore, depression and cognition are also negatively associated with aerobic capacity (44,45), and the severity of depression has been demonstrated to reduce following aerobic exercise (46). Therefore, it is unclear whether changes in aerobic capacity have a direct effect on fatigue or whether this pathway is mediated through changes in depression or cognition. Future studies should explore this pathway in order to determine whether fatigue is associated with aerobic capacity independent of these variables.

In comparison to aerobic capacity, results of this meta-analysis indicated muscle strength demonstrated a weaker negative association with fatigue, and the relationship between these variables was inconsistent as some studies reported a positive, though non-significant, association. Most studies included in this review assessed lower limb muscle strength, which is strongly associated with levels of disability and physical function (e.g. walking performance) (18,19,47). However, no study specifically included the most affected limb in the correlation analysis or accounted for the anthropometric differences of participants by normalizing strength measurements to body weight (48). Furthermore, all studies measured isometric muscle strength and did not include measures of dynamic (e.g. isokinetic) muscle strength. Although one study used manual muscle testing to assess strength, sensitivity analysis indicated that this study did not change the result of the meta-analysis despite the limited precision of this measurement technique in comparison to dynamometry (16).

The weak association between fatigue and muscle strength support the results of a previous meta-analysis which found that resistance training interventions that were designed to improve muscle strength had a heterogeneous, non-significant effect on fatigue outcomes (13). Therefore, it remains unclear whether greater muscle strength is associated with lower levels of fatigue. However, while this present review included only studies that assessed muscle strength, other aspects of neuromuscular function (such as muscle fatigability) can also be used to assess physical fitness (9). In contrast to muscle strength, muscle fatigability refers to the ability to sustain force development over time and can be characterized by a temporal decline in performance during functional tasks (49,50). In a meta-analysis of 19 studies measures of fatigability demonstrated a moderate positive correlation with self-reported fatigue in people with MS, suggesting that increased muscle fatigability may contribute to worsening fatigue (51). Therefore, in order to improve fatigue, perhaps resistance training interventions should aim to improve muscle fatigability rather than muscle strength. However, further longitudinal studies are required to investigate the association between neuromuscular function and fatigue in people with MS.

4.1 Limitations of the evidence

Despite the multidimensional nature of MS-related fatigue, few studies considered confounding variables when analyzing the association between fatigue and constructs of physical fitness. Therefore, it is unclear whether fatigue is independently associated with aerobic capacity/muscle strength or whether other variables (such as depression or disability) moderate this relationship. Accordingly future studies should consider these confounding relationships in multi-variate regression models to better understand the association between these variables. In addition, several different fatigue outcome measures and protocols to measure aerobic capacity/muscle strength were used across the studies included in this review. This may have influenced the accuracy of the pooled correlation coefficients – for example, it is unclear whether the association between fatigue and muscle strength varied depending on the use of upper-limb or lower-limb assessment. Furthermore, this review only included studies that used VO_{2peak} to assess aerobic capacity. While there are other indirect measures that can be used to estimate aerobic capacity, these measures provide less valid assessments of aerobic capacity when compared with the gold-standard VO_{2max}/ VO_{2peak} (52)

and were, therefore, not included in this review. Lastly, the findings of this review are limited by the cross-sectional design of the included studies, meaning it was not possible to determine the direction of causality between fatigue and aerobic capacity/muscle strength – consequently, it is unclear whether changes in fatigue account for differences in these outcomes or whether improvements in aerobic capacity/muscle strength result in reduced fatigue.

5 Conclusions

This systematic review and meta-analysis demonstrated that fatigue has a moderate, negative association with aerobic capacity in people with MS, suggesting that higher levels of aerobic capacity are associated with lower fatigue. Therefore, these results support the potential importance of aerobic exercise interventions in managing MS-related fatigue and suggest that exercise prescription must be sufficient to increase aerobic capacity in order to elicit improvements in fatigue. However, future longitudinal studies are required to determine the direction of causality between these variables. In contrast to aerobic capacity, this review found that fatigue had a weak and inconsistent association with muscle strength. Accordingly, further studies are required to determine whether objectively measured improvements in muscle strength are associated with changes in fatigue in people with MS.

Conflicts of interest: None

References

(1) Lerdal A, Celius EG, Krupp L, Dahl AA. A prospective study of patterns of fatigue in multiple sclerosis. Eur J Neurol 2007;14(12):1338-1343.

(2) Hadjimichael O, Vollmer T, Oleen-Burkey M, North American Research Committee on Multiple Sclerosis. Fatigue characteristics in multiple sclerosis: the North American Research Committee on Multiple Sclerosis (NARCOMS) survey. Health Qual Life Outcomes 2008;6:100-7525-6-100.

(3) Rooney S, Wood L, Moffat F, Paul L. Prevalence of fatigue and its association with clinical features in progressive and non-progressive forms of Multiple Sclerosis. Multiple Sclerosis and Related Disorders 2019;28:276-282.

(4) Multiple Sclerosis Council for Clinical Practice Guidelines. Fatigue and multiple sclerosis: Evidence-based management strategies for fatigue in multiple sclerosis. Washington, DC: Paralyzed Veterans of America; 1998.

(5) Janardhan V, Bakshi R. Quality of life in patients with multiple sclerosis: the impact of fatigue and depression. J Neurol Sci 2002;205(1):51-58.

(6) Bakshi R. Fatigue associated with multiple sclerosis: diagnosis, impact and management. Mult Scler 2003;9(3):219-27.

(7) Moore P, Harding KE, Clarkson H, Pickersgill TP, Wardle M, Robertson NP. Demographic and clinical factors associated with changes in employment in multiple sclerosis. Mult Scler 2013;19(12):1647-1654.

(8) Kos D, Kerckhofs E, Nagels G, D'hooghe MB, Ilsbroukx S. Origin of Fatigue in Multiple Sclerosis: Review of the Literature. Neurorehabil Neural Repair 2008;22(1):91-100.

(9) Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep 1985;100(2):126-131.

(10) National Institute for Health and Care Excellence. Multiple sclerosis in adults: management. National Institute for Health and Care Excellence; 2014.

(11) Andreasen AK, Stenager E, Dalgas U. The effect of exercise therapy on fatigue in multiple sclerosis. Mult Scler 2011(9):1041-1054.

(12) Pilutti LA, Greenlee TA, Motl RW, Nickrent MS, Petruzzello SJ. Effects of exercise training on fatigue in multiple sclerosis: a meta-analysis. Psychosom Med 2013;75(6):575-580.

(13) Heine M, van de Port I, Rietberg MB, van Wegen EEH, Kwakkel G. Exercise therapy for fatigue in multiple sclerosis. Cochrane Database of Systematic Reviews 2015(9):CD009956.

(14) Langeskov-Christensen M, Bisson EJ, Finlayson ML, Dalgas U. Potential pathophysiological pathways that can explain the positive effects of exercise on fatigue in multiple sclerosis: A scoping review. J Neurol Sci 2017;373:307-320.

(15) Platta ME, Ensari I, Motl RW, Pilutti LA. Effect of Exercise Training on Fitness in Multiple Sclerosis: A Meta-Analysis. Arch Phys Med Rehabil 2016;97(9):1564-1572.

(16) Jorgensen M, Dalgas U, Wens I, Hvid LG. Muscle strength and power in persons with multiple sclerosis - A systematic review and meta-analysis. J Neurol Sci 2017;376:225-241.

(17) Langeskov-Christensen M, Heine M, Kwakkel G, Dalgas U. Aerobic capacity in persons with multiple sclerosis: a systematic review and meta-analysis. Sports Med 2015;45(6):905-923.

(18) Broekmans T, Gijbels D, Eijnde BO, Alders G, Lamers I, Roelants M, et al. The relationship between upper leg muscle strength and walking capacity in persons with multiple sclerosis. Mult Scler 2013;19(1):112-119.

(19) Kjolhede T, Vissing K, Langeskov-Christensen D, Stenager E, Petersen T, Dalgas U. Relationship between muscle strength parameters and functional capacity in persons with mild to moderate degree multiple sclerosis. Multiple Sclerosis and Related Disorders 2015;4(2):151-158.

(20) Jeng B, Sandroff BM, Motl RW. Energetic Cost of Walking and Its Physiological Correlates in Persons With Multiple Sclerosis Who Have Moderate Mobility Disability. Arch Phys Med Rehab 2018;99(10):2038-2044.

(21) Motl RW, Sandroff BM, Suh Y, Sosnoff JJ. Energy cost of walking and its association with gait parameters, daily activity, and fatigue in persons with mild multiple sclerosis. Neurorehabil Neural Repair 2012;26(8):1015-1021.

(22) Swain DP. ACSM's resource manual for guidelines for exercise testing and prescription. 7th ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2014.

(23) Aromataris E, Munn Z. Joanna Briggs Institute Reviewer's Manual. Adelaide, Joanna Briggs Institute; 2017.

(24) Hinkle DE, Wiersma W, Jurs SG. Applied statistics for the behavioral sciences. Boston, USA: Houghton Mifflin; 1988.

(25) Fisher RA. Frequency Distribution of the Values of the Correlation Coefficient in Samples from an Indefinitely Large Population. Biometrika 1915;10(4):507-521.

(26) Hedges LV, Olkin I. Statistical methods for meta-analysis. Orlando, USA: Academic Press; 1985.

(27) Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327(7414):557-560.

(28) Ng AV, Miller RG, Gelinas D, Kent-Braun JA. Functional relationships of central and peripheral muscle alterations in multiple sclerosis. Muscle Nerve 2004;29(6):843-852.

(29) Rasova K, Brandejsky P, Havrdova E, Zalisova M, Rexova P. Spiroergometric and spirometric parameters in patients with multiple sclerosis: are there any links between these parameters and fatigue, depression, neurological impairment, disability, handicap and quality of life in multiple sclerosis? Mult Scler 2005;11(2):213-21.

(30) Koseoglu BF, Gokkaya NKO, Ergun U, Inan L, Yesiltepe E. Cardiopulmonary and metabolic functions, aerobic capacity, fatigue and quality of life in patients with multiple sclerosis. Acta Neurol Scand 2006;114(4):261-267.

(31) Konečný L., Pospíšil P., Dufek M., Drlíková L., Anbais F. H., Erajhi A. A., Dob Šák P., Vank P., Siegelová J. Functional impairment in Multiple Sclerosis. Scripta Medica 2007;80(5):225-232.

(32) Trojan D, Arnold D, Collet J, Shapiro S, Bar-Or A, Robinson A, et al. Fatigue in multiple sclerosis: association with disease-related, behavioural and psychosocial factors. Mult Scler 2007;13(8):985-95.

(33) Andreasen AK, Jakobsen J, Petersen T, Andersen H. Fatigued patients with multiple sclerosis have impaired central muscle activation. Mult Scler 2009;15(7):818-827.

(34) Steens A, de Vries A, Hemmen J, Heersema T, Heerings M, Maurits N, et al. Fatigue perceived by multiple sclerosis patients is associated with muscle fatigue. Neurorehabil Neural Repair 2012;26(1):48-57.

(35) Pilutti LA, Sandroff BM, Klaren RE, Learmonth YC, Platta ME, Hubbard EA, et al. Physical Fitness Assessment Across the Disability Spectrum in Persons With Multiple Sclerosis: A Comparison of Testing Modalities. J Neurol Phys Ther 2015;39(4):241-249.

(36) Valet M, Lejeune T, Glibert Y, Hakizimana JC, Van Pesch V, Sankari SE, et al. Fatigue and physical fitness of mildly disabled persons with multiple sclerosis: a cross-sectional study. Int J Rehabil Res 2017;40(3):268-274.

(37) Dalgas U, Stenager E, Jakobsen J, Petersen T, Hansen HJ, Knudsen C, et al. Fatigue, mood and quality of life improve in MS patients after progressive resistance training. Mult Scler 2010;16(4):480-490.

(38) Rooney, S. Wood, L. Moffat, F. Paul, L. Effectiveness of fatigue management interventions in reducing severity and impact of fatigue in people with progressive Multiple Sclerosis. Int J MS Care 2019;21:34-46.

(39) Mills RJ, Young CA. The relationship between fatigue and other clinical features of multiple sclerosis. Mult Scler 2011;17(5):604-612.

(40) Sandroff BM, Klaren RE, Pilutti LA, Motl RW. Oxygen cost of walking in persons with multiple sclerosis: disability matters, but why? Mult Scler Int 2014;2014:162765.

(41) Heesen C, Schulz KH, Fiehler J, Von der Mark U, Otte C, Jung R, et al. Correlates of cognitive dysfunction in multiple sclerosis. Brain Behav Immun 2010;24(7):1148-1155.

(42) Wood B, van der Mei IA, Ponsonby AL, Pittas F, Quinn S, Dwyer T, et al. Prevalence and concurrence of anxiety, depression and fatigue over time in multiple sclerosis. Mult Scler 2013;19(2):217-224.

(43) Nociti V, Losavio FA, Gnoni V, Losurdo A, Testani E, Vollono C, et al. Sleep and fatigue in multiple sclerosis: A questionnaire-based, cross-sectional, cohort study. J Neurol Sci 2017;372:387-392.

(44) Sandroff BM, Pilutti LA, Benedict RHB, Motl RW. Association Between Physical Fitness and Cognitive Function in Multiple Sclerosis: Does Disability Status Matter? Neurorehabil Neural Repair 2015;29(3):214-223.

(45) Ensari I, Pilutti LA, Motl RW. Depressive symptomology in multiple sclerosis: Disability, cardiorespiratory fitness and heart rate variability. Acta Neurol Scand 2017;136(5):440-446.

(46) Ensari I, Motl RW, Pilutti LA. Exercise training improves depressive symptoms in people with multiple sclerosis: results of a meta-analysis. J Psychosom Res 2014;76(6):465-471.

(47) Sandroff BM, Sosnoff JJ, Motl RW. Physical fitness, walking performance, and gait in multiple sclerosis. J Neurol Sci 2013;328(1-2):70-76.

(48) Jaric S. Muscle strength testing: use of normalisation for body size. Sports Med 2002;32(10):615-631.

(49) Zwarts MJ, Bleijenberg G, van Engelen BGM. Clinical neurophysiology of fatigue. Clinical Neurophysiology 2008;119(1):2-10.

(50) Severijns D, Zijdewind I, Dalgas U, Lamers I, Lismont C, Feys P. The Assessment of Motor Fatigability in Persons With Multiple Sclerosis: A Systematic Review. Neurorehabil Neural Repair 2017;31(5):413-431.

(51) Loy B, Taylor R, Fling B, Horak F. Relationship between perceived fatigue and performance fatigability in people with multiple sclerosis: A systematic review and meta-analysis. J Psychosom Res 2017;100:1.

(52) Stickland MK, Butcher SJ, Marciniuk DD, Bhutani M. Assessing exercise limitation using cardiopulmonary exercise testing. Pulm Med 2012;2012:824091.

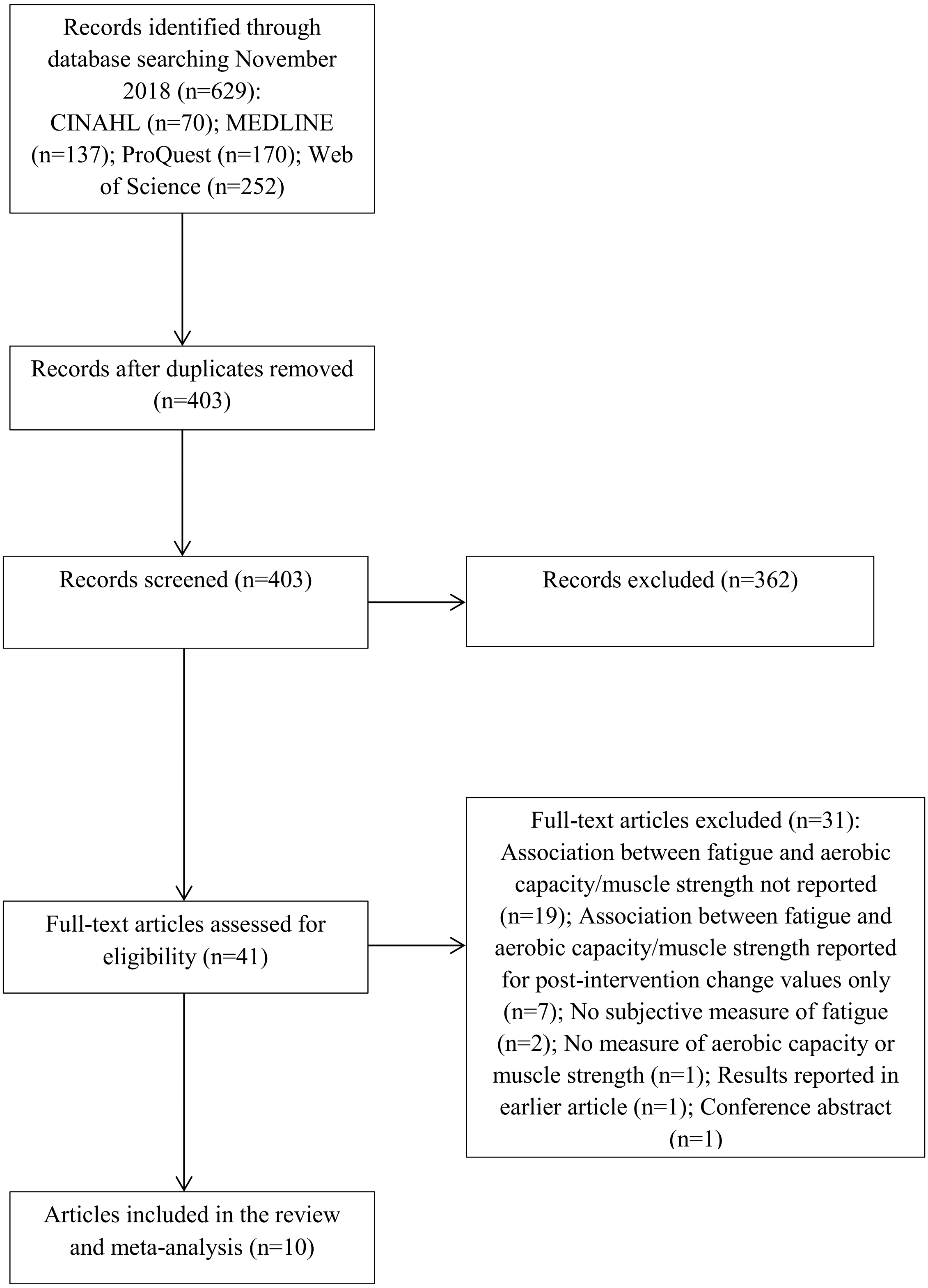

Figure 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram (Moher et al., 2009)

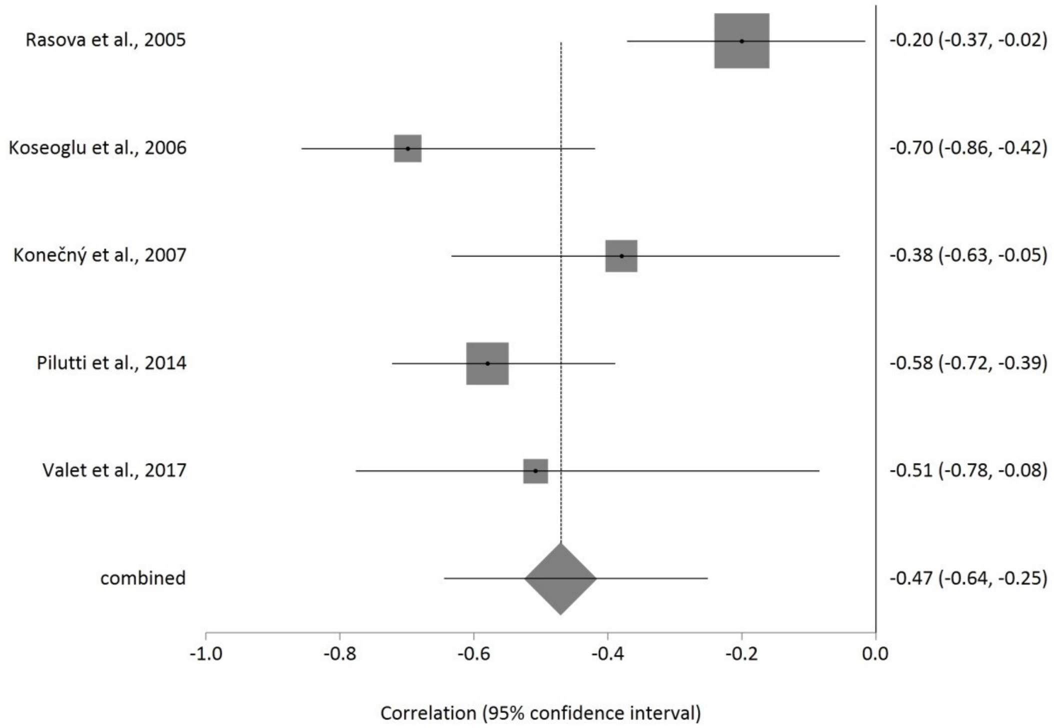

Figure 2 Correlation **(**Hedges-Olkin random effects) meta-analysis for the association between fatigue and aerobic capacity

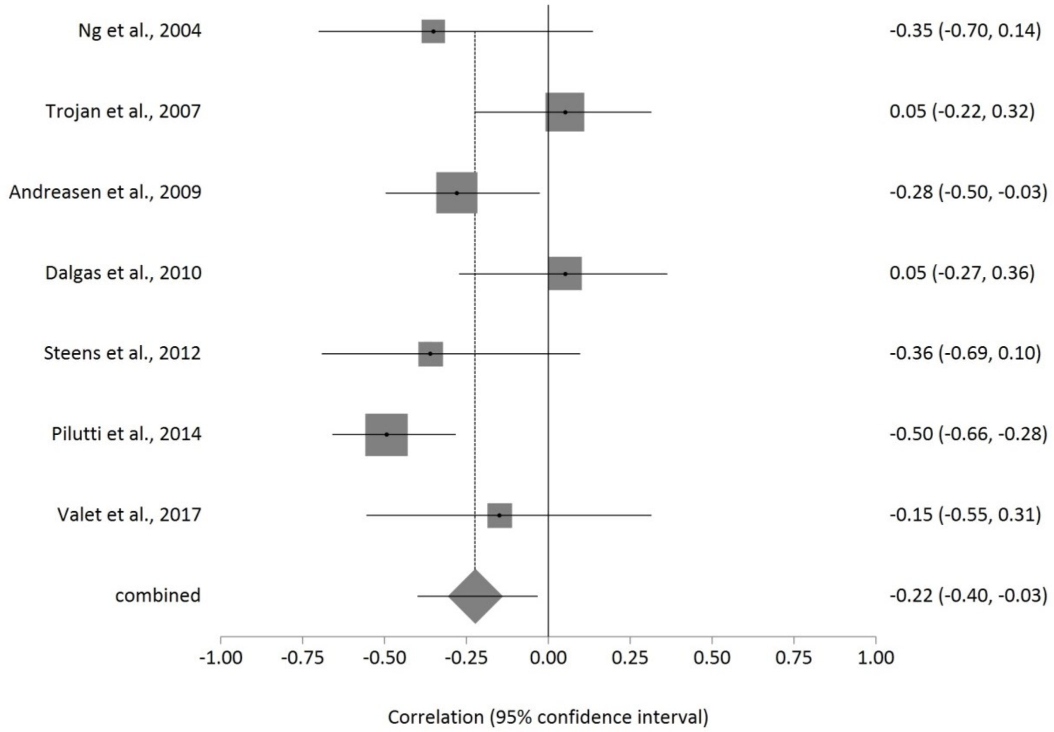

Figure 3 Correlation **(**Hedges-Olkin random effects) meta-analysis for the association between fatigue and muscle strength

Table 1 Characteristics and results of included studies

Author, date, and study design	Participant demographics	Fatigue outcome measure	Aerobic capacity/muscle strength outcome measurement	Main findings
Ng et al., 2004 (28) Cross-sectional	N = 18 (12 F/6 M) MS type: 50% RRMS, 50% SPMS/PPMS EDSS (median (range)) = 3.2 (1.5-6) Height (mean ± SD) = 169±2 cm Weight (mean ± SD) = 73.7±3.4 kg	FSS, VAS (0-10)	<u>Muscle strength</u> *Device used*: Computerised dynamometer *Limb tested*: Right *Contraction type, joint action*: Isometric, ankle dorsiflexion (120° plantarflexion) *Outcome measures*: MVIC (N) *Muscle strength (mean ± SD):* 115±15 N	<u>Correlation with FSS*:</u> MVIC ($r = -0.208$, $p = 0.59$) <u>Correlation with VAS*:</u> MVIC ($r = -0.496$, $p = 0.17$)
Rasova et al., 2005 (29) Cross-sectional	N = 112 (83 F/29 M) MS type: 71% RRMS, 21% SPMS, 8% PPMS EDSS (mean ± SD) = 3.1±1.7 Height (mean ± SD) = 171.4±8 cm Weight (mean ± SD) = 65.8±13.0 kg	MFIS	<u>Aerobic capacity</u> *Ergometer*: Lower limb bicycle, EL800, Ergoline, Germany *Gas exchange measurement*: Oxycon Delta, Jaeger, Germany *Test protocol*: Resistance increment/min *Outcome*: VO_{2peak}(VO_2/kg) *Aerobic capacity (mean ± SD)*: 81.77±23.05 VO_2/kg	<u>Correlation with MFIS:</u> VO_{2peak} ($r = -0.200$, $p>0.05$)
Koseoglu et al., 2006 (30) Cross-sectional	N = 25 (13 F/12 M) MS type: NR EDSS (mean ± SD) = 4.4±2.6 Height: NR Weight: NR	FSS	<u>Aerobic capacity</u> *Ergometer*: Upper limb ergometer, Ergoline, Germany *Gas exchange measurement*: Vmax29, Sensormedics, USA *Test protocol*: Warm-up 25W/3 mins, resistance increment/ 3 mins, 50 rpm *Outcome*: VO_{2peak} (mL/kg/min) *Aerobic capacity (mean ± SD)*: 10.06±24.7 mL/kg/min	<u>Correlation with FSS:</u> VO_{2peak} ($r = -0.699$, $p<0.05$)
Konečný et	N = 35 (28 F/7 M)	MFIS	<u>Aerobic capacity</u>	<u>Correlation with MFIS:</u> VO_{2peak}

al., 2007 (31) Cross-sectional	MS type: 49% RRMS, 46% SPMS, 5% PPMS EDSS (mean ± SD) = 3.0±1.2 Height: NR Weight: NR		*Ergometer*: Lower limb bicycle *Gas exchange measurement*: MedGraphics, USA *Test protocol*: Increments 20W/2 mins *Outcome*: VO_{2peak} (mL/kg) *Aerobic capacity (mean±SD)*: 20.60±5.9 mL/kg/min	(r = -0.380, p<0.05)
Trojan et al., 2007 (32) Cross-sectional	N = 53 (34 F/19 M) MS type: 70% RRMS, 30% SPMS EDSS (mean ± SD) = 3.4±2.2 Height: NR Weight: NR	FSS, MFI	Muscle strength *MRC strength scale*: Physician assessed muscle strength using ordinal scale (0-5), 12 muscle groups assessed (bilateral arm abduction, forearm flexion, wrist extension, leg flexion, knee extension and foot dorsal flexion), final score ranges from 0 (paralysis) to 60 (normal strength) *Muscle strength (mean ± SD):* 56.9±4.7	Correlation with FSS: MRC (r = 0.030, p>0.05) Correlation with MFI: MRC (r = 0.070, p>0.05)
Andreasen et al., 2009 (33) Cross-sectional	N = 60 (F/M NR) MS type: 100% RRMS EDSS (range) = 1-3.5 Height (range) = 158-191 cm Weight (range) = 46-102 kg	FSS	Muscle strength *Device used*: Computerised dynamometer, Biodex System 3, Biodex Medical Systems, USA *Limb tested*: Right *Contraction type, joint action*: Isometric, knee extension (90^{o} flexion) *Outcome measures*: MVIC (Nm) *Muscle strength:* NR	Correlation with FSS: MVIC (r = -0.280, p<0.05)
Dalgas et al., 2010 (37) RCT	N = 38 (25 F/13 M) MS type: 100% RRMS EDSS (mean ± SD) = 3.8±0.8 Height (mean ± SD) = 169.0±10.6 cm Weight (mean ± SD) = 67.7±14.0 kg	FSS, MFI	Muscle strength *Device used*: Computerised dynamometer, Biodex System 3, Biodex Medical Systems, USA *Limb tested*: Least-affected leg (patient reported) *Contraction type, joint action*: Isometric, knee extension and knee flexion (70^{o} flexion) *Outcome measures*: MVIC (Nm) *Muscle strength (mean ± SD):* knee extensors = 171.7±58.1Nm; knee flexors = 70.2±23.8Nm	Correlation with FSS*: *MVIC*: knee extension (r = 0.070, p = 0.690), knee flexion (r = 0.090, p = 0.600) Correlation with MFI*General fatigue: *MVIC*: knee extension (r = 0.030, p = 0.880), knee flexion (r = 0.040, p = 0.800) Physical fatigue: *MVIC*: knee extension (r = 0.050, p = 0.750), knee flexion (r = 0.040, p =

				0.800) Reduced activity: *MVIC*: knee extension (r = 0.210, p = 0.200), knee flexion (r = 0.010, p = 0.950) Reduced motivation: *MVIC*: knee extension (r = 0.210, p = 0.210), knee flexion (r = 0.060, p = 0.730) Mental fatigue: *MVIC*: knee extension (r = -0.010, p = 0.960), knee flexion (r = -0.180, p = 0.300)
Steens et al., 2012 (34) Cross-sectional	N = 20 (13 F/7 M) MS type: 100% RRMS EDSS (median (range)) = 2.5 (0-5) Height: NR Weight: NR	FSS	Muscle strength *Device used*: Computerised dynamometer *Limb tested*: Right *Contraction type, joint action*: Isometric, 2nd metacarpal phalangeal joint flexion *Outcome measures*: MVIC (Nm) *Muscle strength (mean ± SD):* M, 38.9±5.6 Nm; F, 25.8±7.7 Nm	Correlation with FSS: MVIC (r = -0.360, p>0.05)
Pilutti et al., 2014 (35) Cross-sectional	N = 64 (46 F/18 M) MS type: 77% RRMS, 23% SPMS/PPMS EDSS (median (IQR)) = 4.3 (2.5) Height (mean ± SD) = 169.9±10.2 cm Weight (mean ± SD) = 80.1±20.9 kg	MFIS	Aerobic capacity *Ergometer*: Upper limb ergometer, Ergometrics 800 arm ergometer, Ergoline, Germany; Recumbent stepper, Nustep T5^{XR}, Nustep, USA *Gas exchange measurement*: TrueOne 2400, Parvo Medics, USA *Test protocol*: 15W + 5-10W/min *Outcome*: VO_{2peak} (mL/kg/min) *Aerobic capacity*: NR Muscle strength *Device used*: Computerised dynamometer, Biodex System 3, Biodex Medical Systems, USA; hand-held dynamometer, Lafayette Manual Muscle Testing System, Lafayette Instrument Company, USA *Limb tested*: Average of both limbs	Correlation with MFIS: VO_{2peak}: Upper limb ergometry (r = -0.500, p<0.05), recumbent stepper (r = -0.660, p<0.05) *MVIC*: Computerised dynamometry (extensors, r = -0.500, p<0.05; flexors, r = -0.490, p<0.05); hand-held dynamometry (extensors, r = -0.460, p<0.05; flexors, r = -0.460, p<0.05)

			Contraction type, joint action: Isometric, knee extension and flexion (60° flexion) *Outcome measures*: MVIC (Nm) *Muscle strength:* NR	
Valet et al., 2017 (36) Cross-sectional	N = 20 (14 F/6 M) MS type: 70% RRMS, 5% SPMS, 20% PPMS EDSS (median (range)) = 2.5 (0-4) Height: NR Weight: NR	FSS, MFIS	<u>Aerobic capacity</u> *Ergometer*: Lower limb bicycle, Ergomedic 828E, Monark, Sweden *Gas exchange measurement*: Ergocard, Medisoft, Belgium *Test protocol*: 0W + 25W/2min *Outcome*: VO_{2peak} (mL/kg/min) *Aerobic capacity (mean, 95% CI)*: 19.87 (16.95, 22.79) mL/kg/min <u>Muscle strength</u> *Device used*: Computerised dynamometer, Cybex, CSMI, USA *Limb tested*: Average of both limbs *Contraction type, joint action*: Isometric, knee extension *Outcome measures*: MVIC (Nm) *Muscle strength (mean, 95% CI):* 78.73 (64.1, 93.3) Nm	<u>Correlation with FSS:</u> VO_{2peak} ($r = -0.590$, $p<0.05$); MVIC ($r = -0.102$, $p>0.05$) <u>Correlation with MFIS:</u> VO_{2peak} ($r = -0.426$, $p>0.05$); MVIC ($r = -0.196$, $p>0.05$)

*Values obtained from the study author

Abbreviations: EDSS, Expanded Disability Status Scale; F, Female; FSS, Fatigue Severity Scale; M, Male; MFIS, Modified Fatigue Impact Scale; MFI, Multidimensional fatigue inventory ; MRC, Medical Research Council; MS, Multiple Sclerosis; MVIC, Maximal voluntary isometric contraction; NR, Not reported; PPMS, Primary Progressive Multiple Sclerosis; RCT, Randomised Controlled Trail; RRMS, Relapsing Remitting Multiple Sclerosis; SPMS, Secondary Progressive Multiple Sclerosis; VAS, Visual analogue scale; VO_{2peak}, Peak oxygen consumption.

Table 2 Joanna Briggs Institute Appraisal Checklist for Analytical Cross-sectional Studies (23)

Study	**1. Were the criteria for inclusion in the sample clearly defined?**	**2. Were the study subjects and the setting described in detail?**	**3. Was the exposure measured in a valid and reliable way?**	**4. Were objective, standard criteria used for measurement of the condition?**	**5. Were confounding factors identified?**	**6. Were strategies to deal with confounding factors stated?**	**7. Were the outcomes measured in a valid and reliable way?**	**8. Was appropriate statistical analysis used?**
Ng et al., 2004 (28)	U	N	Y	Y	Y	Y	Y	Y
Rasova et al., 2005 (29)	N	Y	U	U	N	N	Y	Y
Koseoglu et al., 2006 (30)	Y	N	Y	U	N	N	Y	Y
Konečný et al., 2007 (31)	N	Y	Y	N	N	N	Y	Y
Trojan et al., 2007 (32)	Y	N	U	Y	N	N	Y	Y
Andreasen et al., 2009 (33)	Y	N	Y	Y	N	N	Y	Y
Dalgas et al., 2010 (37)	Y	Y	Y	Y	Y	Y	Y	Y
Steens et al., 2012 (34)	Y	N	Y	Y	Y	Y	Y	Y
Pilutti et al., 2014 (35)	Y	Y	Y	N	Y	Y	Y	Y
Valet et al., 2017 (36)	Y	Y	Y	Y	N	N	Y	Y

Abbrevaitions: N, No; U, Unclear; Y, Yes

Supplementary table 1

Search terms
(“Multiple Sclerosis”) AND (Fatigue or "physical fatigue" or "mental fatigue" or "central fatigue" or "fatigue impact" or "fatigue severity") AND ("physical fitness" or "maxim* oxygen consumption" or "maxim* oxygen uptake" or "cardiopulmonary exercise testing" or "cardiopulmonary exercise test" or "VO2-max" or "VO2max" or "VO2-peak" or "VO2peak" or "aerobic capacity" or "maxim* aerobic capacity" or "cardiopulmonary fitness" or "muscle strength" or "maxim* voluntary contraction" or "maxim* muscle contraction" or “muscle function” or “mechanical muscle function” or “muscle power” or “explosive strength” or “rate of force development”)