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Oxygen cost of walking in people with Multiple Sclerosis and its association with fatigue: a systematic review and meta-analysis

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Practice Points:

- Oxygen cost of walking is significantly higher in people with Multiple Sclerosis compared to healthy controls.
- Evidence from a small number of studies highlights that oxygen cost of walking may be positively correlated with fatigue suggesting that higher levels of fatigue are associated with greater energy expenditure while walking.
- Future studies should determine whether interventions (e.g. exercise) which reduce energy cost of walking also positively influences fatigue.

Abstract

Background: This systematic review and meta-analysis aimed to: 1) compare the oxygen cost of walking in people with MS to healthy controls; 2) assess the relationship between oxygen cost of walking and fatigue in people with MS.

Methods: Four databases (CINAHL, MEDLINE, ProQuest, Web of Science) were searched up to September 2020. Studies were included if they recruited adults with MS and either compared oxygen cost of walking to a healthy control population or determined the relationship between oxygen cost of walking and fatigue. Meta-analysis of the standardised mean difference in oxygen cost of walking between people with MS and healthy controls was performed.

Results: 9 studies were included in this review of which 7 compared oxygen cost of walking in people with MS (n=176) to healthy controls (n=142), and 4 investigated the relationship between oxygen cost of walking and fatigue. Meta-analysis revealed that people with MS (with predominately mild-moderate disability) had a significantly higher oxygen cost of walking compared to health controls (SMD = 2.21; 95% CI = 0.88, 3.54; $p = 0.001$). In addition, 3 studies found a significant yet weak positive association between oxygen cost of walking and fatigue.

Conclusions: People with MS expend greater amounts of energy when walking compared to healthy controls. This increase in energy expenditure may contribute to the development of fatigue, as a small number found that higher oxygen costs of walking were associated with greater levels of fatigue. Therefore, future studies should investigate whether reducing energy expenditure during movement improves fatigue.

Introduction

Multiple Sclerosis (MS) is a chronic demyelinating disease of the central nervous system which manifests in impaired nerve conduction and dysfunction of neural pathways.[1] The clinical manifestation of MS is heterogeneous and dependent upon the location of demyelination; although, lesions typically impact motor, sensory, visual, and cerebellar function.[2] Consequently, walking impairments are a common feature of MS and are reported in up to 68% of the population.[3] Reductions in walking speed and endurance are often demonstrated by people with MS,[4-6] alongside altered gait kinematics such as lower cadence, shortened stride length, and increase time spent in double-limb support.[7,8] These alterations in gait performance are suggested to reduce the efficiency of movement resulting in increased energy expenditure.[9]

Energy expenditure while walking is commonly quantified by measuring the changes in metabolic rate associated with the movement – i.e. the oxygen cost of walking. The oxygen cost of walking is defined as the volume of oxygen consumed per kilogram of body weight over the distance travelled, and reflects the total energy required for muscle activation and the maintenance of balance and posture in order to sustain locomotion.[9] Increased oxygen costs of walking can be used as a physiological marker of gait impairment to indicate either greater levels of energy expenditure used to travel the same distance or a reduction in the distance travelled for the same level of energy expenditure. In people with MS, disability[10-12] and slower walking speeds[12,13] are positively associated with oxygen cost of walking indicating that people with higher levels of gait impairments expend greater amounts of energy while walking. However, despite the prevalence of gait impairments, it is currently unclear whether energy expenditure during functional tasks such as walking is indeed higher in MS populations.

If oxygen cost of walking is found to be elevated in people with MS, then a consequence of this may be the development of fatigue – particularly with the progression of disability. Fatigue is one of the most common symptoms of MS which is reported by over 70% of the population,[14-16] and 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”.[17] Although the exact causes of MS-related fatigue are unclear it has been proposed that expending greater amounts of energy during activities of daily living may increase the subjective perception of effort and thus lead to increased fatigue.[18] Therefore, reducing the energy cost of movement could present a potential therapeutic target for interventions aimed at improving fatigue. However, despite the potential role of energy expenditure in the development of fatigue, no systematic review has yet evaluated the available evidence to determine the association between fatigue and oxygen cost of walking in MS populations; consequently, the relationship between energy expenditure and fatigue remains unclear.

Accordingly, the aims of this review are to: 1) compare the oxygen cost of walking in people with MS to healthy controls; 2) assess the relationship between oxygen cost of walking and fatigue in people with MS.

Methods

Eligibility criteria

Observational studies (with either a cross-sectional or prospective design) or randomised controlled trials which recruited adults with MS were included in this review if they directly measured oxygen cost of walking using a standardised testing protocol and met one of the following criteria: 1) compared the oxygen cost of walking in people with MS to healthy controls; 2) reported the association between oxygen cost of walking and fatigue (using any self-reported outcome measure) in people with MS. Studies with a longitudinal design were only included if mean difference and/or associations between oxygen cost of walking and fatigue was reported using baseline values. Only full-text articles published in English were included in this review and when the results of the same study were reported in multiple articles, only the original article was included in this review. Grey literature and conference abstracts were excluded.

Search strategy

A review protocol was registered with PROSPERO in September 2020 (CRD42020207500), and searches were conducted of the following databases from inception: CINAHL (via EBSCOhost), MEDLINE (via Ovid), ProQuest (Health & Medical Collection, Nursing &

Allied Health Database, Sports Medicine & Education Index) and Web of Science Core Collections. The following search strategy comprised of keywords was used in each database: ("Multiple Sclerosis") AND ("oxygen cost" OR "oxygen consumption" OR "oxygen uptake" OR "VO2" OR "energy cost" OR "energy expenditure" OR "energy efficiency" OR "energy requirement" OR "metabolic cost") AND ("walking" OR "gait" "locomotion" OR "activit* of daily living" OR "functional task*" OR "mobility task*"). Reference lists of included articles were also hand searched to identify additional articles.

Study selection

Study selection was conducted using Covidence systematic review software. After removing duplicates, the title and abstracts of all articles were screened against the eligibility criteria by one reviewer. Subsequently, two reviewers independently screened full texts of the remaining articles for eligibility. Disagreements were resolved through consensus in consultation with a third reviewer if required.

Quality assessment

Methodological quality of included studies was assessed by two reviewers using the Joanna Briggs Institute Critical Appraisal Checklist for Analytical Cross-Sectional Studies. Quality assessment was completed independently by each reviewer, and any discrepancies between reviewers 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. No studies were excluded based on the result of the quality assessment.

Data extraction

Data extraction was completed independently by one reviewer using a standardised data extraction form. Data extracted from studies included: study details (author, year of publication, study design), participant demographics (total number, age, gender, disability, MS-type), methods of measuring oxygen cost of walking (test duration, over-ground vs. treadmill walking, walking speed, measurement equipment, calculation of oxygen cost, use of walking aids), and the outcome measures used to assess fatigue (if applicable). For studies which compared oxygen cost of walking in people with MS to healthy controls, the mean values for oxygen cost of walking in the MS and control groups were extracted along with the mean difference and associated p-value. Additionally, for studies which report the association between oxygen cost of walking and fatigue, the value of the correlation coefficient was extracted.

Data synthesis

Narrative synthesis

The results of all included studies were analysed through narrative synthesis. Firstly the mean difference in oxygen cost of walking reported by individual studies was classified by direction and statistical significance ($p<0.05$) to determine whether oxygen cost of walking is significantly higher in the control or MS groups, or whether no significant difference was found. These findings were then compared across studies to determine whether a consistent difference was reported. Studies were also categorised according to the method used to measure oxygen cost (e.g. treadmill vs. over-ground walking, fixed vs. self-selected walking speed), and values for mean difference were compared within groups to determine the consistency of the results. Lastly, the association between fatigue and oxygen cost of walking was compared across studies, and findings were classified according to the direction and statistical significance of the reported correlation coefficients – i.e. a significant positive correlation, significant negative correlation, or no significant association.

Meta-analysis

Meta-analysis of the mean difference in oxygen cost of walking between people with MS and healthy controls was performed if oxygen cost of walking was assessed using the same units of measurement (i.e. mL/kg/m) in two or more studies. When data were reported for multiple walking speeds, only the self-selected/comfortable walking speed was included in the meta-analysis – studies which did not identify a self-selected/comfortable walking speed were excluded. Due to differences in methods of calculating oxygen cost (e.g. net oxygen consumption vs. total oxygen consumption), standardised mean differences were calculated using the mean and standard deviation extracted from each study. Summary estimates including 95% CI were then reported for each individual study and overall findings using

Revman software v5.3 (2019, Cochrane Collaboration, UK). Heterogeneity in results across studies was assessed using I^2, and a random effects model was used due to evidence of significant heterogeneity (I^2 >40%). To account for differences in methods used between studies to measure oxygen cost, a sensitivity analysis was performed to compare the results of studies that used fixed vs. self-selected walking speeds.

Results

Search results

The search strategy identified 282 articles and, after removing 120 duplicates, the title and abstracts of 162 articles were screened against the eligibility criteria. Of these articles, 139 were excluded, and the full-texts of the remaining 23 articles were screened. 14 articles were excluded after full-text screening as six articles did not include a control group or fatigue outcome measure, five did not include a measure of oxygen cost of walking, one did not report the difference in oxygen cost of walking between people with MS and healthy controls, one did not report the relationship between oxygen cost of walking and fatigue, and the results of one study were reported in another article. Therefore, nine articles were included in this review (Figure S1).[10,12,13,19-24] Of the included articles, all reported the results of cross-sectional studies with seven examining the difference in oxygen cost of walking in people with MS compared to healthy controls (Table S1),[10,19-24] and four examining the association between oxygen cost of walking and fatigue in people with MS (including two of the studies that examined the difference in oxygen cost of walking in people with MS compared to healthy controls;[23,24] Table S2).[12,13,23,24]

Participants

In total, 302 people with MS were included in the nine articles in this review with sample size ranging from 10-82. Participants were mostly female (77%) with a relapsing-remitting diagnosis of MS (79%), and the mean age of participants ranged from 39.0-54.1 years. Disability was measured using the Expanded Disability Status Scale (EDSS) in two articles,[21,23] and the Patient Determined Disease Steps (PDDS) in four articles,[10,12,13,22] with scores indicating mild-moderate levels of disability.

Oxygen cost of walking measurement

Walking protocol

Of the studies included in this review, five used a treadmill walking protocol when measuring oxygen cost of walking[10,13,19,22,23] and four used an over-ground walking protocol.[12,20,21,24] The duration of walking trials was six minutes in the majority of studies (n=6),[10,12,13,19,21,22] with remaining studies using a five minute protocol (n=3).[20,23,24] Of the studies that used a treadmill protocol, participants walked at a constant speed throughout the trial with the exception of the study by Olgiati et al.[19] where participants walked at 1.5 km/h for three minutes followed by 2.0 km/h for another three minutes. Three studies included multiple treadmill walking trials at various speeds, with Chung et al.[23] and Motl et al.[10] including three different walking speeds, and Sandroff et al.[22] including five different walking speeds. All over-ground walking trials were performed at the participant's self-selected walking speed (range of means = 0.43-1.33 m/s). All of the participants in the studies by Paul et al.[20] and Devasahayam et al.[24] used walking aids, whereas no walking aids were used by participants in the study by Franceschini et al.[21]

Calculation of oxygen cost

All studies measured oxygen consumption while walking using metabolic measurement systems with the exception of Olgiati et al.[19] which used rubber balloons to collect expired gas that was then analysed using a dry gas meter. The majority of studies used the mean steady-state oxygen consumption when calculating oxygen cost of walking – this was defined as the mean oxygen consumption during the final two minutes,[23,24] final three minutes,[10,12,13,22] or 4th minute (out of five) of the walking trial.[20] Only two studies used the mean oxygen consumption during the full duration of the walking trial when calculating oxygen cost.[19,21] The method used to calculate oxygen cost of walking varied between studies, as four studies calculated oxygen cost as net oxygen consumption (i.e. oxygen consumption while walking – oxygen consumption at rest) divided by walking speed,[12,13,19,23] whereas four studies calculated oxygen cost as gross oxygen consumption (i.e. oxygen consumption while walking) divided by walking speed.[10,20-22,24]

Study quality

The number of items that were adequately addressed on the Joanna Briggs Institute Critical Appraisal Checklist for Analytical Cross-Sectional Studies ranged from 6-8 (Table S3). Of the studies that included a control group, all adjusted for confounding variables by recruiting age and sex matched healthy controls. In addition, all studies used valid and reliable methods to assess oxygen cost of walking. However, three studies did not include a clear description of the criteria used to confirm diagnosis of MS.[19,20,23] Furthermore, one study did not adequately report the demographic characteristics of the study population.[19]

Oxygen cost of walking in Multiple Sclerosis vs. healthy controls

Oxygen cost of walking was found to be significantly higher in people with MS compared to healthy controls by all studies included in this review. Of the studies that measured oxygen cost of walking at self-selected walking speeds, mean values ranged from 0.10-0.60 ml/kg/m in people with MS and 0.06-0.22 ml/kg/m in healthy controls.[20,21,23,24] The studies which reported the largest difference in oxygen cost of walking between MS and healthy controls at self-selected speeds (-0.280 ml/kg/m; -0.380 ml/kg/m) also reported the highest values for oxygen cost of walking in those with MS (0.46 ml/kg/m; 0.60 ml/kg/m);[20,24] both studies used an over-ground walking protocol and predominantly included people with progressive forms of MS (83-93%) – all of whom required walking aids. Conversely, the study which reported the lowest value for oxygen cost of walking (0.10 ml/kg/m) used a treadmill protocol where participants did not use any walking aids.[23] Of the studies which measured oxygen cost of walking across various treadmill speeds, a consistent significant difference between people with MS and healthy controls was found at speeds of 54 m/min to 94 m/min,[10,22] but not at 107 m/min.[22] Similarly, using different walking speeds, Chung et al. only found a significant difference in the oxygen cost of walking between people with MS and healthy controls at slower gait speeds (mean difference: 0.6 m/s = -0.110 ml/kg/m, $p \leq 0.001$; 1.4 m/s = -0.010 ml/kg/m, $p > 0.05$).[23]

When the standardized mean difference was pooled in a meta-analysis (Figure 1), oxygen cost of walking was found to be significantly greater in people with mild to moderate MS compared to healthy controls (SMD (95% CI) = 2.21 (0.88, 3.54), $p = 0.001$). However, there was evidence of significant heterogeneity as the magnitude of difference varied across studies within the meta-analysis (I^2 = 91%, $p < 0.001$). In line with the methods of this review, two studies were excluded from this meta-analysis as these studies measured oxygen cost across various walking speeds and did not identify a self-selected/comfortable walking speed.[10,22] When only the results from studies that measured oxygen cost of walking at self-selected walking speeds were pooled,[20,21,23,24] a smaller, more consistent effect was found (SMD (95% CI) = 1.32 (0.73, 1.90), $p < 0.001$). Similarly, a smaller yet significant effect was found in studies that measured oxygen cost of walking at variable walking speeds (SMD (95% CI) = 1.53 (0.86, 2.20), $p < 0.001$)[20,21,24] compared to fixed speeds (SMD (95% CI) = 3.29 (-1.96, 8.55), $p > 0.05$).[19,23] However, due to small number of studies with variable sample sizes and population demographics, it is unclear whether the differences in measurement methods indeed account for the difference in results.

Figure 1 near here

Relationship between oxygen cost of walking and fatigue

Across the studies which investigated the association between oxygen cost of walking and fatigue, three studies measured fatigue using outcomes which required participants to recall symptoms over a period of time (e.g. Fatigue Severity Scale, Modified Fatigue Impact Scale),[12,13,24] whereas two studies measured fatigue immediately following completion of a walking test.[23,24] Of these studies, two reported a significant weak relationship ($r \leq 0.3$, $p \leq 0.05$) between oxygen cost of walking and Fatigue Severity Scale scores, suggesting that higher oxygen costs of walking may be associated with greater levels of fatigue.[12,13] While, the study by Devasahayam et al.[24] found no significant association between oxygen cost of walking and fatigue (measured using the Fatigue Severity Scale and Modified Fatigue Impact Scale), this study had a considerably smaller sample size compared to those which found a significant association (14[24] vs. 44-82[12,13]). Of the studies which measured fatigue immediately following completion of a walking task,[23,24] only one found fatigue to be moderately associated with oxygen cost of walking – this study included people with higher levels of mobility disability and greater energy costs of walking.[24]

Discussion

The evidence from the nine articles included in this systematic review and meta-analysis highlights that people with MS expend greater amounts of energy during walking, as oxygen cost of walking was found to be significantly higher in people with MS compared to healthy controls. In addition, evidence from a small number of studies suggests that higher oxygen costs of walking may be weakly associated with greater levels of fatigue, indicating a potential role of energy expenditure in the development of fatigue symptoms. Therefore, reducing energy expenditure during functional tasks such as walking could present a potential therapeutic target for interventions aimed at improving fatigue in people with MS. However, the relationship between oxygen cost of walking and fatigue remains unclear due to inconsistent evidence from a small number of studies that used various different fatigue outcome measures likely measuring different aspects of fatigue. Accordingly further research is required to determine the impact of increased energy cost of walking on the clinical features of MS such as fatigue.

Despite the prevalence of walking impairments in people with MS,[3] only seven studies were found that compared oxygen cost of walking in people with MS to healthy control populations. However, the evidence from this small number of studies consistently demonstrated higher oxygen costs in people with MS. At self-selected walking speeds (ranging between 0.43-1.33 m/s), people with MS were found to consume 30%-170% more oxygen per meter walked compared to healthy controls; this approximately equates to an increase of 0.011-0.108 METs/m. Therefore, the evidence presented in this review confirms the hypothesis that people with MS with mild to moderate disability expend greater amounts of energy while walking; this finding is similar to evidence from other neurological diseases including Stroke, Cerebral Palsy, and Parkinson's disease.[25-27]

While oxygen cost of walking was found to be consistently higher in people with MS, the mean value for oxygen cost and the magnitude of difference compared to healthy controls varied across the studies included in this review depending on the population recruited and walking protocol used. For instance, studies which recruited predominantly people with progressive MS reported higher oxygen costs of walking, and thus a greater difference compared to healthy controls.[20,24] As people with progressive MS generally present with more severe mobility impairments,[28] this finding is in line with previous evidence which demonstrates that oxygen cost of walking is higher in people with greater levels of disability.[10,12] In addition, differences in walking test protocols may also account for the variation in oxygen cost, as when walking at matched speeds, oxygen cost of walking was only found to be higher in people with MS at slower walking speeds. Although there were differences in oxygen cost of walking between studies that used treadmill or over-ground walking protocols, it is unclear whether these differences can be attributed to changes in movement patterns while treadmill walking[29,30] or the use of walking aids in over-ground tests.[11,12]

The mechanisms through which the oxygen cost of functional tasks such as walking are increased in people with MS are not yet determined but likely include factors related to disability, lower-limb spasticity, deconditioning, and walking impairments. As previously stated, studies included in this review reported higher oxygen costs of walking in populations with greater levels of disability. Furthermore, previous studies report that disability and oxygen cost of walking are positively associated, further indicating people with higher levels of disability expend greater amounts of energy during walking.[10,12] While the causal influence of this relationship is unclear, it is likely that disability directly influences energy expenditure due to the association between oxygen cost and gait and balance impairments.[12,13,31,32] Additionally, people with MS have a reduction in the number and size of fatigue resistant type 1 muscle fibres along with a decrease in muscle oxidative capacity;[33-36] consequently, these changes in muscle structure and function may also increase oxygen consumption during functional tasks due to changes in mitochondrial function and the ability to meet the energy requirements of the task. However, no study has yet determined whether these factors indeed contribute to the greater energy expenditure observed in MS populations. Therefore, further research is required to investigate the mechanisms that cause increased oxygen cost of walking in order to identify effective interventions to reduce energy expenditure.

The evidence presented in this systematic review also highlights the possible role of deconditioning in the development of fatigue due the positive association found between oxygen cost of walking and fatigue. People with MS are generally found to be deconditioned as previous systematic reviews have reported that both cardiorespiratory fitness and muscle strength are lower in MS populations compared to healthy controls.[37,38] Furthermore, higher levels of deconditioning are associated with greater energy costs during activities of daily living – particularly during walking.[39] Therefore, greater oxygen cost of walking as a result of deconditioning may increase the perception of effort during functional tasks, thus leading to fatigue. However, due to the small number of studies included in this review, differences in fatigue outcome measures used across studies, and cross-sectional nature of the evidence, the presence and magnitude of association and direction of causality between oxygen cost of walking and fatigue is unclear. Accordingly, further studies are required to evaluate the association between oxygen cost of walking and fatigue to determine the relative roles of energy expenditure and deconditioning in the development of fatigue. Furthermore, future studies should also evaluate whether reversing the effects of deconditioning and improving walking performance in people with MS positively affects energy expenditure and fatigue.

If oxygen cost of walking is indeed associated with fatigue in people with MS, then interventions such as exercise which aim improve cardiorespiratory fitness have the potential to reduce fatigue. For example, as higher levels of aerobic capacity are associated with lower energy expenditure during functional tasks,[39] then reducing relative energy expenditure (i.e. expending energy at a lower percentage of maximal energy expenditure) through sufficiently intense aerobic exercise training may also lead to improvements in fatigue.[18] However, it is important to consider the increased energy demand in people with MS when prescribing exercise and modify the type and intensity of exercise prescription in line with current exercise recommendations.[40]

Limitations

There are several important limitations to consider when interpreting the findings of this review. Firstly, the methods used to measure oxygen cost of walking were inconsistent across the included studies. While some studies controlled for resting metabolic rate by calculating net oxygen consumption, other studies used gross oxygen consumption values to calculate oxygen cost of walking. Additionally, while most studies used steady-state oxygen consumption in determining oxygen cost of walking, the criteria used to define steady-state varied between studies, and it was unclear whether participants had indeed achieved steady-state oxygen consumption in each study. As a result of the variance in measurement methods, standardised mean difference in oxygen costs of walking were used in this meta-analysis which limits the interpretability of the results. Accordingly, standardised methods of measuring oxygen cost should be defined for future research. Secondly, the findings of this review are based on a small number of studies – most of which included participants with low-moderate levels of disability. Therefore, further research is required to measure oxygen cost of walking in MS populations with more severe levels of disability and gait impairment. 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 oxygen cost of walking and fatigue; consequently, it is unclear whether changes in fatigue account for differences in oxygen costs or whether reductions in oxygen costs result in improved fatigue.

Conclusions

This systematic review and meta-analysis found that oxygen cost of walking was higher in people with MS who have mild to moderate disability compared to healthy controls, which highlights that people with MS expend greater amounts of energy during walking. In addition, a small number of studies found that a higher oxygen cost of walking was associated with greater levels fatigue. Therefore, these findings suggest that rehabilitation interventions which aim to reduce oxygen cost of walking may have a positive impact on fatigue symptoms. However, further research is needed to investigate the impact of increased energy cost of walking on the clinical features of MS such as fatigue in order to determine whether reducing energy expenditure improves overall fatigue symptoms.

Conflicts of interest: None

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Study or Subgroup	Multiple Sclerosis Mean	SD	Total	Healthy controls Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Olgiati et al., 1988 [19]	0.27	0.02	33	0.16	0.01	12	17.8%	6.01 [4.55, 7.47]	1988
Paul et al., 2008 [20]	0.46	0.16	12	0.18	0.03	12	19.7%	2.35 [1.27, 3.43]	2008
Franceschini et al., 2010 [21]	0.22	0.05	46	0.17	0.03	36	22.0%	1.17 [0.69, 1.64]	2010
Chung et al., 2016 [23]	0.1	0.08	10	0.06	0.04	14	20.7%	0.65 [-0.19, 1.48]	2016
Devasahayam et al., 2019 [24]	0.6	0.3	14	0.22	0.04	7	19.9%	1.46 [0.43, 2.50]	2019
Total (95% CI)			**115**			**81**	**100.0%**	**2.21 [0.88, 3.54]**	

Heterogeneity: Tau² = 2.04; Chi² = 45.02, df = 4 (P < 0.00001); I² = 91%
Test for overall effect: Z = 3.26 (P = 0.001)

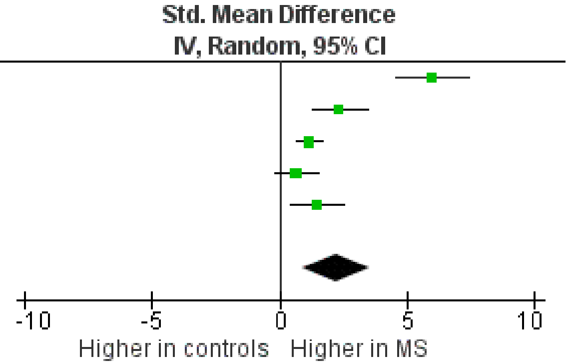

Figure 1 Meta-analysis comparing the standardised mean difference of oxygen cost of walking in people with Multiple Sclerosis to healthy controls

Table S1 Characteristics and main findings of the studies which investigated the difference in oxygen cost of walking between people with MS and healthy controls

Author, date, study design, quality	**Participant demographics**	**Control demographics**	**Oxygen cost of walking measurement**	**Main findings***
Olgiati et al.[19], 1988 Cross-sectional JBI = 6	N = 33 (F/M NR) MS type: NR EDSS: NR Age, years (mean ± SD) = 41.0 ± 1.7 Weight, kg (mean ± SD) = 67.0 ± 2.1	N = 12 (6 F/6 M) Age, years (mean ± SD) = 36.0 ± 2.0 Weight, kg (mean ± SD) = 67.0 ± 3.5	*Walking test*: Treadmill protocol; 6 mins of walking starting at 1.5 km/h with 0.5 km/h increase in speed after 3 mins *Walking speed*: 1.5 km/h, 2.0 km/h *Gas exchange measurement*: Open circuit spirometry using rubber balloon, expired gas measured using dry gas meter (Singer model DTM 115, American Meter Division, USA) *Calculation method*: Net VO_2/walking speed *Walking aids*: No aids used	<u>Oxygen cost (ml/kg/m)</u> MS: 0.267 ± 0.018 Controls: 0.162 ± 0.008 Mean difference (95% CI): **-0.105 (-0.116, -0.094), p < 0.001**
Paul et al.[20], 2008 Cross-sectional JBI = 7	N = 12 (F/M NR) MS type: 17% RRMS, 83% SPMS EDSS: NR Age, years (mean ± SD) = 53.0 ± 8.0 Weight, kg (mean ± SD) = 81.8 ± 18.3	N = 12 (F/M NR) Age, years (mean ± SD) = 52.0 ± 7.3 Weight, kg (mean ± SD) = 69.2 ± 13.6	*Walking test*: Overground walking; 5 mins *Walking speed*: Preferred walking speed (mean ± SD = 0.43 ± 0.15 m/s) *Gas exchange measurement*: COSMED K4b2 (Cosmed, Italy) *Calculation method*: Gross VO_2/walking speed *Walking aids*: 67% unilateral aid, 33% bilateral aid	<u>Oxygen cost (ml/kg/m)</u> MS: 0.46 ± 0.16 Controls: 0.18 ± 0.03 Mean difference (95% CI): **-0.280 (-0.378, -0.183), p < 0.001**

Franceschini et al.[21], 2010 Cross-sectional JBI = 8	N = 46 (27 F/19 M) MS type: NR EDSS (median (range)): 3 (1-4) Age, years (mean ± SD) = 39.0 ± 8.0 Weight: NR	N = 36 (21 F/ 15M) Age, years (mean ± SD) = 40.0 ± 9.0 Weight: NR	*Walking test*: Overground walking; 6MWT *Walking speed*: Self-selected walking speed (mean ± SD = 1.33 ± 0.25 m/s) *Gas exchange measurement*: Oxycon Mobile (Jäger, Germany) *Calculation method*: Gross VO_2/walking speed *Walking aids*: No aids used	Oxygen cost (ml/kg/m) MS: 0.219 ± 0.050 Controls: 0.170 ± 0.030 Mean difference: **-0.049 (-0.068, -0.030), p < 0.05**
Motl et al.[10], 2011 Cross-sectional JBI = 8	N = 18 (14 F/4M) MS type: 83% RRMS, 11% benign MS, 6% PPMS PDDS (median (range)): 1 (0-4) Age, years (mean ± SD) = 41.9 ± 12.6 Weight, kg (mean ± SD) = 72.1 ± 16.4	N = 18 (14 F/4 M) Age, years (mean ± SD) = 39.1 ± 11.9 Weight, kg (mean ± SD) = 72.8 ± 15.0	*Walking test*: Treadmill walking; three 6-min walking trials at a constant speed separated by 6 mins *Walking speed*: 54 m/min, 80 m/min, 107 m/min *Gas exchange measurement*: TrueOne (Parvo Medics, USA) *Calculation method*: Gross VO_2/walking speed *Walking aids*: No aids used	54 m/min oxygen cost (ml/kg/m) MS: 0.202 ± 0.023 Controls: 0.186 ± 0.010 Mean difference: **-0.016 (-0.028, -0.004), p < 0.05** 80 m/min oxygen cost (ml/kg/m) MS: 0.179 ± 0.020 Controls: 0.163 ± 0.013 Mean difference: **-0.016 (-0.027, -0.005), p < 0.05** 107 m/min oxygen cost (ml/kg/m) MS: 0.190 ± 0.024 Controls: 0.172 ± 0.011 Mean difference: **-0.018 (-0.031, -0.005), p < 0.05**

Sandroff et al.[22], 2012 Cross-sectional JBI = 8	N = 43 (38 F/5 M) MS type: 88% RRMS, 6% SPMS, 6% PPMS PDDS (median (range)): 1 (0-5) Age, years (mean ± SD) = 47.2 ± 9.1 Weight, kg (mean ± SD) = 75.7 ± 19.4	N = 43 (38 F/5 M) Age, years (mean ± SD) = 46.5 ± 10.0 Weight, kg (mean ± SD) = 75.4 ± 16.2	*Walking test*: Treadmill walking; five 6-min walking trials at a constant speed separated by 6 mins *Walking speed*: 54 m/min, 67 m/min, 80 m/min, 94 m/min, 107 m/min *Gas exchange measurement*: TrueOne (Parvo Medics, USA) *Calculation method*: Gross VO_2/walking speed *Walking aids*: No aids used	54 m/min oxygen cost (ml/kg/m) MS: 0.200 ± 0.026 Controls: 0.187 ± 0.027 Mean difference: **-0.013 (-0.024, -0.001), p < 0.05** 67 m/min oxygen cost (ml/kg/m) MS: 0.184 ± 0.025 Controls: 0.169 ± 0.022 Mean difference: **-0.015 (-0.025, -0.005), p <0.01** 80 m/min oxygen cost (ml/kg/m) MS: 0.171 ± 0.019 Controls: 0.156 ± 0.019 Mean difference: **-0.015 (-0.023, -0.007), p < 0.01** 94 m/min oxygen cost (ml/kg/m) MS: 0.167 ± 0.014 Controls: 0.157 ± 0.021 Mean difference: **-0.010 (-0.018, -0.002), p < 0.05** 107 m/min oxygen cost (ml/kg/m) MS: 0.167 ± 0.016 Controls: 0.162 ± 0.026 Mean difference: -0.005 (-0.014, 0.004), p > 0.05

Chung et al.[23], 2016 Cross-sectional JBI = 7	N = 10 (9 F/1 M) MS type: 90% RRMS, 10% PPMS EDSS (mean ± SD) = 4.6 ± 1.1 Age, years (mean ± SD) = 45.0 ± 8.0 Weight, kg (mean ± SD) = 74.4 ± 14.0	N = 14 (11 F/3 M) Age, years (mean ± SD) = 46.0 ± 7.0 Weight, kg (mean ± SD) = 73.4 ± 16.3	*Walking test*: Treadmill walking; three 5-min walking trials at a constant speed separated by 5-10 mins *Walking speed*: 0.6 m/s, 1.4 m/s, preferred walking speed *Gas exchange measurement*: TrueMax2400 Metabolic Measurement System (Parvo Medics, USA) *Calculation method*: Net VO_2/walking speed *Walking aids*: No aids used	<u>0.6 m/s oxygen cost (ml/kg/m)</u> MS: 0.25 ± 0.09 Controls: 0.14 ± 0.06 Mean difference: **-0.110 (-0.173, -0.047), p ≤ 0.001** <u>1.4 m/s oxygen cost (ml/kg/m)</u> MS: 0.11 ± 0.03 Controls: 0.10 ± 0.03 Mean difference: -0.010 (-0.036, 0.016), p > 0.05 <u>Preferred speed oxygen cost (ml/kg/m)</u> MS: 0.10 ± 0.08 Controls: 0.06 ± 0.04 Mean difference: -0.040 (-0.091, 0.011), p > 0.05
Devasahayam et al.[24], 2016 Cross-sectional JBI = 8	N = 14 (10 F/4 M) MS type: 7% RRMS, 71% SPMS, 22% PPMS EDSS: NR Age, years (mean ± SD) = 54.1 ± 8.5 Weight: NR	N = 7 (4 F/3 M) Age, years (mean ± SD) = 50.7 ± 12.1 Weight: NR	*Walking test*: Overground walking; 5 mins *Walking speed*: self-selected speed (mean ± SD = 0.53 ± 0.32 m/s) *Gas exchange measurement*: VmaxST, v1.0 (Sensor Medics, USA) *Calculation method*: Gross VO_2/walking speed *Walking aids*: 43% unilateral aid, 43 % bilateral aid, 14% unilateral or bilateral aid	<u>Oxygen cost (ml//kg/m)</u> MS: 0.60 ± 0.30 Controls: 0.22 ± 0.04 Mean difference: **-0.380 (-0.621, -0.139), p < 0.01**

* Values presented as mean ± SD unless stated otherwise

Abbreviations: 6MWT, 6-Minute Walk Test; EDSS, Expanded Disability Status Scale; F, Female; JBI, Joanna Briggs Institute Critical Appraisal Checklist for Analytical Cross-Sectional Studies; M, Male; MS, Multiple Sclerosis; NR, Not reported; PDDS, Patient Determined Disease Steps; PPMS, Primary Progressive Multiple Sclerosis; RRMS, Relapsing Remitting Multiple Sclerosis; SPMS, Secondary Progressive Multiple Sclerosis; VO_2, oxygen consumption

Table S2 Characteristics and main findings of the studies which investigated the association between oxygen cost of walking and fatigue in people with MS

Author, date, study design, quality	Participant demographics	Oxygen cost of walking measurement	Fatigue outcome measure	Main findings
Motl et al.[13], 2012 Cross-sectional JBI = 6	N = 44 (38 F/6 M) MS type: 90% RRMS, 5% SPMS, 5% PPMS PDDS (median (range)): 1 (0-3) Age, years (mean ± SD) = 47.2 ± 9.1 Weight, kg (mean ± SD) = 75.7 ± 19.4	*Walking test*: Treadmill walking; 6 mins at constant speed *Walking speed*: 54 m/min *Gas exchange measurement*: TrueOne (Parvo Medics, USA) *Calculation method*: Net VO_2/walking speed *Walking aids*: No aids used	FSS	Correlation with FSS: $r = 0.306$, $p \leq 0.05$
Sandroff et al.[12], 2014 Cross-sectional JBI = 6	N = 82 (63 F/19 M) MS type: 78% RRMS, 22% SPMS/PPMS PDDS (median (range)): 3 (0-6) Age, years (mean ± SD) = 49.1 ± 9.0 Weight, kg (mean ± SD) = 80.3 ± 21.7	*Walking test*: Overground walking; 6MWT *Walking speed*: Self-selected walking speed (mean ± SD = 0.98 ± 0.33 m/s) *Gas exchange measurement*: COSMED K4b2 (Cosmed, Italy) *Calculation method*: Net VO_2/walking speed *Walking aids*: NR	FSS	Correlation with FSS: $r = 0.223$, $p < 0.05$

Chung et al. [23], 2016 Cross-sectional JBI = 7	N = 10 (9 F/1 M) MS type: 90% RRMS, 10% PPMS EDSS (mean ± SD) = 4.6 ± 1.1 Age, years (mean ± SD) = 45.0 ± 8.0 Weight, kg (mean ± SD) = 74.4 ± 14.0	*Walking test*: Treadmill walking; three 5-minute walking trials at a constant speed separated by 5-10 minutes *Walking speed*: 0.6 m/s, 1.4 m/s, preferred walking speed *Gas exchange measurement*: TrueMax2400 Metabolic Measurement System (Parvo Medics, USA) *Calculation method*: Net VO_2/walking speed *Walking aids*: No aids used	VAS (immediately post-walking trial)	<u>Correlation with VAS</u>: 0.6 m/s: $r \leq 0.350$, $p \geq 0.1$ 1.4 m/s: $r \leq 0.350$, $p \geq 0.1$ Preferred speed: $r \leq 0.350$, $p \geq 0.1$
Devasahayam et al. [24], 2016 Cross-sectional JBI = 8	N = 14 (10 F/4 M) MS type: 7% RRMS, 71% SPMS, 22% PPMS EDSS: NR Age, years (mean ± SD) = 54.1 ± 8.5 Weight: NR	*Walking test*: Overground walking; 5 mins *Walking speed*: self-selected speed (mean ± SD = 0.53 ± 0.32 m/s) *Gas exchange measurement*: VmaxST, v1.0 (Sensor Medics, USA) *Calculation method*: Gross VO_2/walking speed *Walking aids*: 43% unilateral aid, 43 % bilateral aid, 14% unilateral or bilateral aid	FSS, MFIS, SF-36 vitality subscale, VAS (before, immediately post-walking trial)	<u>Correlation with FSS</u>: $r = -0.432$, $p > 0.05$ <u>Correlation with MFIS</u>: $r = -0.154$, $p > 0.05$ <u>Correlation with SF-36</u>: $r = 0.160$, $p > 0.05$ <u>Correlation with change in VAS:</u> $r = 0.626$, $p < 0.05$

Abbreviations: 6MWT, 6-Minute Walk Test; EDSS, Expanded Disability Status Scale; F, Female; FSS, Fatigue Severity Scale; JBI, Joanna Briggs Institute Critical Appraisal Checklist for Analytical Cross-Sectional Studies; M, Male; MFIS, Modified Fatigue Impact Scale; MS, Multiple Sclerosis; NR, Not reported; PDDS, Patient Determined Disease Steps; PPMS, Primary Progressive Multiple Sclerosis; RRMS, Relapsing Remitting Multiple Sclerosis; SF-36 Medical Outcomes Study 36-item Short Form Health Survey; SPMS, Secondary Progressive Multiple Sclerosis; VAS, Visual Analogue Scale; VO_2, oxygen consumption

Table S3 Quality assessment using the Joanna Briggs Institute Critical Appraisal Checklist for Analytical Cross-Sectional Studies

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?
Olgiati et al.[19]	Y	N	U	Y	Y	Y	Y	Y
Paul et al.[20]	Y	Y	U	Y	Y	Y	Y	Y
Franceschini et al.[21]	Y	Y	Y	Y	Y	Y	Y	Y
Motl et al.[10]	Y	Y	Y	Y	Y	Y	Y	Y
Motl et al.[13]	Y	Y	Y	Y	N/A	N/A	Y	Y
Sandroff et al.[22]	Y	Y	Y	Y	Y	Y	Y	Y
Sandroff et al.[12]	Y	Y	Y	Y	N/A	N/A	Y	Y
Chung et al. [23]	Y	Y	U	Y	Y	Y	Y	Y
Devasahayam et al. [24]	Y	Y	Y	Y	Y	Y	Y	Y

Abbrevaitions: N, No; N/A, Not applicable U, Unclear; Y, Yes

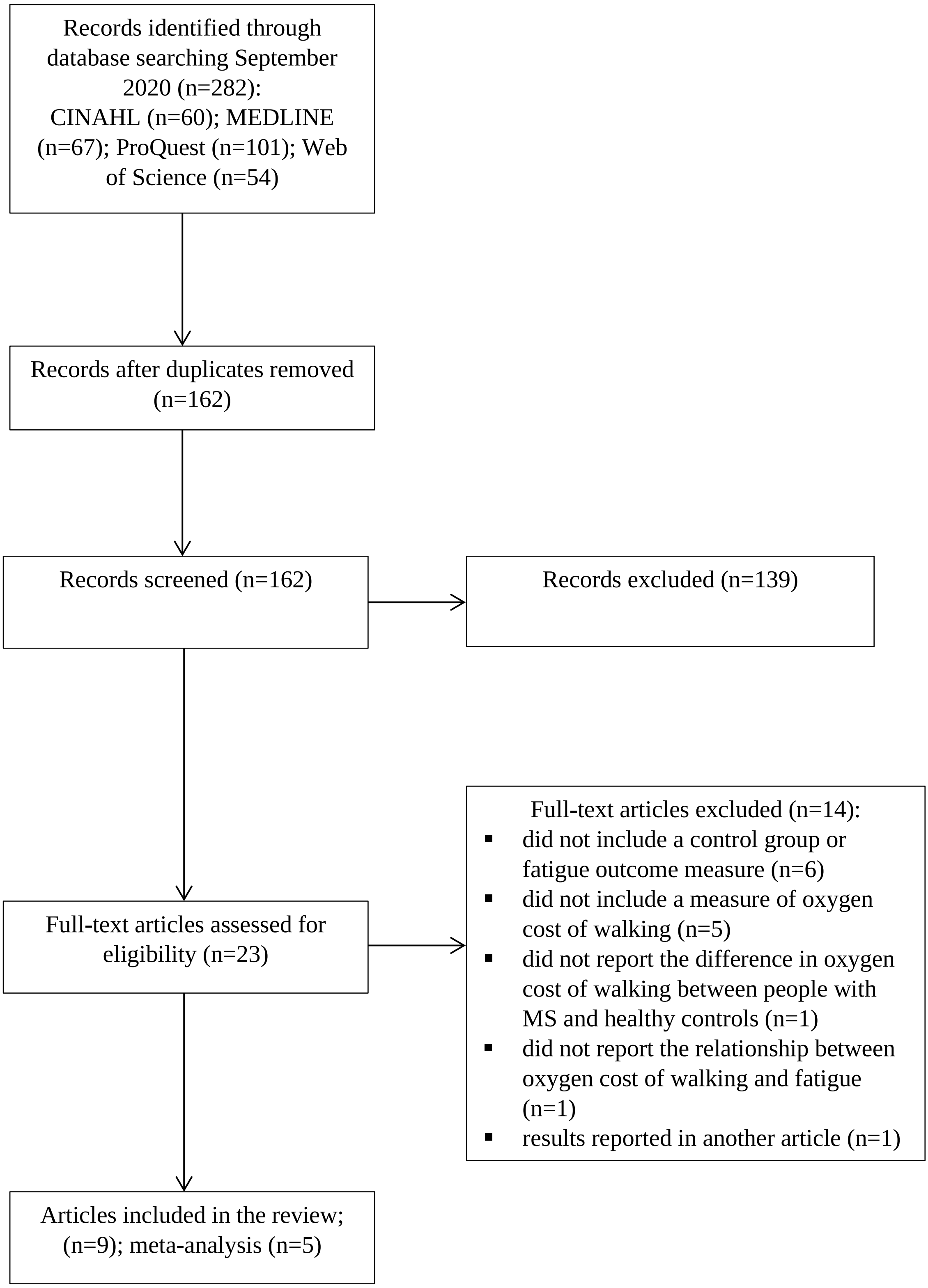

Figure S1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram