Oxygen Cost of Walking in People With Multiple Sclerosis and Its Association With Fatigue: A Systematic Review and Meta-analysis

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Background: **This systematic review and meta-analysis aimed to compare the oxygen cost of walking in individuals with multiple sclerosis (MS) and controls and to assess the relationship between oxygen cost of walking and fatigue in individuals 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 in those with MS and a control population or determined the relationship between oxygen cost of walking and fatigue. Meta-analysis of the standardized mean difference in oxygen cost of walking between individuals with MS and controls was performed.**

Results: **Nine studies were included in this review, of which 7 compared oxygen cost of walking in individuals with MS (n = 176) and controls (n = 142) and 4 investigated the relationship between oxygen cost of walking and fatigue. Meta-analysis revealed that individuals with MS (with predominantly mild-to-moderate disability) had a significantly higher oxygen cost of walking compared with controls (standardized mean difference = 2.21, 95% CI = 0.88 to 3.54, *P* = .001). In addition, 3 studies found a significant yet weak positive association between oxygen cost of walking and fatigue.**

Conclusions: **Individuals with MS expend more energy when walking compared with controls. This increase in energy expenditure may contribute to the development of fatigue, as some studies found that higher oxygen costs of walking were associated with greater fatigue. Future studies should investigate whether reducing energy expenditure during movement improves fatigue.** ***Int J MS Care. 2022;24(2):74-80. doi:10.7224/1537-2073.2020-128***

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system that manifests in impaired nerve conduction and dysfunction of neural pathways.[1] The clinical manifestation of MS is heterogeneous and depends on the location of demyelination, although lesions typically affect 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 individuals with MS,[4-6] alongside altered gait kinematics such as lower cadence, shortened stride length, and increased 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, ie, 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 traveled and reflects the total energy required for muscle activation and the maintenance of balance and posture 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 traveled for the same level of energy expenditure. In

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individuals with MS, disability[10-12] and slower walking speeds[12,13] are positively associated with oxygen cost of walking, indicating that individuals 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 individuals 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 and is reported by more than 70% of the population.[14-16] It 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 individuals with MS and controls and (2) assess the relationship between oxygen cost of walking and fatigue in individuals with MS.

Methods

Eligibility Criteria

Observational studies (with either a cross-sectional or prospective design) or randomized controlled trials that recruited adults with MS were included in this review if they directly measured oxygen cost of walking using a standardized testing protocol and met one of the following criteria: (1) compared the oxygen cost of walking in individuals with MS and controls or (2) reported the association between oxygen cost of walking and fatigue (using any self-reported outcome measure) in individuals with MS. Studies with a longitudinal design were included only if mean difference and/or associations between oxygen cost of walking and fatigue were 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. Gray literature and conference abstracts were excluded.

Search Strategy

A review protocol was registered with PROSPERO in September 2020 (ID: 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 Collection. The following search strategy composed 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* OR *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 systematic review software (Covidence). After removing duplicates, the titles and abstracts of all the articles were screened against the eligibility criteria by 1 reviewer (S.R.). Subsequently, 2 reviewers (S.R., G.M.) independently screened full texts of the remaining articles for eligibility. Disagreements were resolved through consensus in consultation with a third reviewer (L.P.) if required.

Quality Assessment

The methodological quality of included studies was assessed by 2 reviewers (S.R., G.M.) using the Joanna Briggs Institute Critical Appraisal Checklist for Analytical Cross-Sectional Studies. Quality assessment was completed independently by each reviewer, and discrepancies between reviewers were resolved through consensus in consultation with a third reviewer (L.P.) if required. Before 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 results of the quality assessment.

Data Extraction

Data extraction was completed independently by 1 reviewer (SR) using a standardized data extraction form. Data extracted from studies included study details (author, year of publication, study design), participant demographics (total number, age, sex, disability, MS type), methods of measuring oxygen cost of walking (test duration, overground vs treadmill walking, walking speed, measurement equipment, calculation of oxygen cost, use of walking aids), and outcome measures used to assess fatigue (if applicable). For studies that compared oxygen cost of walking in individuals with MS and 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. In addition, for studies that reported 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 analyzed through narrative synthesis. First, the mean difference in oxygen cost of walking reported by individual studies was classified by direction and statistical significance ($P < .05$) to determine whether oxygen cost of walking is significantly higher in the control or MS group 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 categorized according to the method used to measure oxygen cost (eg, treadmill vs overground walking, fixed vs self-selected walking speed), and values for mean difference were compared within groups to determine the consistency of the results. Last, 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, ie, 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 individuals with MS and controls was performed if oxygen cost of walking was assessed using the same units of measurement (ie, milliliters per kilogram per meter) in 2 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 that did not identify a self-selected/comfortable walking speed were excluded. Due to differences in methods of calculating oxygen cost (eg, net oxygen consumption vs total oxygen consumption), standardized mean differences (SMDs) were calculated using the mean and SD extracted from each study. Summary estimates, including 95% CIs, were then reported for each individual study and overall findings using RevMan software v5.3 (Cochrane Collaboration). 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 versus self-selected walking speeds.

Results

Search Results

The search strategy identified 282 articles and, after removing 120 duplicates, the titles 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. Fourteen articles were excluded after full-text screening: 6 did not include a control group or a fatigue outcome measure, 5 did not include a measure of oxygen cost of walking, 1 did not report the difference in oxygen cost of walking between individuals with MS and controls, 1 did not report the relationship between oxygen cost of walking and fatigue, and the results of 1 were reported in another article. Therefore, 9 articles were included in this review (**Figure S1**, which is published in the online version of this article at IJMSC.org).[10,12,13,19-24] Of the included articles, all reported the results of cross-sectional studies, with 7 examining the difference in oxygen cost of walking in individuals with MS compared with controls (**Table S1**)[10,19-24] and 4 examining the association between oxygen cost of walking and fatigue in individuals with MS (including 2 of the studies that examined the difference in oxygen cost of walking in individuals with MS compared with controls[23,24]) (**Table S2**).[12,13,23,24]

Participants

In total, 302 individuals with MS were included in the 9 articles in this review, with sample sizes ranging from 10 to 82. Participants were mostly female (77%) with a relapsing-remitting diagnosis of MS (79%), and the mean participant age ranged from 39.0 to 54.1 years. Disability was measured in 6 of the 9 studies (2 using the Expanded Disability Status Scale[21,23] and 4 using the Patient-Determined Disease Steps scale[10,12,13,22]) with scores indicating mild to moderate levels of disability.

Oxygen Cost of Walking Measurement

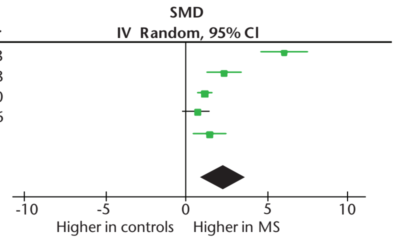
Walking Protocol

Of the studies included in this review, 5 used a treadmill walking protocol when measuring oxygen cost of walking[10,13,19,22,23] and 4 used an overground walking protocol.[12,20,21,24] The duration of the walking trials was 6 minutes in most studies (n = 6),[10,12,13,19,21,22] with the remaining studies using a 5-minute protocol (n = 3).[20,23,24] Of the studies that used a treadmill protocol, participants walked at a constant speed throughout the trial except in the study by Olgiati et al,[19] where participants walked at 1.5 km/h for 3 minutes followed by 2.0 km/h for another 3 minutes. Three studies included multiple treadmill walking trials at various speeds, with Chung et al[23] and Motl et al[10] including 3 different walking speeds and Sandroff et al[22] including 5 different walking speeds. All overground walking trials were performed at the participant's self-selected walking speed (range of means = 0.43-1.33 m/s). All 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]

Figure 1. Meta-Analysis Comparing the Standardized Mean Difference (SMD) (with inverse variance [IV]) of Oxygen Cost of Walking in Individuals With Multiple Sclerosis and Controls

Study or subgroup	Multiple sclerosis Mean	SD	Total	Controls Mean	SD	Total	Weight %	SMD 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: $Tau^2 = 2.04$; $\chi^2 = 45.02$, df = 4 (P <.00001); I^2 = 91 %
Test for overall effect Z = 3.26 (P = .001)



Calculation of Oxygen Cost

All the studies measured oxygen consumption while walking using metabolic measurement systems except the study by Olgiati et al,[19] which used rubber balloons to collect expired gas that was then analyzed using a dry gas meter. Most studies used the mean steady-state oxygen consumption when calculating oxygen cost of walking, which was defined as the mean oxygen consumption during the final 2 minutes,[23,24] final 3 minutes,[10,12,13,22] or minute 4 (of 5 minutes) of the walking trial.[20] Only 2 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: 4 studies calculated oxygen cost as net oxygen consumption (ie, oxygen consumption while walking – oxygen consumption at rest) divided by walking speed[12,13,19,23] and 5 studies calculated oxygen cost as gross oxygen consumption (ie, 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 to 8 (**Table S3**). Of the studies that included a control group, all adjusted for confounding variables by recruiting age- and sex-matched controls. In addition, all the studies used valid and reliable methods to assess oxygen cost of walking. However, 3 studies did not include a clear description of the criteria used to confirm the diagnosis of MS.[19,20,23] Furthermore, 1 study did not adequately report the demographic characteristics of the study population.[19]

Oxygen Cost of Walking in Individuals With MS Versus Controls

Oxygen cost of walking was found to be significantly higher in individuals with MS compared with controls in all the 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 to 0.60 mL/kg/m in individuals with MS and from 0.06 to 0.22 mL/kg/m in controls.[20,21,23,24] The studies that reported the largest difference in oxygen cost of walking between the MS and control groups at self-selected speeds (–0.280 mL/kg/m and –0.380 mL/kg/m) also reported the highest values for oxygen cost of walking in those with MS (0.46 mL/kg/m and 0.60 mL/kg/m)[20,24]; both studies used an overground walking protocol and predominantly included individuals with progressive forms of MS (83% to 93%), all of whom required walking aids. Conversely, the study that 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 that measured oxygen cost of walking across various treadmill speeds, a consistent significant difference between individuals with MS and controls was found at speeds of 54 to 94 m/min[10,22] but not at 107 m/min.[22] Similarly, using different walking speeds, Chung et al[23] found a significant difference in the oxygen cost of walking between individuals with MS and controls only at slower gait speeds (mean difference: 0.6 m/s = –0.110 mL/kg/m, $P \leq .001$; 1.4 m/s = –0.010 mL/kg/m, $P > .05$).

When the SMD was pooled in a meta-analysis (**Figure 1**), oxygen cost of walking was found to be significantly greater in individuals with mild to moderate MS compared with controls (SMD = 2.21, 95% CI = 0.88 to 3.54, P = .001). However, there was evidence of significant heterogeneity as the magnitude of difference varied across studies in the meta-analysis (I^2 = 91%, $P < .001$). In line with the methods of this review, 2 studies were excluded from this meta-analysis because they 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 = 1.32, 95% CI = 0.73 to 1.90, $P < .001$). Similarly, a smaller yet significant effect was found in studies that measured oxygen cost of walking at variable walking speeds (SMD = 1.53, 95% CI = 0.86 to 2.20, $P < .001$)[20,21,24] compared with fixed speeds (SMD = 3.29, 95% CI = –1.96 to 8.55, $P > .05$).[19,23] However, due to the 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.

Relationship Between Oxygen Cost of Walking and Fatigue

Across the studies that investigated the association between oxygen cost of walking and fatigue, 3 studies measured fatigue using outcomes that required participants to recall symptoms over time (eg, Fatigue Severity Scale, Modified Fatigue Impact Scale),[12,13,24] whereas 2 studies measured fatigue immediately after completion of a walking test.[23,24] Of these studies, 2 reported a significant weak relationship ($r \leq 0.3$, $P \leq .05$) 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] Whereas 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 with those that found a significant association (14[24] vs 44-82[12,13]). Of the studies that measured fatigue immediately after completion of a walking task,[23,24] only 1 found fatigue to be moderately associated with oxygen cost of walking, and this study included individuals with higher levels of mobility disability and greater energy costs of walking.[24]

Discussion

The evidence from the 9 articles included in this systematic review and meta-analysis highlights that individuals with MS expend greater amounts of energy during walking, as oxygen cost of walking was found to be significantly higher in individuals with MS compared with 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 individuals 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 individuals with MS,[3] only 7 studies were found that compared oxygen cost of walking in individuals with MS and control populations. However, the evidence from this small number of studies consistently demonstrated higher oxygen costs in individuals with MS. At self-selected walking speeds (range, 0.43-1.33 m/s), individuals with MS were found to consume 30% to 170% more oxygen per meter walked compared with controls; this approximately equates to an increase of 0.011 to 0.108 metabolic equivalents per meter. Therefore, the evidence presented in this review confirms the hypothesis that individuals with MS with mild to moderate disability expend greater amounts of energy while walking; this finding is similar to evidence in other neurologic diseases, including stroke, cerebral palsy, and Parkinson disease.[25-27]

Whereas oxygen cost of walking was found to be consistently higher in individuals with MS, the mean value for oxygen cost and the magnitude of difference compared with controls varied across the studies included in this review depending on the population recruited and the walking protocol used. For example, studies that recruited predominantly individuals with progressive MS reported higher oxygen costs of walking, and thus a greater difference compared with controls.[20,24] Because individuals with progressive MS generally present with more severe mobility impairments,[28] this finding is in line with previous evidence that demonstrates that oxygen cost of walking is higher in individuals 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 found to be higher in individuals with MS only at slower walking speeds. Although there were differences in oxygen cost of walking between studies that used treadmill or overground 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 overground tests.[11,12]

The mechanisms through which the oxygen cost of functional tasks such as walking are increased in individuals 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 that individuals with higher levels of disability expend greater amounts of energy during walking.[10,12] Although 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] In addition, individuals with MS have a reduction in the number and size of fatigue-resistant type 1 muscle fibers 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 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 to the positive association found between oxygen cost of walking and fatigue. Individuals with MS are generally found to be deconditioned, as previous systematic reviews have reported that cardiorespiratory fitness and muscle strength are lower in MS populations compared with 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 the cross-sectional nature of the evidence, the presence and magnitude of association and direction of causality between oxygen cost of walking and fatigue are 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 individuals with MS positively affects energy expenditure and fatigue.

If oxygen cost of walking is indeed associated with fatigue in individuals with MS, then interventions such as exercise that aim to 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 (ie, 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 individuals with MS when prescribing exercise and to modify the type and intensity of exercise prescription in line with current exercise recommendations.[40]

PRACTICE POINTS

- Oxygen cost of walking is significantly higher in individuals with MS compared with controls.
- Evidence from a small number of studies highlights that the 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 (eg, exercise) that reduce energy cost of walking also positively influence fatigue.

Limitations

There are several important limitations to consider when interpreting the findings of this review. First, the methods used to measure oxygen cost of walking were inconsistent across the included studies. Whereas 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. In addition, whereas most studies used steady-state oxygen consumption in determining oxygen cost of walking, the criteria used to define steady-state varied among 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, SMDs in oxygen costs of walking were used in this meta-analysis, which limits the interpretability of the results. Accordingly, standardized methods of measuring oxygen cost should be defined for future research. Second, the findings of this review are based on a small number of studies, most of which included participants with low to 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. Last, due to the cross-sectional design of the studies included in this review it was not possible to determine the direction of causality between oxygen cost of walking and fatigue.

Conclusions

This systematic review and meta-analysis found that oxygen cost of walking was higher in individuals with MS who have mild to moderate disability compared with controls, which highlights that individuals 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 that aim to reduce oxygen cost of walking may have a positive effect 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 to determine whether reducing energy expenditure improves overall fatigue symptoms. □

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