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Review

Oxygen cost of walking in multiple sclerosis: Review and future directions

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ABSTRACT

One of the hallmark features of multiple sclerosis (MS) involves the impairment of walking. The impairment of walking becomes particularly concerning when it co-occurs with an increase in physiological energy expenditure, and this process is expressed as the energetic or oxygen (O_2) cost of walking. This review presents data on the O_2 cost of walking in MS, including comparisons with healthy controls, its association with other factors that represent influences and consequences, and approaches for management. We end the paper by identifying limitations of the existing research and potential directions for future examinations of the O_2 cost of walking in MS.

KEYWORDS: multiple sclerosis, energy expenditure, walking, disability, fatigue.

ABBREVIATIONS

MS, Multiple sclerosis; O_2, Oxygen; CNS, Central nervous system; 6MW, 6-Minute Walk; VO_2, Oxygen consumption; PDDS, Patient Determined Disease Status; FSS, Fatigue Severity Scale; FES, Functional electrical stimulation; AFO, Ankle foot orthoses; QOL, Quality of life; HITT, High-intensity interval training; LITT, Low-intensity interval training.

1. Introduction

Multiple sclerosis (MS) is a chronic neurological disease characterized by immune-mediated demyelination and transection of axons as well as neurodegenerative processes involving loss of neurons within the central nervous system (CNS) [1]. The disease process results in white matter damage and grey matter atrophy in the CNS and ultimately mobility disability [2]. Walking impairment is one of the most prevalent and life-altering consequences of MS, and is often documented and tracked over time based on performance tests such as the Timed 25-Foot Walk and 6-Minute Walk (6MW) [3-5]. Such performance tests, particularly the 6MW, can further be conducted with instrumentation for measuring mechanical movement (e.g., accelerometers or gyroscopes) and/or physiological efficiency (e.g., oxygen [O_2] consumption). This is important, as walking impairment seemingly becomes more concerning when it co-occurs with an increase in energy expenditure, and this process is expressed as the energetic or O_2 cost of walking. There is long-standing interest in O_2 cost of walking as an outcome measure in MS (c.f., Olgiati), and this interest has expanded over the past decade. To that end, we provided an overview of existing research on the O_2 cost of walking in MS. This review establishes a research agenda directed toward better understanding the O_2 cost of walking and its influences and consequences in MS, and then informing interventions that may reduce O_2 cost of walking and its secondary consequences in persons with MS. We structure the review based on defining the O_2 cost of walking and its measurement. We then discuss the O_2 cost of walking in MS, including comparisons with healthy controls, its association with other

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factors that represent influences and consequences, and approaches for management. We end the paper by identifying limitations of the existing research and potential directions for future examination in MS.

2. O_2 cost of walking

2.1. Definition

Walking (i.e., bipedal movement of the body on foot through alternating and advancing footsteps) involves the sequential and rhythmical contraction of the upper and lower leg and arm musculature resulting in physiological energy expenditure (i.e., O_2 consumption). The physiological energy expenditure is necessary for locomotion or ambulatory movement and scaled based on the internal and external demands of traveling through space. The O_2 cost of walking, therefore, is defined as the amount of O_2 consumed per kilogram of body weight per unit distance traveled [6]. Conceptually, the O_2 cost of walking reflects the energy required for walking and can increase as a function of shorter distance traveled while expending the same amount of energy, or as a function of increased energy expenditure for walking the same distance. By extension, two people may walk the same distance, yet, the O_2 demand of the body may differ between them resulting in differential O_2 cost of walking (i.e., the same bout of walking is more or less energetically costly for one person than the other). This permits a quantitative assessment of the interaction between rates of O_2 consumption and walking speed/distance with values of the O_2 cost of walking that are comparable with those of the general population for understanding influences on pathological gait and gait efficiency. Collectively, the O_2 cost of walking represents a physiological marker of walking impairment that reflects the contributions of pathological gait abnormalities and other manifestations caused by disability [6] and its interaction with external constraints.

2.2. Measurement

The study of the O_2 cost of walking requires accurate measurement of expired respiratory gases through indirect calorimetry as well as walking distance/speed; the latter component is easily measured using a distance wheel or precisely controlled on a calibrated, motor driven treadmill. Of note, some researchers have focused on the Physiological Cost Index, or the difference between resting and active heart rate, as a measure of energy efficiency during walking, yet MS may result in cardiovascular autonomic dysregulation through lesions in the brainstem (i.e., medulla or cardiovascular control center), for example, that can influence heart rate and its regulation during walking [7]. Accordingly, the O_2 cost of walking is typically measured based on O_2 consumption using a stationary telemetric metabolic cart while walking on a treadmill or a portable metabolic system while walking over-ground. Importantly, there are many metabolic systems for capturing measurements of O_2 consumption, and values for O_2 consumption may vary by device manufacturer [8]. For example, the True One 2400 (Parvo Medics, Salt Lake City, UT, USA), a telemetric metabolic cart, and the K4b^2 (COSMED, Rome, Italy), a portable metabolic system, are both systems that have been validated in healthy controls for measuring O_2 consumption, and have often been utilized in studies involving persons with MS. We utilized both a telemetric metabolic cart during treadmill walking and portable metabolic system during over-ground walking and reported comparable values in O_2 cost of walking in persons with mild MS [9]. The O_2 cost of walking on a treadmill at 80 m·m-1 was 0.179 $ml \cdot kg^{-1} \cdot m^{-1}$, and the O_2 cost of walking over-ground at 77 $m \cdot m^{-1}$ was 0.172 $ml \cdot kg^{-1} \cdot m^{-1}$ in persons with mild MS. Beyond metabolic systems, researchers must select an approach for administering walking such as over-ground or on a treadmill. The use of a treadmill precisely controls speed, and may be a good approach based on factors such as limited laboratory space. Of note, treadmill walking and over-ground walking may involve substantially different gait mechanics, and persons with walking impairments may have difficulty walking on a treadmill; this suggests that treadmill walking may not be an accurate reflection of free-living walking in persons with MS. Regarding test duration, researchers often opt for 6 minutes of walking, as it clearly allows for the achievement of steady-state O_2 consumption (VO_2) in the last 3 minutes of a 6-minute bout of walking (see Figure 1). Net steady-state VO_2, or the difference between average steady-state VO_2 and average resting-state VO_2 values, is measured as a control

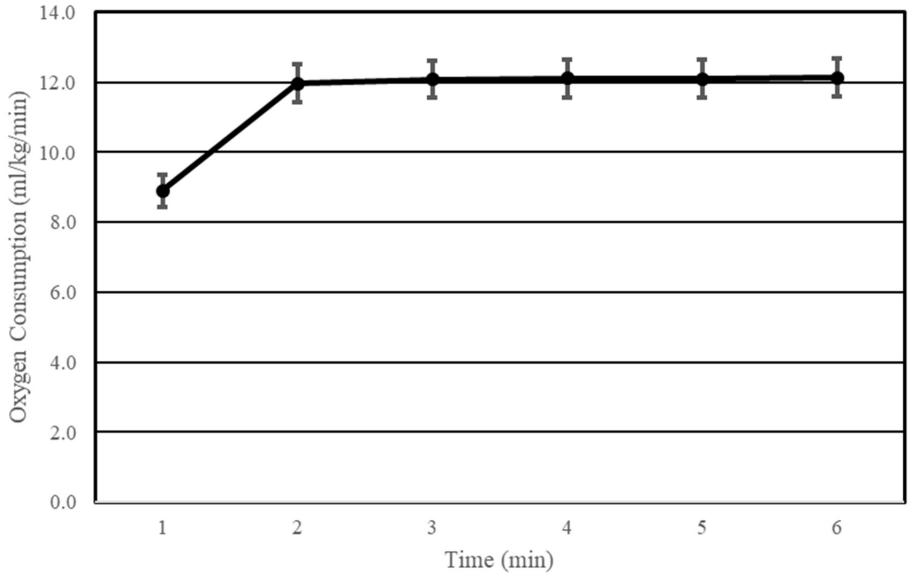

Figure 1. Oxygen consumption (VO_2) over a six-minute walk test in persons with MS. The data are from a paper involving a sample of 44 persons with MS [10].

for influential factors such as physical activity and food intake on resting energy expenditure. The O_2 cost of walking is then expressed as $ml \cdot kg^{-1} \cdot m^{-1}$ by dividing steady-state VO_2 in $ml \cdot kg^{-1} \cdot min^{-1}$ by actual walking speed in $m \cdot min^{-1}$ (O_2 cost of walking = (steady-state VO_2 – resting VO_2)/speed).

3. O_2 cost in MS

3.1. MS vs. control

There has been interest in determining the difference in O_2 cost of walking between persons with MS and controls without MS. There is consistent evidence that persons with MS have elevated O_2 cost of walking compared with healthy controls. For example, one study reported that the O_2 cost of treadmill walking at slow speeds was between two and three times higher in persons with MS compared with controls [11]. Those with MS demonstrated mean values (standard error of the mean) for the O_2 cost of walking of 0.299 (0.019) $ml \cdot kg^{-1} \cdot m^{-1}$ at 2 $km \cdot h^{-1}$ and 0.285 (0.042) $ml \cdot kg^{-1} \cdot m^{-1}$ at 4 $km \cdot h^{-1}$, whereas controls demonstrated values of 0.147 (0.006) $ml \cdot kg^{-1} \cdot m^{-1}$ at 2 $km \cdot h^{-1}$ and 0.110 (0.005) $ml \cdot kg^{-1} \cdot m^{-1}$ at 4 $km \cdot h^{-1}$. Similar results have been reported in another study regarding the O_2 cost of treadmill walking in persons with MS compared with controls at slow (36 $m \cdot m^{-1}$) speeds [12]. Another study extended the results of aforementioned research by measuring the difference in O_2 cost of treadmill walking at slow (54 $m \cdot m^{-1}$), moderate (80 $m \cdot m^{-1}$), and fast (107 $m \cdot m^{-1}$) speeds in persons with mild MS and healthy controls [9]. Persons with mild MS demonstrated significantly higher mean O_2 cost values (standard deviation) of 0.202 (0.023), 0.179 (0.020), and 0.190 (0.024) $ml \cdot kg^{-1} \cdot m^{-1}$ at 54, 80, and 107 $m \cdot m^{-1}$, respectively, than healthy controls with values of 0.186 (0.010), 0.163 (0.013), and 0.172 (0.011) $ml \cdot kg^{-1} \cdot m^{-1}$, respectively. Another study assessed the O_2 cost of over-ground walking and reported a significantly higher value for the O_2 cost of walking in persons with mild MS (0.19 [0.05] $ml \cdot kg^{-1} \cdot m^{-1}$) compared with controls (0.17 [0.03] $ml \cdot kg^{-1} \cdot m^{-1}$) [13]. Collectively, the research supports that the O_2 cost of walking is higher across a range of conditions in persons with MS than controls, even in those with MS who have mild disability.

3.2. Disability status

Mobility disability is a defining feature of MS that has been associated with the O_2 cost of walking. We located two studies that examined the O_2 cost of walking as a function of disability status in MS. One study measured the O_2 cost of over-ground

walking across three speeds, namely comfortable (76.6 ± 13.0 $m \cdot m^{-1}$), slower (64.2 ± 12.3 $m \cdot m^{-1}$), and faster (89.0 ± 13.8 $m \cdot m^{-1}$) walking [9]. The results indicated that disability status, based on Patient Determined Disease Status (PDDS) scores, was strongly correlated with O_2 cost of walking at comfortable (r = 0.60), fast (r = 0.65), and slow (r = 0.53) speeds in persons with MS. The correlations indicated that those with worse disability had a higher energetic cost of walking. Another study replicated and extended those findings among a sample of persons with MS who had a broader range of disability and reported that persons with MS who had worse disability, as indicated by the PDDS scores, demonstrated greater O_2 cost of walking (r = 0.55) [14]. Overall, the evidence suggests that the O_2 cost of walking increases as a function of worsening mobility disability.

3.3. Outcomes

The O_2 cost of walking presumably influences fatigue in persons with MS; that is, those who expend more physiological energy during walking probably experience more severe and frequent fatigue. Indeed, fatigue is one of the most commonly reported symptoms of MS, and the O_2 cost of walking may influence the severity of fatigue experienced by a person with MS. We identified two studies examining the relationship between O_2 cost of walking and fatigue. One study examined the association between O_2 cost of treadmill walking and fatigue in 44 persons with mild MS [15]. The results indicated that O_2 cost of walking was positively associated with fatigue (ρ = 0.31), as indicated by scores on the Fatigue Severity Scale (FSS). One final study reported an association between FSS scores and the O_2 cost of walking (r = 0.22) in 82 persons with MS [14]. Collectively, the evidence suggests that fatigue severity may be influenced by the O_2 cost of walking and highlight the importance of designing interventions that reduce the O_2 cost of walking to lessen fatigue severity.

Persons with MS who demonstrate higher O_2 cost of walking may be less physically active based on output from accelerometers; accelerometry has been utilized as an appropriate measure of free-living ambulation in persons with MS [16]. One study examined the association between the output from accelerometers and the O_2 cost of walking in a sample of 256 persons with a broad range of MS [16]. There was a significant negative correlation reported between movement counts from the accelerometers and the O_2 cost of walking (ρ = -0.46), suggesting that persons who demonstrate a higher O_2 cost of walking were less physically active under free-living conditions. Another study examined daily activity as a correlate of the O_2 cost of walking in a sample of 44 persons with mild MS [15]. The results indicated that persons who are in the early stages of MS and demonstrate elevated O_2 cost of walking engage in less daily activity based on free-living accelerometry (r = -0.35). This pattern suggests that those who require more energy for walking may have lower levels of physical activity.

3.4. Predictors

Persons with MS may demonstrate altered gait patterns in the early stages of the disease, and researchers have suggested a possible relationship among the O_2 cost of walking, spatiotemporal gait parameters, and spasticity in MS. For example, one study examined spatiotemporal gait parameters as variables that explain the association between disability status and O_2 cost of walking in 82 persons with MS [14]. Cadence was identified as the intermediate or mediating variable in the relationship between disability status and O_2 cost of walking; this suggests that cadence should be the target of rehabilitation for reducing O_2 cost of walking as a function of worsening disability in MS. Other researchers have reported an association between spasticity (i.e., velocity-dependent increase in muscle resistance in response to a passive stretch) and the O_2 cost of walking (ρ = 0.34); those with worse spasticity had a higher O_2 cost of walking [17]. Another study examined the relationship between spasticity of the lower extremities and O_2 cost of treadmill walking in 33 persons with MS [18]. The results indicated a significant association between spasticity and O_2 cost of walking in MS (r = 0.51). Such results have informed other research that examined spatiotemporal gait parameters as factors explaining the relationship between spasticity and O_2 cost of walking in MS. One paper focused on ankle plantarflexor spasticity and the O_2 cost of walking and examined spatiotemporal gait parameters

as possible factors to explain this association in 44 persons with MS who had moderate disability [10]. The results indicated that persons with higher levels of spasticity in the ankle plantarflexors had slower cadence and shorter step length that resulted in a higher O_2 cost of over-ground walking in moderate MS. Such evidence highlights the importance of interventions that target gait and/or spasticity for reducing the O_2 cost of walking in MS.

Gait variability, another quantitative measure of gait for movement consistency or stability, may be associated with a higher O_2 cost of walking. Variability of both stance time and step length have been identified as significant predictors of the O_2 cost of walking in 86 persons with MS [19]. These findings suggest developing interventions that aim to reduce gait variability to lower the O_2 cost of walking in MS.

There is some research focusing on other putative modifiable variables such as fitness parameters that may be associated with the O_2 cost of walking in persons with MS. Indeed, persons with MS demonstrate compromised physical fitness (i.e., aerobic capacity, upper leg muscular strength, and postural control) compared with controls, and the magnitude of reductions in those outcomes increases as a function of worsening disability status. To that end, one study examined aerobic capacity, knee muscular strength, and postural control as correlates of the O_2 cost of walking in 44 persons with MS who have moderate disability based on Expanded Disability Status Scale scores between 4.0 and 6.0 [20]; that is a benchmark of moderate disability reflecting the 2nd stage of MS [21]. Aerobic capacity was measured using an incremental exercise test performed on an electronically braked, computer-driven cycle ergometer with an open circuit spirometry system, knee muscular strength with a computerized dynamometer, and postural control with a force platform. The results indicated that persons who had lower VO_2 peak, peak power output, and muscular strength of the knee had greater O_2 cost of walking; however, aerobic power, namely peak power output, was the strongest independent predictor of the O_2 cost of walking in persons with MS. Such results suggest that future research should consider interventions that focus on increasing aerobic power for reducing the O_2 cost of walking in MS.

3.5. Management

To date, limited research exists on approaches for reducing the O_2 cost of walking in persons with MS. One study has examined the feasibility of an aerobic treadmill exercise program and its effect on O_2 cost of walking in 3 persons with mild MS [22]. O_2 cost of walking was calculated from VO_2 and walking speed from 3 minutes of treadmill walking at 4 different speeds, namely 1 $km \cdot h^{-1}$, 3 $km \cdot h^{-1}$, 4 $km \cdot h^{-1}$, and 5 $km \cdot h^{-1}$. The intervention consisted of aerobic training for a total of 10 sessions over a 4-week period. All three participants demonstrated reductions in O_2 cost of walking at 4 $km \cdot h^{-1}$ (from 0.157 to 0.137; 0.169 to 0.146; 0.149 to 0.128), and two of the three participants at 6 $km \cdot h^{-1}$ (from 0.174 to 0.139; 0.198 to 0.17). The results indicate that O_2 cost of walking is reduced following treadmill training in persons with MS. However, the O_2 cost of walking was not measured from steady-state VO_2, and the small sample of persons recruited for the study had mild MS-related disability. There are few rehabilitation options that have been established for the subgroup of persons with MS who have moderate to severe MS; exercise training, as an example of a rehabilitation approach, is typically studied in persons with mild MS [23, 24]. Another study examined the effect of aquatic therapy on the O_2 cost of walking in a mixed sample of 12 persons with MS and spinal cord injury who have spastic paresis [25]. O_2 cost of walking was measured following two weeks of 45-minute hydro-kinesi therapy sessions (i.e., active and passive movements in water). The findings indicate that persons who are characterized by slower self-selected speeds at baseline demonstrate greater reductions in the O_2 cost of walking from the hydro-kinesi therapy compared to those with faster self-selected speeds.

Functional electrical stimulation (FES), a method of delivering electrical stimuli through surface electrodes, and ankle foot orthoses (AFO) have been used to assist with walking for persons with MS and other populations who have drop foot, and research have reported lower O_2 cost of walking while using these devices. We located

cross-sectional studies that compared the O_2 cost of walking with FES and AFO against that of walking without FES and AFO. One study compared the O_2 cost of walking with and without FES in persons with MS who used FES regularly [26]. The results indicated that persons with MS demonstrate lower values of 0.41 (0.15) $ml \cdot kg^{-1} \cdot m^{-1}$ while using FES compared to values of 0.46 (0.16) $ml \cdot kg^{-1} \cdot m^{-1}$ while not using the FES system. Another study examined the O_2 cost of walking for 5 minutes of different speeds with and without FES [27]. Persons with MS demonstrated a lower O_2 cost of walking with the use of FES compared to walking without FES. However, persons with MS who walked at speeds faster than 0.8 $m \cdot s^{-1}$ demonstrated a significant increase in the O_2 cost of walking when using FES. Another cross-sectional study reported that walking with an AFO may reduce the amount of O_2 cost required for walking compared to walking without an AFO in a mixed sample of 10 persons with MS and those post-stroke, possibly as the result of the spring-like characteristic of the AFO reducing the amount of work required for ankle push-off [28].

4. Future research directions

To date, the O_2 cost of walking has not been thoroughly studied in MS. We believe there are more opportunities for research that can identify the degree of change in O_2 cost of walking in MS and its correlates, consequences, and management!

Regarding the expression of the O_2 cost of walking in MS, one research direction involves examining if the O_2 cost of walking differs across sub-populations with MS. For example, researchers might examine if the O_2 cost of walking differs between clinical courses of MS, as relapsing-remitting MS is more commonly studied than progressive MS, yet progressive courses of the disease often express with more severe mobility disability. Researchers might consider examining the O_2 cost of movement in persons with MS who use wheelchairs for daily mobility; this would require examining the O_2 cost of arm movement for wheelchair propulsion or transport. Other directions include examining the O_2 cost of walking based on demographic characteristics (i.e., age, sex, ethnicity, disease duration), and this is particularly important for age as the population of persons with MS is greying and older age has a number of co-occurring conditions that could influence the energetic cost of walking (e.g., aerobic deconditioning, sarcopenia, and altered gait and balance). Such analyses will help identify the sub-populations of MS who have impaired efficiency with walking and mobility for future, targeted interventions.

The design of targeted interventions requires an understanding of the modifiable correlates of the O_2 cost of walking. One obvious category of modifiable variables involves physical fitness (i.e., aerobic capacity, muscular strength, postural control); these are characteristic of persons that can become the direct target of exercise training interventions for management of the O_2 cost of walking. Of particular note, future studies might examine ankle plantarflexor strength as a correlate of O_2 cost of walking considering that reduced push-off might influence the worsening of walking impairments in MS [29]. Another related pair of modifiable factors include physical activity and sedentary behavior as overlapping or independent risk factors for an elevated O_2 cost of walking. Other modifiable correlates might include spasticity and gait as well as adiposity and body weight status. There might even be a basis for examining variables from magnetic resonance imaging of the brain and its tracts as correlates of the O_2 cost of walking; this could inform the study of neurorehabilitation for managing the energetic cost of walking in MS. Clearly, identifying modifiable correlates will inform the development of targeted interventions for possibly reducing the O_2 cost of walking and its consequences in MS.

There are countless opportunities for future research that examines the consequences of the elevated O_2 cost of walking. For example, there should be a strong focus on fatigue as a consequence of O_2 cost of walking in MS, as well as consideration of depression and pain as possible correlates, and potential consequences, of the O_2 cost of walking. Sleep quality and sleep disorders may further be associated directly or indirectly with the O_2 cost of walking in MS. The O_2 cost of walking may further influence employment, participation in the community, and activities of daily living. Of further note, these consequences may negatively

influence overall quality of life (QOL) and independence of persons with MS, and those outcomes should be examined as consequences of the O_2 cost of walking.

To date, there is limited research that has examined the effects of exercise programs on O_2 cost of walking in MS, but studies have reported reductions in O_2 cost of walking following exercise programs in persons post-stroke. With the use of FES, persons post-stroke demonstrated lower O_2 cost of walking following a fast treadmill training program through faster and more symmetric walking [30]. Another study compared the effects of a high-intensity treadmill training (HITT) and low-intensity treadmill training (LITT) on O_2 cost of walking in persons post-stroke [31]. Both groups completed sessions 3 times per week for 3 months, and individuals who participated in HITT demonstrated greater reductions in O_2 cost of walking when compared to those who completed the LITT. As peak power output has been identified as a predictor of O_2 cost of walking in moderate MS [20], we see potential for research conducting interventions that focus on increasing peak power output to reduce the O_2 cost of walking, considering the limited number of interventions in this area and the importance of the consequences of elevated O_2 cost of walking.

Future research might consider two refinements over previous research regarding the mode of exercise interventions for reducing the O_2 cost of walking. The available research that aims to reduce the O_2 cost of walking incorporated treadmill walking as the mode of exercise; however, treadmill walking may not be the most appropriate for persons with moderate mobility disability, or even accessible for those with severe mobility disability. An alternative mode for aerobic training for persons with MS who have moderate to severe mobility disability is a total body recumbent stepper that utilizes both the upper and lower body with coupled arm levers and foot pedals. The total body recumbent stepper has been established as a feasible and valid mode in populations such as post-stroke [32, 33]. Of important note, future research should consider the recruitment of persons who have moderate MS, as this subgroup has a level of disability wherein disease-modifying medications have limited influences on the manifestations of MS [34]. We further note that interventional research should recruit persons with an elevated O_2 cost of walking, as other research in MS does not always pre-screen and recruit persons with a focal problem for randomized controlled trials [24]. Another limitation of previous research is the short duration of the intervention period in MS (e.g., 4 weeks). Exercise interventions of longer periods may yield larger improvements in the O_2 cost of walking and, in turn, clinically meaningful changes in outcomes necessary for improving participation and QOL.

5. Conclusion

Overall, the O_2 cost of walking is higher in persons with MS than healthy persons without MS, even in the early stages of the disease, and it increases as a function of worsening disability status, lower aerobic fitness, gait dysfunction, and spasticity. The higher O_2 cost of walking may result in higher levels of fatigue and reduce participation in free-living daily activities. To date, very few research studies have examined rehabilitation approaches, such as exercise training or other targeted interventions, that may reduce the O_2 cost of walking in MS. To that end, research on therapeutic approaches for reducing the O_2 cost of walking and managing its consequences may advance the management of mobility disability and, ultimately, improve the QOL and independence of persons living with MS.

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CONFLICT OF INTEREST STATEMENT

None.

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