Sex-Based Differences in Oxygen Cost of Walking and Energy Equivalents in Minimally Disabled Individuals With Multiple Sclerosis and Controls

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Background: Elevated oxygen cost of walking and energy equivalents are reported for highly and moderately disabled individuals with multiple sclerosis (MS). However, less is known about minimally impaired individuals. Moreover, no sex-based data on the metabolic rates of individuals with MS are available. In this cross-sectional study, the metabolic rates and temporospatial parameters of gait during overground walking in minimally disabled individuals with MS versus matched controls were quantified and whether sex-based differences occur was examined.

Methods: Sixty-nine minimally impaired adults with MS (37, relapsing-remitting MS [RRMS]; 32, clinically isolated syndrome [CIS]) and 25 matched controls completed two 6-minute walking bouts at comfortable and fast speeds. The oxygen cost of walking, energy equivalents, and respiratory exchange ratio were recorded through breath-by-breath open-circuit spirometry. Gait analysis was performed via a portable electronic walkway.

Results: At comfortable but not at fast speed, men with RRMS showed higher oxygen cost of walking than men with CIS (+17.9%, $P = .04$) and male controls (+21.3%, $P = .03$). In the RRMS group, men showed higher oxygen cost of walking (+19.2%, $P = .04$) and energy equivalents (+19.2%, $P = .02$) than women. Elevated oxygen cost of walking and energy equivalents in men were paralleled by significantly larger base of support and step time asymmetry during walking.

Conclusions: Metabolic demands are elevated while walking in minimally disabled individuals with RRMS. Furthermore, higher energy demands occur in men, probably due to increased step symmetry and base of support. Clinicians are advised to follow energy expenditure metrics collected while walking because they can indicate a decrease in fitness, even in the early phase of MS.
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Individuals with multiple sclerosis (MS) exhibit increased energy demands during walking as a result of subclinical and/or clinical gait abnormalities.[1] Aside from gait deficits, metabolic demands are increased by disease-related symptoms, including muscular and neuromuscular impairment, deconditioning, and fatigability. However, clinically based tests evaluating fitness and metabolic features cannot discern between mildly disabled patients and controls,[2] often leading to ignoring initial signs of metabolic or gait alteration.

Oxygen cost of walking and oxygen consumption (VO_2 rate) while walking are established metabolic markers of gait efficiency and economy. These

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parameters can distinguish not only severely and moderately but also mildly disabled individuals with MS from controls.[1]

The oxygen cost of walking is measured in milliliters of oxygen consumed per kilogram of body weight per meter traveled (mL O_2 kg^{-1} m^{-1}) and provides a measure of the relationship between walking distance/speed and VO_2 rate.[1] The VO_2 rate is an index of the body's efficiency during physical performance and expresses the rate of energy expenditure when converted into energy equivalents of oxygen (kilocalories per liter).[3] Both oxygen cost of walking and energy equivalents are elevated in individuals with MS with high[4] and moderate[5,6] disability, whereas findings from less disabled patients are controversial, ranging from significant increase[1] to no difference[7] compared with controls. Nevertheless, a significant relationship was found between gait variability and energy cost of walking also in minimally disabled individuals with MS.[7] Given that metabolic rates are associated with the degree of gait abnormality and variability,[8] their evaluation is increasingly supported in individuals with MS displaying ambulatory impairments.[1]

Another aspect that is still unaddressed in MS is whether differences between men and women exist in the energy demands of walking. Covering this issue has potential clinical implications, as we have entered the era of personalized strategies to optimize health and performance.[9] In addition, given the higher prevalence of MS in women, it is important to investigate this issue depending on the sex characteristics. Sex-based differences are observed among seemingly healthy people in response to exercise of moderate intensity.[9] A common parameter estimating energy utilization is the respiratory exchange ratio (RER), that is, the ratio between the amount of carbon dioxide produced and oxygen consumed at rest or during a predefined physical activity.[10] When carbohydrates are the predominant energy source, the RER value is 1.0, whereas a value of 0.7 indicates that lipids are the main energy substrate. Values between 0.7 and 1.0 suggest that a combination of the 2 is used. In healthy adults, the RER is higher in men than in women during low-to-moderate aerobic exercise (ie, up to 65% of VO_2 peak), confirming higher reliance on carbohydrates (by ~25%-50%).[9-13] Conversely, enhanced lipid metabolism seems more dominant in women, demonstrated by the lower RER during aerobic exercise.[11,14,15] Nevertheless, energy expenditure and metabolic rates of walking according to sex has yet to be investigated in individuals with MS.

The present study was aimed at comparing metabolic rates (oxygen cost of walking, energy equivalents, and RER) during comfortable and fast overground walking in minimally disabled individuals with relapsing-remitting MS (RRMS), in those defined as having clinically isolated syndrome (CIS), and in a group of matched controls. Based on the previously described background, we hypothesized that (1) significant differences would emerge among the groups in the metabolic rates of walking, (2) sex-based differences in these outcomes would be observed, (3) the selected measures would differentiate not only individuals with MS from controls but also between the 2 MS subgroups, and (4) metabolic demands would be associated with the gait pattern.

Methods

Study Approval and Participants

The study was approved by Sheba Medical Center's research ethics committee and was conducted at the Multiple Sclerosis Center, Sheba Medical Center. This cross-sectional study included patients with MS (RRMS and CIS) and matched (by sex, age, and body mass index) controls. Patients with a definite diagnosis of MS were treated with immunomodulatory drugs. Inclusion criteria were (1) neurologist-confirmed diagnosis of definite MS or CIS according to the 2017 revised McDonald criteria[16]; (2) walking without mobility aids, equivalent to a score of less than 6.0 on the Expanded Disability Status Scale[17]; (3) relapse-free for at least 90 days before testing; (4) being on a stable course of immunomodulatory drugs for at least 6 months; and (5) age 18 years or older. Exclusion criteria included (1) orthopedic disorders affecting balance and walking, (2) pregnancy, (3) blurred vision, (4) cardiovascular disorders, (5) respiratory disorders, (6) taking corticosteroids or fampridine, and (7) women in luteal phase. Written consent was obtained from all the participants.

Outcome Measures

Metabolic Rates

The VO_2 rate was measured separately at rest and during self-selected comfortable and fast walking speeds. Gas exchange values were acquired continuously by open spirometry and indirect calorimetry during each test period. Measurements were collected via a portable metabolic device using breath-by-breath technology (COSMED K5, COSMED).

Participants breathed through a silicone face mask equipped with inspiratory valves. Before each test, the oxygen and carbon dioxide analyzers and the flow turbine were calibrated according to the device manufacturer's instructions. Data from each participant were telemetrically transferred to a laptop and analyzed through the device software. Participants were asked to avoid eating 4 hours before

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measurements and not to consume alcohol or engage in exercise during the 24 hours before testing. The VO_2 rate at rest was calculated by averaging 30-second VO_2 values during 5 minutes of seated rest; higher values indicated a greater rate of resting energy expenditure. Participants then performed two walking trials with their own footwear along an indoor 30-m corridor. The two walking trials differed in terms of speed instruction. In the first trial, participants were instructed to "walk at your own comfortable speed" with the intention to reflect daily mobility,[18] ensuring stronger validity compared with walking on a treadmill.[19] Instruction for the second trial was "walk at a fast pace attempting to cover as much ground as possible, without endangering yourself." Each trial was performed continuously for 6 minutes. The total distance was recorded for each trial. Seated rest periods of 5 to 10 minutes were provided between the two walking trials. No encouragement or feedback was provided while walking. Gas exchange values were calculated by averaging 30-second values over the final 3 minutes of a 6-minute period (minutes 4-6). Research studies have confirmed that the last 3 minutes of a 6-minute period of walking at a predetermined speed yield a steady-state VO_2 rate in people with MS.[1] The VO_2 rate was then used to calculate the oxygen cost of walking during comfortable and fast walking speeds.[1] Moreover, energy equivalent of gait was determined by calculating the energy equivalent for oxygen according to the method of Jeukendrup and Wallis.[3] In addition, the pattern of energy substrate utilization was estimated through determination of the RER during both walking speeds. The RER was also constantly monitored to control the validity and accuracy of the energy equivalent and VO_2 measurements during the walking tests. When the ratio was found to be 1 or greater, the test was discarded.

Gait Assessments

Walking performance was subjectively assessed using the following patient-rated scales: the 12-item Multiple Sclerosis Walking Scale and the visual analogue scale of perceived efficacy of gait and balance.

Gait Analysis

To characterize the gait patterns and identify potential subclinical gait disorders, the two subgroups of patients with MS (RRMS and CIS) underwent gait analysis using the GAITRite electronic walkway, version 4.0.3 (CIR Systems Inc). The system integrates footprints and provides spatiotemporal parameters. In the present study, we extracted the asymmetry and variability of the following parameters: step length, step time, stance time, single support, and base of support. These parameters were selected in line with previous studies demonstrating their relevance to gait difficulties in the MS population.[20,21] A single valid walking trial was defined once the participant independently walked in one direction, at his or her self-selected speed, across the electronic mat without stopping. Each participant performed six consecutive walking trials, with each trial estimated to be 4 to 6 gait cycles. The values from all the trials were consequently averaged to produce the final results.

Data Analysis

All the analyses were performed using SPSS Statistics for Windows, version 25.0 (IBM Corp). The outcome assessors (AK, LF) and statistician (AM) were blinded to the participants' status.

An a priori power analysis was conducted using G*Power 3.1.9.2 software[22] to identify the least number of participants to be enrolled. Considering 3 groups (RRMS, CIS, controls) and 2 subgroups (males and females), and assuming a moderate to large effect size for the expected differences in spiroergometric measurements (partial □2 = 0.4), 92 participants were needed to achieve the least statistical power of 0.80 at $\alpha = .05$.

Compound symmetry of data was evaluated using the Mauchly sphericity test. The Greenhouse-Geisser correction was used to compensate for nonspherical data. Normality of data was analyzed using the Shapiro-Wilk test. Box plots determined outliers for each outcome. Group differences in sex distribution were determined using the χ^2 test. Between-group differences in demographic, anthropometric, and spiroergometric variables were tested by analysis of variance (ANOVA) for main effects (group, sex) and group × sex interactions. In case of significant differences, Bonferroni-adjusted comparisons were run to locate the differences. Given the expected differences in body weight and self-selected walking speed between individuals with MS and controls, and also between men and women, we planned to conduct the comparisons for oxygen cost of walking, energy equivalents, and RER by analysis of covariance (ANCOVA), setting walking speed and body weight as covariates in all the comparisons.

Two-way ANOVAs (sex, MS course) along with Bonferroni-adjusted pairwise comparisons were performed to analyze differences in temporospatial parameters of gait.

For all the hypothesis-testing analyses, the significance level was set at $P < .05$. To estimate the magnitude of effect of the significant differences observed, the standardized effect size was calculated (Hedges *g*), taking 0.2 as small, 0.5 as medium, and 0.8 as large effect sizes. Unless otherwise stated, data are reported as mean ± SD.

Bivariate correlation analyses were performed to examine potential relationships of association between the primary outcome of the study (oxygen cost of walking) and gait parameters and between gait characteristics and established functional mobility rating scales (the 12-item Multiple Sclerosis Walking Scale and the visual analogue scale of perceived efficacy of gait and balance).

Results

Of the 102 potentially eligible candidates, 8 did not enter the study for personal reasons and 94 were

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Table 1. Demographic and Clinical Measures of the Cohort Under Study (N = 94)

Variable	Sex	RRMS group (n = 37)	CIS group (n = 32)	Controls (n = 25)	Statistics
Sex, F/M		22/15	19/13	15/10	$P = .90$
Age, y	M	38.62 ± 10.91	37.43 ± 13.40	38.40 ± 9.69	$F_{2,37} = 0.044, P = .96$
	F	36.40 ± 9.53	37.03 ± 13.12	29.53 ± 5.91[a]	$F_{2,55} = 2.755, P = .07$
Height, m	M	1.77 ± 0.05	1.71 ± 0.05	1.72 ± 0.10	$F_{2,37} = 1.001, P = .38$
	F	1.65 ± 0.09	1.63 ± 0.06	1.64 ± 0.09	$F_{2,55} = 0.269, P = .77$
Weight, kg	M	74.72 ± 12.39	75.48 ± 29.78	79.64 ± 11.50	$F_{2,37} = 0.197, P = .82$
	F	65.48 ± 13.33	68.13 ± 14.60	65.58 ± 8.86[a]	$F_{2,55} = 1.373, P = .20$
Disease duration, y	M	5.61 ± 7.39	0.88 ± 2.02	NA	$P = .04$
	F	7.94 ± 8.03	2.60 ± 4.09	NA	$P = .03$
EDSS total score	M	2.52 [1.02]	1.00 [2.41]	NA	$P = .009$
	F	2.03 [0.52]	1.79 [1.52]	NA	$P = .19$
MFIS score	M	34.60 ± 22.01	26.68 ± 19.62	NA	$P = .32$
	F	31.64 ± 22.10	25.50 ± 18.85	NA	$P = .34$
Comfortable walking speed, m/s[b]	M	1.17 ± 0.19	1.12 ± 0.16	1.29 ± 0.26	$F_{2,37} = 2.033, P = .15$
	F	1.16 ± 0.16	1.04 ± 0.12	1.23 ± 0.20	$F_{2,56} = 5.762, P = .005$ CIS < control, $P = .008$
Fast walking speed, m/s[b]	M	1.52 ± 0.30	1.51 ± 0.25	1.87 ± 0.17	$F_{2,36} = 6.985, P = .003$
	F	1.49 ± 0.26	1.44 ± 0.16	1.62 ± 0.21	$F_{2,55} = 3.734, P = .03$ CIS < control, $P = .03$
MSWS score (0-60)	M	30.00 [29.25]	22.00 [22.75]	NA	$P = .32$
	F	21.00 [19.50]	23.00 [18.25]	NA	$P = .92$
VAS gait score (0-10)	M	7.00 [5.75]	10.00 [3.50]	NA	$P = .18$
	F	9.00 [3.25]	9.00 [4.00]	NA	$P = .73$
VAS balance score (0-10)	M	6.50 [7-25]	9.50 [2.75]	NA	$P = .18$
	F	9.00 [4.25]	8.00 [3.75]	NA	$P = .75$

CIS, clinically isolated syndrome; EDSS, Expanded Disability Status Scale; MFIS, Modified Fatigue Impact Scale; MSWS, Multiple Sclerosis Walking Scale; NA, not applicable; RRMS, relapsing-remitting multiple sclerosis; VAS, visual analogue scale.
Note: Data are reported as number, mean ± SD, or, for the EDSS, MSWS, and VAS, as median [interquartile range] and analyzed using nonparametric Mann-Whitney *U* test.
[a]Significant sex-based difference within group ($P < .05$).
[b]Assessed during 2 separate 6-Minute Walk Tests.

enrolled and analyzed; there were 69 patients with MS (37 with RRMS [mean ± SD age, 37.3 ± 10.0 years], 32 with CIS [mean ± SD age, 37.2 ± 13.0 years]) and 25 controls (mean ± SD age, 33.1 ± 8.7 years). All the participants reported to perform usual activities with no steady participation in exercise-based programs. Demographic, anthropometric, and clinical characteristics of the participants are reported in **Table 1**. The Shapiro-Wilk test revealed that data were normally distributed. Groups were comparable for all demographic and anthropometric characteristics except for body weight, which proved to be significantly higher in men than in women and, in the latter group, in controls than in those with RRMS or CIS ($P = .02$). To compensate for the significant weight differences, the spiroergometric measurements were normalized to body weight, which was also set as a covariate in all the ANCOVAs performed. Individuals with RRMS or CIS exhibited a median (95% CI) Expanded Disability Status Scale score of 2 (2.1-2.9) and 1.5 (1.1-2.0), respectively, indicating minimal neurologic disability. No differences by MS course or sex were detected in the functional systems scores except for the pyramidal functions, with male patients with RRMS displaying on average a significantly higher mean ± SD score than their female counterparts (men: 1.6 ± 1.19, women: 0.82 ± 0.85, $P = .04$). Regarding the perceived burden of fatigue, as assessed using the Modified Fatigue Impact Scale, no difference was detected between the RRMS and CIS subgroups because they both displayed scores corresponding to mild to moderate fatigue impact.

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Table 2. Spiroergometric Measurements From Study Cohort (N = 94)

Condition and variable	Sex	RRMS group (n = 37)	CIS group (n = 32)	Controls (n = 25)	Between-group statistics[a]
At rest (sitting)					
VO_2, mL O_2 kg^{-1} min^{-1}	M	4.74 ± 0.99	4.58 ± 0.91	4.75 ± 0.81	NS
	F	4.66 ± 0.84	4.79 ± 1.37	4.82 ± 1.11	NS
Comfortable walking speed					
Oxygen cost of walking ,mL O_2 kg^{-1} m^{-1}	M	0.21 ± 0.03	0.18 ± 0.03	0.17 ± 0.03	RRMS > CIS, *P* = .03 RRMS > control, *P* = .04 CIS vs control, NS
	F	0.18 ± 0.03[b]	0.18 ± 0.05	0.19 ± 0.04	NS
Energy equivalents, kcal/L	M	5.02 ± 0.91	4.38 ± 0.91	4.29 ± 0.96	NS
	M	5.02 ± 0.91	4.38 ± 0.91	4.29 ± 0.96	NS
RER	M	0.76 ± 0.07	0.78 ± 0.07	0.83 ± 0.07	RRMS < control, *P* = .03 CIS vs control, NS
	F	0.78 ± 0.07	0.79 ± 0.07	0.79 ± 0.07	NS
Fast walking speed					
Oxygen cost of walking, mL O_2 kg^{-1} m^{-1}	M	0.22 ± 0.04	0.19 ± 0.04	0.20 ± 0.02	NS
	F	0.19 ± 0.04	0.19 ± 0.05	0.21 ± 0.03	NS
Energy equivalents, kcal/L	M	6.90 ± 1.29	6.85 ± 1.34	7.09 ± 1.45	NS
	F	6.02 ± 1.29	5.74 ± 1.33	6.42 ± 1.34	NS
RER	M	0.88 ± 0.08	0.86 ± 0.09	0.93 ± 0.09	NS
	F	0.85 ± 0.08	0.84 ± 0.09	0.86 ± 0.08	NS

CIS, clinically isolated syndrome; NS, not significant; RER, respiratory exchange ratio; RRMS, relapsing-remitting multiple sclerosis; VO_2, oxygen consumption.
Note: Data are reported as mean ± SD.
[a]Between-group differences assessed by analysis of covariance (covariate: walking speed) comparing main effects of group (RRMS vs CIS vs control), sex (men, women), and group × sex interaction. Significant at *P* < .05. In case of significant differences, Bonferroni-adjusted pairwise comparisons were performed to locate source of difference.
[b]Significant sex-based differences within group (*P* < .05).

Main results for the measurement of VO_2 rate at rest and the oxygen cost of walking for the walking trials are summarized in **Table 2** by group (RRMS, CIS, control), condition (comfortable and fast walking speed), and sex (men, women).

At rest (sitting), a 3 (RRMS, CIS, control) × 2 (males, females) ANOVA revealed no main effects and interactions for VO_2 rate and no differences by group and sex.

At self-selected comfortable and fast speeds, one-way ANOVA detected a main effect of group for walking speed (comfortable: $F_{2,93}$ = 7.004, *P* = .001; fast: $F_{2,91}$ = 8.686, *P* < .0005). Bonferroni-adjusted pairwise comparisons revealed that controls walked at a significantly faster mean ± SD speed (comfortable: 4.50 ± 0.80 km/h; fast: 6.19 ± 0.83 km/h) than the RRMS group only for fast walking (comfortable: 4.18 ± 0.61 km/h; *P* = .16; fast: 5.41 ± 0.97 km/h; *P* = .002) and than the CIS group at comfortable (4.09 ± 0.50 km/h; *P* = .001) and fast (5.30 ± 0.72 km/h; *P* = .001) speeds. To counteract such discrepancies, walking speed was set as a covariate in the 2-way (group, sex) ANCOVAs conducted for oxygen cost of walking comparisons.

Two-way ANCOVA (covariate: walking speed) detected a significant group × sex interaction (*F* = 5.827, *P* = .004) for oxygen cost of walking during self-selected comfortable walking speed. After controlling for the same velocity for all groups, Bonferroni-adjusted pairwise comparisons revealed that in the subgroup of men, patients with RRMS had a significantly higher oxygen cost of walking than those with CIS (+17.9%, *P* = .04, *g* = 0.9) and controls (+21.3%, *P* = .03, *g* = 1.1), whereas no difference emerged between the CIS and control groups (*P* = .85). In the subgroup of women, no significant differences were detected by group. However, for RRMS, after controlling for the same body weight for all groups, ANCOVA showed that female patients exhibited a significantly lower oxygen cost of walking than male patients (–18.0%, *P* = .04), at a large effect size (*g* = 0.9),

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whereas no sex-based differences emerged for the CIS and control groups.

Two-way ANCOVA (covariate: walking speed) revealed a significant group × sex interaction ($F = 5.536$, $P = .005$) for energy equivalents during comfortable walking speed. Bonferroni-adjusted pairwise comparisons revealed no significant differences between groups in either men or women. In the RRMS group, after controlling for speed and body weight for the 2 sexes, female patients exhibited significantly lower mean ± SD energy equivalents than male patients (4.213 ± 0.91 kcal/L vs 5.022 ± 0.91 kcal/L, $P = .02$), at a large effect size ($g = 0.9$).

The RER during comfortable walking was lower in men with RRMS compared with controls (–9.4%, $P = .03$), revealed by 2-way ANCOVA (covariate: walking speed). No differences were observed among women. In addition, no sex-based differences were demonstrated in the RER in the study cohort. Regarding oxygen cost of walking, energy equivalents, and RER at self-selected fast speed, two-way ANCOVAs (covariate: walking speed) revealed no significant main effects of sex and group and no interactions (**Table 2**).

Temporospatial Parameters of Gait

The results of the quantitative assessment of temporospatial parameters of gait are presented in **Table S1**, which is published in the online version of this article at ijmsc.org. Groups were comparable for gait velocity and cadence. Two-way ANOVA (sex, MS course) detected a trend toward significance for sex ($F_{1,63} = 3.908$, $P = .053$) and MS course ($F_{1,63} = 2.838$, $P = .097$). Although the sex × MS course interaction proved nonsignificant ($F_{1,63} = 1.990$, $P = .164$), Bonferroni-corrected pairwise comparisons revealed that in the RRMS group only, men walked with a significantly wider base of support than women (+35.4%, $P = .04$), at a large effect size.

Significant main effects of sex ($F_{1,57} = 14.068$, $P < .0001$) and MS course ($F_{1,57} = 4.769$, $P = .033$) were detected for step time asymmetry. Although no significant sex × MS course interaction was found ($F_{1,57} = 0.275$, $P = .602$), Bonferroni-adjusted pairwise comparisons revealed that men walked with increased asymmetry in step time compared with women in both the RRMS (+48.7%, $P = .012$) and CIS (+53.5%, $P = .04$) courses. No differences by sex and MS course were detected for any of the gait variability parameters (**Table S1**).

Correlation Analyses

The oxygen cost of walking was significantly and positively associated with base of support width ($r = 0.44$, $P = .006$) and step time asymmetry ($r = 0.532$, $P = .004$). No statistically significant correlations were detected at fast walking speed.

When examining the degree of association between gait biomechanics and the scores obtained through selected patient-reported scales evaluating fall risk, walking ability, and balance, statistically significant correlations were detected for step length, step time and single support variability, base of support width, and step time asymmetry (**Table S2**).

Given the difference between men and women with RRMS in the pyramidal functional system score, we examined its association with the gait parameters. Significant correlations were demonstrated between the pyramidal score and asymmetry of step length ($r = 0.385$, $P = .003$), step time ($r = 0.379$, $P = .004$), and stance time ($r = 0.309$, $P = .02$).

Discussion

Metabolic and energy demands of walking have been previously shown to differentiate between highly disabled individuals with MS and controls.[4] More recently, elevated oxygen cost of walking was observed also in mildly disabled individuals with MS,[1] introducing this measure as an early physiological marker of walking impairment in MS and an indirect indicator of other disease-related symptoms, such as neuromuscular impairment and fatigue.

The first finding of this study is that despite no apparent gait abnormality, men with RRMS displayed significantly higher oxygen cost of walking than patients with CIS and matched controls, at large effect sizes in both cases, possibly indicating a practical relevance of the observed differences. This occurred at comfortable (4.1-4.2 km/h) but not fast (5.3-5.6 km/h) speed, and only in men, whereas women did not differ from their matched controls.

There is evidence that even mildly impaired individuals with MS exhibit subclinical balance and gait abnormalities,[23,24] which have been shown to significantly correlate with elevated costs of walking.[7] Kalron and colleagues[7] examined 88 mildly impaired individuals with MS and found a significant association between elevated oxygen cost of walking and increased gait variability. Individuals with MS who ambulate with increased variability between steps may preserve walking speed, but they expend more energy than normal to control the body's irregular center

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of mass sway[7] because of poor stability, inadequate foot clearance, imperfect prepositioning of the foot in terminal swing, and short step length. The elevated costs displayed by male patients with RRMS might be explained by the presence of subclinical gait impairments, as suggested by the pyramidal functional system score calculated for this cohort. Indeed, the median score was 1.6, which stands right between a score of 1, indicating abnormal signs without disability, and 2, indicating minimal disability.

The present finding of elevated oxygen cost of walking and energy equivalents during comfortable walking is in line with previous reports in individuals with MS. Olgiati and colleagues[4] examined the oxygen cost of treadmill walking in 24 individuals with MS with mobility aids and found that oxygen cost of walking was 2.5 times greater than in controls. A similar but smaller difference was observed in the present study between men with RRMS and control men (at 4 km/h: patients, 0.211 mL O_2 kg^{-1} m^{-1}; controls, 0.174 mL O_2 kg^{-1} m^{-1}). The smaller difference in the present study can be explained by the different disability level of the participants with MS between the 2 studies. Olgiati and colleagues[4] examined individuals with moderate to high disability and ankle plantarflexor spasticity, whereas we focused on minimally impaired patients without spasticity.

The present findings add to previous evidence from a case-control study[1] that examined mildly disabled individuals with MS likewise reporting elevated oxygen cost of walking. Unlike that study, where patients with single-point walking assistance were also included, we enrolled only persons with no walking supports and no apparent gait impairment, which may explain the slightly lower oxygen cost of walking values that we observed at approximately 4 km/h. Moreover, whereas Motl and colleagues[1] tested both treadmill and overground walking, reporting no differences in oxygen cost between the 2 methods, we focused on the latter, which is considered more ecologically and kinematically valid and more generalizable to real-life walking,[19] although some heterogeneity can be introduced due to self-selected speed. In addition to oxygen and energy cost, we evaluated the RER. We observed lower scores in men with RRMS compared with controls, suggesting that these individuals rely less on carbohydrates to obtain energy. Surprisingly, no sex-based differences were observed for the RER between and within population groups. This observation is in disagreement with previous studies reporting lower RER values in control women due to less use of carbohydrates and enhanced lipolysis.[9,11-15]

Unlike Olgiati and colleagues,[4] who enrolled only men, and Motl and colleagues,[1] whose cohort mainly consisted of women, we also balanced groups by sex composition to test the hypothesis that sex-based differences would emerge in the metabolic rates of walking. Although men with RRMS showed higher metabolic rates than men with CIS and controls, no differences were detected among RRMS, CIS, and control women. However, in the RRMS group, women had significantly lower metabolic demands than men during comfortable walking speed.

A possible explanation for the sex-based difference observed in the RRMS group may concern the step asymmetry demonstrated in men. Men exhibited higher pyramidal signs, which suggest increased muscle weakness. Taking into account that muscle weakness is almost never identical between the lower limbs, this observation might be related to the asymmetrical gait pattern.[24] In addition, men exhibited a wider base of support while walking. In most cases, a wider base of support is considered a compensation strategy to cope with poor balance.[25] Interestingly, both increased step asymmetry and wider base of support were found to be associated with elevated oxygen cost of walking.

PRACTICE POINTS

- Oxygen cost of walking provides physiological information on gait efficiency and is increasingly supported in individuals with MS displaying ambulatory impairments.
- This study found that even minimally disabled individuals with MS display elevated oxygen cost and energy consumption during comfortable walking.
- Men with MS with a relapsing-remitting course displayed higher metabolic demands than female patients and were associated with subclinical gait disorders.
- Elevated metabolic rates and sex-based differences need to be considered when devising retraining programs in MS populations.

Practical Implications

The results of this study showed that even minimally disabled individuals with RRMS (but not CIS) exhibit higher metabolic rates. Although the present participants did not exhibit evident gait impairments, gait asymmetry was associated with increased metabolic demands, in line with previous studies.[7,26] We advise clinicians to be aware of subclinical walking impairments that may exist even in the early stages of the disease. In this context, metabolic and gait assessments, even in asymptomatic individuals with MS, seem relevant because evaluating energy expenditure during walking (and/or other daily living activities) might improve management of individuals with MS

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at the early phase of disease. Such information may be of practical utility in designing aerobic training programs for minimally impaired individuals with MS.

Regarding the sex-based differences in the metabolic demand of walking, the present findings, which are novel to MS, confirm the need to control the sex factor also in this population because the 2 sexes may exhibit differential trajectories of neuromuscular dysfunction and physical disability that need to be captured when devising rehabilitation and retraining programs.

Study Limitations

This study has limitations that warrant attention. First, we assessed oxygen cost of walking and energy equivalents during overground walking, which is more generalizable to real-life walking than treadmill walking but introduced heterogeneity in walking speed that prompted statistical corrections. Second, we interpreted metabolic data on oxygen cost of walking and energy equivalents from participants within a biochemical/nutritional framework in the absence of direct determinations of the content of organic polymers and their constituting monomers (ie, liver and muscle glycogen, glycerol, and free fatty acids) and body composition, which would have allowed normalization of oxygen and energy data to fat mass and metabolically active tissues. The inclusion of these elements in future sex-based comparative studies will likely boost an advance in this literature. Finally, the study was limited to patients with RRMS and CIS forms of disease, with minimal disability. Therefore, the conclusions should be cautiously generalized to individuals with MS with moderate to severe disability.

Conclusions

The present study provides the first evidence that oxygen cost of walking and energy equivalents are elevated even in minimally disabled individuals with MS. Moreover, metabolic measures differentiate between patients classified with RRMS versus CIS. The sex-based differences in the metabolic measures of gait should encourage future research to examine the benefits of aerobic and gait training interventions in this segment of the MS population. □

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