

**Table S1. Characteristics and Main Findings of the Studies Which Investigated the Difference in Oxygen Cost of Walking Between People With MS and Controls**

Author, date, study design, quality	Participant demographics	Control demographics	Oxygen cost of walking measurement	Main findings*
Olgiati et al <sup>19</sup> , 1988 Cross-sectional JBI = 6	N = 33 (F/M NR) MS type: NR EDSS: NR Age, years (mean ± SD) = 41.0 ± 1.7 Weight, kg (mean ± SD) = 67.0 ± 2.1	N = 12 (6 F/6 M) Age, years (mean ± SD) = 36.0 ± 2.0 Weight, kg (mean ± SD) = 67.0 ± 3.5	<i>Walking test:</i> Treadmill protocol; 6 min of walking starting at 1.5 km/h with 0.5 km/h increase in speed after 3 min <i>Walking speed:</i> 1.5 km/h, 2.0 km/h <i>Gas exchange measurement:</i> Open circuit spirometry using rubber balloon, expired gas measured using dry gas meter (Singer model DTM 115, American Meter Division, USA) <i>Calculation method:</i> Net VO <sub>2</sub> /walking speed <i>Walking aids:</i> No aids used	<u>Oxygen cost (mL/kg/m)</u> MS: 0.267 ± 0.018 Controls: 0.162 ± 0.008 Mean difference (95% CI): <b>-0.105 (-0.116, -0.094), P &lt; .001</b>
Paul et al <sup>20</sup> , 2008 Cross-sectional JBI = 7	N = 12 (F/M NR) MS type: 17% RRMS, 83% SPMS EDSS: NR Age, years (mean ± SD) = 53.0 ± 8.0 Weight, kg (mean ± SD) = 81.8 ± 18.3	N = 12 (F/M NR) Age, years (mean ± SD) = 52.0 ± 7.3 Weight, kg (mean ± SD) = 69.2 ± 13.6	<i>Walking test:</i> Overground walking; 5 min <i>Walking speed:</i> Preferred walking speed (mean ± SD = 0.43 ± 0.15 m/s) <i>Gas exchange measurement:</i> COSMED K4b2 (Cosmed, Italy) <i>Calculation method:</i> Gross VO <sub>2</sub> /walking speed <i>Walking aids:</i> 67% unilateral aid, 33% bilateral aid	<u>Oxygen cost (mL/kg/m)</u> MS: 0.46 ± 0.16 Controls: 0.18 ± 0.03 Mean difference (95% CI): <b>-0.280 (-0.378, -0.183), P &lt; .001</b>

Franceschini et al <sup>21</sup> , 2010	N = 46 (27 F/19 M) MS type: NR Cross-sectional EDSS (median (range)): 3 (1-4) Age, years (mean ± SD) = 39.0 ± 8.0 Weight: NR JBI = 8	N = 36 (21 F/15 M) Age, years (mean ± SD) = 40.0 ± 9.0 Weight: NR	<i>Walking test:</i> Overground walking; 6MWT <i>Walking speed:</i> Self-selected walking speed (mean ± SD = 1.33 ± 0.25 m/s) <i>Gas exchange measurement:</i> Oxycon Mobile (Jäger, Germany) <i>Calculation method:</i> Gross VO <sub>2</sub> /walking speed <i>Walking aids:</i> No aids used	<u>Oxygen cost (mL/kg/m)</u> MS: 0.219 ± 0.050 Controls: 0.170 ± 0.030 Mean difference: <b>-0.049 (-0.068, -0.030), P &lt; .05</b>
Motl et al <sup>10</sup> , 2011	N = 18 (14 F/4M) MS type: 83% RRMS, 11% benign MS, 6% PPMS PDDS (median (range)): 1 (0-4) Age, years (mean ± SD) = 41.9 ± 12.6 Weight, kg (mean ± SD) = 72.1 ± 16.4 JBI = 8	N = 18 (14 F/4 M) Age, years (mean ± SD) = 39.1 ± 11.9 Weight, kg (mean ± SD) = 72.8 ± 15.0	<i>Walking test:</i> Treadmill walking; three 6-min walking trials at a constant speed separated by 6 min <i>Walking speed:</i> 54 m/min, 80 m/min, 107 m/min <i>Gas exchange measurement:</i> TrueOne (Parvo Medics, USA) <i>Calculation method:</i> Gross VO <sub>2</sub> /walking speed <i>Walking aids:</i> No aids used	<u>54 m/min oxygen cost (mL/kg/m)</u> MS: 0.202 ± 0.023 Controls: 0.186 ± 0.010 Mean difference: <b>-0.016 (-0.028, -0.004), P &lt; .05</b>  <u>80 m/min oxygen cost (mL/kg/m)</u> MS: 0.179 ± 0.020 Controls: 0.163 ± 0.013 Mean difference: <b>-0.016 (-0.027, -0.005), P &lt; .05</b>  <u>107 m/min oxygen cost (mL/kg/m)</u> MS: 0.190 ± 0.024 Controls: 0.172 ± 0.011 Mean difference: <b>-0.018 (-0.031, -0.005), P &lt; .05</b>

Sandroff et al <sup>22</sup> , 2012 Cross-sectional JBI = 8	N = 43 (38 F/5 M)	N = 43 (38 F/5 M)	<i>Walking test:</i> Treadmill walking; five 6-min walking trials at a constant speed separated by 6 min <i>Walking speed:</i> 54 m/min, 67 m/min, 80 m/min, 94 m/min, 107 m/min <i>Gas exchange measurement:</i> TrueOne (Parvo Medics, USA) <i>Calculation method:</i> Gross VO <sub>2</sub> /walking speed <i>Walking aids:</i> No aids used	<u>54 m/min oxygen cost (mL/kg/m)</u>
	MS type: 88% RRMS, 6% SPMS, 6% PPMS	Age, years (mean ± SD) = 46.5 ± 10.0		MS: 0.200 ± 0.026 Controls: 0.187 ± 0.027 Mean difference: <b>-0.013 (-0.024, -0.001), P &lt; .05</b>
	PDDS (median (range)): 1 (0-5)	Weight, kg (mean ± SD) = 75.4 ± 16.2		<u>67 m/min oxygen cost (mL/kg/m)</u>
	Age, years (mean ± SD) = 47.2 ± 9.1			MS: 0.184 ± 0.025 Controls: 0.169 ± 0.022 Mean difference: <b>-0.015 (-0.025, -0.005), P &lt; .01</b>
	Weight, kg (mean ± SD) = 75.7 ± 19.4			<u>80 m/min oxygen cost (mL/kg/m)</u>
				MS: 0.171 ± 0.019 Controls: 0.156 ± 0.019 Mean difference: <b>-0.015 (-0.023, -0.007), P &lt; .01</b>
				<u>94 m/min oxygen cost (ml/kg/m)</u>
				MS: 0.167 ± 0.014 Controls: 0.157 ± 0.021 Mean difference: <b>-0.010 (-0.018, -0.002), P &lt; .05</b>
				<u>107 m/min oxygen cost (mL/kg/m)</u>
				MS: 0.167 ± 0.016 Controls: 0.162 ± 0.026 Mean difference: -0.005 (-0.014, 0.004), P > .05

Chung et al <sup>23</sup> , 2016 Cross- sectional JBI = 7	N = 10 (9 F/1 M) MS type: 90% RRMS, 10% PPMS EDSS (mean ± SD) = 4.6 ± 1.1 Age, years (mean ± SD) = 45.0 ± 8.0 Weight, kg (mean ± SD) = 74.4 ± 14.0	N = 14 (11 F/3 M) Age, years (mean ± SD) = 46.0 ± 7.0 Weight, kg (mean ± SD) = 73.4 ± 16.3	<i>Walking test:</i> Treadmill walking; three 5-min walking trials at a constant speed separated by 5-10 min <i>Walking speed:</i> 0.6 m/s, 1.4 m/s, preferred walking speed <i>Gas exchange measurement:</i> TrueMax2400 Metabolic Measurement System (Parvo Medics, USA) <i>Calculation method:</i> Net VO <sub>2</sub> /walking speed <i>Walking aids:</i> No aids used	<u>0.6 m/s oxygen cost (mL/kg/m)</u> MS: 0.25 ± 0.09 Controls: 0.14 ± 0.06 Mean difference: <b>-0.110 (-0.173, - 0.047), P ≤ .001</b>  <u>1.4 m/s oxygen cost (mL/kg/m)</u> MS: 0.11 ± 0.03 Controls: 0.10 ± 0.03 Mean difference: -0.010 (-0.036, 0.016), P > .05  <u>Preferred speed oxygen cost (mL/kg/m)</u> MS: 0.10 ± 0.08 Controls: 0.06 ± 0.04 Mean difference: -0.040 (-0.091, 0.011), P > .05
Devasahayam et al <sup>24</sup> , 2019 Cross- sectional JBI = 8	N = 14 (10 F/4 M) MS type: 7% RRMS, 71% SPMS, 22% PPMS EDSS: NR Age, years (mean ± SD) = 54.1 ± 8.5 Weight: NR	N = 7 (4 F/3 M) Age, years (mean ± SD) = 50.7 ± 12.1 Weight: NR	<i>Walking test:</i> Overground walking; 5 min <i>Walking speed:</i> self-selected speed (mean ± SD) = 0.53 ± 0.32 m/s) <i>Gas exchange measurement:</i> VmaxST, v1.0 (Sensor Medics, USA) <i>Calculation method:</i> Gross VO <sub>2</sub> /walking speed <i>Walking aids:</i> 43% unilateral aid, 43 % bilateral aid, 14% unilateral or bilateral aid	<u>Oxygen cost (mL/kg/m)</u> MS: 0.60 ± 0.30 Controls: 0.22 ± 0.04 Mean difference: <b>-0.380 (-0.621, - 0.139), P &lt; .01</b>

6MWT, 6-Minute Walk Test; EDSS, Expanded Disability Status Scale; F, Female; JBI, Joanna Briggs Institute Critical Appraisal Checklist for Analytical Cross-Sectional Studies; M, Male; MS, multiple sclerosis; NR, not reported; PDDS, Patient-Determined Disease Steps; PPMS, primary progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; VO<sub>2</sub>, oxygen consumption

\* Values are presented as mean ± SD unless stated otherwise

**Table S2. Characteristics and Main Findings of the Studies Which Investigated the Association Between Oxygen Cost of Walking and Fatigue in People With MS**

Author, date, study design, quality	Participant demographics	Oxygen cost of walking measurement	Fatigue outcome measure	Main findings
Motl et al <sup>13</sup> , 2012 Cross-sectional JBI = 6	N = 44 (38 F/6 M) MS type: 90% RRMS, 5% SPMS, 5% PPMS PDDS (median (range)): 1 (0-3) Age, years (mean ± SD) = 47.2 ± 9.1 Weight, kg (mean ± SD) = 75.7 ± 19.4	<i>Walking test:</i> Treadmill walking; 6 min at constant speed <i>Walking speed:</i> 54 m/min <i>Gas exchange measurement:</i> TrueOne (Parvo Medics, USA) <i>Calculation method:</i> Net VO <sub>2</sub> /walking speed <i>Walking aids:</i> No aids used	FSS	<u>Correlation with FSS:</u> $r = 0.306, P \leq .05$

Sandroff et al <sup>12</sup> , 2014 Cross-sectional JBI = 6	N = 82 (63 F/19 M) MS type: 78% RRMS, 22% SPMS/PPMS PDDS (median (range)): 3 (0-6) Age, years (mean ± SD) = 49.1 ± 9.0 Weight, kg (mean ± SD) = 80.3 ± 21.7	<i>Walking test:</i> Overground walking; 6MWT <i>Walking speed:</i> Self-selected walking speed (mean ± SD = 0.98 ± 0.33 m/s) <i>Gas exchange measurement:</i> COSMED K4b2 (Cosmed, Italy) <i>Calculation method:</i> Net VO <sub>2</sub> /walking speed <i>Walking aids:</i> NR	FSS	<u>Correlation with FSS:</u> $r = 0.223, P < .05$
Chung et al <sup>23</sup> , 2016 Cross-sectional JBI = 7	N = 10 (9 F/1 M) MS type: 90% RRMS, 10% PPMS EDSS (mean ± SD) = 4.6 ± 1.1 Age, years (mean ± SD) = 45.0 ± 8.0 Weight, kg (mean ± SD) = 74.4 ± 14.0	<i>Walking test:</i> Treadmill walking; three 5-min walking trials at a constant speed separated by 5-10 minutes <i>Walking speed:</i> 0.6 m/s, 1.4 m/s, preferred walking speed <i>Gas exchange measurement:</i> TrueMax2400 Metabolic Measurement System (Parvo Medics, USA) <i>Calculation method:</i> Net VO <sub>2</sub> /walking speed <i>Walking aids:</i> No aids used	VAS (immediately post-walking trial)	<u>Correlation with VAS:</u> 0.6 m/s: $r \leq 0.350, P \geq .1$ 1.4 m/s: $r \leq 0.350, P \geq .1$ Preferred speed: $r \leq 0.350, P \geq .1$

Devasahayam et al <sup>24</sup> , 2019	N = 14 (10 F/4 M) MS type: 7% RRMS, 71% SPMS, 22% PPMS EDSS: NR Age, years (mean ± SD) = 54.1 ± 8.5 Weight: NR	Walking test: Overground walking; 5 min Walking speed: self-selected speed (mean ± SD = 0.53 ± 0.32 m/s) Gas exchange measurement: VmaxST, v1.0 (Sensor Medics, USA) Calculation method: Gross VO <sub>2</sub> /walking speed Walking aids: 43% unilateral aid, 43 % bilateral aid, 14% unilateral or bilateral aid	FSS, MFIS, SF-36 vitality subscale, VAS (before, immediately post-walking trial)	<u>Correlation with FSS:</u> $r = -0.432, P > .05$  <u>Correlation with MFIS:</u> $r = -0.154, P > .05$  <u>Correlation with SF-36:</u> $r = 0.160, P > .05$  <u>Correlation with change in VAS:</u> $r = 0.626, P < .05$
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6MWT, 6-Minute Walk Test; EDSS, Expanded Disability Status Scale; F, female; FSS, Fatigue Severity Scale; JBI, Joanna Briggs Institute Critical Appraisal Checklist for Analytical Cross-Sectional Studies; M, male; MFIS, Modified Fatigue Impact Scale; MS, multiple sclerosis; NR, not reported; PDDS, Patient-Determined Disease Steps; PPMS, primary progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SF-36 Medical Outcomes Study 36-item Short Form Health Survey; SPMS, secondary progressive multiple sclerosis; VAS, visual analogue scale; VO<sub>2</sub>, oxygen consumption

**Table S3. Quality Assessment Using the Joanna Briggs Institute Critical Appraisal Checklist for Analytical Cross-Sectional Studies**

<b>Study</b>	<b>1. Were the criteria for inclusion in the sample clearly defined?</b>	<b>2. Were the study subjects and the setting described in detail?</b>	<b>3. Was the exposure measured in a valid and reliable way?</b>	<b>4. Were objective, standard criteria used for measurement of the condition?</b>	<b>5. Were confounding factors identified?</b>	<b>6. Were strategies to deal with confounding factors stated?</b>	<b>7. Were the outcomes measured in a valid and reliable way?</b>	<b>8. Was appropriate statistical analysis used?</b>
Olgiati et al <sup>19</sup>	Y	N	U	Y	Y	Y	Y	Y
Paul et al <sup>20</sup>	Y	Y	U	Y	Y	Y	Y	Y
Franceschini et al <sup>21</sup>	Y	Y	Y	Y	Y	Y	Y	Y
Motl et al <sup>10</sup>	Y	Y	Y	Y	Y	Y	Y	Y
Motl et al <sup>13</sup>	Y	Y	Y	Y	N/A	N/A	Y	Y
Sandroff et al <sup>22</sup>	Y	Y	Y	Y	Y	Y	Y	Y
Sandroff et al <sup>12</sup>	Y	Y	Y	Y	N/A	N/A	Y	Y
Chung et al <sup>23</sup>	Y	Y	U	Y	Y	Y	Y	Y
Devasahayam et al <sup>24</sup>	Y	Y	Y	Y	Y	Y	Y	Y

N/A, not applicable U, unclear; Y, yes



**Figure S1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Flow Diagram**

