

## **Efficacy of high-intensity aerobic exercise on fatigue, walking, and quality of life in people with multiple sclerosis: A randomized controlled trial**

Martin Langeskov-Christensen, PhD<sup>1</sup> (main author), Lars Grøndahl Hvid, PhD<sup>1</sup>, Henrik Boye Jensen, PhD<sup>2,7</sup>, Helle Hvilsted Nielsen, PhD<sup>3-5</sup>, Thor Petersen, DMSc<sup>6</sup>, Egon Stenager, PhD<sup>7</sup>, and Ulrik Dalgas, PhD<sup>1</sup>.

<sup>1</sup> Exercise Biology, Department of Public Health, Aarhus University, Aarhus, Denmark.

<sup>2</sup> Brain and Nerve Diseases, Lillebaelt Hospital, Kolding, Denmark.

<sup>3</sup> Department of Neurobiology Research, Institute of Molecular Medicine, University of Southern Denmark, Odense, Denmark

<sup>4</sup> Department of Neurology, Odense University Hospital, Odense, Denmark

<sup>5</sup> BRIDGE - Brain Research - Inter-Disciplinary Guided Excellence, Department of Clinical Research, University of Southern Denmark, Odense, Denmark

<sup>6</sup> The multiple sclerosis clinic, Department of Neurology, Aarhus University Hospital, Aarhus, Denmark

<sup>7</sup> Department of Regional Health Research, University of Southern Denmark, Odense, Denmark

## **Abstract**

**Objectives:** Fatigue and walking impairment are two of the most common and disabling symptoms of multiple sclerosis (MS). We aimed to investigate the effects of a 24-week progressive aerobic exercise (PAE) intervention on fatigue impact and severity, walking ability and capacity, and quality of life in people with MS.

**Methods:** This was a randomized controlled trial (1:1 ratio, stratified by sex) with a 24-week crossover follow-up, including an exercise (24 weeks of supervised PAE followed by self-guided physical activity) and a waitlist (24 weeks of habitual lifestyle followed by supervised PAE) group. PAE consisted of two supervised sessions per week; session duration = 30-60min, intensity = 65%-95% of maximum heart rate. Fatigue impact (Modified Fatigue Impact Scale; MFIS) and severity (Fatigue Severity Scale; FSS), walking ability (12-item MS Walking Scale; MSWS-12) and capacity (6-Minute Walk Test; 6MWT, Six Spot Step Test; SSST), quality of life (Short Form (36) health survey; SF-36), and cardiorespiratory fitness ( $VO_2\text{max}$ ) were measured at 0, 24, and 48 weeks. Data were analyzed using intention-to-treat linear mixed effects models.

**Results:** A total of 86 mildly to severely impaired people with MS were enrolled. Following 24 weeks of PAE, between group differences showed reductions in MFIS<sub>total</sub> score (-5.3 [95% CI: -10.9;0.4]; mean value > clinical relevance), MFIS<sub>physical</sub> subscore (-2.8 [-5.6;-0.1]), MFIS<sub>psychosocial</sub> subscore (-0.9 [-1.6;-0.2]), and MSWS-12 (-5.9 [-11.9; 0.2]), and increases in  $VO_2\text{max}$  (+3.5 mL  $O_2/\text{min}/\text{kg}$  [2.0;5.1]) and 6MWT (+14 m [-5;33]). These improvements were maintained at follow-up after 48 weeks. No changes were observed in FSS, SSST, SF-36<sub>Physical</sub> subscore, or SF-36<sub>Mental</sub> subscore.

**Conclusions:** In a representative sample of people with MS, 24 weeks of PAE induced a clinically relevant and long-lasting reduction in fatigue impact along with small improvements in walking. These findings justify recommending long-term PAE as a possible treatment for MS fatigue impact.