

# Cardiorespiratory fitness and moderate-to-vigorous physical activity in older adults with multiple sclerosis

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## Abstract

**Background:** Cardiorespiratory fitness ( $VO_{2peak}$ ) may be a modifiable indicator of health status and well-being in older adults with multiple sclerosis.

**Purpose:** We examined differences in  $VO_{2peak}$  and moderate-to-vigorous physical activity between older adults with multiple sclerosis and healthy controls, and whether moderate-to-vigorous physical activity accounted for group differences in  $VO_{2peak}$ .

**Methods:** Older adults with multiple sclerosis ( $n = 31$ ) and healthy controls ( $n = 29$ ) completed a cardiopulmonary exercise test and wore an accelerometer for measuring moderate-to-vigorous physical activity. The data were analyzed using the Baron and Kenny approach for examining moderate-to-vigorous physical activity as a mediator of group differences in  $VO_{2peak}$ .

**Results:** The multiple sclerosis group had significantly lower  $VO_{2peak}$  and moderate-to-vigorous physical activity than healthy controls.  $VO_{2peak}$  had a large correlation with moderate-to-vigorous physical activity ( $r = .59$ ). Group initially explained 8% of the variance in  $VO_{2peak}$  ( $\beta = -0.29$ ). The inclusion of moderate-to-vigorous physical activity accounted for an additional 27% of the variance in  $VO_{2peak}$ , but only moderate-to-vigorous physical activity ( $\beta = 0.57$ ) was a statistically significant correlate of  $VO_{2peak}$ . The effect of Group was attenuated and non-significant with the addition of moderate-to-vigorous physical activity in Step 2 (Group  $\beta$  Step 1 =  $-0.29$ , Group  $\beta$  Step 2 =  $-0.05$ ).

**Conclusions:** Our results provide initial support for targeting moderate-to-vigorous physical activity as an approach for improving  $VO_{2peak}$  in older adults with multiple sclerosis.

**Keywords:** Multiple sclerosis, aging, aerobic fitness, physical activity, rehabilitation

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There has been a demographic shift in the landscape of persons living with multiple sclerosis (MS) in the United States (US). The most recent prevalence estimates indicated nearly 1 million adults living with MS in the US, and further highlighted a change in the demography of MS by age. Those 55–64 years of age were the most prevalent group of women and men with MS in the US, and those 65–74 years of age were the third and second most prevalent groups for women and men with MS, respectively.<sup>1</sup> This indicates a greater number of older adults than young and middle-aged adults living with MS in the

US, and such a shift likely has major implications for health status and well-being.<sup>2,3</sup>

People with MS are living longer, but not necessarily better.<sup>4,5</sup> Indeed, there are many changes in health status among older adults with MS,<sup>4,5</sup> including higher rates of comorbid conditions such as hypertension, hyperlipidemia, heart disease, and diabetes.<sup>6</sup> There further is evidence for reduced lower-extremity physical function, walking and cognitive dysfunction, and compromised health-related quality of life (HRQOL) in older adults with MS.<sup>4</sup>

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Another important, yet seemingly understudied outcome of aging with MS may be reduced cardiorespiratory fitness. Cardiorespiratory fitness is measured using an incremental exercise test performed until volitional exhaustion (i.e. fatigue) with expired gases analyzed via calorimetry for estimating peak oxygen consumption ( $VO_{2peak}$ ).  $VO_{2peak}$  represents the highest rate of oxygen uptake and extraction by the body during maximal exercise based on cardiovascular and skeletal muscle oxidative function and pulmonary ventilation and diffusion capacity. There are data indicating that  $VO_{2peak}$  is reduced in young and middle-aged adults with MS compared with healthy controls<sup>7</sup> and as a function of increasing age in healthy adults.<sup>8</sup> We note that  $VO_{2peak}$  has been associated with outcomes such as comorbidity, walking, cognition, and HRQOL in young and middle-aged adults with MS<sup>9</sup> and older adults from the general population.<sup>10</sup> To that end,  $VO_{2peak}$  may be an important indicator of health status and well-being in older adults with MS, and may be modifiable through participation in moderate-to-vigorous physical activity (MVPA).

MVPA includes a range of human movements from walking for transportation through leisure-time exercise and sports that may benefit health and/or reduce chronic disease.<sup>11</sup> MVPA has been associated with a range of clinical and symptomatic outcomes in MS<sup>4</sup> and represents a primary determinant of  $VO_{2peak}$ ,<sup>11</sup> yet it is reduced in older adults with MS. Indeed, there are data supporting lower levels of MVPA in older adults with MS compared with healthy controls,<sup>12</sup> and further data of declines in MVPA with increasing age in MS.<sup>13</sup> We note that MVPA has been associated with  $VO_{2peak}$  in older adults from the general population<sup>14</sup> as well as young and middle-aged adults with MS.<sup>15</sup> This supports the idea that MVPA might be associated with  $VO_{2peak}$  in older adults with MS and thereby represents an important target of behavior change interventions for improving cardiorespiratory fitness. To date, there is limited research either concurrently comparing  $VO_{2peak}$  and MVPA between groups of older adults with MS and healthy controls or examining whether levels of MVPA explain group differences in  $VO_{2peak}$ .

The current study examined levels of  $VO_{2peak}$  and device-measured MVPA in older adults with MS compared with healthy controls. We hypothesized differences in  $VO_{2peak}$  and device-measured MVPA between groups, and that MVPA would account for group differences in  $VO_{2peak}$ , even when controlling

for walking performance as a confounding variable (i.e. extraneous or third variable that is associated with independent and dependent variables and that may bias or distort the association between those variables). We note that walking performance, as measured by the Timed 25-Foot Walk (T25FW), differs between older adults with MS and healthy controls<sup>2,4</sup> and correlates with both fitness and MVPA in MS.<sup>16</sup> To that end, the inclusion of walking performance as a confounding variable is important as this consequence of aging with MS may result in a spurious association between  $VO_{2peak}$  and device-measured MVPA (see Figure 1 for a conceptual representation of T25FW as a confounding variable). If our hypotheses are correct, the results would support future research examining behavior change interventions for increasing MVPA as an approach for improving  $VO_{2peak}$  as a major health indicator in this population.

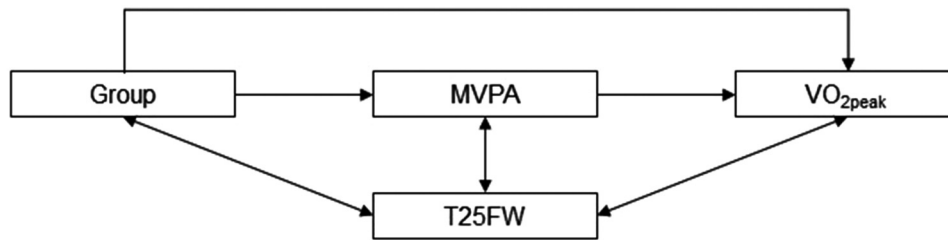
## Methods

### Participants

Participants were recruited through flyers posted in the local community, mailing lists of interested volunteers, and word of mouth. Those who were interested in participating contacted the laboratory and were screened for inclusion criteria. The inclusion criteria for persons with MS were: (a) physician-confirmed diagnosis of MS; (b) no relapses over the 30 days before engaging in the research; (c) 55+ years of age; (d) ambulatory with or without an assistive device; (e) no contraindications for magnetic resonance imaging (e.g. free of metal implants); and (f) low risk of contraindications for strenuous exercise based on the Physical Activity Readiness Questionnaire<sup>17</sup> along with physician's approval for participation, as necessary. The control participants were matched on age ( $\pm 5$  years) and sex, but not walking performance, and inclusion criteria were the same, except for the diagnosis of MS and relapse status; controls further were free of neurological disorders (e.g. stroke, Parkinson's disease).

### Measures

$VO_{2peak}$  was assessed using an incremental exercise protocol with a recumbent stepper (NustepT5 recumbent stepper; Nustep Inc, Ann Arbor, MI). Expired gases were collected using a 2-way, non-rebreathable valve and oxygen consumption ( $VO_2$ ) was measured using an open circuit spirometry system (VMAX Encore CareFusion; Vyair Medical, Inc, Yorba Linda, CA). Participants completed a warm-up for 1 min at a work rate of 15 W. The initial work rate during the first minute of the test was set to 15 W



**Figure 1.** Diagram depicting the hypothesized mediation of group differences in aerobic fitness ( $VO_{2peak}$ ) through device-measured moderate-to-vigorous physical activity (MVPA), and conceptualization of walking performance (T25FW) as a possible confounding variable of associations among group, MVPA, and  $VO_{2peak}$ .

and gradually increased  $\sim 10$  W every minute until the participant reached volitional fatigue. Heart rate (Polar Electro; Oy, Kempele, Finland) and rating of perceived exertion were recorded every minute.  $VO_{2peak}$  (ml/kg/min) was determined as the highest recorded 20 s  $VO_2$  value when at least 1 of the following criteria was met: (1) respiratory exchange ratio of 1.10 or greater reflecting a greater level of  $CO_2$  production than  $O_2$  consumption, based on ventilatory expired gas analysis, and indicating muscle lactate accumulation and substantial effort by a participant during the test protocol; (2) peak heart rate within 10 beats per minute of age predicated maximum (220-age); or (3) rating of perceived exertion of 17 (very hard) or greater indicating that a participant provided a substantial effort during the test protocol. This protocol was developed for exercise testing in persons with spinal cord injury and validated for adults with MS.<sup>18</sup>

MVPA was measured with accelerometry (ActiGraph, model GT3X+; ActiGraph LLC, Pensacola, FL). Accelerometers were worn at the waist over the non-dominant hip and were secured by an elastic belt. The raw data were downloaded using ActiLife 8 software, and processed with a low-frequency extension into 60 s epochs. Time spent engaging in MVPA was based on group-specific cut points wherein a minute increment was designated as MVPA if the number of activity counts/min exceeded 1584 and 1950 for MS and healthy controls, respectively.<sup>19</sup> The number of minutes of MVPA were summed per day and averaged across all valid days providing a final measure of MVPA in minutes/day. To be considered a valid day and included in the analysis, there was a minimum threshold of 10 h of wear time/day. We included all persons who had 1 or more valid days of accelerometer data, as is common in research involving device-measured MVPA (e.g. National Health and Nutrition Examination Survey). There was 1 person with only

1 valid day of data, and 4, 9, 21, and 25 persons had 4, 5, 6, and 7 days of valid data, respectively; the mean number of valid days of data was 6.0 (1.4) days for the overall sample, and 5.9 (1.5) and 6.0 (1.2) for older health controls and persons with MS, respectively.

Walking speed was assessed by the Timed 25-Foot Walk (T25FW).<sup>20</sup> Participants were instructed to walk as quickly and safely as possible from a static start position across a clearly marked 25 ft course. Two trials were administered. The average time (seconds) for walking the 25 ft course was recorded and converted into a measure of speed (ft/s).

#### Procedure

The study procedure was approved by a University Institutional Review board and administered as part of a study examining predictors of brain structure in older adults with MS.<sup>21</sup> All participants provided written informed consent prior to enrolling in the study. Participants completed three study visits. The first visit took place at our laboratory where all participants completed a demographics questionnaire that included clinical characteristics for those with MS, and the T25FW. Participants with MS further underwent a neurological evaluation by a Neurostatus certified examiner (level C) for establishing disability status based on the Expanded Disability Status Scale (EDSS). At the end of the initial visit, participants were provided the accelerometer and instructed to wear it during waking hours for 7 days. Additionally, participants were instructed to record wear time on a log sheet for cross-referencing valid days identified by the accelerometer software. Participants returned the accelerometer at one of the two subsequent study visits. One visit was for exercise testing completed at a University site that specializes in clinical exercise testing. On a separate day, participants underwent MRI, although this was not the focus in the current paper. The initial visit was

**Table 1.** Demographic and clinical characteristics of the samples of older adults with multiple sclerosis and healthy controls.

Variable	Multiple sclerosis ( <i>n</i> = 31)	Healthy controls ( <i>n</i> = 29)	<i>p</i> -value
Age (years)	63.0 (5.8)	63.9 (5.4)	0.54
Sex ( <i>n</i> /% female)	25/81%	24/83%	0.95
Race ( <i>n</i> /% Caucasian)	26/84%	21/72%	0.33
MS clinical course ( <i>n</i> /% RRMS)	29/94%	N/A	
Disease duration (years)	18.3 (6.1)	N/A	
EDSS (0–10)	4.0 (1.5)	N/A	

*Note.* Values are median (IQR) for EDSS, and mean (SD) or *n*/% for all other variables. RRMS: relapsing-remitting multiple sclerosis. EDSS: Expanded Disability Status Scale.

always completed first, but the order of the remaining two visits was based on availability. Visits were not completed on the same day, and were completed within 1 week from the initial visit.

#### Data analysis

Data were analyzed in SPSS Statistics version 25 with an unadjusted significance level of  $p < 0.05$ . We first examined differences between MS and control groups in age, sex, and race using independent sample *t*-tests or chi-square tests as appropriate. We then examined the data using the Baron and Kenny<sup>22</sup> approach for investigating MVPA as a possible explanatory variable (i.e. mediator) of group differences in cardiorespiratory fitness. The first step involved testing group differences in cardiorespiratory fitness, MVPA, and walking performance using independent sample *t*-tests. The magnitude of differences between groups was expressed as Cohen's *d* with values of 0.2, 0.5, and 0.8 interpreted as small, moderate, and large, respectively.<sup>23</sup> The second step involved a bivariate Pearson correlation (*r*) performed between cardiorespiratory fitness, MVPA, and walking performance in the overall sample. Values of 0.1, 0.3, and 0.5 were interpreted as small, moderate, and large, respectively.<sup>23</sup> The last step involved a linear regression analysis with direct entry of variables in Steps (i.e. blocks), whereby we regressed cardiorespiratory fitness on Group (MS and control) in Step 1, and then added MVPA in Step 2, if scores for MVPA differed between groups and correlated with cardiorespiratory fitness. We lastly added walking speed in Step 3 as a confounding variable, if scores for T25FW differed between groups and correlated with both cardiorespiratory fitness and MVPA. We examined the  $\beta$ -coefficients for identifying the independent contributions of the variables in the model as well as model fit based on  $R^2$  and

change in  $R^2$  ( $\Delta R^2$ ). The decision on mediation was determined based on comparison of the standardized  $\beta$ -coefficient for Group between Steps 1 and 2 of the regression and attenuation toward zero and non-significance indicated full mediation. The decision on confounding was based on inspection of standardized  $\beta$ -coefficients in Step 3, and the attenuation toward zero and non-significance of coefficients would support walking speed as a confounding variable.

## Results

### Participant characteristics

Demographic and clinical characteristics are provided in Table 1. The MS group ( $n = 31$ ) and the control group ( $n = 29$ ) were similar in age ( $t = 0.62$ ,  $p = .54$ ), sex ( $X^2 = 0.01$ ,  $p = .95$ ), and race ( $X^2 = 2.21$ ,  $p = .33$ ); we did not present data on assistive device use for comparison between groups. The MS group had mostly relapsing-remitting MS, a mean disease duration of 18.3 years, and mild through moderate disability based on a median EDSS score of 4.0 (range of scores = 2.0–6.5).

### Group differences

The descriptive statistics for  $VO_{2peak}$ , MVPA, and T25FW for the MS and healthy control groups are provided in Table 2. The MS group had significantly lower values for  $VO_{2peak}$  ( $t = 2.20$ ,  $p < .05$ ), MVPA ( $t = 3.47$ ,  $p < .001$ ), and T25FW ( $t = 5.68$ ,  $p < .001$ ) than healthy controls; the group difference in MVPA satisfies the criterion for an association between Group and MVPA (i.e. presumed mediator). The difference between groups in  $VO_{2peak}$  was moderate in magnitude ( $d = .58$ ), whereas the differences in MVPA ( $d = .88$ ) and T25FW ( $d = 1.5$ ) were large in magnitude; the difference in T25FW indicated

**Table 2.**  $VO_{2peak}$ , MVPA, and T25FW values for the samples of older adults with multiple sclerosis and healthy controls.

Variable	Multiple sclerosis ( $n = 31$ )	Healthy controls ( $n = 29$ )	$p$ -value
$VO_{2peak}$ (ml/kg/min)	18.8 (5.9)	22.3 (6.6)	<0.05
MVPA (min/d)	14.4 (15.4)	30.1 (19.6)	<0.001
T25FW (ft/s)	4.5 (1.4)	6.2 (0.9)	<0.001

*Note.* Values are mean (SD).  $VO_{2peak}$ , peak aerobic capacity; MVPA: moderate-to-vigorous physical activity; T25FW: timed 25-foot walk.

that the older adults with MS presented with greater physical limitations than the older healthy controls.

### Bivariate correlations

$VO_{2peak}$  had a large correlation with device-measured MVPA ( $r = .59, p < .001$ ) and a moderate correlation with T25FW speed ( $r = .47, p < .001$ ). MVPA had a large correlation with T25FW speed ( $r = .59, p < .001$ ).

### Regression analyses

The results for the linear regression analysis examining MVPA as a mediator of group differences in  $VO_{2peak}$  while controlling for T25FW as a confounding variable are in Table 3. Group (coded as 1 = MS and 0 = healthy controls) initially explained 8% of the variance in  $VO_{2peak}$  ( $\beta = -0.29$ ). The inclusion of MVPA in Step 2 of the model accounted for an additional 27% of the variance in  $VO_{2peak}$ , but only MVPA ( $\beta = 0.57$ ) was a statistically significant correlate of  $VO_{2peak}$ . The effect of Group was attenuated and non-significant with the addition of MVPA in Step 2 (Group  $\beta$  Step 1 =  $-0.29$ , Group  $\beta$  Step 2 =  $-0.05$ ) and this is consistent with full mediation. The inclusion of T25FW in Step 3 of the model accounted for an additional 3% of the variance in  $VO_{2peak}$ , but only MVPA ( $\beta = 0.47$ ) was a statistically significant correlate of  $VO_{2peak}$ . The effects of Group and T25FW were non-significant in Step 3 and this suggests that T25FW did not confound the results of MVPA as a mediator of Group differences in  $VO_{2peak}$ .

### Discussion

This study examined levels of cardiorespiratory fitness and MVPA in older adults with MS compared with age and sex-matched healthy controls. We observed differences in  $VO_{2peak}$ , MVPA, and T25FW between groups, and further observed that MVPA accounted for group differences in  $VO_{2peak}$  even when controlling for T25FW as a possible confounding variable. These results provide initial

support for future research examining approaches for increasing MVPA and possibly improving  $VO_{2peak}$  as a major health indicator among older adults with MS.

Older adults with MS had lower  $VO_{2peak}$  than age and sex-matched healthy controls. The difference was moderate in magnitude, and was consistent with previous reports of lower cardiorespiratory fitness in MS.<sup>7</sup> Importantly, the novel component of the current study involved older adults with MS who had a lower  $VO_{2peak}$  than age and sex matched controls, and the mean value of 18.8 ml/kg/min was nearly 1 MET lower than the mean of  $\sim 22.0$  ml/kg/min estimated from previous research using a similar exercise test protocol in middle-aged adults with mild-moderate disability based on EDSS.<sup>18</sup> Such data may support the possibility of combined effects of MS and aging on  $VO_{2peak}$ , and this should be directly examined in future research that includes samples of MS and healthy controls across young, middle-aged, and older age-groups. The clinical importance of  $VO_{2peak}$  has not yet been established in older adults with MS, but it has been associated with magnetic resonance imaging volumes of subcortical deep-grey brain regions, walking and cognitive performance, symptoms, HRQOL, participation, and comorbidity in young and middle-aged adults with MS<sup>9</sup>; the same pattern of clinical relevance might apply in older adults with MS and thereby identify  $VO_{2peak}$  as an important target for clinical rehabilitation involving physical activity and/or exercise training interventions.

Older adults with MS further demonstrated a reduction in MVPA compared with age and sex-matched healthy controls. The difference between groups in device-measured MVPA was large in magnitude, and this was consistent with previous research reporting reductions in physical activity as a function of aging in MS<sup>13</sup> and when comparing older adults with MS and healthy controls.<sup>12</sup> The reduction in

**Table 3.** Regression analysis examining MVPA as a mediator of group differences in the  $VO_{2peak}$  between samples of older adults with multiple sclerosis and healthy controls statistically controlling for T25FW.

Step	Variable	<i>B</i>	Standard error of <i>B</i>	$\beta$	<i>p</i> -value	$R^2$	$\Delta R^2$
Step 1	Group	−3.725	1.647	−0.289	0.028	.08	N/A
Step 2	Group	−0.612	1.720	−0.050	0.693	.35	.27
	MVPA	0.193	0.040	0.572	0.001		
Step 3	Group	0.646	1.720	0.050	0.709	.38	.03
	MVPA	0.160	0.045	0.474	0.001		
	T25FW	1.028	0.656	0.235	0.123		

*Note.*  $VO_{2peak}$ : peak aerobic capacity; MVPA: moderate-to-vigorous physical activity; T25FW: timed 25-foot walk.

physical activity among older adults with MS has been explained, in part, by social-cognitive theory (SCT) variables.<sup>24,25</sup> SCT identifies self-efficacy, outcome expectations, barriers/facilitators, and goal setting and action planning as core determinants of behavior, including physical activity, and those variables can be directly targeted by behavior change techniques for increasing MVPA. Accordingly, our results may support future efforts toward the design and delivery of SCT-based behavior change interventions targeting physical activity in older adults with MS. The measurement of MVPA may represent an important metric for characterizing the efficacy of such interventions for behavior change and the necessary dose for changes in  $VO_{2peak}$ .

We examined MVPA as a mediator of group differences in  $VO_{2peak}$ , and further controlled for T25FW as it differed between groups and correlated with  $VO_{2peak}$  and MVPA (i.e. possible confounding variable). We observed that MVPA satisfied the preconditions for examining mediation and fully accounted for the effect of group on  $VO_{2peak}$ , even when controlling for T25FW. This suggests that physical activity may be an important target for improving  $VO_{2peak}$  in older adults with MS. MVPA may be mechanistically associated with improvements in  $VO_{2peak}$  through consideration of the Fick principle that indicates that  $VO_{2peak}$  is the product of cardiac output (delivery) times the differential  $O_2$  content of the arterial and mixed venous blood (extraction). Cardiac output is the product of stroke volume and heart rate, and regular MVPA may increase stroke volume through expanded plasma volume and increased ventricular end-diastolic volume and cardiac contractility (Frank-Starling mechanism). MVPA may further promote changes in local muscle blood flow dynamics through metabolic vasodilation and visceral sympathetic vasoconstriction, and increased  $O_2$  extraction through changes in capillary density, mitochondrial

density, and oxidative enzymes within the muscle. Such results and mechanisms lend further support for developing theory-based behavior change interventions for increasing physical activity and examining the secondary effects on the  $VO_{2peak}$  in older adults with MS.

There are important limitations of the current study. The most significant limitation was the cross-sectional research design. The cross-sectional design precludes inferences regarding causality among variables. This limitation can be overcome in future research using longitudinal or intervention designs. Another limitation was that the sample was primarily female and Caucasian, and the results cannot be broadly generalized among older adults with MS or healthy controls. The last limitation is that we did not include young and middle-aged adults with MS or healthy controls for examining the pattern of change in variables as a function of age cohort between groups. We included persons with as few as 1 day of valid accelerometer data, and this might not provide a representative measure of typical physical activity in MS.

Overall, this study reported differences in  $VO_{2peak}$ , MVPA, and T25FW between groups of older adults with MS and age and sex-matched healthy controls, and further observed that MVPA accounted for the group difference in  $VO_{2peak}$ , even after controlling for T25FW. Such results provide support for future research examining approaches for increasing health-promoting physical activity behavior and examining secondary effects on  $VO_{2peak}$  among older adults with MS. This is important as  $VO_{2peak}$  is a key indicator of health and well-being in all populations, including those aging with chronic disabling disease and conditions such as MS. Collectively, this line of research may support efforts toward maximizing longevity and independence among the growing population of older adults with MS in the US.<sup>4</sup>


## Declaration of conflicting interests


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