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Predictors of positive outcomes following resistive inspiratory muscle training in non-ambulatory persons with advanced multiple sclerosis

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Abstract

Background: Inspiratory muscle training (IMT) using a threshold device improves inspiratory muscle strength. What factors influence the IMT outcome has not been examined.

Objective: To identify predictors of the positive outcome following IMT in persons with advanced multiple sclerosis (PwAMS).

Methods: Inclusion criteria were non-ambulatory PwAMS, Expanded Disability Status Scale (EDSS) ≥6.5, age >18 years, no acute medical conditions, current non-smokers, and ability to consent. Participants (n = 38) performed daily inspiratory exercises using a resistive threshold device for 10 weeks. Baseline measurements included age, sex, body mass index, year post multiple sclerosis diagnosis, comorbidities, EDSS, Modified Fatigue Impact Scale-5, and oral Symbol Digit Modality Test. The percentage of completed prescribed exercise trials (Trials%) during the 10-week intervention was calculated. Age- and sex-adjusted predicted values of maximum inspiratory pressure (MIP%pred) and maximum expiratory pressure (MEP%pred) were obtained before and after the 10-week intervention. Backward multivariable regression analyses for the primary outcome (MIP%pred) were conducted.

Results: After controlling for the initial MIP%pred, perceived fatigue at the baseline and Trial% were significant and independent predictors of MIP%pred after IMT.

Conclusion: Less fatigue at the baseline and higher adherence to the prescribed exercise repetitions were positive predictors of the positive outcome following IMT in PwAMS.

Keywords: Exercise, respiratory muscles, multiple sclerosis

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Introduction

Multiple sclerosis is associated with a variety of impairments, including muscle weakness, fatigue, cognitive deficits, sensory disturbances, pain, spasticity, visual changes, and bladder and bowel dysfunction.[1] In persons with multiple sclerosis (MS), weakness of respiratory muscles emerges early in the disease course without respiratory symptoms[2,3] and worsens as the disease progresses.[4] Approximately 60% of ambulatory persons with MS experience respiratory muscle weakness[5] that negatively impacts respiratory function, physical performance, exercise capacity, balance, and fatigue.[6,7] Rehabilitation intervention is essential for optimizing physical function and quality of life in this population.

Among various types for respiratory muscle training programs, inspiratory muscle training (IMT) with the emphasis on strength and using a resistive threshold device has a moderate effect on improving inspiratory muscle strength in persons with MS.[5,7–10] Compared to breathing and maximum exhalation exercises, 12-week IMT resulted in a significantly greater improvement in inspiratory muscle pressure and dyspnea in ambulatory and non-ambulatory persons with MS.[10] A recent study confirmed the benefits of IMT without adverse effects in non-ambulatory persons with advanced MS (PwAMS), defined as the Expanded Disability Status Scale (EDSS) ≥6.5.[11] Despite the research evidence, IMT has not been routinely integrated into the rehabilitation management in PwMS.[12] Because persons with

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MS with respiratory muscle weakness often do not report subjective complaints of dyspnea,[2,3] one challenge may relate to identifying appropriate candidates for IMT. Delineating the individuals' characteristics associated with the responses to IMT may provide insight into the prescription of this intervention in clinical practice. IMT may be particularly suitable for persons with MS with positive prognostic factors. Co-treatment to address negative and potentially modifiable prognostic factors, such as fatigue,[13] comorbidity, and cognition,[14] may be considered prior to or concurrently with the IMT. Given that the MS disease course, pathology, impairments, and symptoms are diverse,[1] a better understanding about the predictors of the response to IMT may guide the development of individually tailored interventions to optimize the outcome.

The findings of response heterogeneity following resistive exercise interventions in persons with MS[15] further supports the need to evaluate the influence of participant characteristics on the positive outcome following IMT. In a study of 12-week progressive resistive exercise training in persons with MS, three out of the 15 participants showed a decline in isometric knee extensor muscle strength after training, although the improvement in strength in the training groups overall was significant compared to the control group.[16] Conversely, in a study of IMT, all seven participants with advanced MS improved inspiratory muscle strength after the 10-week intervention.[17] Plausible links between the participant characteristics with the positive outcome of inspiratory exercise interventions likely exist but have not been investigated prospectively. Cross-sectional observations have revealed significant associations between respiratory muscle strength with MS-related disability,[5] perceived fatigue,[6] and cognition.[18] Lower aerobic fitness, slower walking speed, and cognitive processing speed prior to starting the exercise intervention were linked to larger improvements in these respective outcomes, indicating that persons with MS with poorer baseline performance experienced greater training benefits.[19] In summary, there is a gap in knowledge about the factors that may influence the positive outcome of IMT in the MS population.

The purpose of this study was to identify independent factors associated with improvements in inspiratory muscle strength following IMT using a resistive threshold device in PwAMS. In light of the paucity of relevant research, clinical characteristics of persons with MS that are commonly evaluated by clinicians and reported in the literature[5,6,13–19] were considered as the potential predictors relating to the positive outcome following IMT.

Materials and Methods

Design

This study was a secondary analysis of data from a previous trial investigating the effects of IMT.[11] Data being analyzed in this study were collected prospectively.

Participants

We recruited individuals with advanced MS at The Boston Home, a facility with the designation of "Center for Excellence in Long-term Care" from the National Multiple Sclerosis Society. Inclusion criteria were: age > 18 years, MS diagnosis confirmed via medical record, EDSS score ≥ 6.5, and ability to provide consent. Exclusion criteria were hospitalization for MS exacerbation within two months before or during enrollment, an oral temperature greater than 100°F, unstable heart, lung, or other physical conditions (e.g. shortness of breath with light activities or chest pain), and current smoking history. All participants provided their written consent before enrolling in the study. Franklin Pierce University and University of Michigan-Flint Institutional Review Boards approved the study.

Intervention

Participants performed three sets of 15 repetitions of IMT daily for 10 weeks using the threshold inspiratory muscle trainer (Philips, Andover, MA). The device has a spring-loaded valve that provides consistent resistance to exercise inspiratory muscle, regardless of how quickly or slowly the user breathes. During inhalation, the user must generate pressure at the preset threshold load to open the valve and allow the airflow through the device for each breath.

The intervention protocol was adapted from a previous study in persons with mild-moderate MS.[5] The threshold device resistance was initiated at 30% of each participant's baseline maximum inspiratory pressure (MIP), or at 9 cm H2O when their 30% of baseline MIP was less than the lowest resistance level of 9 cm H2O on the device. The participant used a nose clip and inhaled deeply through the mouth from the functional residual capacity to the prescribed resistance on the device. The participant continued inhaling and exhaling without removing the device from the mouth for 15 repetitions in a set and completed three sets with rest as necessary in a day. The progression of device resistance was

Table 1. Ten-week resistive inspiratory training protocol.[a]

Frequency: Exercises performed daily for 10 weeks.				
Overload: Three sets of 15 repetitions[b]				
Resistance: Initial resistance (cmH2O) of the IMT was set at 30% of the participant's baseline MIP.				
Progression: Resistance was adjusted weekly by the research team according to the participant's baseline MIP, Borg RPE, and symptoms.				
Participant's Baseline MIP < 50 cmH2O				
Borg RPE	**<13**	**13–15**	**16–17**	**>17**
Pressure resistance (cmH2O)	Increase by 2	Increase by 1	Maintain at same level	Reduce by 2
Participant's Baseline MIP ≥50 cmH2O				
Borg RPE	**<13**	**13–15**	**16–17**	**>17**
Pressure resistance (cmH2O)	Increase by 4	Increase by 2	Maintain at same level	Reduce by 2
If subjects developed symptoms (i.e. dizziness, lightheadedness, or shortness of breath) while performing exercises, the resistance was adjusted as follows until no symptoms persisted.				
Symptoms	Two or more symptomatic episodes in a row per week		One to two isolated symptomatic episodes per week	
IMT Resistance	Reduce by 2 Participants were checked 3 days later to monitor response		Maintain at the same level Participants were checked 3 days later to monitor response	

IMT: inspiratory muscle trainer; MIP: maximum inspiratory pressure; RPE: rating of perceived exertion.
aAdapted with permission from Fry et al.[5]
bIf a subject achieved the maximum IMT resistance of 41 cmH2O and resistance could no longer be increased, a fourth set of exercises was added along with an increased number of repetitions up to a maximum of 15 repetitions.

adjusted weekly by the research team based on symptoms (e.g. shortness of breath, light-headedness, dizziness, or discomfort), rate of perceived exertion,[20] and baseline MIP (Table 1).

After the research team provided the exercise instruction, the participants performed the exercise on their own unless they had difficulty handling the threshold device due to motor impairments of the upper extremities. In such instances, the rehab personnel held the device for the participants to complete exercises.

Measurements

Demographics and health information of participants. The participants' age, sex, body mass index (BMI), years post MS diagnosis, and comorbidities were collected by interviews and reviews of medical charts at the baseline. The BMI, calculated as body weight/body height (kg/m^2), is a commonly used measurement of body composition in PwMS.[21] The number of comorbidities was determined using the Functional Comorbidity Index, a self-report of 18 medical conditions that impact physical function.[22]

EDSS. The EDSS was measured at the baseline. EDSS total functional score was determined by a clinician with experience administering the test following the standardized procedures.[23] The participants were given a neurologic examination and their scores were determined based on the examination findings and individual's functional abilities. EDSS has demonstrated excellent inter-rater reliability (intraclass correlation coefficient (ICC) = 0.99) and intra-rater reliability (ICC = 0.99), and excellent construct validity in activities of daily living ($r = -0.74$ with the Barthel Index) and health-related quality of life ($r = -0.82$ with physical functioning items of SF-36).[24]

Modified Fatigue Impact Scale-5 Item. The MFIS5, an abbreviated version of Modified Fatigue Impact Scale,[25] was measured at the baseline and at the end of 10-week intervention. The MFIS5 asks the individual to rate the impact of fatigue on cognitive, physical, and psychosocial function during the past four weeks. In PwMS, the MFIS5 has good test–retest reliability (ICC = 0.76) with minimal detectable change at 95% CI (MDC_{95}) of 6.92.[25] The participants completed the MFIS5 through verbal interviews.

Symbol Digit Modalities Test. The Symbol Digit Modalities Test (SDMT) was measurd at the baseline and at the end of 10-week intervention. It is a reliable and valid measure of cognitive processing speed and working memory in PwMS.[26] The SDMT requires the test-takers to use a coded key to match abstract symbols paired with numerical digits.[27] The oral version of SDMT is recommended for PwMS[26] and was used in this study because a majority of the participants had upper extremity impairments with difficulty in writing. The total number of correct responses within 90 seconds was the score of SDMT.[27]

The oral version of SDMT was found to have excellent test–retest reliability (r = 0.97), adequate validity (r = 0.70–0.71 with magnetic resonance imaging measurements of brain atrophy), and clinically meaningful change of 4 points in persons with MS.[28]

Percentage of Completed Prescribed Exercise Trials (Trial%). The total number of completed inspiratory exercise repetitions as a percentage of the total number of prescribed repetitions during the 10-week intervention was the percentage of completed prescribed exercise trials. Each participant was provided with a paper exercise schedule and a log to record the number of exercise repetitions performed daily. If the participants had difficulty in writing, the rehabilitation personnel helped with log entries. Many participants benefitted from the written schedule and/or verbal reminders to complete the exercises.

Respiratory Muscle Strength. The MIP and maximum expiratory pressure (MEP) are indirect measures of inspiratory and expiratory muscle strength, respectively.[29] Using the MicroRPM Pressure Meter (measurement range = −300 to 300 cmH2O, resolution = 1.0 cmH2O, and accuracy = 0.03 cmH2O) (Micro Direct, Inc. Lewiston, ME), three trials of MIP and MEP were measured following the American Thoracic Society and the European Respiratory Society standardized procedures to ensure the reliability of the results.[29] The best value from three trials was analyzed.[29] The MIP and MEP were measured at the baseline and at the end of 10-week intervention. The MIP and MEP were converted to age- and sex-adjusted MIP (MIP%pred) and MEP (MEP%pred) predicted values, respectively.[30] The psychometrics of MIP and MEP measurements using the MicroRPM have not been established in PwMS. The test–retest reliability for measuring the MIP and MEP using the MicroRPM was good in healthy adults (ICC ≥ 0.92).[31]

Primary Outcome

Exercises using the resistive threshold device primarily involve inspiratory muscles. This training has demonstrated a task-specific gain in inspiratory muscle strength in PwAMS.[11] Because normative values of MIP differ by age and sex,[29,30] the MIP% pred at the end of the intervention was used as the primary outcome.

Statistical Analysis

IBM SPSS version 26 (Armonk, NY: IBM Corp) was used for statistical analyses. The normality of data distribution was examined using Shapiro–Wilk test. Descriptive statistics were calculated for all measurements. Depending on the normality of data, paired t-test or Wilcoxon signed ranks test was used to compare fatigue, cognitive processing speed, and respiratory muscle strength before and after the 10-week intervention.

Correlation Analysis. The relations among predictor variables and between predictor variables and primary outcome (MIP%pred) were examined using Person r or Spearman σ values based on the normality of data distribution. The significance level for these analyses using the conservative Bonferroni correction was $p < 0.0045$ for the correlations between the predictor variables and $p < 0.0042$ for the correlations between the predictor variables and primary outcome.

Univariable Regression Analysis. In order to build a parsimony multivariable regression model for the primary outcome, univariable regression models with each predictor variable were constructed with the baseline MIP%pred as the covariate in the models to control for differences in baseline inspiratory muscle strength.

Multivariable Regression Analysis. The backward regression approach was employed to construct the multivariable model by including the predictor variables that had a p-value <0.1 in the previous univariable regression analyses.[31] The backward elimination of independent variables was determined by Akaike's information criterion corrected (AICC) for a small sample size to avoid overfitting.[31] The model with the smallest AICC was the final model. Multicollinearity of independent variables in the model was determined by covariate correlation matrix (r or ρ ≥ 0.6) and variance inflation factor (VIF ≥ 4).[32]

Standardized coefficients (β) for independent variables in the regression models were reported as an

Table 2. Characteristics of participants ($n = 38$; 29 female and 9 male).

Variables	Mean (SD)
Age, year	60.2 (8.5)
Functional Comorbidity Index, number of commodities	2.3 (2.0)
Body mass index, kg/m^2	26.8 (6.1)
Year since multiple sclerosis diagnosis, year	28.3 (11.0)
Expanded Disability Status Scale score	8.5 (0.4)
Modified Fatigue Impact Scale-5	6.6 (4.7)
Symbol Digit Modality Test	18.4 (10.3)
Maximum inspiratory pressure, cmH2O	27.9 (16.7)
Age- and sex-adjusted maximum inspiratory pressure, %	36.1% (21.3%)
Maximum expiratory pressure, cmH2O	23.7 (15.3)
Age- and sex-adjusted maximum expiratory pressure, %	26.1% (14.1%)
Percentage of completed prescribed exercise trials, %	45.9% (29.0%)

estimate of effect size.[33] A larger absolute value of standardized coefficient indicates a stronger effect of the independent variable on the primary outcome.[33] In the context of multiple regression, $\beta \geq 0.1$, $\beta \geq 0.3$, and $it > \beta \geq 0.5$ were used as the criteria to determine the small, medium, and large effect sizes, respectively.[34]

Results

Characteristics of Participants

Two participants missed post-tests and one participant dropped out due to illness unrelated to respiratory function. Data from the remaining 38 participants were analyzed. Table 2 presents the characteristics of participants. Twenty-four participants began the training at the lowest level of resistance (9 cmH2O) on the device. All participants were breathing room air without supplementary oxygen or ventilation assist during the study period. No adverse events were reported during the intervention. Figure 1 shows the change scores of each participant on the primary outcome. The mean change score on MIP%pred was 5.3%.

Fatigue, Cognitive Processing Speed, and Respiratory Muscle Strength Before and After Intervention

As shown in Table 3, MIP%pred increased significantly after the 10-week intervention ($p = 0.01$). In contrast, MEP%pred and scores of MFIS5 and SDMT did not differ before and after the intervention.

Relations among Predictors Variables

As shown in Table 4, MIP%pred at the baseline was correlated with Trial% during the 10-week intervention. The correlation between MEP%pred at the baseline and Trial% ($p = 0.005$) was not significant but approached the significance level with Bonferroni adjustment ($p < 0.0045$). Age was correlated with the year of MS diagnosis. Cognitive processing speed was correlated with MEP%pred. Comorbidity was correlated with MS-related disability measured by EDSS. No other statistically significant associations were found.

Relations between Predictor Variables and Primary Outcome

Baseline MIP%pred and cognitive processing speed and Trial% were correlated with MIP%pred (Table 5). No other significant associations between the predictor variables and primary outcome were found.

Regression Modeling

In univariable regression models, the baseline MIP%pred and MFIS5 and Trial% were significant predictors of MIP%pred at the end of intervention (Table 6). SDMT ($p = 0.05$) and EDSS ($p = 0.059$) approached the significance level. No other significant predictors were found in the univariable models. In the multivariable regression analyses, all variables with a p-value <0.1 from the univariable analyses (baseline MIP%pred, EDSS, MFIS5, SDMT, and Trial%) were entered into the initial model. No violation of multicollinearity was found. Table 7 shows the final model using the backward regression analyses. Baseline MIP%pred and fatigue and Trials% together explain 83.6% of the variance in the model for MIP%pred at the end of intervention ($F_{3,23} = 26.246$, $p < 0.001$). After controlling for the initial MIP%pred, less fatigue at the baseline and higher adherence in completing prescribed exercise trials during the intervention was associated with a better outcome in inspiratory muscle strength. All predictors had $\beta > 0.5$, reflecting a large effect size.

Discussion

This prospective study examined the relationship between the participant characteristics and the positive outcome in inspiratory muscle strength after 10-week IMT using a resistive threshold device among non-ambulatory PwAMS. Multivariable regression analyses revealed that after controlling the initial inspiratory muscle strength, baseline

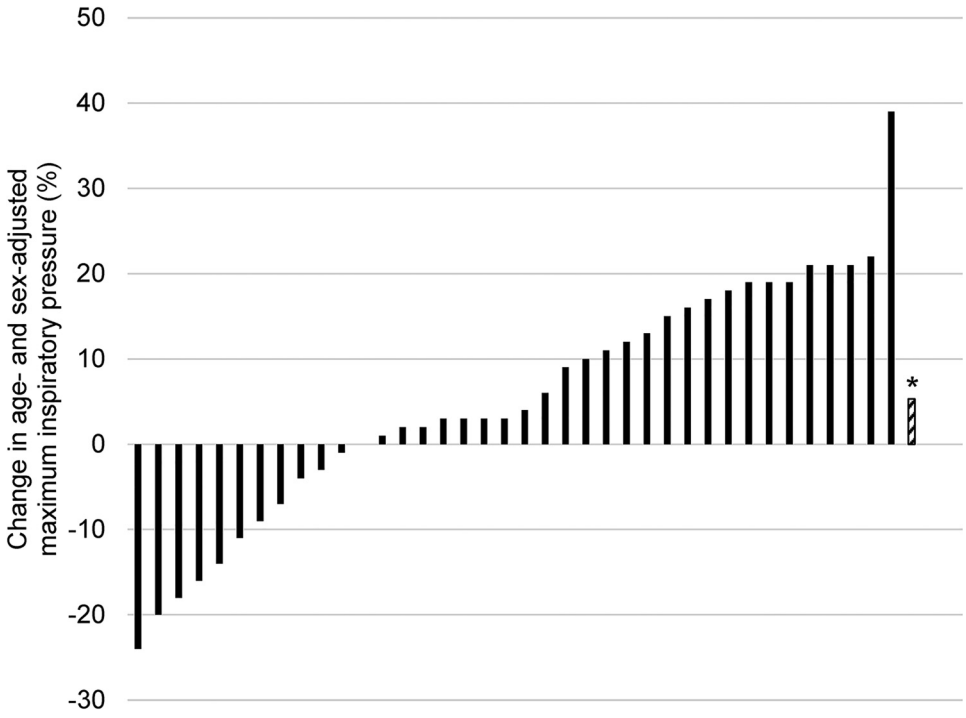

Figure 1. The change in age- and sex-adjusted maximum inspiratory pressure (MIP%pred) from the baseline to the end of 10-week inspiratory muscle training using a resistive threshold device for each participant. Each bar represents the change in MIP%pred of an individual participant. A higher percentage indicates a greater improvement in MIP%pred after the intervention. **Represents the average change in MIP%pred for all participants.

fatigue and percentage of completed prescribed exercise trials were significant and independent predictors of inspiratory muscle strength at the end of the intervention. In light of limited evidence for IMT in non-ambulatory persons with advanced MS-related disability (EDSS ≥ 6.5), current findings have significant clinical implications. Persons with MS rarely report symptoms of dyspnea even though respiratory muscle weakness can develop early in the disease course.[2,3] Interventions to strengthen respiratory muscles are important in order to reduce respiratory complications in this population.[3] Regardless of the demographic or clinical characteristics, including age, sex, BMI, years post MS diagnosis, comorbidity, cognitive processing speed, or EDSS score, PwAMS may be suitable candidates for IMT. More importantly, fatigue and exercise adherence are potentially modifiable factors that can be managed prior to or concurrently with the intervention in order to achieve a better outcome following IMT.

Table 3. Comparisons of fatigue, cognition, age-, and sex-adjusted maximum inspiratory pressure and maximum expiratory pressure before and after the 10-week intervention.

Variable	Before	After	*p*-value
Modified Fatigue Impact Scale-5	6.4 (4.4)	5.6 (4.9)	0.099
Symbol Digit Modalities Test	19.2 (10.8)	19.2 (10.3)	0.978
Age- and sex-adjusted maximum inspiratory pressure, %	33.3 (19.8)	39.6 (22.3)	0.010*
Age- and sex-adjusted maximum expiratory pressure, %	25.8 (14.6)	27.6 (12.8)	0.182

Variable values shown are mean (SD).
*$p < 0.0125$ (Bonferroni adjusted).
Data were not normally distributed based on Shapiro–Wilk's test. *p*-values were comparisons of variables before and after the 10-week intervention using paired t-test (Symbol Digit Modalities Test, age- and sex-adjusted maximum inspiratory pressure) and Wilcoxon signed ranks test (Modified Fatigue Impact Scale-5, age- and sex-adjusted maximum expiratory pressure).

Table 4. Relationships among baseline variables.

	MIP% pred	MEP% pred	Age	Gender	BMI	Year of diagnosis	Comorbidity	EDSS	MFIS5	SDMT	Trial %
MIP%pred	1										
MEP%pred	0.535*	1									
Age	−0.168	0.004	1								
Gender	−0.127	0.006	−0.048	1							
BMI	0.071	0.096	−0.157	0.014	1						
Year of diagnosis	−0.022	−0.019	0.557*	−0.212	−0.015	1					
Comorbidity	−0.144	−0.008	0.078	0.313	0.100	−0.029	1				
EDSS	0.034	−0.310	−0.043	−0.118	−0.167	−0.760	−0.416*	1			
MFIS5	−0.294	−0.328	−0.321	−0.119	−0.161	−0.391	0.023	0.109	1		
SDMT	0.414	0.452*	−0.293	0.387	0.221	−0.273	0.009	−0.064	−0.099	1	
Trial%	0.455*	0.442	0.012	−0.147	−0.104	−0.118	−0.230	0.136	−0.188	0.302	1

BMI: body mass index; EDSS: Expanded Disability Status Scale; MIP%pred: age- and sex-adjusted maximum inspiratory pressure; MEP%pred: age- and sex-adjusted maximum expiratory pressure; MFIS5: Modified Fatigue Impact Scale-5 Item; SDMT: Symbol Digit Modalities Test; Trial%: percentage of completed prescribed exercise trials during the 10-week exercise intervention; Year of diagnosis: year of multiple sclerosis diagnosis.
Correlation coefficients (r or σ) are shown. * $p < 0.0045$ (Bonferroni adjusted).

Table 5. Correlation of predictor variables with primary outcome (MIP%pred).

Predictor variable	Correlation coefficient (r or σ)	*p*
MIP%pred	0.780*	<0.001
MEP%pred	0.420	0.009
Age	−0.144	0.389
Gender	0.113	0.499
Body mass index	−0.091	0.586
Year of multiple sclerosis diagnosis	−0.089	0.596
Comorbidity	−0.074	0.657
Expanded Disability Status Scale	−0.188	0.258
Modified Fatigue Impact Scale-5	−0.428	0.007
Symbol Digit Modalities Test	0.507*	0.001
Percentage of completed prescribed exercise trials %	0.540*	<0.001

MIP%pred: age- and sex-adjusted maximum inspiratory pressure; MEP%pred: age- and sex-adjusted maximum expiratory pressure.
* $p < 0.0042$ (Bonferroni adjusted).
The primary outcome was MIP%pred at the end of 10-week inspiratory muscle training. All predictor variables, except for the percentage of completed prescribed exercise trials, were measured at the baseline.

Self-reported perception of fatigue is a common outcome of interest in studies of exercise interventions for persons with MS.[12,35] The current work extended previous research by examining the role of fatigue on the responses to IMT. In a study of physical activity and fatigue management programs in persons with MS, baseline fatigue, age, income, comorbidity, physical activity level, and self-efficacy for exercises did not influence the level of fatigue at the end of the intervention.[36] The impact of these variables on other outcomes, such as muscle strength, was not examined.[36] Fatigue is associated with various demographic and biopsychosocial factors. Studies in the MS population reported that greater self-reported fatigue was associated with living alone,[13] lower income,[37] shorter disease duration,[37] greater disability,[37] greater sleep disturbance,[37] poor motor performance,[38,39] and weaker expiratory muscle strength.[6] In this study, the participants had a low level of fatigue at the baseline that remained unchanged after the intervention, suggesting that IMT alone may not impact self-reported fatigue in PwAMS. However, baseline fatigue had a large and independent effect on the inspiratory muscle strength following IMT. Managing fatigue as a co-treatment of IMT may be a promising approach to optimize the outcome and warrants further investigation.

This study demonstrated that the participants who completed more prescribed exercise repetitions during the 10-week intervention had a better outcome on inspiratory muscle strength, likely indicating a dose–response relationship for the intervention. In a study examining the adherence to the Physical Activity Guidelines over 16 weeks in persons with MS, the participants achieving an adherence rate of ≥75%, defined as meeting the weekly aerobic and resistive exercise recommendations for at least 12 weeks, had higher self-efficacy for exercise at the baseline in comparison with those with lower adherence.[40] The EDSS score, time since diagnosis, fatigue, or fitness level at the baseline did not influence exercise adherence.[40] This study did not examine self-efficacy at the baseline but did not find any significant correlations between the percentage of completed prescribed exercise trials with baseline variables, including age, gender, BMI, comorbidity, years of MS diagnosis, EDSS scores, perceived fatigue, or cognitive processing speeds. Collectively, these results indicate that higher adherence to the prescribed repetitions for IMT may contribute to positive outcomes in PwAMS with a broad range of demographic and clinical characteristics. In this study, the level of exercise adherence was low. It cannot be ruled out that some participants or their assistants forgot to enter the completed exercise trials on the paper tracking log. Although using a paper log is a standard clinical practice, a different tracking mechanism may need to be considered. The barriers and facilitators to exercise adherence were not examined among the participants. In persons with MS, competing interests on time, symptoms, and lack of support and motivation were identified as the reasons for failing to meet exercise recommendations.[41] The participants in this study performed the exercises on their own once they learned how to use the threshold device correctly. The lack of direct supervision for exercises could have influenced exercise adherence. Further research on the role of exercise parameters, such as the exercise repetitions and resistance, is necessary in order to inform the clinicians about the

Table 6. Univariable regression models for the primary outcome.

Variable	Standardized coefficients (β)	*t*	*p*	R^2
MIP%pred	0.780	7.478	<0.001*	0.780
MEP%pred	0.107	0.930	0.359	0.786
Age	−0.013	−0.125	0.901	0.780
Gender	0.057	0.535	0.596	0.782
BMI	−0.125	−1.190	0.242	0.790
Year of diagnosis	−0.015	−0.145	0.886	0.780
Comorbidity	−0.024	−0.223	0.825	0.780
EDSS	−0.196	−1.954	0.059	0.804
MFIS5	−0.217	−2.079	0.045*	0.807
SDMT	0.223	2.027	0.050	0.806
Trial%	0.262	2.291	0.028*	0.812

BMI: body mass index; EDSS: Expanded Disability Status Scale; MIP%pred: age- and sex-adjusted maximum inspiratory pressure; MEP%pred: age- and sex-adjusted maximum expiratory pressure; MFIS5: Modified Fatigue Impact Scale-5 Item; SDMT: Symbol Digit Modalities Test; Trial%: percentage of completed prescribed exercise trials during the 10-week intervention; Year of diagnosis: year of multiple sclerosis diagnosis.
*$p < 0.05$.
MIP%pred at baseline is included in the model as a covariate. The primary outcome for the model is MIP%pred at the end of 10-week inspiratory muscle training using the resistive threshold device.

appropriate dosage for the IMT using a threshold device in PwAMS.

This study has limitations. The sample size was relatively small but was adequate to detect a significant change in inspiratory muscle strength. Based on the analysis using G*Power,[42] the minimum number of participants is 34 for a repeated measure design in this study ($\alpha = 0.05$, power = 0.80, effect size = 0.69 from previously published data[5]). Because the participants were non-ambulatory and residing in a specialized long-term care facility, the results should not be generalized to ambulatory persons with mild to moderate MS living in the community. Future studies with larger sample size and from various settings are necessary to investigate a broader range of clinical characteristics of the participants that may influence the outcome following IMT in order to develop a more targeted, precise, and individualized intervention.

Table 7. Multivariable regression models for the primary outcome.

Variable	Standardized coefficients (*β*)	*p*
Age- and sex-adjusted maximum inspiratory pressure	5.280	<0.001
Modified Fatigue Impact Scale-5 Item	−2.096	0.044
Percentage of completed prescribed exercise trials	2.302	0.028
Model statistics: $F_{3,34}$ =26.246; p <0.001; R^2 =0.836.		

Conclusion

In non-ambulatory PwAMS, after controlling for the initial inspiratory muscle strength, less self-reported fatigue at the baseline and higher adherence in completing prescribed exercise trials were independent and significant factors associated with a better outcome on inspiratory muscle strength at the end of 10-week IMT using a resistive threshold device. The benefit of IMT was not influenced by other demographic or clinical characteristics, including age, sex, BMI, year post-MS diagnosis, MS-related disability, and cognitive processing speed. For PwAMS with EDSS ≥ 6.5, IMT may be considered as a part of the rehabilitation program. Additionally, applying strategies to manage fatigue and improve exercise adherence likely promote a better outcome following the IMT intervention.

Declaration of conflicting interests

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