PHYSICAL ACTIVITY AND MULTIPLE SCLEROSIS

THE EFFECT OF PHYSICAL ACTIVITY PARTICIPATION ON OVERALL HEALTH IN ADULTS WITH MULTIPLE SCLEROSIS

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A Thesis Submitted to the School of Graduate Studies in Partial Fulfillment of the Requirements for the Degree Doctor of Philosophy

DOCTOR OF PHILOSOPHY (2017)
(KINESIOLOGY)
McMaster University
Hamilton, Ontario

TITLE: The Effect of Physical Activity Participation on Overall Health in Adults with Multiple Sclerosis
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Number of pages: xiii, 134

ABSTRACT

Multiple Sclerosis (MS) is an autoimmune disease characterized by demyelination and axon degeneration of the central nervous system that is accompanied by a wide range of symptoms. It is well established that physical activity is associated with a wide variety of health benefits, including improving fitness, MS-related symptoms and function in the MS population. However, despite the potential benefits associated with physical activity participation, most people living with MS remain physically inactive. In 2012, new evidence-based physical activity guidelines (PAGs) for adults with MS were released. The PAGs suggest that for health benefits, adults aged 18-64 years with mild to moderate disability need at least 30 minutes of moderate intensity aerobic physical activity two days per week and strength training for major muscle groups two times per week. The purpose of this dissertation was to determine the association between physical activity and health and to explore physical activity as a potential disease-modifying therapy in the MS population. This was completed through a series of three projects focusing on the PAGs for adults with MS.

The focus of the first study of this dissertation was on the implementation of the PAGs. The results from this study revealed that direct referral to physical activity from a physician is twice as effective as simply providing information about physical activity with respect to adhering to the PAG recommendations in people with MS (65.2 % vs. 32.8 % for direct referral and control groups, respectively). Further, the results revealed that a high self-efficacy for exercise at baseline may be an additional predictor to PAG adherence.

The purpose of the second study of this dissertation was to validate the PAGs for people with MS within a community-based intervention, and to affirm that following the PAGs for 16 weeks would result in improvements in fitness, mobility, fatigue symptoms and quality of life.

The results from the second study confirm the effectiveness of the PAGs for people with MS for improving health, as significant improvements were observed in VO_2 peak (+32 %), strength (+8-20 %), mobility (+14 %), fatigue symptoms (-40 %) and quality of life (+10-24 %).

The purpose of the third and final study was to determine the effect of exercise on brain function and cognition in a sample of adults living with MS. Following the PAGs for 16 weeks led to significant improvements in processing speed and memory in adults living with MS.

Overall, the results from this dissertation are extremely promising and highlight the importance of physical activity with respect to improving aspects of health and the effect it can have on MS-related symptoms and cognition in the MS population. Novel findings in this dissertation present convincing evidence that physicians should refer patients with MS to participate in exercise to improve MS-related symptoms and overall well-being.

ACKNOWLEDGEMENTS

First off, I would like to sincerely thank my supervisor, Dr. Audrey Hicks. Thank-you for taking a chance on me 4 years ago! I am so grateful for the opportunity to complete my PhD in an area that I am so passionate about. Thank-you for your patience, guidance and mentorship. I will cherish our New Orleans memories forever! Secondly, I would like to thank my committee, Dr. Jennifer Heisz and Dr. Maureen MacDonald for your continued support, advice and patience.

Third, to my PAMS family; participants, incredible research coordinators and passionate volunteers. Not many people can say that they gained a second family while completing their PhD, but I can. I have met some of the most incredible people over the past 4 years and I am forever indebted to you all for your support, belief and friendship. I truly believe you cross paths in life with people for a reason, and I was supposed to cross paths with you all. Our little PAMS fam we have created is something I will cherish forever. The work we do as researchers would not be possible without individuals like you, so thank-you from the bottom of my heart. At the end of the day you are our reason "why."

Lastly, but most importantly, thank-you to my friends and family for their continued support and love no matter what; without you this all would not be possible. Momma Bear, you are the light that ignites my passion every single day and the reason I do what I do. Thanks for showing me how to be a strong woman and to rise up, no matter how many times you fall. Your strength, adversity, confidence and positive attitude are characteristics I absolutely admire and strive to possess. Kyle, my loving and genuine

husband, thank-you from the bottom of my heart. There are no words to express how much I appreciate all that you do for me and the love and support you show me, day in and day out. You are my rock and my whole world.

TABLES OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
CON	Control Group
EDSS	Expanded Disability Status Score
FSS	Krupp's Fatigue Severity Scale
HR	Heart Rate
IQR	Interquartile Range
MetS	Metabolic Syndrome
MFIS	Modified Fatigue Impact Scale
MFIS-5	Modified Fatigue Impact Scale 5 Factor Questionnaire
MS	Multiple Sclerosis
MSQOL-54	Multiple Sclerosis Quality of Life 54 Questionnaire
PAGs	Physical Activity Guidelines
PPMS	Primary Progressive Multiple Sclerosis
QOL	Quality of Life
RAVLT	Rey Auditory Verbal Learning Test
RCT	Randomized Controlled Trial
REF	Direct Referral Group
RPE	Rating of Perceived Exertion
RRMS	Relapsing Remitting Multiple Sclerosis
RT	Reaction Time
SD	Standard Deviation
SDMT	Symbol Digits Modalities Test
SPMS	Secondary Progressive Multiple Sclerosis
VO_2 peak	Peak Oxygen Consumption
1RM	One Repetition Maximum
25FTW	25 Foot Walk Test

DECLARATION OF ACADEMIC ACHEIVEMENT

K.L. Canning's Role:

- Recruited study participants
- Trained and supervised Research Coordinators, staff and volunteers who assisted with data collection and training of participants
- Led data collection, analysis and interpretation
- Responsible for manuscript preparation

A.L. Hicks's Role:

- Study conception, design and measurement selection
- Obtained study funding
- Responsible for editing manuscripts

CHAPTER 1:

INTRODUCTION

1.0 *Multiple Sclerosis*

Multiple Sclerosis (MS) is a chronic autoimmune, inflammatory condition wherein the central nervous system experiences demyelination in the neurons of the brain and spinal cord thus affecting the electrical conduction of nerve signals (1,2). The degenerative nature of this neurological disease is associated with a wide range of debilitating symptoms including muscle weakness, extreme fatigue, loss of balance, impaired speech, double vision, declining cognitive function, and paralysis (1). There are four different types of multiple sclerosis; relapsing and remitting, primary progressive, secondary progressive and progressive relapsing MS. Relapsing and remitting MS is defined by specific ‘attacks’ that result in exacerbated symptoms or new symptoms followed by recovery periods also known as ‘remission’ where the symptoms are stable (2). Primary progressive MS is defined as disability occurring slowly without relapses. However, there is no period of remission and therefore disability increases over time. Secondary progressive MS is defined by relapses and remissions at the beginning of the course of disease which eventually leads to a progressive decline without remissions. Progressive relapsing MS is the rarest form wherein individuals experience progressive worsening of the disease with specific attacks or episodes without periods of recovery (2).

1.1 Prevalence and Epidemiology

Canada has the highest rate of MS in the world with approximately 100,000 Canadians living with the disease (3,4). Currently, the prevalence rates for MS in Canada are 291 cases per 100 000 (5) and 2.5 million adults are affected by MS worldwide (6). The symptoms that are manifested in those with MS lead to poor quality of life and increased health care costs. It is estimated that health care costs associated with MS in Canada is a staggering $1.7 billion annually (7). It is unknown what causes MS however there is research to suggest that there are strong associations between immunologic, environmental, infectious and genetic factors and the diagnosis of MS (8). There are many risk factors that increase one's risk of developing MS which include age (most commonly affects people aged 15-60), sex (affects females two times more than males), family history, infections, ethnic background (Northern European descent), climate, autoimmune diseases and smoking (9).

1.2 Symptoms & Treatments

As mentioned previously, MS is associated with a wide range of debilitating symptoms including muscle weakness, extreme fatigue, loss of balance, impaired speech, double vision, declining cognitive function, and paralysis (1). The most prevalent and disabling symptom associated with MS is fatigue (10). Fatigue affects almost all people living with MS with up to 90% of people living with MS reporting MS related fatigue (10).

Given the fact that there is still no cure for MS, the current approach to treatment is to manage symptoms through medications and other disease modifying therapies that focus on speeding up recovery from attacks and slowing down the progression of the disease (11). However, most of the available disease modifying therapies available today are for relapsing-remitting MS; to date, there are no available therapies for primary progressive MS. Alternative treatments for managing symptoms of MS include exercise, muscle relaxants and fatigue minimizing medications.

The neuro-degenerative nature of MS is associated with cognitive decline in people living with MS (12). Cognitive function has been previously reported to be correlated with the amount of overall brain damage including lesions in the brain and brain atrophy as a result of the MS (13). Approximately 40-65% of people living with MS experience cognitive dysfunction demonstrated by slower cognitive processing speeds, problems with executive functioning and impairments in learning and memory (14,15), and this cognitive dysfunction is associated with poor quality of life (QOL), depression and dependant living (16).

2.0 *Physical Activity and MS*

Two decades ago, when patients were first diagnosed with MS, physicians would advise their patients to not participate in physical activity. Physicians would err on the side of caution when it came to physical activity promotion as it was thought physical activity might worsen symptoms and increase fatigue in people living with MS. It is now known that physical activity participation does not worsen symptoms or fatigue, in fact it has been proposed by many to aid in counteracting the disabling effects of MS (17). Current evidence surrounding physical activity suggests a wide variety of benefits, including improvement or maintenance of QOL, fatigue, depression, fitness and function (18,19). However, despite the potential benefits associated with physical activity participation, most people living with MS remain physically inactive (20). Klaren et al. (2013) objectively quantified physical activity in people living with MS and concluded that only 19% of individuals living with MS are meeting the current public health guidelines for moderate to vigorous physical activity (21) compared to 47% of the general population meeting the guidelines.

2.1 Inactivity in MS Population & Associated Health Risk

It is well-established in the literature that a physically inactive lifestyle is associated with major health risks. This is no different for those living with MS, in fact, the health risks of inactivity may be even greater for the MS population. For example, the increased risks of cardio-metabolic chronic diseases associated with living a sedentary lifestyle may be even more detrimental to those with MS as they already have higher risks associated with their chronic disease (22–24). It has been suggested that the presence of comorbidities in this population can affect the clinical phenotype, disability progression and QOL (22). A recent comparison of adults with MS with matched controls showed higher levels of various clinical markers indicative of atherosclerosis in the people with MS, and that differences in physical activity levels accounted for most of the difference between the two groups (25). Additionally, previous evidence suggests that common comorbidities like depression and sleep disorders affect more than 50% of patients with multiple sclerosis compared to ~17% in the general population (23). Fibromyalgia, insomnia, irritable bowel syndrome, ischemic heart disease, obstructive sleep apnea and restless legs syndrome are also estimated to have an increased prevalence in individuals with MS compared to the general population (23). Physical activity has been reported to combat most of these comorbidities, therefore engaging in physical activity may be of utmost importance in people living with MS.

2.2 Barriers to Exercise in MS

Individuals living with MS are more likely to live sedentary lives compared to their healthy counterparts. A potential explanation for that may be in the fact that there are many barriers to exercise associated with this debilitating disease. The most commonly reported barriers to engaging in health promotion activities in the MS population are fatigue, impairment, lack of accessible fitness centers and lack of time (26,27). Plow and colleagues (2009) conducted a study where they interviewed thirteen individuals living with MS gathering information on perceived barriers to physical activity. The authors reported that barriers to physical activity in this population include physical environment, social environment and one's perceived health and symptoms. For physical environment as a barrier, individuals reported that exercising indoors was helpful as hot weather increases fatigue however they also reported limited accessibility to recreational exercise centers was an additional barrier for individuals with mild to moderate disability (27). Social environment barriers included the individuals' role in society and their role within their families. Their societal obligations hindered their physical activity participation especially if they did not have a supportive social group. Lastly, typical symptoms of MS including fatigue followed by depression influenced the degree to which individuals participated in physical activity (27). Other studies have also suggested that beliefs about physical activity, emotional responses, mental fatigue and self efficacy can all influence the decision to participate in physical activity in individuals living with MS (28,29).

3.0 *Physical Activity as Disease Modifying Treatment in MS*

Research confirms that individuals with MS have poorer physical fitness compared to their healthy counterparts (30,31). This may be as a result of the disease itself, poorer physical function, and the resultant inactive lifestyle. A proposed relationship between MS, physical activity and physiological and functional impairment was put forward by Motl in 2010. The authors suggest that in this model deficits associated with MS, such as muscle weakness and fatigue, result in a reduced ability to participate in physical activity. Physical inactivity, in turn, contributes to aerobic and muscular deconditioning, which subsequently results in mobility limitations. As mobility impairments progress, the participation in physical activity becomes more and more difficult, creating a vicious cycle that individuals with MS constantly battle with (32).

Impairments in cardiorespiratory, metabolic, and muscular fitness have been documented in persons with MS compared to non-MS controls, which is most likely related to their lower activity levels (24,33). Given the relatively young age at diagnosis, coupled with only slightly reduced life expectancies, optimizing health and function through regular physical activity is clearly important. It is noteworthy that the low levels of physical activity in the MS population are not necessarily due to a lack of interest in being active, in fact, information about physical activity and programs are among the most desired yet least available resources for people with MS (34).

Dalgas and colleagues (2008) completed a review summarizing the effects of engaging in exercise in individuals living with MS. They concluded that physical exercise is an important component of MS rehabilitation, however the evidence demonstrating the positive benefits with resistance training is less substantial compared to the evidence that surrounds aerobic or endurance training (31). As for combined exercise training (resistance and aerobic training), more research needs to be conducted as the number of studies that evaluate this are limited.

3.1 Cardiovascular Benefits of Physical Activity

Respiratory muscles are weakened, functional exercise capacity is reduced and pulmonary function is affected in people living with MS (35). However, aerobic training is one way affected patients can improve these limiting physiological impairments. Improvements in peak oxygen consumption and functional capacity after exercise interventions in the MS population have been documented by many (36–38). Specifically, there is level 1 evidence to suggest that aerobic training programs 2 to 3 times per week for 30 to 60 minutes at a moderate intensity significantly improves aerobic capacity in people living with MS (37–40).

3.2 Muscular Benefits of Physical Activity

MS negatively influences skeletal muscle fiber cross-sectional area, muscle mass and muscle strength of the lower limbs in people with mild disability (41). Wens et al. (2014) reported smaller mean muscle fiber cross sectional-area (-17 %) and significantly smaller type I (-16 %), II (-19 %) and IIa (-22 %) fibers in patients with MS compared to healthy controls (41). Several studies have evaluated the effects of resistance training in the MS population. The overall effect of resistance training on muscular fitness was statistically significant but small in magnitude (36). Overall changes in muscular fitness in the knee extensors (9.5 %) and flexors (11.6 %) may be associated with clinically significant improvements in mobility (36). Increases in muscle fiber cross-sectional area, muscle strength and functional capacity have been observed in several studies evaluating resistance exercise training programs in the MS population (36,42–45).

3.3 Metabolic Benefits of Physical Activity

Individuals living with MS predominately lead sedentary lifestyles and this is very concerning since physical inactivity is a major risk factor for several chronic conditions such as obesity, type 2 diabetes, cardiovascular disease and some cancers (46,47). Physical activity along with dietary interventions are strongly recommended to aid in weight management in addition to reducing the risk for metabolic aberrations in the general population (48). Whether this holds true for people living with MS is unclear. Subclinical markers of atherosclerosis have been demonstrated in people living with MS, suggesting a higher level of cardiovascular disease in this population (25). The most common metabolic comorbidities in the MS population include hypertension and hyperlipidemia (23,49). Further, previous research suggests that about one third of the MS population has Metabolic Syndrome (MetS) (50). Few studies have investigated how exercise influences metabolism in the MS population however research conducted in the general population suggests that regular participation in physical activity is associated with better glucose tolerance and blood lipid profiles and overall favorable body composition (51,52). Wens et al. 2017 reported that high intensity aerobic exercise in combination with resistance exercise improves glucose tolerance in people living with MS (53).

3.4 Physical Activity and Fatigue

Fatigue affects almost all individuals living with MS and it can significantly impact overall well-being and functioning (10). Even if an individual has minimal disability, their fatigue can be completely disabling, preventing them from completing activities of daily living and maintaining independence at work and home. Therefore managing fatigue is very important and necessary for people living with MS. Heine and colleagues (2015) completed a review on exercise therapy for fatigue in MS and concluded that exercise can be safely prescribed and is moderately effective at reducing fatigue in the MS population (54). Findings from exercise studies determining the impact on fatigue are very heterogeneous. One possible explanation for this variability may be the different questionnaires used to measure fatigue in the MS population. Commonly used questionnaires include The Chalder Fatigue Scale (55), Krupp's Fatigue Severity Scale (FSS) (56) and the Modified Fatigue Impact Scale (MFIS) (10). Some questionnaires are more sensitive to change than others, which might explain. To date, no RCT has been completed to determine the effect on exercise training to specifically reduce fatigue symptoms in people living with MS.

3.5 Physical Activity and Mobility

MS is associated with decreased physical function including altered gait and impaired mobility (57,58). There is evidence to demonstrate that altered walking ability and impaired mobility significantly affect QOL in individuals with MS (58). Mobility is commonly assessed by use of the 25 foot walk test, in which the time in seconds (or speed) to walk 25 feet as quickly as possible is reported. Goldman et al. (2013) reported a cut-off time of 6 seconds to be predictive of significant disability as a result of MS and a cut-off time of 8 seconds to be associated with the need for walking aids and an inability to work or complete activities of daily living (59). Further, Cohen and colleagues (2014) suggest that a decline in walking speed of 20 to 25 % may be a clinically meaningful threshold for monitoring patients with MS and aid to determine progression of the disease (60).

Walking impairments and decreased mobility not only affect QOL, engaging in daily activities, social function, employment and socioeconomic status have also been shown to be affected by decreased walking ability and reduced physical function (61). Therefore physical functioning is an important parameter to understand and improve for individuals living with MS. To further demonstrate the importance, approximately 70% of the participants in the previous study reported that walking difficulties was the most challenging aspect of battling with their disease (58).

Exercise training has been associated with improvements in balance and gait (43). Previous research on physical functioning and exercise in MS for the most part is positive with regards to ambulation and walking ability. Dodd and colleagues (2011) conducted a randomized controlled trial evaluating a progressive resistance training program in individuals with MS. The results of the study suggests that while a resistance training program may improve QOL, muscular strength and fatigue, it does not seem to be associated with improved walking ability. However, several other studies have reported improved walking speed or endurance as a result of aerobic or resistance training programs (42,62,63).

3.6 Physical Activity and QOL

Abrams (1973) defines QOL as the "degree of satisfaction or dissatisfaction felt by people with various aspects of their lives." Patients living with MS report decreased QOL compared to their healthy counterparts (65). In the MS population, health-related QOL is most commonly measured by the MSQOL-54 questionnaire which consists of 54 questions assessing physical, sexual and cognitive health (66). Two overall composite QOL scores are calculated, mental health-related QOL and physical health-related QOL composite scores. Lower physical or mental health-related QOL scores have been associated with worsening fatigue and depression whereas disease progression assessed by EDSS has been associated with lower physical health-related QOL scores (67). Wynia and colleagues (2008) reported that impairment in mental health functions was the most important predictor of health-related QOL (68). Evidently, people living with MS are affected in both areas of mental health- and physical health-related QOL which can have a significant effect on other disease-related symptoms and independence.

Previous research suggests that increases in structured exercise participation and increases in physical activity levels are associated with increased QOL scores (39,40,69). However, it is unclear as to which exercise modality is most effective, as both positive or null findings have been found after both aerobic and resistance training programs. The role of social support during an exercise intervention is a potential confounder to interpretation of the evidence (70).

A variety of exercise interventions have been employed to evaluate the potential effects on QOL. Pilutti and colleagues (2011) conducted a 12 week clinical trial consisting of individuals with progressive MS engaging in body weight supported treadmill training, 30 minute sessions, three times per week. The results of the study suggest that a body weight supported treadmill training program produces increases in QOL and reductions in fatigue in individuals with progressive MS (71). Giacobbi and colleagues (2012) conducted a 4-month mixed methods study using a progressive resistance training program for people with MS. The results indicated that while there were improvements in the study participants' responses toward QOL, no causal relationship was determined. Therefore it is unclear if it was the engagement in the resistance training program that caused the improvements in QOL (72). Jackson et al. (2012) conducted a study evaluating the effectiveness of a group kickboxing program for improvements in QOL in people with MS. They found no changes in QOL after this intervention. Thus, it is still unclear as to which exercise intervention is the most beneficial for producing improvements in QOL and it may be the delivery of the intervention (and the social support) that is most important.

3.7 Physical Activity as Treatment for Impaired Cognition

A positive association between exercise and cognitive function has been demonstrated in both young and healthy populations (74). It is currently unclear whether exercise has a role to play to improve cognition in adults with MS but there is some evidence of its potential benefit. Preliminary evidence that aerobic exercise can induce increases in both hippocampal volume and brain connectivity, both of which play significant roles in improving memory, has been reported, however larger studies are required to confirm this (75). Briken et al. (2014) concluded that aerobic training is feasible, and could be beneficial in the MS population, as authors reported correlations associated between improvements in aerobic fitness and measures of cognition (12). Further, Sandroff et al. (2017) provided novel evidence of an association between cardiorespiratory fitness and processing speed in people living with MS (76), and treadmill walking has been associated with improvements in executive control (77). To date, only three RCTs have been conducted evaluating the effect of exercise on cognition in the MS population however none of these studies have produced convincing evidence of any beneficial effect exercise on cognition (12,69,78).

4.0 Adherence to Physical Activity

Despite the many benefits that have been reported for physical activity in the MS population, physical activity rates are extremely low. While most studies calculate adherence rates as the number of sessions attended over the total number of sessions for the duration of the study (79), the definition of what constitutes “adherence” to a physical activity intervention is variable. Currently there is no gold standard defining what constitutes physical activity adherence or what number of training sessions are needed to reap the benefits of physical activity. **Table 1.1** displays comparisons of definitions and justifications of adherence across a variety of studies.

Table 1.1 Comparison of Adherence Definitions and Justifications across Studies

Author	Title	Purpose	Definition of Adherence	Justification
De Jesus et al. (2017) (80)	Feasibility of an exercise intervention for fatigued breast cancer patients at a community-based cardiac rehabilitation program.	To determine the feasibility of an oncology rehabilitation exercise program in a cardiac rehabilitation program.	**>80% at the exercise sessions**, and compliance rate of >80% of the Actical® accelerometer readings at follow-up	NO JUSTIFICATION
Deka et al. (2017) (81)	Adherence to recommended exercise guidelines in patients with heart failure.	Review to summarize exercise guidelines and adherence for heart failure patients.	Meeting at least **80 % of the recommended exercise dose.** **"**Non-adherent": adherence <20 % "Partially adherent": ≥ 20 and <80%	The designation of 80 % is consistent with the medication adherence literature.
Freiberger et al. (2013) (82)	Effects of a complex intervention on fall risk in the general practitioner setting: a cluster randomized controlled trial.	To study the feasibility of older persons at risk of falls through their general practitioner (GP) and to reduce fall risk factors with a complex exercise intervention.	Participation in **>75% of all supervised exercise sessions.**	NO JUSTIFICATION
Geraedts et al. (2014) (83)	Adherence to and effectiveness of an individually tailored home-	To present the rationale and design of a study evaluating the adherence to and	Adherence to exercise program and **wearing of the sensor exceeds**	Although a general cut-off point for sufficient adherence has not

	based exercise program for frail older adults, driven by mobility monitoring: design of a prospective cohort study.	effectiveness of an individually tailored, home-based physical activity program for frail older adults.	**70%.**	yet been defined, in the literature a cut-off value of 70% adherence is often used.
Hicks et al. (2012) (84)	Adherence to a community-based exercise program is a strong predictor of improved back pain status in older adults: an observational study.	To identify factors that were predictive of improved pain status among older adults with chronic back pain.	Participation in **>75% of all exercise sessions for the entire 12 month study period**	NO JUSTIFICATION
Kampshoff et al. (2016) (85)	Participation in and adherence to physical exercise after completion of primary cancer treatment.	To identify demographic, clinical, psychosocial, physical and environmental factors that are associated with participation and adherence exercise program in cancer survivors.	**Attending at least 80 % of the sessions**	In line with previous studies.

Kronish et al. (2017) (86)	Objectively measured adherence to physical activity guidelines after acute coronary syndrome.	To determine if patients adherence to physical activity guidelines after discharge acute coronary syndrome.	≥30 min of moderate-to-vigorous physical activity bout minutes (none; insufficient (1% to 65% of days; **met guidelines ≥ 66% of days**))	NO JUSTIFICATION FOR THIS %
Shubert, Altpeter, & Busby-Whitehead (2011) (87)	Using the RE-AIM framework to translate a research-based falls prevention intervention into a community-based program: lessons learned.	To translate a research-based intervention into a community program, and to assess if similar outcomes were achieved.	Participation in **>75% of all exercise sessions**	75% chosen because of previous research. Authors reference Shumway-Cook et al., 2007 (greatest reduction in fall risk at 75%).
Shumway-cook et al. (2007) (88)	Effectiveness of a Community-Based Multifactorial Intervention on Falls and Fall Risk Factors in Community-Living Older Adults: A RCT.	To evaluate the effectiveness of a 12-month community-based intervention on falls and risk factors in older adults.	Split cohort into 3 levels of adherence > **75%, 75%–33%, ≤ 33% attendance**.	NO JUSTIFICATION
Sjösten et al. (2007) (89)	A multifactorial fall prevention programme in the community-dwelling aged: predictors of adherence.	To determine the adherence rates and the predictors of adherence in four key activities of a multifactorial fall prevention trial.	Non-Adherence: 0% Low Adherence: 0.1–33.3% Moderate Adherence: 33.4–66.6% **High/Full Adherence: 66.7–100% adherence rate**	NO JUSTIFICATION

The results from **Table 1** demonstrate the variable adherence rates used to define adherence in other populations from as low as 66% to as high as 100%. The average adherence threshold across all 10 studies was 74.8%.

4.1 Effect of Direct Referral on Adherence

Commitment and adherence to community-based physical activity can be a challenge for people living with MS as they have to overcome numerous barriers on a daily basis (with respect to disease symptoms, transportation issues, fatigue) (26). In cardiac patients, there is evidence to suggest that direct referral to community-based exercise from a physician (or member of the healthcare team) is a strong predictor for adherence (90). Previous research suggests that patients who reported receiving a physician referral rated the strength of the referral high by which significantly predicted exercise participation, indicating the powerful effect positive endorsement of exercise by a physician can have (91). People living with MS consider physicians to be the most credible (yet least accessible) source for physical activity information specific to their needs, with allied health professionals and peers also ranking quite highly as a desired source of information (92). Therefore, there is potential for physical referral to physical activity programs (with appropriate exercise prescription) to have a positive effect on physical activity participation rates in the MS population.

5.0 *Physical Activity Guidelines for People with MS*

The Canadian Society for Exercise Physiology in conjunction with Public Health Canada have developed evidence-based physical activity guidelines that recommend the proper dose of physical activity Canadians should be engaging in to accumulate health benefits (93). However, up until recently no physical activity guidelines specifically for individuals living with MS were available. The Consensus Conference White Paper from the Consortium of Multiple Sclerosis Centers (CMSC) highlighted the scientific evidence supporting the wide variety of benefits of exercise and/or physical activity for people with MS, and made a strong recommendation that it should become integrated within the usual standard of care for this clinical population (94). One of the key recommendations to come out of the CMSC White Paper was to develop evidence-informed physical activity guidelines (PAGs) to improve physical fitness and decrease comorbidities in people with MS (94). The new PAGs for adults with MS were released in 2012. The guidelines recommend that for health benefits, adults with MS who have mild to moderate disability should participate in at least 30 minutes of moderate intensity aerobic activity 2 times per week and engage in strength-training activities for major muscle groups 2 times per week (95).

The literature surrounding the positive effects of exercise and MS rehabilitation paints a clear picture regarding the innumerable benefits that can be reaped from engaging in physical activity. An intervention that can both manage symptoms and improve function is so important for a disease that has no known cure. There has been evidence to suggest that, in healthy Canadians, participating in the recommended amounts of physical activity will produce improvements in aerobic fitness and strength, reduce fatigue, improve mobility and improve overall well-being (18,19). However, no study to date has determined the effectiveness of the prescribed physical activity dosage for people with MS and whether this amount of physical activity will elicit the aforementioned improvements in QOL, function and fitness.

6.0 *Summary and Statement of Purpose*

The purpose of this dissertation was to explore the association between physical activity and health in the MS population. This was completed through a series of three projects focusing on the PAGs for adults with MS. The first objective was to determine how best to implement the PAGs for people with MS. Despite common knowledge that physical activity is good for you, commitment and adherence to community-based physical activity can be a challenge, especially for people living with MS who have to overcome numerous barriers on a daily basis. Physicians will typically recommend regular physical activity to their patients through referral to physical therapy (11), but utilization of physical therapy by adults with MS is reportedly quite low (10). Therefore, our first objective was to determine if direct referral to regular exercise by a physician in MS patients predicts successful adherence to the PAGs. We also wanted to determine if there were other important factors that may predict adherence to the PAGs in the MS population. The second objective was to test the validity of the PAGS; to affirm that following the PAGs for people with MS would result in improvements in fitness, function, mobility and QOL. Lastly, the third objective was to determine if following the PAGs results in significant improvements in cognitive function, specifically executive functioning, memory and processing speed.

The PAGs for adults with MS have the potential to influence healthcare practice and delivery in this population. Healthcare and service providers now know the types, frequencies and amounts of physical activity to prescribe to their patients with MS. The goal of this dissertation is to provide new information on how best to implement these guidelines in order to maximize adherence. It will also provide information on the validity (and effectiveness) of the PAGs in a community-based, as opposed to laboratory, setting. The hypotheses for this dissertation are as follows. For the first study, we hypothesized that adherence would be higher in people who have been directly referred to a community-based exercise program compared to those individuals who are just given a print copy of the guidelines. For the second study, we hypothesized that following the PAGs for adults with MS for 4 months would result in improvements in fitness, function and quality of life, and lastly for the final study, we hypothesized that cognitive function would improve in adults with MS who follow the PAGs for 4 months.

7.0 References

1. Compston A, Coles A. Multiple sclerosis. Lancet. 2008 25;372(9648):1502–17.

2. MS Society of Canada. What is MS? [Internet]. 2016. [cited 2017 Apr 3] Available from: https://mssociety.ca/about-ms/what-is-ms

3. MS Society of Canada. About MS [Internet]. 2017 [cited 2017 Apr 3]. Available from: https://mssociety.ca/about-ms

4. Statistics Canada. Table 105-1300 Neurological Conditions, by age group and sex, household population aged 0 and over, 2010/2011 [Internet]. 2012 [cited 2017 Apr 4]. Available from: http://www5.statcan.gc.ca/cansim/a26?lang=eng&id=1051300

5. Multiple Sclerosis International Federation. Atlas of MS 2013. 2013.

6. Beck CA, Metz LM, Svenson LW, Patten SB. Regional variation of multiple sclerosis prevalence in Canada. Mult Scler. 2005 1;11(5):516–9.

7. Multiple Sclerosis International Federation. Global Economic Impact of Multiple Sclerosis Global Economic Impact of Multiple Sclerosis. 2010.

8. National MS Society. What Causes MS? [Internet]. 2017 [cited 2017 Apr 3]. Available from: http://www.nationalmssociety.org/What-is-MS/What-Causes-MS

9. Mayo Clinic. Multiple Sclerosis [Internet]. 2017. [cited 2017 Mar 15]. Available from: http://www.mayoclinic.org/diseases-conditions/multiple-sclerosis/symptoms-causes/dxc-20131884

10. Fisk JD, Ritvo PG, Ross L, Haase DA, Marrie TJ, Schlech F, et al. Measuring the Functional Impact of Fatigue : Initial Validation of the Fatigue Impact Scale. Clin Infect Dis. 1994;18(S1):S79–83.

11. Boissy AR, Cohen JA. Multiple sclerosis symptom management. Exepert Rev Neurother. 2007;7(9):1213–22.

12. Briken S, Gold SM, Patra S, Vettorazzi E, Harbs D, Tallner A, et al. Effects of exercise on fitness and cognition in progressive MS: a randomized , controlled pilot trial. Mult Scler J. 2014;20(3):382–90.

13. Fisher E, Rudick RA., Simon JH, Cutter G, Baier M, Lee J-C, et al. Eight-year follow-up study of brain atrophy in patients with MS. Neurology. 2002 12;59(9):1412–20.

14. Guimarães J, Sá MJ. Cognitive dysfunction in Multiple Sclerosis. Front Neurol. 2012;3(74):1–8.

15. Benedict RHB, Holtzer R, Motl RW, Foley FW, Kaur S, Hojnacki D, et al. Upper and Lower Extremity Motor Function and Cognitive Impairment in Multiple Sclerosis. J Int Neuropsychol Soc. 2011;17:643–53.

16. Benedict RHB, Wahlig E, Bakshi R, Fishman I, Munschauer F, Zivadinov R, et al. Predicting quality of life in multiple sclerosis: accounting for physical disability, fatigue, cognition, mood disorder, personality, and behavior change. J Neurol Sci. 2005;231:29–34.

17. Sutherland G, Andersen MB. Exercise and multiple sclerosis: physiological, psychological, and quality of life issues. J Sports Med Phys Fitness. 2001 Dec;41(4):421–32.

18. Ready AE, Butcher JE, Dear JB, Fieldhouse P, Harlos S, Katz A, et al. Canada's physical activity guide recommendations are a low benchmark for Manitoba adults. Appl Physiol Nutr Metab. 2009 May;34(2):172–81.

19. Public Health Agency of Canada. Benefits of Physical Activity [Internet]. 2007. Available from: http://www.phac-aspc.gc.ca/hp-ps/hl-mvs/pa-ap/02paap-eng.php

20. Motl RW, McAuley E, Snook EM. Physical activity and multiple sclerosis: a meta-analysis. Mult Scler. 2005 Aug 1;11(4):459–63.

21. Klaren RE, Motl RW, Dlugonski D, Sandroff BM, Pilutti LA. Objectively Quantified Physical Activity in Persons With Multiple Sclerosis. Arch Phys Med Rehabil. 2013;94(12):2342–8.

22. Marrie RA, Horwitz RI. Emerging effects of comorbidities on multiple sclerosis. Lancet Neurol. 2010 Aug;9(8):820–8.

23. Marrie RA, Hanwell H. General health issues in multiple sclerosis: comorbidities, secondary conditions, and health behaviors. Continuum. 2013 Aug;19(4):1046–57.

24. Koseoglu BF, Gokkaya NKO, Ergun U, Inan L, Yesiltepe E. Cardiopulmonary and metabolic functions, aerobic capacity, fatigue and quality of life in patients with multiple sclerosis. Acta Neurol Scand. 2006;114(4):261–7.

25. Ranadive SM, Yan H, Weikert M, Lane AD, Linden MA, Baynard T, et al. Vascular dysfunction and physical activity in multiple sclerosis. Med Sci Sports Exerc. 2012;44(2):238–43.

26. Becker H, Stuifbergen A. What makes it so hard? Barriers to health promotion experienced by people with multiple sclerosis and polio. Fam Community Health. 2004;27(1):75–85.

27. Plow MA, Resnik L, Allen SM. Exploring physical activity behaviour of persons with multiple sclerosis: a qualitative pilot study. Disabil Rehabil. 2009;31(20):1652–65.

28. Kayes NM, McPherson KM, Schluter P, Taylor D, Leete M, Kolt GS. Exploring the facilitators and barriers to engagement in physical activity for people with multiple sclerosis. Disabil Rehabil. 2011;33(12):1043–53.

29. Kayes NM, McPherson KM, Taylor D, Schlüter PJ, Kolt GS. Facilitators and barriers to engagement in physical activity for people with multiple sclerosis: a qualitative investigation. Disabil Rehabil. 2011;33(8):625–42.

30. Motl RW, McAuley E, Wynn D, Suh Y, Weikert M, Dlugonski D. Symptoms and physical activity among adults with relapsing-remitting multiple sclerosis. J Nerv Ment Dis. 2010;198(3):213–9.

31. Dalgas U, Stenager E, Ingemann-Hansen T. Multiple sclerosis and physical exercise: recommendations for the application of resistance-, endurance- and combined training. Mult Scler. 2008;14(1):35–53.

32. Motl RW. Physical activity and irreversible disability in multiple sclerosis. Exerc Sport Sci Rev. 2010;38(4):186–91.

33. Ng AV, Miller RG, Gelinas D, Kent-Braun JA. Functional relationships of central and peripheral muscle alterations in multiple sclerosis. Muscle Nerve. 2004;29(6):843–52.

34. Somerset M, Campbell R, Sharp DJ, Peters TJ. What do people with MS want and expect from health-care services? Heal Expect. 2001;4(1):29–37.

35. Bosnak-Guclu M, Gunduz AG, Nazliel B, Irkec C. Comparison of functional exercise capacity, pulmonary function and respiratory muscle strength in patients with multiple sclerosis with different disability levels and healthy controls. J Rehabil Med. 2012 Jan;44(1):80–6.

36. Platta ME, Ensari I, Motl RW, Pilutti LA. Effect of Exercise Training on Fitness in Multiple Sclerosis : A Meta-Analysis. Arch Phys Med Rehabil. 2016;97(9):1564–72.

37. Rampello A, Franceschini M, Piepoli M, Antenucci R, Lenti G, Olivieri D, et al. Effect of aerobic training on walking capacity and maximal exercise tolerance in patients with Multiple Sclerosis: A randomzied crossover controlled study. Phys Ther. 2007;87(5):545–55.

38. Petajan JH, Gappmaier E, White AT, Spencer PMK, Mino L, Hicks RW. Impact of Aerobic Training on Fitness and Quality of Life in Multiple Sclerosis. Ann Neurol. 1996;39(4):432–41.

39. Mostert S, Kesselring J. Effects of a short-term exercise training program on aerobic fitness, fatigue, health perception and activity level of subjects with multiple sclerosis. Mult Scler. 2002;8(2):161–8.

40. Schulz K-H, Gold SM, Witte J, Bartsch K, Lang UE, Hellweg R, et al. Impact of aerobic training on immune-endocrine parameters, neurotrophic factors, quality of life and coordinative function in multiple sclerosis. J Neurol Sci. 2004;225(1-2):11–8.

41. Wens I, Dalgas U, Vandenabeele F, Krekels M, Grevendonk L, Eijnde BO. Multiple Sclerosis Affects Skeletal Muscle Characteristics. PLoS One. 2014;9(9):1–5.

42. Dalgas U, Stenager E, Jakobsen J, Petersen T, Hansen HJ, Knudsen C, et al. Resistance training improves muscle strength and functional capacity in multiple sclerosis. Neurology. 2009;73(18):1478–84.

43. Motl RW, Pilutti LA. The benefits of exercise in MS. Nat Rev Neurol. 2012;8:487–97.

44. Dodd KJ, Taylor NF, Shields N, Prasad D, McDonald E, Gillon a. Progressive resistance training did not improve walking but can improve muscle performance, quality of life and fatigue in adults with multiple sclerosis: a randomized controlled trial. Mult Scler. 2011;17(11):1362–74.

45. Taylor NF, Dodd KJ, Prasad D, Denisenko S, Dodd KJ, Prasad D, et al. Progressive resistance exercise for people with multiple sclerosis. Disabil Rehabil. 2006;28(18):1119–26.

46. Osypuk TL, Diez Roux A V, Hadley C, Kandula NR. Are immigrant enclaves healthy places to live? The Multi-ethnic Study of Atherosclerosis. Soc Sci Med. 2009;69(1):110–20.

47. Macfarlane D, Chan A, Cerin E. Examining the validity and reliability of the Chinese version of the International Physical Activity Questionnaire, long form (IPAQ-LC). Public Health Nutr. 2010;14(3):1–8.

48. Expert Panel on the Identification Evaluation and Treatment of Overweight in Adults. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: executive summary. Am J Clin Nutr. 1998;68:899–917.

49. Marrie RA. Comorbidity in Multiple Sclerosis Some Answers, More Questions. Int J MS Care. 2016;18(6):271–2.

50. Pinhas-hamiel O, Livne M, Harari G, Achiron A. Prevalence of overweight , obesity and metabolic syndrome components in multiple sclerosis patients with significant disability. Eur J Neurol. 2015;22:1275–9.

51. Warburton DER, Nicol CW, Bredin SSD. Health benefits of physical activity: the evidence. Can Med Assoc J. 2006 Mar 14;174(6):801–9.

52. Blair SN, Kohl HW, Gordon NF, Paffenbarger RS. How much physical activity is good for health? Annu Rev Public Health. 1992 Jan;13:99–126.

53. Wens I, Dalgas U, Vandenabeele F, Verboven K, Hansen D, Deckx N, et al. High Intensity Aerobic and Resistance Exercise Can Improve Glucose Tolerance in Persons With Multiple Sclerosis A Randomized Controlled Trial. Am J Phys Med Rehabil. 2017;96:161–6.

54. Heine M, Van De Port I, Rietberg M, Van Wegen E, Kwakkel G. Exercise therapy for fatigue in multiple sclerosis (Review). Cochrane Database Syst Rev. 2015;(9):1–127.

55. Chalder T, Berelowitz G, Pawlikowska T, Watts L, Wright D, Wallace EP. Development of a Fatigue Scale. J Psychosom Res. 1993;37(2):147–53.

56. Krupp LB, Larocca NG, Muir-nash J, Steinberg AD. The Fatigue Severity Scale Application to Patients With Multiple Sclerosis and Systemic Lupus Erythematosus. Arch Neurol. 1989;46(10):1121–3.

57. Heesen C, Segal J, Reich C, Hämäläinen P, Broemel F, Niemann S, et al. Patient information on cognitive symptoms in multiple sclerosis - acceptability in relation to disease duration. Acta Neurol Scand. 2006 Oct;114(4):268–72.

58. LaRocca NG. Impact of walking impairment in Multiple Sclerosis Perspectives of Patients and Care Partners. Patient. 2011;4(3):198–201.

59. Goldman MD, Motl RW, Scagnelli J, Pula JH, Sosnoff JJ, Cadavid D. Clinically meaningful performance benchmarks in MS Timed 25-Foot Walk and the real world. Neurology. 2013;81:1856–63.

60. Cohen JA, Krishnan A V, Goodman AD, Potts J, Wang P, Havrdova E, et al. The Clinical Meaning of Walking Speed as Measured by the Timed 25-Foot Walk in Patients With Multiple Sclerosis. JAMA Neurol. 2014;71(11):1386–93.

61. La Rocca NG. Impact of Walking Impairment in Multiple Sclerosis Perspectives of Patients and Care Partners. Patient. 2011;4(3):189–201.

62. Cakt BD, Nacir B, Genç H, Saraçoğlu M, Karagöz A, Erdem HR, et al. Cycling progressive resistance training for people with multiple sclerosis: a randomized controlled study. Am J Phys Med Rehabil. 2010;89(6):446–57.

63. van den Berg M, Dawes H, Wade DT, Newman M, Burridge J, Izadi H, et al. Treadmill training for individuals with multiple sclerosis: a pilot randomised trial. J Neurol Neurosurg Psychiatry. 2006;77(4):531–3.

64. Abrams M. Subjective Social Indicators. 1973.

65. Mitchell AJ, Benito-León J, González J-MM, Rivera-Navarro J. Quality of life and its assessment in multiple sclerosis: integrating physical and psychological components of wellbeing. Lancet Neurol. 2005;4(9):556–66.

66. Vickrey BG, Hays RD, Harooni R, Myers LW, Ellison GW, Quality S, et al. A Health-Related Quality of Life Measure for Multiple Sclerosis. Qual life Res. 1995;4(3):187–206.

67. Bueno A-M, Sayao A-L, Yousefi M, Devonshire V, Traboulsee A, Tremlett H. Health-related quality of life in patients with longstanding “benign multiple sclerosis”. Mult Scler Relat Disord. 2015;4(1):31–8.

68. Wynia K, Middel B, Dijk JP van, Keyser JHA De, Reijneveld SA. The impact of disabilities on quality of life in people with multiple sclerosis. Mult Scler. 2008;14:972–80.

69. Oken BS, Kishiyama S, Zajdel D, Bourdette D, Carlsen J, Haas M, et al. Randomized controlled trial of yoga and exercise in multiple sclerosis. Neurology. 2004. 7;62(11):2058–64.

70. Motl RW, Gosney J. Effect of exercise training on quality of life in multiple sclerosis: a meta-analysis. Mult Scler. 2008;14:129–35.

71. Pilutti LA, Lelli DA, Paulseth JE, Crome M, Jiang S, Rathbone MP, et al. Effects of 12 weeks of supported treadmill training on functional ability and quality of life in progressive multiple sclerosis: a pilot study. Arch Phys Med Rehabil. 2011;92(1):31–6.

72. Giacobbi PR, Dietrich F, Larson R, White LJ. Exercise and quality of life in women with multiple sclerosis. Adapt Phys Activ Q. 2012;29(3):224–42.

73. Jackson K, Edginton-Bigelow K, Cooper C, Merriman H. A group kickboxing program for balance, mobility, and quality of life in individuals with multiple sclerosis: a pilot study. J Neurol Phys Ther. 2012;36(3):131–7.

74. Smith PJ, Blumenthal JA, Hoffman BM, Cooper H, Strauman TA, Welsh-Bohmer K, et al. Aerobic exercise and neurocognitive performance: a meta-analytic review of randomized controlled trials. Psychosom Med. 2010;72(3):239–52.

75. Leavitt VM, Cirnigliaro C, Cohen A, Farag A, Brooks M, Wecht JM, et al. Aerobic exercise increases hippocampal volume and improves memory in multiple sclerosis: Preliminary findings. Neurocase. Routledge; 2013;00(00):1–3.

76. Sandroff BM, Motl RW, Deluca J. The Influence of Cognitive Impairment on the Fitness – Cognition Relationship in MS. Med Sci Sport Exerc. 2017; DOI:10.1249/MSS.0000000000001215

77. Sandroff BM, Hillman CH, Benedict RHB, Motl RW. Acute effects of walking, cycling, and yoga exercise on cognition in persons with relapsing- remitting multiple sclerosis without impaired cognitive processing speed. J Clin Exp Neuropsychol. 2015;37(2):209–19.

78. Romberg A, Virtanen A, Ruutiainen J. Long-term exercise improves functional impairment but not quality of life in multiple sclerosis. J Neurol. 2005;252:839–45.

79. Heesen C, Bruce J, Gearing R, Moss-morris R, Weinmann J, Hamalainen P, et al. Adherence to behavioural interventions in multiple sclerosis: Follow-up meeting report (AD@MS-2). Mult Scler J. 2015;1:1–4.

80. De Jesus S, Fitzgeorge L, Unsworth K, Massel D, Suskin N, Prapavessis H, et al. Feasibility of an exercise intervention for fatigued breast cancer patients at a community-based cardiac rehabilitation program. Cancer Manag Res. 2017;9:29–39.

81. Deka P, Pozehl B, Williams MA, Yates B. Adherence to recommended exercise guidelines in patients with heart failure. Heart Fail Rev. 2017;22(1):41–53.

82. Freiberger E, Blank WA, Salb J, Geilhof B, Hentschke C, Landendoerfer P, et al. Effects of a complex intervention on fall risk in the general practitioner setting: a cluster randomized controlled trial. Clin Interv Aging. 2013;8:1079–88.

83. Geraedts HAE, Zijlstra W, Zhang W, Bulstra S, Stevens M. Adherence to and effectiveness of an individually tailored home-based exercise program for frail older adults, driven by mobility monitoring: design of a prospective cohort study. BMC Public Health. 2014;14(570):1–7.

84. Hicks G, Benvenuti F, Fiaschi V, Lombardi B, Segenni L, Stuart M, et al. Adherence to a community-based exercise program is a strong predictor of improved back pain status in older adults: an observational study. Clin J Pain. 2013;28(3):195–203.

85. Kampshoff CS, Mechelen W Van, Schep G, Nijziel MR, Witlox L, Bosman L, et al. Participation in and adherence to physical exercise after completion of primary cancer treatment. Int J Behav Nutr Phys Act. Int J Behav Nutr Phys Act; 2016;13(100):1-12.

86. Kronish IM, Diaz KM, Goldsmith J, Moise N, Schwartz JE. Objectively Measured Adherence to Physical Activity Guidelines After Acute Coronary Syndrome. JACC. 2017;69(9):1205–7.

87. Shubert TE, Altpeter M, Busby-whitehead J. Using the RE-AIM Framework to translate a research-based falls prevention intervention into a community-based program : Lessons Learned. J Safety Res. 2011;42(6):509–16.

88. Shumway-cook A, Silver IF, LeMier M, York S, Cummings P, Koepsell TD. Effectiveness of a Community-Based Multifactorial Intervention on Falls and Fall Risk Factors in Controlled Trial. J Gerontol Med Sci. 2007;62A(12):1420–7.

89. Sjosten NM, Salonoja M, Piirtola M, Vahlberg TJ, Isoaho R, Hyttinen HK, et al. A multifactorial fall prevention programme in the community-dwelling aged: predictors of adherence. Eur J Public Health. 2007;17(5):464–70.

90. Jackson L, Leclerc J, Erskine Y, Linden W. Getting the most out of cardiac rehabilitation: a review of referral and adherence predictors. Heart. 2005;91(1):10–4.

91. Dunn SL, Dunn LM, Buursma MP, Clark JA, Berg L Vander, Devon HA, et al. Home- and Hospital- Based Cardiac Rehabilitation Exercise: The Important Role of Physician Recommendation. West J Nurs Res. 2017;39(2):214–33.

92. Sweet SN, Perrier M-J, Podzyhun C, Latimer-cheung AE. Identifying physical activity information needs and preferred methods of delivery of people with multiple sclerosis. Disabil Rehabil. 2013;35(24):2056–63.

93. Canadian Society for Exercise Physiology. Canadian Physical Activity Guidelines [Internet]. 2011. Available from: http://www.csep.ca/CMFiles/Guidelines/CSEP-InfoSheets-adults-ENG.pdf

94. Vollmer T, Benedict R, Bennett S, Motl R, White A, Bombardier C, et al. Exercise as prescriptive therapy in multiple sclerosis: A consensus conference white paper. Int J MS Care. 2012;14(Suppl 3):2–14.

95. Canadian Society for Exercise Physiology. Canadian Physical Activity Guidelines for Adults with Multiple Sclerosis [Internet]. 2012. Available from: http://www.csep.ca/CMFiles/Guidelines/specialpops/CSEP_MS_PAGuidelines_adults_en.pdf

CHAPTER 2:

Factors That Predict Adherence to the Physical Activity Guidelines for Adults with Multiple Sclerosis: A Randomized Controlled Trial

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Abstract

Objectives: Commitment and adherence to community-based physical activity can be a challenge, especially for clinical populations. The purpose of this study was to determine the effect of physician referral on physical activity guidelines (PAGs) adherence in people with Multiple Sclerosis (MS) and to explore additional factors that might also predict adherence to the PAGs.

Methods: Seventy-seven participants with MS were recruited to participate in a 16wk RCT (age: 47.7 ± 10.4 years, EDSS score: 3.5 ± 1.8, time since diagnosis: 12.2 ± 10.1 years). Participants were randomized into a direct referral to PAGs from a physician group (REF) or control (CON). Adherence to the PAGs was assessed through weekly physical activity logs. VO_2 peak, strength, mobility, fatigue symptoms, quality of life (QOL) and self-efficacy for exercise were assessed at baseline and after 16 weeks. After 16 weeks of observation participants were categorized as either PAG "Adherers" (n=28) or "Non-Adherers" (n=49) based on achieving an adherence rate of ≥ 75 %.

Results: Adherence to the PAGs was significantly higher in the REF group (65.2 ± 29.2 %) compared with the CON (32.8 ± 34.1 %) ($p < 0.05$). At baseline, the Adherers had greater self-efficacy for exercise compared to the Non-Adherers ($p < 0.0001$). There were no differences in baseline EDSS scores, time since diagnosis, VO_2 peak, strength, fatigue symptoms, mobility or health-related QOL between the Adherers and Non-Adherers ($p > 0.05$).

Conclusion: Direct referral to physical activity from a physician is twice as effective as simply providing information about physical activity with respect to adhering to the PAG prescription in people with MS. Further, a high self-efficacy for exercise at baseline may be an additional predictor to PAG adherence.

Introduction

Physical activity is a powerful tool that can be utilized in the Multiple Sclerosis (MS) population for symptom management through modifying fatigue, mobility, depression and pain (1, 2). Two-thirds of people living with MS do not participate in regular physical activity despite its reported benefits (3, 4). Commitment and adherence to community-based physical activity can be a challenge for people living with MS as they have to overcome numerous barriers on a daily basis (with respect to disease symptoms, transportation issues, fatigue) (5). In other clinical populations, like cardiac patients, there is evidence to suggest that direct referral to community-based exercise from a physician (or member of the healthcare team) is a strong predictor for adherence (6). Dunn and colleagues examined predictors of home- and hospital-based cardiac rehabilitation exercise and concluded that patients who reported receiving a physician referral rated the strength of the referral high. Further, this highly rated referral by a physician significantly predicted exercise participation, indicating the powerful effect positive endorsement of exercise by a physician can have (7). Sweet et al. (2013) revealed that adults with MS consider physicians to be the most credible (yet least accessible) source for physical activity information specific to their needs, with allied health professionals and peers also ranking quite highly as a desired source of information (8). Therefore, there is potential for physical referral to physical activity programs (with appropriate exercise prescription) to have a positive effect on physical activity participation rates in the MS population.

Characterizing or defining what constitutes physical activity adherence across exercise studies is variable, although most studies calculate adherence rates as the number of sessions attended over the total number of sessions for the duration of the study (9). Currently there is no gold standard defining what constitutes physical activity adherence or the number of training sessions that is required to significantly benefit from physical activity. Studies evaluating adherence to physical activity in other populations have defined successful adherence as attending between 66-100 % of prescribed sessions (10–19). A comparison of definitions and justifications for physical activity adherence across those 10 studies produced an average benchmark of 75 %; this threshold was then used to define adherence in the current study.

Identifying physical activity determinants and what other factors may predict adherence to physical activity will aid in getting people to adopt physically active lifestyles. Self-efficacy; the belief to execute or accomplish a task, has been correlated to physical activity behaviours in adults (20) in the general population and it is also a novel area of research in the MS population garnishing attention. Previous studies have concluded that self-efficacy was positively and moderately correlated with physical activity adherence in adults with MS (21–23).

The objectives of this study were to determine the effect of physician referral on adherence to the Physical Activity Guidelines (PAGs) for people living with MS in a community setting and to identify what other factors may also predict adherence to the PAGs. The results from this study will help to determine whether or not a model of referral to a defined program is more effective than simply providing information about the PAGs to adults with MS. If direct referral to community-based exercise proves to result in greater adherence to PAGs, this will not only be a strong argument in support of the development of specialized community-based exercise programs for this population, but will also emphasize the value patients place on physician advice with respect to the importance of physical activity for overall health and wellbeing.

Methods

Participants

Detailed recruitment and enrollment information is provided in the flow diagram **(Figure 2.1)**. Participants were recruited to participate in a 16wk RCT at McMaster University in Hamilton, ON from July 2014 - March 2017. Inclusion criteria consisted of; i) EDSS score between 1 and 7, ii) aged 18 to 64 years and iii) medical clearance to participate in exercise. Exclusion criteria included; i) participation in physical activity (≥ twice weekly) and ii) other serious medical condition that would impair ability to participate in strength or aerobic training. All participants provided written informed consent and all procedures were approved and conducted in accordance with the ethical guidelines of the Hamilton Integrated Research Ethics Board. Participants were randomized to a direct referral group (REF) or a control group (CON) after baseline testing was completed and randomization allocation was blinded to testers. Participants randomized to the REF group were prescribed exercise based on the PAG recommendations by a physician and referred to a community-based exercise program at McMaster University. Participants randomized to the CON group were given a print copy of the PAGs and an online link for information about physical activity and MS. CON participants had to use their own initiative to seek out community based exercise opportunities.

Physician Referral

The physician referral form was filled out by the lead Neurologist at Hamilton Health Science's MS Clinic. The referral form replicated a physicians' prescription pad wherein participants were prescribed exercise in accordance with the PAGs for adults living with MS (24). The form also included a referral to an appropriate exercise program at McMaster University. Participants who joined the exercise program participated in supervised, twice-weekly exercise sessions that involved both aerobic and resistance exercise. Each participant worked one-on-one with an exercise trainer who monitored each exercise session, recorded the details pertaining to all exercises completed and progressed the intensity of the prescription as appropriate. There was membership fee for this program (similar to other exercise programs in the area, \$55/month + \$20/month parking if required) to truly represent a real-world, community-based setting.

Demographics and Questionnaires

Participants completed a variety of questionnaires assessing demographics, quality of life (QOL), fatigue symptoms and self-efficacy for exercise at baseline and post-testing. QOL was assessed using the MS Quality of Life 54 (MSQOL-54) (25). Fatigue was assessed using the Modified Fatigue Impact Scale (MFIS-5) (26). The 5 item scale was used instead of the full version to reduce burden to participants. A questionnaire previously used in the spinal cord injury population was used to determine self-efficacy for exercise. This questionnaire has demonstrated reliability, predictive validity and sensitivity to change in an intervention study evaluating perceptions of PAGs for a clinical population with mobility impairment (27). Questionnaire items included items assessing participants' perceptions of the value of the PAGs, expectations about the benefits of meeting the guidelines and confidence to engage in the recommended amount of physical activity. The questionnaire assessed participants' confidence and intentions to follow the PAGs, addressing both the aerobic and strengthening portions of the guidelines separately (28). All self-efficacy items were rated on a 7 point Likert scale from 1 (strongly disagree/not at all confident) to 7 (strongly agree/completely confident). One total score was reported for outcome expectation and 4 total scores were reported for self-efficacy beliefs regarding strengthening and aerobic exercise.

Peak Aerobic Capacity

To measure peak oxygen consumption, a progressive VO_2 peak test to peak oxygen consumption or volitional exhaustion on an arm cycle ergometer (Lode B.V., Groningen, Netherlands) was completed by participants. The resistance started at 0 W and increased thereafter by 10 W every minute and participants were asked to keep their RPMs between 50-60 RPM. Heart rate (Polar Electro, Lachine, QC, Canada) and VO_2 (Moxus Metabolic System, AEI Technologies, Pittsburgh, PA, USA) were continuously measured. The test was terminated if a) the participant reached volitional exhaustion, b) the cycling rate dropped below 50 RPM c) a plateau in VO_2 was observed, or d) heart rate was greater than 90% of the participants' age predicted maximum heart rate.

Muscle Strength

One repetition maximum (1RM) strength testing using established procedures (29) was completed on a multi-station (wheelchair accessible) weight training system

(Equalizer Multi-Station, Equalizer Exercise Machines, Red Deer, AB, Canada), unilateral wall pulleys (Endorphin Pulleys, Patterson Medical Supply, Mississauga, ON, Canada) and using the HUR leg extension/flexion machine (HUR Health & Fitness Canada INC, Canada). 1RM was assessed in the back, chest, biceps, triceps, shoulder flexors, shoulder extensors, hamstrings and quadriceps muscles and a composite strength score was calculated.

Mobility

Mobility was assessed using the 25 ft walk test. Participants were instructed to walk 25 ft as quickly as possible but safely and in their usual manner and they repeated this twice. An average of the walking speeds for the 2 attempts was calculated (7.62 m divided by the time it took to complete the test (m/s).

Adherence to PAGs

Adherence was assessed over 16 weeks by weekly physical activity logs. Participants were emailed weekly logs for aerobic and strengthening exercises. If participants were unable to access internet, hard copies of 16 weeks of logs were provided at baseline testing and participants were instructed to return the physical activity logs at post-testing. Detailed information about type, duration and intensity of exercise was provided by participants in the logs for analysis of adherence. Adherence to the PAGs was calculated as the number of weeks (calculated as a percentage) participants achieved both the aerobic and resistance exercise recommendations over the 16 week period. At the end of the study, participants were then categorized as “Adherers” or “Non-Adherers” to assist in our analysis of additional factors that may predict adherence to the PAGs.

Participants were classified as an "Adherer" if they met the PAGs recommendations for 12 out of 16 weeks, or had a calculated adherence rate of 75 %.

Data Analyses

Continuous variables are reported as means and standard deviations and categorical variables are presented as frequencies and prevalence values**.** Differences in baseline values were compared using independent samples t-tests. Stepwise multiple regression analyses were used to determine what factors predict adherence. Pearson R correlational analyses were used to assess relationships between outcome variables and adherence. All statistical analyses were performed using IBM SPSS Statistics v24. Statistical significance was set at alpha < 0.05.

Results

Participant Characteristics

Seventy-four participants (age 47.7 ± 10.4 years, EDSS score 3.5 ± 1.8, 12.2 ± 10.1 years living with MS) completed follow-up; 41 were randomized into the REF group and 36 were randomized into the CON group. There were no significant differences in demographic characteristics between the two groups, presented in **Table 2.1.** Wide ranges of baseline characteristics were observed; age (range: 22-64 years), EDSS score (range: 1-7), time since diagnosis (range: 1 month-39 years), fatigue scores (range: 2-20), mobility (range: 0.08-2.25 m/s), physical health-related QOL scores (range: 8.66-85.73) and mental health-related QOL scores (range: 9.37-93.22).

Adherence

The effect of direct referral on adherence is displayed in **Figure 2.2.** Participants in the REF group had twice the adherence rate to the PAGs as those in the CON group ($p < 0.05$; 65.2 ± 29.2 %, range: 0-100 % versus 32.8 ± 34.1 %, range: 0-100 %). Thirty-six people in the REF group joined either the community-based exercise program at McMaster University or another fitness center whereas only 15 people in the CON group joined a community-based program. Due to the range in adherence, participants were categorized as “Adherers” if calculated adherence rates were ≥ 75 % (i.e. met the PAGs for at least 12/16 weeks). Twenty-eight participants were classified as Adherers and 49 were classified as Non-Adherers. Participants who adhered to the PAGs over the 16 week study period significantly improved aerobic fitness, strength in major muscle groups, mobility, fatigue symptoms and overall health-related QOL ($p < 0.05$) (30).

Baseline Characteristics in Adherers and Non-Adherers

There were no significant differences in demographics, fitness or functional outcomes at baseline between Adherers and Non-Adherers ($p > 0.05$) **Table 2.2.** No significant correlations were observed between any of the baseline demographic, fitness or functional outcomes and adherence ($p > 0.05$).

Self-Efficacy

The results for self-efficacy are presented in **Table 2.3.** Participants who adhered to the PAGs at least 75 % of the time had greater self-efficacy for exercise at baseline compared to the Non-Adherers ($p < 0.0001$). Significant moderate correlations were observed between baseline self-efficacy scores for meeting the aerobic and strengthening portions of the PAGs and adherence ($r = 0.479$, $p < 0.0001$; $r = 0.489$, $p < 0.0001$, respectively). Higher self-efficacy scores at baseline were associated with greater adherence to the PAGs.

Significant Predictors for Adherence

Group (direct referral) and self-efficacy for completing the aerobic component of the PAGs for adults living with MS significantly predicted adherence, accounting for 23 % of variance in the model ($R = 0.472$, $R^2 = 0.223$, $p < 0.05$).

Discussion

The objectives of this study were to determine the effect of physician referral on adherence to the PAGs in a community-based exercise setting and to identify other factors that may also predict PAG adherence in the MS population. The findings suggest that physician referral to an exercise program is far more effective than simply providing information about the PAGs to adults living with MS. Further, we found that baseline self-efficacy for exercise is an additional predictor of adherence to the PAGs in this population. These results have clear implications for the important role physicians can play in promoting physical activity to their patients with MS.

Patients with MS identify physicians and allied healthcare professionals as the most credible source for physical activity information (8), and the results from this RCT certainly support this observation. It is well known that people living with MS are physically inactive and physical inactivity is associated with negative health consequences (3, 31, 32). Our results highlight the importance of physician referral in improving physical activity adherence, and align with what has been observed in the cardiac rehabilitation setting (6, 7). There is a need for physicians and health care professionals to start stressing the value of exercise to their patients living with MS and to incorporate the prescription of regular exercise in their patient visits. Exercise has been shown to not only improve physical fitness, but it can positively modify MS-related symptoms like fatigue, mobility and improve the QOL in those living with the disease (2, 33). No single pharmaceutical prescription can make the same claims. Having disease specific PAGs (24) should make it much easier for physicians to talk about the importance of physical activity to their patients.

One of the most interesting results from this current study was that there were no baseline differences in EDSS score, time since diagnosis, fitness parameters, fatigue symptoms or overall health-related QOL between participants who ended up being an Adherer or a Non-Adherer. We believe this is a positive finding as MS related symptoms do not seem to predict adherence to physical activity. This is unlike previous research where authors reported that individuals with MS who reported a greater number of symptoms during the past 30 days engaged in lower amounts of physical activity (22). However, similar to the results from the current study, Kayes et al. (2011) found that greater exercise and household chores self-efficacy and lower number of perceived barriers to physical activity were significantly associated with increased participation in physical activity in their cross-sectional analysis (34). More longitudinal studies are needed to understand adherence to physical activity and exercise over the long term in the MS population (9).

Apart from physician referral, a higher self-efficacy for exercise was the only additional predictor of PAG adherence in this randomized, community-based sample of adults living with MS. Social Cognitive Theory is a theoretical framework that describes behaviour by personal self-control and can be used to identify constructs (i.e., self-efficacy and outcome expectations) as targets for changing health behaviours (i.e., physical activity) (35). Research by Motl and colleagues has demonstrated these constructs from Social Cognitive Theory as being important determinants of physical activity behaviour among adults with MS (36, 37). Self-efficacy for exercise has been shown to be a strong predictor of adherence to physical activity in previous cross-sectional studies in the MS population (21, 38, 39). We have now validated this association longitudinally, by showing positive correlations between baseline self-efficacy and PAG adherence over a 16 wk period. It is also important to highlight that participants in the current study had to take the initiative to join (and pay for) the exercise program, enhancing its ecological validity. Whereas the current study examined the role of baseline self-efficacy as a predictor of PAG adherence, future studies could also target self-efficacy as a potential modifiable risk factor after exercise interventions, as well as investigating in the MS population how self-efficacy for exercise impacts long-term physical activity participation.

Conclusions

Adherence to the PAGs for people living with MS is twice as high in people who receive a direct referral from a physician. Further, baseline self-efficacy for exercise is an additional predictor. Given the multiple benefits associated with regular physical activity, and the fact that there now exists evidence-based PAGs for people with MS, the results from this study send a strong message to the medical community regarding the importance of physical activity referral by a physician.

References

1. Sutherland G, Andersen M. Exercise and multiple sclerosis: Physiological, psychological, and quality of life issues. J. Sports Med. Phys. Fitness 2001;41:421–32.

2. Latimer-Cheung AE, Pilutti LA, Hicks AL, et al. Effects of exercise training on fitness, mobility, fatigue, and health-related quality of life among adults with multiple sclerosis: a systematic review to inform guideline development. Arch. Phys. Med. Rehabil. 2013;94:1800–1828.e3.

3. Motl RW, Mcauley E, Sandroff B, Hubbard E. Descriptive epidemiology of physical activity rates in multiple sclerosis. Acta Neurol. Scand. 2015;131:422–425.

4. Motl RW, McAuley E, Snook EM. Physical activity and multiple sclerosis: a meta-analysis. Mult. Scler. 2005;11:459–463.

5. Becker H, Stuifbergen A. What makes it so hard? Barriers to health promotion experienced by people with multiple sclerosis and polio. Fam. Community Health 2004;27:75–85.

6. Jackson L, Leclerc J, Erskine Y, Linden W. Getting the most out of cardiac rehabilitation: a review of referral and adherence predictors. Heart 2005;91:10–4.

7. Dunn SL, Dunn LM, Buursma MP, et al. Home- and Hospital- Based Cardiac Rehabilitation Exercise: The Important Role of Physician Recommendation. West. J. Nurs. Res. 2017;39:214–233.

8. Sweet SN, Perrier M-J, Podzyhun C, Latimer-cheung AE. Identifying physical activity information needs and preferred methods of delivery of people with multiple sclerosis. Disabil. Rehabil. 2013;35:2056–2063.

9. Heesen C, Bruce J, Gearing R, et al. Adherence to behavioural interventions in multiple sclerosis: Follow-up meeting report (AD@MS-2). Mult. Scler. J. 2015;1:1–4.

10. De Jesus S, Fitzgeorge L, Unsworth K, et al. Feasibility of an exercise intervention for fatigued breast cancer patients at a community-based cardiac rehabilitation program. Cancer Manag. Res. 2017;9:29–39.

11. Deka P, Pozehl B, Williams MA, Yates B. Adherence to recommended exercise guidelines in patients with heart failure. Heart Fail. Rev. 2017;22:41–53.

12. Freiberger E, Blank WA, Salb J, et al. Effects of a complex intervention on fall risk in the general practitioner setting: a cluster randomized controlled trial. Clin. Interv. Aging 2013;8:1079–1088.

13. Geraedts HAE, Zijlstra W, Zhang W, Bulstra S, Stevens M. Adherence to and effectiveness of an individually tailored home-based exercise program for frail older adults, driven by mobility monitoring: design of a prospective cohort study. BMC Public Health 2014;14:1–7.

14. Hicks G, Benvenuti F, Fiaschi V, et al. Adherence to a community-based exercise program is a strong predictor of improved back pain status in older adults: an observational study. Clin. J. Pain 2013;28:195–203.

15. Kampshoff CS, Mechelen W Van, Schep G, et al. Participation in and adherence to physical exercise after completion of primary cancer treatment. Int. J. Behav. Nutr. Phys. Act. 2016;13:1–12.

16. Kronish IM, Diaz KM, Goldsmith J, Moise N, Schwartz JE. Objectively Measured Adherence to Physical Activity Guidelines After Acute Coronary Syndrome. JACC 2017;69:1205–1207.

17. Shubert TE, Altpeter M, Busby-whitehead J. Using the RE-AIM Framework to translate a research-based falls prevention intervention into a community-based program : Lessons Learned. J. Safety Res. 2011;42:509–516.

18. Shumway-cook A, Silver IF, LeMier M, York S, Cummings P, Koepsell TD. Effectiveness of a Community-Based Multifactorial Intervention on Falls and Fall Risk Factors in Controlled Trial. J. Gerontol. Med. Sci. 2007;62A:1420–1427.

19. Sjosten NM, Salonoja M, Piirtola M, et al. A multifactorial fall prevention programme in the community-dwelling aged: predictors of adherence. Eur. J. Public Health 2007;17:464–470.

20. McAuley E, Blissmer B. Self efficacy determinants and consequences of physical activity. Exerc. Sport Sci. Rev. 2000;28:85–88.

21. Motl RW, Mcauley E, Doerksen S, Hu L, Morris KS. Preliminary evidence that self-efficacy predicts physical activity in multiple sclerosis. Int. J. Rehabil. Res. 2009;32:260–263.

22. Motl RW, Snook EM, Mcauley E, Gliottoni RC. Symptoms, Self-Efficacy, and Physical Activity Among Individuals With Multiple Sclerosis. Res. Nurs. 2006;29:597–606.

23. Streber R, Peters S, Pfeifer K. Systematic Review of Correlates and Determinants of Physical Activity in Persons With Multiple Sclerosis. Arch. Phys. Med. Rehabil. 2016;97:633–45.

24. Canadian Society for Exercise Physiology. Physical Activity Guidelines for Adults with MS. 2012.

25. Vickrey BG, Hays RD, Harooni R, et al. A Health-Related Quality of Life Measure for Multiple Sclerosis. Qual. life Res. 1995;4:187–206.

26. Fisk JD, Ritvo PG, Ross L, et al. Measuring the Functional Impact of Fatigue : Initial Validation of the Fatigue Impact Scale. Clin. Infect. Dis. 1994;18:S79–S83.

27. Gainforth HL, Latimer-cheung AE, Athanasopoulos P, Ginis KAM. Examining the effectiveness of a knowledge mobilization initiative for disseminating the physical activity guidelines for people with spinal cord injury. Disabil. Health J. 2013;6:260–265.

28. Latimer AE, Ginis KAM, Arbour KP. The Efficacy of an Implementation Intention Intervention for Promoting Physical Activity Among Individuals With Spinal Cord Injury : A Randomized Controlled Trial. Rehabil. Psychol. 2006;51:273–280.

29. Kraemer W, Ratamess N, Fry A, French D. Strength Training: development and evaluation of methodology. In: Maud P, Foster C, editors. Physiological assessment of human fitness. Champaign, IL: Human Kinetics, 2006:119–50.

30. Canning KL, Hicks AL. The Validity of the Physical Activity Guidelines for People with Multiple Sclerosis. 2017.

31. Marrie RA, Horwitz RI. Emerging effects of comorbidities on multiple sclerosis. Lancet Neurol. 2010;9:820–8.

32. Sandroff B, Dlugnski D, Weikert M, Suh Y, Balantrapu S, Motl R. Physical activity and multiple sclerosis : new insights regarding inactivity. Acta Neurol. Scand. 2012;126:256–262.

33. Motl RW, Gosney J. Effect of exercise training on quality of life in multiple sclerosis: a meta-analysis. Mult. Scler. 2008;14:129–135.

34. Kayes NM, McPherson KM, Schluter P, Taylor D, Leete M, Kolt GS. Exploring the facilitators and barriers to engagement in physical activity for people with multiple sclerosis. Disabil. Rehabil. 2011;33:1043–53.

35. Bandura A. Health Promotion by Social Cognitive Means. Heal. Educ. Behav. 2004;31:143–164.

36. Motl RW, McAuley E, Sandroff BM. Longitudinal change in physical activity and its correlates in relapsing-remitting multiple sclerosis. Phys. Ther. 2013;93.

37. Suh Y, Weikert M, Dlugonski D, Balantrapu S, Motl RW. Social Cognitive Variables as Correlates of Physical Activity in Persons with Multiple Sclerosis: Findings from a Longitudinal, Observational Study. Behav. Med. 2011;37:87–94.

38. Nickel D, Spink K, Andersen M, Knox K. Attributions and self-efficacy for physical activity in multiple sclerosis. Psychol. Health Med. 2014;19:433–441.

39. Plow MA, Resnik L, Allen SM. Exploring physical activity behaviour of persons with multiple sclerosis: a qualitative pilot study. Disabil. Rehabil. 2009;31:1652–65.

Table 2.1. Participant Characteristics of 77 Adults Living with MS

Characteristic	Mean ± SD	
	REF (n = 41)	**CON (n = 36)**
Age (y)	46.8 ± 10.5	48.9 ± 10.3
Female (N, %)	26 (63)	22 (63)
EDSS	3.5 ± 1.8	3.5 ± 1.8
Time Since Diagnosis (y)	10.9 ± 8.9	13.8 ± 11.1
RRMS (N, %)	27 (66)	23 (59)

REF, Referral Group
CON, Control Group
EDSS, Expanded Disability Status Score
RRMS, Relapsing-Remitting MS

Table 2.2. Baseline Demographic, Fitness & Functional Characteristics of Adherers and Non-Adherers

Characteristic	Mean ± SD		p Value
	Adherers (n = 28)	**Non-Adherers (n = 49)**	
Age (y)	49.7 ± 8.1	46.6 ± 11.4	p = 0.179
EDSS	3.6 ± 1.7	3.5 ± 1.9	p = 0.781
Time Since Diagnosis (y)	12.6 ± 8.1	12.0 ± 11.1	p = 0.816
VO_2 Peak (ml/kg/min)	13.8 ± 5.6	14.1 ± 4.2	p = 0.783
Composite Strength (1RM, kg)	16.4 ± 5.0	17.0 ± 5.7	p = 0.626
25FTW Speed (m/s)	1.4 ± 0.5	1.2 ± 0.5	p = 0.258
MFIS-5	11.0 ± 4.5	11.0 ± 3.3	p = 0.964
Physical Health QOL	53.5 ± 17.8	51.8 ± 16.7	p = 0.320
Mental Health QOL	68.2 ± 15.3	61.5 ± 21.3	p = 0.681

EDSS, Expanded Disability Status Score
1RM, One Repetition Maximum
25FTW, 25 Foot Walk Test
MFIS-5, 5 item Modified Fatigue Impact Scale
QOL, Quality of Life

Table 2.3. Baseline Self-Efficacy for Exercise Constructs of Adherers and Non-Adherers

Characteristic	Mean ± SD		p Value
	Adherers (n = 28)	**Non-Adherers (n = 49)**	
Total Score 1	64.5 ± 7.3	60.6 ± 8.4	$p = 0.078$
Total Score 2	27.5 ± 1.6	24.0 ± 4.6	$p < 0.0001$
Total Score 3	13.7 ± 0.8	11.6 ± 2.4	$p < 0.0001$
Total Score 4	27.2 ± 2.1	22.9 ± 5.9	$p < 0.0001$
Total Score 5	34.1 ± 2.3	28.8 ± 6.7	$p < 0.0001$

Total Score 1, Overall Outcome Expectations
Total Score 2, Self-Efficacy Beliefs for Completing Aerobic Exercise at Targeted Intensities & Durations
Total Score 3, Self-Efficacy Beliefs for Completing Aerobic Exercise Sessions
Total Score 4, Self-Efficacy Beliefs for Completing Resistance Exercise
Total Score 5, Self-Efficacy Beliefs for Completing Exercise Program Over Time

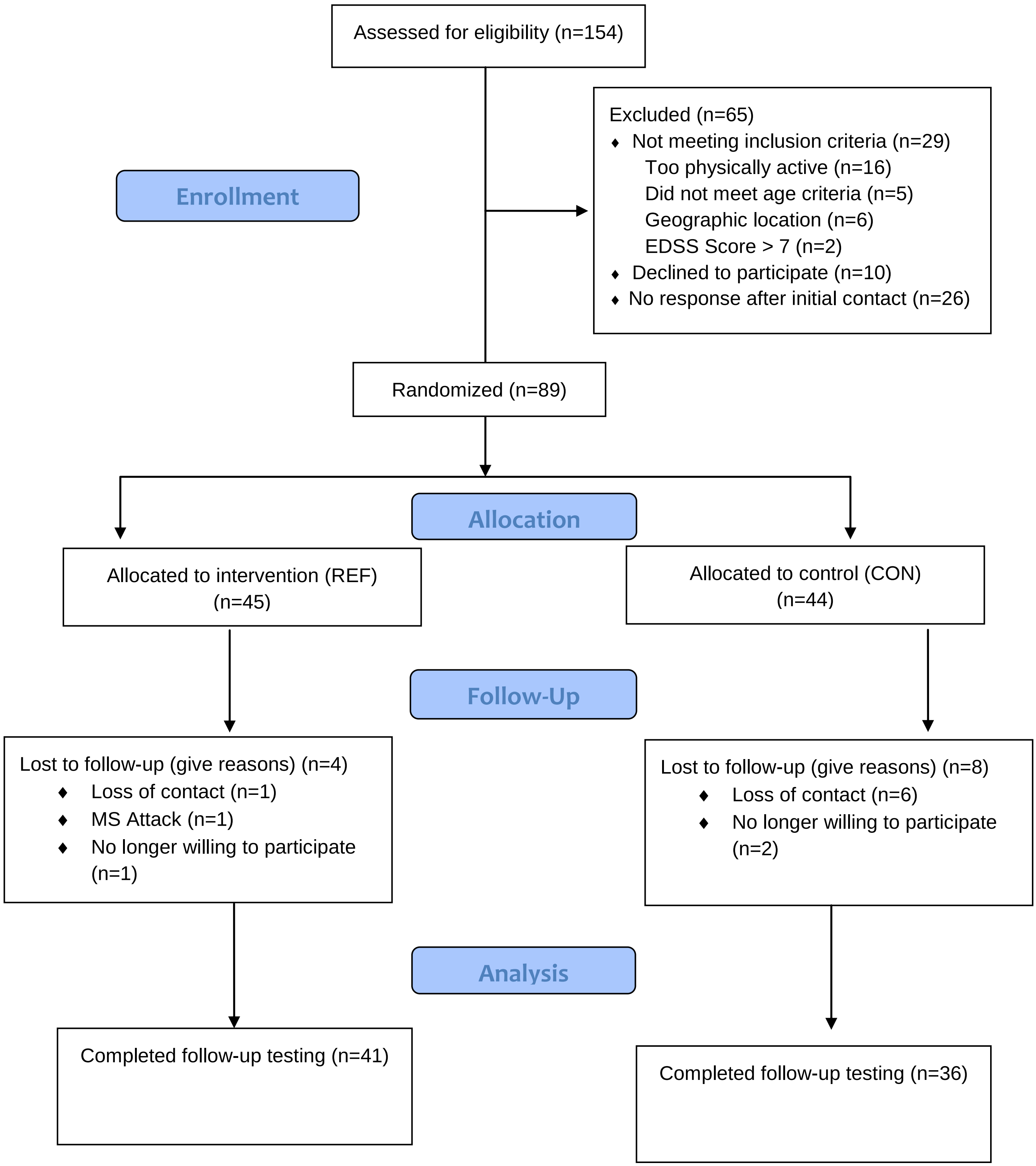
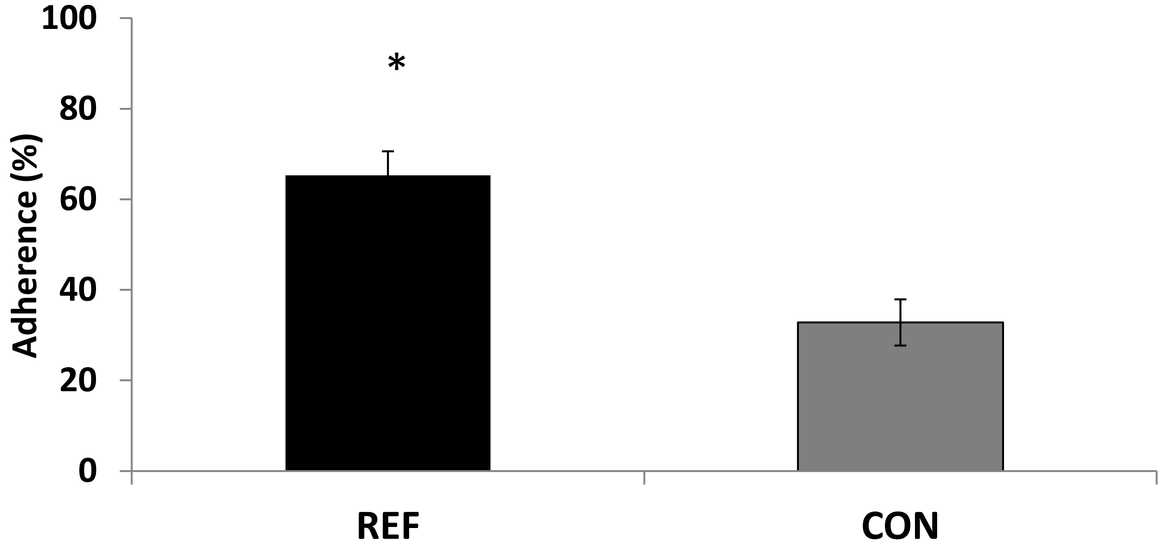


Figure 2.1. CONSORT Flow Diagram of Participant Recruitment and Enrollment



* significant difference $p < 0.05$

Figure 2.2. The Effect of Direct Referral on Adherence

CHAPTER 3:

The Validity of the Physical Activity Guidelines for People with Multiple Sclerosis

Karissa L. Canning, MSc & Audrey L. Hicks, PhD

Abstract

Objectives: New evidence-based physical activity guidelines (PAGs) for people with MS were released in 2012. The objective of this study was to affirm that following the PAGs for people with MS would result in improvements in fitness, mobility, fatigue symptoms and quality of life (QOL).

Methods: As part of an ongoing RCT examining the implementation of the PAGs, participants were randomized to either a direct referral group (REF (n=41): doctor referral to a centre-based exercise program and prescribed an exercise program following the PAGs) or a control group (CON (n=36): provided a copy of the PAGs and a link to an online resource with MS specific physical activity information). VO_2 peak (arm ergometer), strength, mobility (25FW test), fatigue symptoms (MFIS-5) and QOL (MS-QOL54) were assessed at baseline and after 16 weeks.

Results: Seventy-seven people living with MS from the Hamilton area (age: 47.7 ± 10.4 years, EDSS score: 3.5 ± 1.8, time since diagnosis: 12.2 ± 10.1 years) were recruited. Adherence to the PAGs was assessed through weekly physical activity logs. Adherence to the PAGs was higher in the REF group (65.2 ± 29.2 %) compared with the CON (32.8 ± 34.1%) ($p < 0.05$). After 16 weeks of observation, participants were categorized as either PAG “Adherers” (n=28) or “Non-Adherers” (n=49) based on achieving the PAG recommendations at least 75% of the time (ie. at least 12/16 weeks). Adherers saw improvements in VO_2 peak (+32%), strength (+8-20%), mobility (+14%), fatigue symptoms (-40%) and QOL (+10-24%) compared to the Non-Adherers ($p < 0.05$).

Conclusions: Following the PAGs for at least 12 out of 16 weeks results in improvements in fitness, mobility, fatigue symptoms and QOL, confirming the validity of the PAGs for people with MS for improving health. **ClinicalTrials.gov Identifier: NCT02100020**

Introduction

An estimated 100,000 Canadians currently are living with multiple sclerosis (MS), a degenerative neurological disease that has a wide range of debilitating symptoms including muscle weakness, extreme fatigue, loss of balance, impaired speech, double vision, declining cognitive function, and paralysis (1). These symptoms lead to poor quality of life and high health care costs. Physical activity is one strategy that has been proposed to counteract the disabling symptoms of MS, and it is gaining increasing attention for its potential as a disease-modifying intervention. Accumulating evidence indicates that engaging in physical activity can improve and/or maintain functional ability, aerobic fitness, strength, fatigue, quality of life, depression, cognitive function, and chronic disease risk profiles among people with MS (2, 3). Unfortunately, despite the benefits of physical activity, the majority of people with MS are physically inactive, a behaviour which is now known to carry its own specific risk with respect to the development of cardio-metabolic chronic diseases (4, 5).

Health care and service providers have struggled in the past providing recommendations for physical activity for people with MS as there were no evidence-based guidelines on appropriate doses, intensities, and types of exercises to perform in this population. One of the key recommendations to come out of the 2011 Consensus Conference White Paper from the Consortium of Multiple Sclerosis Centers was to identify evidence-informed physical activity guidelines to improve physical fitness and decrease co-morbidities in people with MS (6). In 2012, evidence-based physical activity guidelines (PAGs) for people living with MS were released. These guidelines suggest that to achieve important fitness benefits, adults aged 18-64 years with MS who have mild to moderate disability need at least 30 minutes of moderate intensity aerobic activity 2 times per week and strength training exercises for major muscle groups 2 times per week. Not only is this dose of physical activity suggested to improve fitness, it is also suggested that meeting the PAGs may also reduce fatigue, improve mobility, and enhance elements of health-related quality of life (QOL) (7).

Improvements in cardiovascular fitness and strength after a physical activity intervention have been demonstrated by many (2, 8, 9). However, the difficulty with interpreting these studies is the fact that authors have used different doses of and types of physical activity. Having disease-specific guidelines can help researchers conduct studies using the same dose of stimulus and provide a clear physical activity promotion message to patients. It is imperative to promote positive health behaviours amongst the MS population as there is no cure currently and people are living much longer with the disease.

No study has validated the PAGs and provided scientific evidence that the recommended dose does in fact improve the health of people living with MS. Therefore, the objective of this study was to validate the PAGs for people with MS within a randomized community-based intervention, and to affirm that following the PAGs for 16 weeks would result in improvements in fitness, mobility, fatigue symptoms and QOL.

Methods

Participants

Detailed recruitment and enrollment information is provided in the CONSORT diagram **Figure 3.1**. Participants with MS with an EDSS score between 1 and 7, who were 18-64 years, were recruited to participate from July 2014-March 2017 through advertisements at the local MS Society of Canada chapter in Hamilton, Ontario. Exclusion criteria included any medical condition that would impair ability to participate in strength or aerobic exercises and participation in regular exercise (at least twice weekly). All participants provided written informed consent and all procedures were approved and conducted in accordance with the ethical guidelines of the Hamilton Integrated Research Ethics Board. After baseline tests were completed, participants were randomized to a direct referral group (REF) or a control group (CON). All testers were blinded to randomization until after baseline tests were completed. Participants randomized to the REF group were prescribed exercise based on the PAGs by a physician and referred to a community-based exercise program at McMaster University. Participants randomized to the CON group were given the PAGs, an online link for information about physical activity and MS and they had to seek out community based exercise themselves. In both groups, no monetary funds were given to pay for exercise program memberships or transportation costs, to replicate a real-world, community-based setting.

Community-based Exercise Program

Participants randomized to the REF group were referred to a community-based exercise program at McMaster University in Hamilton, Ontario. Participants who were in the CON group were not given the referral to the community-based exercise program, however, if they asked about the program after hearing about it in the community, they were able to join. All participants were expected to pay the regular membership fees to join the community-based exercise program, and they were unaware of the randomization allocation of other participants. The program ran two times per week with 1-1.5 hour one-on-one sessions with a trained exercise professional. Participants were prescribed exercise based on the PAGs for people living with MS, achieving 30 minutes of moderate intensity aerobic activity and strength training for major muscle groups, 2 times per week. Every program was individualized to participants' needs and changed every 4 weeks to keep progression and stimulus constant. Participants were prompted regularly for their ratings of perceived exertion (RPE) after aerobic and resistance exercises to determine intensity of the exercise program. Exercise trainers aimed to have participants between 4-6 on the 10-point RPE scale (10) with weights and reps adjusted to achieve this. The equipment used for the aerobic exercise included an arm cycle ergometer (Monark Arm Ergometer, Patterson Medical Supply Inc., Mississauga, ON, Canada) and a hybrid recumbent stepper (NuStep T5XR Recumbant Cross Trainer, NuStep Inc., Ann Arbor, MI, United States). Resistance exercise was completed using a combination of multi-station accessible weight stacks (Equalizer Exercise Machines, Red Deer, AB, Canada), wall pulleys (Endorphin Pulleys, Patterson Medical Supply, Mississauga, ON, Canada) and free weights.

Survey and Anthropometrics Assessment

At baseline and post-testing, participants completed a series of questionnaires assessing demographics, quality of life and fatigue symptoms. Quality of life (QOL) was assessed using the MS Quality of Life 54 (MSQOL-54) questionnaire which contains 54 questions relating to physical, cognitive and sexual functioning (11). A composite score for both physical and mental health-related QOL was determined with higher scores indicating better QOL. Fatigue was assessed using the Modified Fatigue Impact Scale (MFIS-5), a 5 item questionnaire asking about fatigue symptoms and how it has impacted the participant's life during the past month (12). The 5 item scale was used instead of the full version to reduce burden to participants. A final score out of 20 is reported with a higher score indicating greater impact of fatigue on daily life.

A questionnaire to determine participants' satisfaction with the PAGs was administered at post-testing. All items were rated on a 7 point likert scale from 1 (strongly disagree) to 7 (strongly agree). Satisfaction with the aerobic and strengthening portions of the guidelines were evaluated along with perception of pain (*I was able to complete the exercises without any additional pain or discomfort*) and enjoyment of exercise.

Fitness and Mobility Assessment

To measure peak oxygen consumption (VO_2 peak), participants performed a progressive exercise test on an arm cycle ergometer to peak oxygen consumption or exhaustion (Lode B.V., Groningen, Netherlands). The resistance started at 0 W and increased thereafter by 10 W every minute and participants were asked to keep their RPMs between 50-60 RPM. Expired gas and ventilatory parameters were acquired throughout the protocol using the MOXUS Metabolic System (Moxus Metabolic System, AEI Technologies, Pittsburgh, PA, USA). Continuous measures of heart rate were measured throughout the entire test (Polar Electro, Lachine, QC, Canada). Central (e.g., breathing) and peripheral (e.g., arm fatigue) RPE were acquired every minute. Participants continued to cycle for a 2 minute rest period after completion of the peak test to assess heart rate recovery (HR recovery). HR recovery was calculated by MAX HR-2 min post VO_2 peak test HR (13). The test was terminated if a) the participant reached volitional exhaustion, b) the cycling rate dropped below 50 RPM c) plateau in VO_2 was observed, or d) heart rate was greater than 90% of the participants' age predicted maximum heart rate.

Muscle strength testing was completed on a multi-station (wheelchair accessible) weight training system (Equalizer Multi-Station, Equalizer Exercise Machines, Red Deer, AB, Canada), unilateral wall pulleys (Endorphin Pulleys, Patterson Medical Supply, Mississauga, ON, Canada) and using the HUR leg extension/flexion machine (HUR Health & Fitness Canada INC, Canada). One repetition maximum (1RM) was assessed using established procedures (14) in latissimus pull down, chest press, bicep curl, shoulder flexion and extension, and knee flexion and extension exercises. The order of exercises was standardized and participants were provided with enough rest between exercises to ensure muscles did not fatigue before reaching maximum. A composite strength score was calculated as the sum of the 1RMs for each muscle group divided by the total number of muscle groups.

Mobility was assessed using the 25 ft walk test. Participants were instructed to walk 25 ft as quickly as possible but safely and in their usual manner and they repeated this twice. An average of the walking speeds for the 2 attempts was calculated (7.62 m divided by the time it took to complete the test (m/s).

Adherence

Adherence was assessed by having participants fill out weekly physical activity logs for 16 weeks. There were separate log entries for aerobic and strengthening exercises, which included information about the type, duration and intensity of the exercise. Participants were instructed to provide as much information as possible for all of the days they participated in exercise. By evaluating the weekly logs, adherence to the PAGs was calculated based on the number of weeks in which the guideline recommendations were achieved over the 16 week period. To determine the validity of the PAGs, participants were categorized into "Adherers" and "Non-Adherers." Participants were classified as an "Adherer" if they met the PAGs recommendations for 12 out of 16 weeks, or had a calculated adherence rate of ≥75 %.

Statistical Analyses

Continuous variables are reported as means and standard deviations and categorical variables are presented as frequencies and prevalence values**.** Baseline and post-testing values were compared using two-way (group by time) repeated measures analysis of variance. All statistical analyses were performed using IBM SPSS Statistics v24. Statistical significance was set at alpha <0.05.

Results

Participant Characteristics

Seventy-seven participants completed the 16 week RCT (age 47.7 ± 10.4 years, EDSS score 3.5 ± 1.8, 12.2 ± 10.1 years living with MS). Participant characteristics stratified by group (REF vs. CON) are presented in **Table 3.1.** There were no significant differences in demographic characteristics between groups. Forty-one participants were randomized to the REF group and 36 participants were randomized to the CON group. See the CONSORT diagram in **Figure 3.1** for enrollment and drop out explanations.

Adherence

Adherence rate in the REF group was 65.2 ± 29.2 % versus 32.8 ± 34.1 % in the CON group ($p < 0.05$). There was a considerable range in adherence rate within each group; for example, 20 people in the REF group did not adhere and 7 people in the CON group did adhere. Thus, to test the validity of the PAGs, post-hoc categorization into adherers and non-adherers was warranted for analysis of fitness and functional outcomes. Using a 75% adherence rate to define an "Adherer," 28 people were categorized as Adherers and 49 people were categorized as Non-Adherers. There were no significant differences in baseline characteristics between the Adherers and Non-Adherers.

Peak Aerobic Capacity

Changes in aerobic capacity are presented in **Figure 3.2A.** There was a significant increase in VO_2 peak (group by time interaction; $F = 51.06$, $p < 0.0001$) in the Adherers after 16 weeks of following the PAGs. The Non-Adherers experienced no change in VO_2 peak after the 16 week training period. Individual training responses in VO_2 peak after 16 weeks of following the PAGs in Adherers and Non-Adherers are represented in **Figure 3.2B.**

Muscle Strength

Changes in muscle strength in different muscle groups are presented in **Figure 3.3A.** Both Adherers and Non-Adherers improved strength in every muscle group (main effect of time; $p < 0.05$). However greater improvements were observed in the Adherers for the chest, biceps, shoulder extensors and quadriceps muscles (group by time interaction; $F = 9.30$, $p = 0.010$, $F = 4.85$, $p = 0.033$, $F = 6.74$, $p = 0.013$ and $F = 4.92$, $p = 0.028$, respectively). Individual training responses in composite muscle strength after 16 weeks of following the PAGs in Adherers and Non-Adherers are presented in **Figure 3.3B.**

Mobility

Changes in mobility assessed by the 25 ft walk test are presented in **Figure 3.4A.** There was a significant increase in walking speed for the 25 ft walk test (group by time interaction; $F = 11.02$, $p = 0.002$) in the Adherers after 16 weeks of following the PAGs for people with MS.

Fatigue

Changes in fatigue assessed are presented in **Figure 3.4B.** There was a significant reduction in fatigue symptoms in both groups (main effect of time; $p < 0.0001$) however a greater reduction was seen in the Adherers (group by time interaction; $F = 4.60$, $p = 0.041$) after 16 weeks of following the PAGs. This was demonstrated by a change in score on the MFIS-5 of 4.4 for the Adherers versus 1.8 for the Non-Adherers.

Health-Related Quality of Life

Changes in mental and physical health-related QOL are presented in **Figure 3.5.** Both Adherers and Non-Adherers significantly improved their mental and physical health-related quality of life after following the PAGs for 16 weeks (main effect of time; $p < 0.0001$). However, greater improvements in both aspects of QOL were observed in the Adherers (group by time interaction Mental QOL; $F = 4.58$, $p = 0.038$, group by time interaction Physical QOL; $F = 7.28$, $p = 0.010$) compared to the Non-Adherers, reflective of 24 % change in both mental and physical QOL for the Adherers versus only a 9 % change in the Non-Adherers.

Satisfaction with PAGs

Responses to the satisfaction with PAGs questionnaire are displayed in **Figure 3.6**. Satisfaction with the aerobic (6.2 ± 1.0) and resistance (6.3 ± 1.0) portions of the PAGs for people living with MS was high (maximum score of 7). Overall enjoyment of the exercise program was also very high (6.6 ± 1.0, maximum score of 7). Participants were able to complete the exercise program without any additional increases in pain or discomfort.

Discussion

This is the first study to validate the PAGs for people living with MS that were released in 2012. The purpose of this study was to determine the effectiveness of following the PAGs for 16 weeks on improving aspects of fitness, fatigue symptoms, mobility and QOL in a community-based sample. Our findings suggest that adhering to the PAGs at least 75 % of the time over 16wks results in clinically significant improvements in aerobic capacity (+32%), strength (range: +8-20%), fatigue (-40%), mobility (+14%) and quality of life (+10-24%). Currently there is no gold standard defining what constitutes physical activity adherence or the number of training sessions needed to reap the benefits of physical activity. An adherence rate of 75 % was chosen as the threshold to classify an Adherer after comparing definitions and justifications for physical activity adherence across a variety of studies in other populations. (15–24).

It is well-established in the literature that individuals living with MS characteristically have low aerobic fitness levels compared to healthy counterparts (25, 26). However, exercise training programs can improve aerobic fitness in the MS population by as much as 22% (25). Previous studies evaluating aerobic training in the MS population have ranged in duration of trial (3 to 26 weeks), number of sessions per week (2 to 5 times per week) and the length of each training session (15 to 45 minutes) (25). Participants in our study who adhered to the PAGs had a 32% increase in VO_2 peak. This is greater than the ~10-22% increase reported in previous studies (16-22), but could be partly due to the fact that we measured VO_2 peak on an arm ergometer. Regardless, completing aerobic exercise at a moderate intensity 2 times per week (as per the PAG recommendation) significantly improves aerobic capacity. As reflected in Figures 2 and 3, there was considerable individual variability in the change in fitness observed in our participants, which supports previous literature in other populations (27–29). To our knowledge, this is the first study to demonstrate individual variability in response to aerobic and resistance training in the MS population. Closer examination of individual participants who showed improvements in aerobic fitness or strength without being labeled as an "Adherer" indicated that these individuals were often just under our threshold criteria of ≥ 75% adherence. These individual response graphs nicely illustrate that fitness improvements occur on a continuum, and people who may not have quite met the "Adherer" criterion could still experience improvements in aerobic capacity and overall strength.

The improvements in muscle strength in this study are similar to previous work in the MS population indicating that 8 to 20 weeks of resistance training, 2 to 3 times per week at a moderate intensity significantly improves muscular strength (8, 30, 31). An interesting and positive finding from this study regarding muscular strength is the fact that, on average, both Adherers and Non-Adherers improved strength in all muscle groups, suggesting that participating in exercise that is below the guideline recommendation may still result in gains in strength. The greater improvements in strength across all muscle groups in the Adherers is likely indicative of the dose-response associated with a greater volume of training (more sessions attended, greater strength improvements). Completing resistance exercise at a moderate intensity 2 times per week as stated in the PAGs, significantly improves strength in major muscle groups for people living with MS, is enjoyable and is not associated with any increase in pain in this population.

The improvements seen in aerobic fitness and overall strength after following the PAGs were expected, but arguably, the results that may be of even more importance are the improvements in fatigue symptoms, mobility and health-related QOL. One of the most commonly reported and debilitating symptoms in the MS population is fatigue (12). Sixty-six percent of participants in this study were characterized by high levels of fatigue, having scores ≥10 on MFIS-5 (32). After 16 weeks of following the PAGs, fatigue symptoms were significantly reduced to what would be categorized as low levels of fatigue. This is an extremely important result, countering previous two decade old precautions that exercising may actual increase fatigue symptoms. Research summarized by Heine and colleagues (2015) confirm these findings as well, indicating the association between exercising and improvements in fatigue symptoms in the MS population (33).

People living with MS report decreased QOL compared to the general population (34), although physical activity participation has been demonstrated to improve health-related QOL in people living with MS (3, 35–37). The results from this RCT confirm that the PAG prescription is sufficient to improve QOL in people living with MS, in fact, this is the first study to observe such large improvements in QOL after exercise training in the MS population (37–39). A mean difference in score of +16 was observed in the mental health composite score and mean difference of +13 in the physical health composite score for the Adherers after 16 weeks of following the PAGs. These mean differences in scores represent a +24 % increases in mental and physical health-related QOL, translating to a significantly improved overall well-being.

Mobility impairment in the MS population results in difficulties in maintaining independence and is one of the most life-altering symptoms associated with MS (40). Walking ability is commonly used to track disease progression by neurologists. The 25 ft walk test is regularly used in both clinical and research based settings (41) to assess walking mobility. Studies using resistance and/or aerobic training programs in the MS population have reported improvements in walking speed and endurance (8, 42, 43). The results from this study are aligned with previous research suggesting 16 weeks of following the PAGs for people with MS is associated with improved walking speed. These improvements may translate to improvements in completing activities of daily living, community independence and overall quality of life in people living with MS.

The responses from the satisfaction with PAGs questionnaire indicate that participants rated the PAGs for adults with MS quite highly. Participants enjoyed following both the aerobic and resistance portion of the guidelines and they were able to complete the exercise sessions without any pain or discomfort. The results from this trial demonstrate not only that the PAGs for adults with MS are valid, but they too are palatable in adults living with MS.

Conclusion

In conclusion, the new PAGs for people living with MS are effective in inducing significant improvements in physical fitness, fatigue symptoms, mobility and QOL. Moreover, the PAGs are very feasible and palatable to this patient population, as seen by the high satisfaction scores. Physicians and health care professionals should highly encourage their patients to participate in physical activity to improve health while living with MS.

References

1. MS Society of Canada. What is MS? 2016. Available at: https://mssociety.ca/about-ms/what-is-ms.

2. Latimer-Cheung AE, Pilutti LA, Hicks AL, et al. Effects of exercise training on fitness, mobility, fatigue, and health-related quality of life among adults with multiple sclerosis: a systematic review to inform guideline development. Arch. Phys. Med. Rehabil. 2013;94:1800–1828.e3.

3. Mostert S, Kesselring J. Effects of a short-term exercise training program on aerobic fitness, fatigue, health perception and activity level of subjects with multiple sclerosis. Mult. Scler. 2002;8:161–168.

4. Motl RW, Mcauley E, Sandroff B, Hubbard E. Descriptive epidemiology of physical activity rates in multiple sclerosis. Acta Neurol. Scand. 2015;131:422–425.

5. Sandroff B, Dlugnski D, Weikert M, Suh Y, Balantrapu S, Motl R. Physical activity and multiple sclerosis : new insights regarding inactivity. Acta Neurol. Scand. 2012;126:256–262.

6. Vollmer T, Benedict R, Bennett S, et al. Exercise as prescriptive therapy in multiple sclerosis: A consensus conference white paper. Int. J. MS Care 2012;14:2–14.

7. Latimer-Cheung AE, Martin Ginis KA, Hicks AL, et al. Development of evidence-informed physical activity guidelines for adults with multiple sclerosis. Arch. Phys. Med. Rehabil. 2013;94:1829–1836.e7.

8. Dalgas U, Stenager E, Jakobsen J, et al. Resistance training improves muscle strength and functional capacity in multiple sclerosis. Neurology 2009;73:1478–84.

9. Platta ME, Ensari I, Motl RW, Pilutti LA. Effect of Exercise Training on Fitness in Multiple Sclerosis : A Meta-Analysis. Arch. Phys. Med. Rehabil. 2016;97:1564–1572.

10. Borg G. Psychophysical bases of perceived exertion. Med Sci Sport. Exerc. 1982;14:377–381.

11. Vickrey BG, Hays RD, Harooni R, et al. A Health-Related Quality of Life Measure for Multiple Sclerosis. Qual. life Res. 1995;4:187–206.

12. Fisk JD, Ritvo PG, Ross L, et al. Measuring the Functional Impact of Fatigue : Initial Validation of the Fatigue Impact Scale. Clin. Infect. Dis. 1994;18:S79–S83.

13. Shetler K, Marcus R, Froelicher VF, et al. Heart Rate Recovery : Validation and Methodologic Issues. J. Am. Coll. Cardiol. 2001;38:1980–7.

14. Kraemer W, Ratamess N, Fry A, French D. Strength Training: development and evaluation of methodology. In: Maud P, Foster C, editors. Physiological assessment of human fitness. Champaign, IL: Human Kinetics, 2006:119–50.

15. Deka P, Pozehl B, Williams MA, Yates B. Adherence to recommended exercise guidelines in patients with heart failure. Heart Fail. Rev. 2017;22:41–53.

16. De Jesus S, Fitzgeorge L, Unsworth K, et al. Feasibility of an exercise intervention for fatigued breast cancer patients at a community-based cardiac rehabilitation program. Cancer Manag. Res. 2017;9:29–39.

17. Freiberger E, Blank WA, Salb J, et al. Effects of a complex intervention on fall risk in the general practitioner setting: a cluster randomized controlled trial. Clin. Interv. Aging 2013;8:1079–1088.

18. Geraedts HAE, Zijlstra W, Zhang W, Bulstra S, Stevens M. Adherence to and effectiveness of an individually tailored home-based exercise program for frail older adults, driven by mobility monitoring: design of a prospective cohort study. BMC Public Health 2014;14:1–7.

19. Hicks G, Benvenuti F, Fiaschi V, et al. Adherence to a community-based exercise program is a strong predictor of improved back pain status in older adults: an observational study. Clin. J. Pain 2013;28:195–203.

20. Kampshoff CS, Mechelen W Van, Schep G, et al. Participation in and adherence to physical exercise after completion of primary cancer treatment. Int. J. Behav. Nutr. Phys. Act. 2016;13:1–12.

21. Kronish IM, Diaz KM, Goldsmith J, Moise N, Schwartz JE. Objectively Measured Adherence to Physical Activity Guidelines After Acute Coronary Syndrome. JACC 2017;69:1205–1207.

22. Shubert TE, Altpeter M, Busby-whitehead J. Using the RE-AIM Framework to translate a research-based falls prevention intervention into a community-based program : Lessons Learned. J. Safety Res. 2011;42:509–516.

23. Shumway-cook A, Silver IF, LeMier M, York S, Cummings P, Koepsell TD. Effectiveness of a Community-Based Multifactorial Intervention on Falls and Fall Risk Factors in Controlled Trial. J. Gerontol. Med. Sci. 2007;62A:1420–1427.

24. Sjosten NM, Salonoja M, Piirtola M, et al. A multifactorial fall prevention programme in the community-dwelling aged: predictors of adherence. Eur. J. Public Health 2007;17:464–470.

25. Langeskov-Christensen M, Heine M, Kwakkel G, Dalgas U. Aerobic capacity in persons with multiple sclerosis: a systematic review and meta-analysis. Sports Med. 2015;45:905–23.

26. Koseoglu BF, Gokkaya NKO, Ergun U, Inan L, Yesiltepe E. Cardiopulmonary and metabolic functions, aerobic capacity, fatigue and quality of life in patients with multiple sclerosis. Acta Neurol. Scand. 2006;114:261–7.

27. Ross R, Lannoy L De, Stotz PJ. Separate Effects of Intensity and Amount of Exercise on Interindividual Cardiorespiratory Fitness Response. Mayo Clin. Proc. 2015;90:1506–1514.

28. Hautala A, Kiviniemi A, Makikallio T, et al. Individual differences in the responses to endurance and resistance training. Eur. J. Appl. Physiol. 2006;96:535–542.

29. Sisson SB, Katzmarzyk PT, Earnest CP, Bouchard C, Blair SN, Church TS. Volume of Exercise and Fitness Nonresponse in Sedentary, Postmenopausal Women. Med. Sci. Sport. Exerc. 2009;41:539–545.

30. Kjølhede T, Vissing K, Dalgas U. Multiple sclerosis and progressive resistance training: a systematic review. Mult. Scler. 2012;18:1215–28.

31. Broekmans T, Roelants M, Feys P, et al. Effects of long-term resistance training and simultaneous electro-stimulation on muscle strength and functional mobility in multiple sclerosis. Mult. Scler. J. 2010;17:468–477.

32. Garg H, Bush S, Gappmaier E. Associations Between Fatigue and Disability, Functional Mobility, Depression, and Quality of Life in People with Multiple Sclerosis. Int. J. MS Care 2016;18:71–77.

33. Heine M, Van De Port I, Rietberg M, Van Wegen E, Kwakkel G. Exercise therapy for fatigue in multiple sclerosis (Review). Cochrane Database Syst. Rev. 2015:1–126.

34. Mitchell AJ, Benito-León J, González J-MM, Rivera-Navarro J. Quality of life and its assessment in multiple sclerosis: integrating physical and psychological components of wellbeing. Lancet Neurol. 2005;4:556–66.

35. Oken BS, Kishiyama S, Zajdel D, et al. Randomized controlled trial of yoga and exercise in multiple sclerosis. Neurology 2004;62:2058–2064.

36. Schulz K-H, Gold SM, Witte J, et al. Impact of aerobic training on immune-endocrine parameters, neurotrophic factors, quality of life and coordinative function in multiple sclerosis. J. Neurol. Sci. 2004;225:11–8.

37. Motl RW, Gosney J. Effect of exercise training on quality of life in multiple sclerosis: a meta-analysis. Mult. Scler. 2008;14:129–135.

38. Rampello A, Franceschini M, Piepoli M, et al. Effect of aerobic training on walking capacity and maximal exercise tolerance in patients with Multiple Sclerosis: A randomzied crossover controlled study. Phys. Ther. 2007;87:545–555.

39. Pilutti LA, Lelli DA, Paulseth JE, et al. Effects of 12 weeks of supported treadmill training on functional ability and quality of life in progressive multiple sclerosis: a pilot study. Arch. Phys. Med. Rehabil. 2011;92:31–6.

40. La Rocca NG. Impact of Walking Impairment in Multiple Sclerosis Perspectives of Patients and Care Partners. Patient 2011;4:189–201.

41. Goldman MD, Motl RW, Scagnelli J, Pula JH, Sosnoff JJ, Cadavid D. Clinically meaningful performance benchmarks in MS Timed 25-Foot Walk and the real world. Neurology 2013;81:1856–1863.

42. Cakt BD, Nacir B, Genç H, et al. Cycling progressive resistance training for people with multiple sclerosis: a randomized controlled study. Am. J. Phys. Med. Rehabil. 2010;89:446–57.

43. van den Berg M, Dawes H, Wade DT, et al. Treadmill training for individuals with multiple sclerosis: a pilot randomised trial. J. Neurol. Neurosurg. Psychiatry 2006;77:531–3.

Table 3.1. Participant Characteristics of 77 Adults Living with MS

Characteristic	Mean ± SD	
	REF (n = 41)	**CON (n = 36)**
Age (y)	46.8 ± 10.5	48.9 ± 10.3
Female (N, %)	26 (63)	22 (63)
EDSS	3.5 ± 1.8	3.5 ± 1.8
Time Since Diagnosis (y)	10.9 ± 8.9	13.8 ± 11.1
RRMS (N, %)	27 (66)	23 (59)

REF, Referral Group
CON, Control Group
EDSS, Expanded Disability Status Score
RRMS, Relapsing-Remitting MS

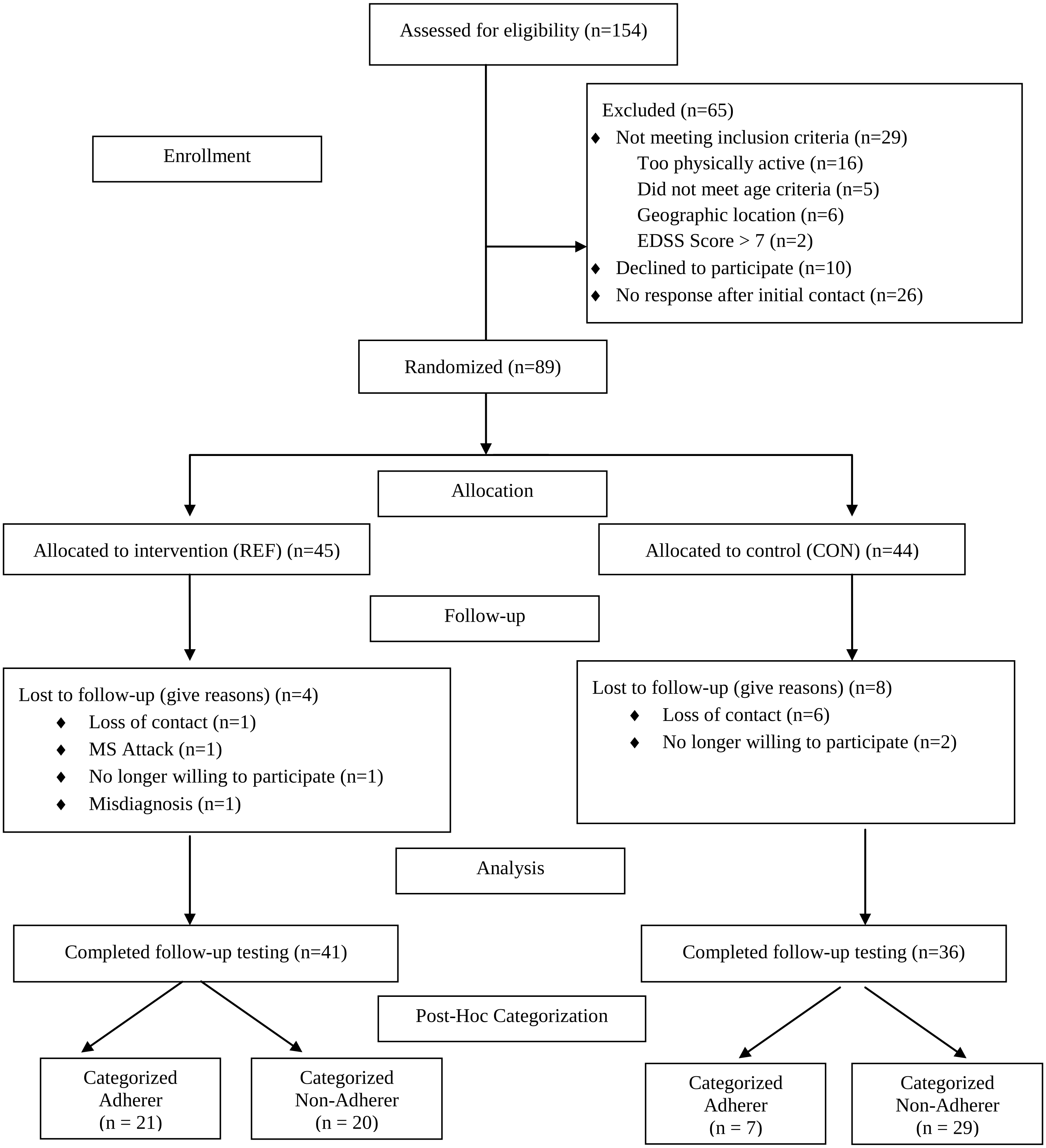


Figure 3.1. CONSORT Diagram of Participant Recruitment and Enrollment

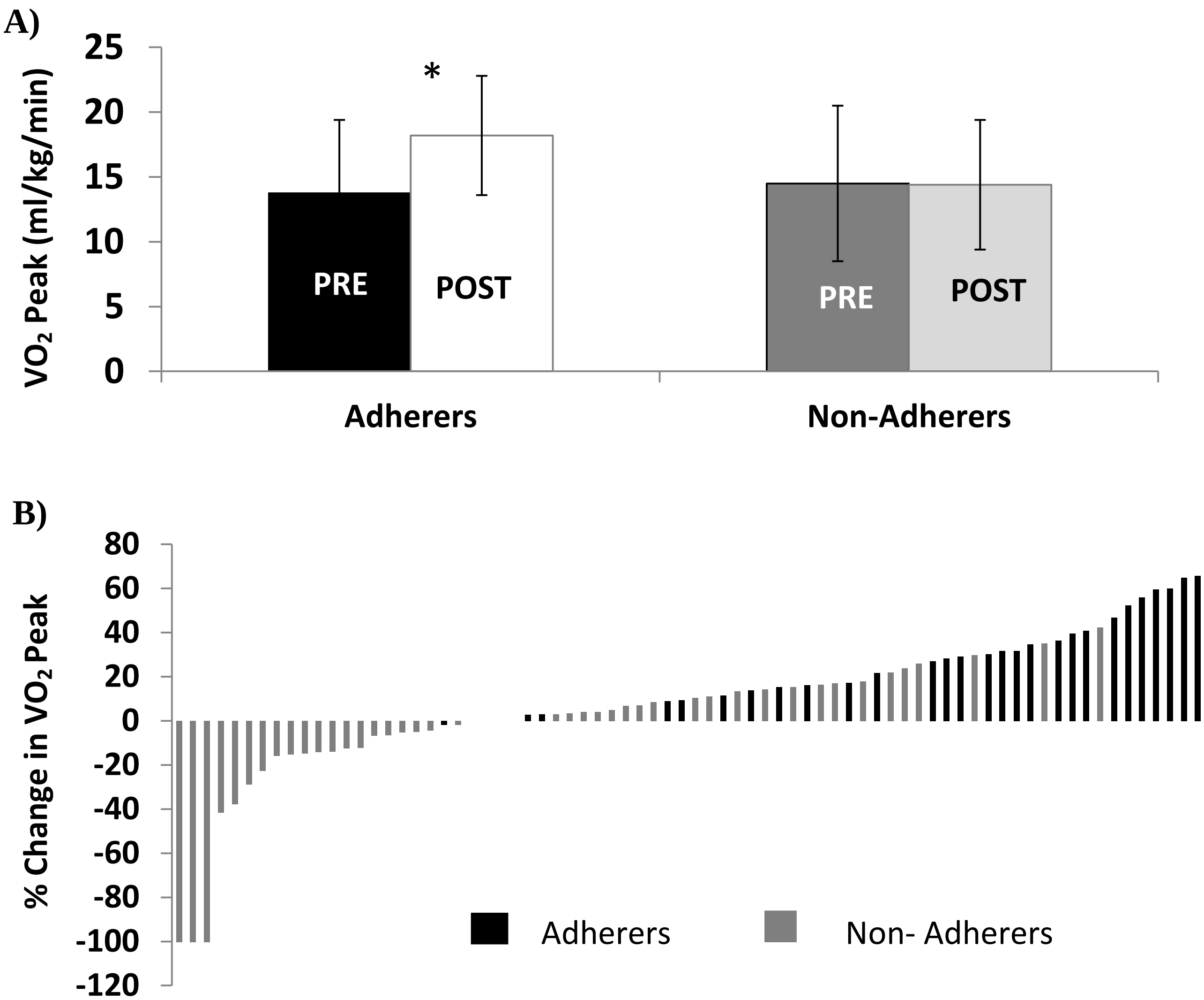


Figure 3.2. Changes in VO_2 Peak in Adherers versus Non-Adherers **A)** and Individual Training Responses in VO_2 Peak for Each Participant **B)** after Following PAGs for 16 Weeks**.**

* significant group by time interaction $p < 0.05$

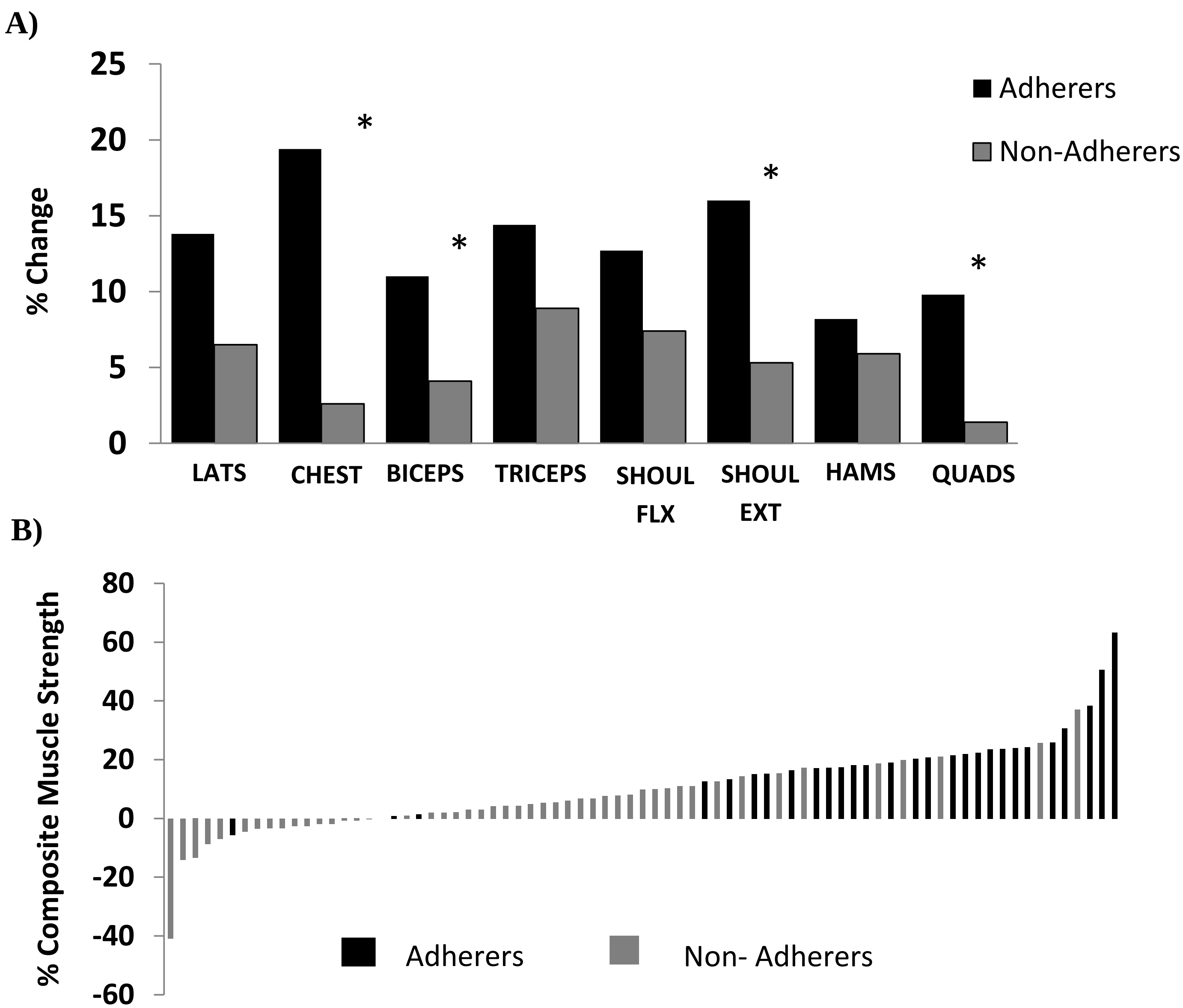


Figure 3.3. Changes in Strength in Each Muscle Group in Adherers versus Non-Adherers **A)** and Individual Training Responses in Overall Strength for Each Participant **B)** after Following PAGs for 16 Weeks

* significant group by time interaction $p < 0.05$

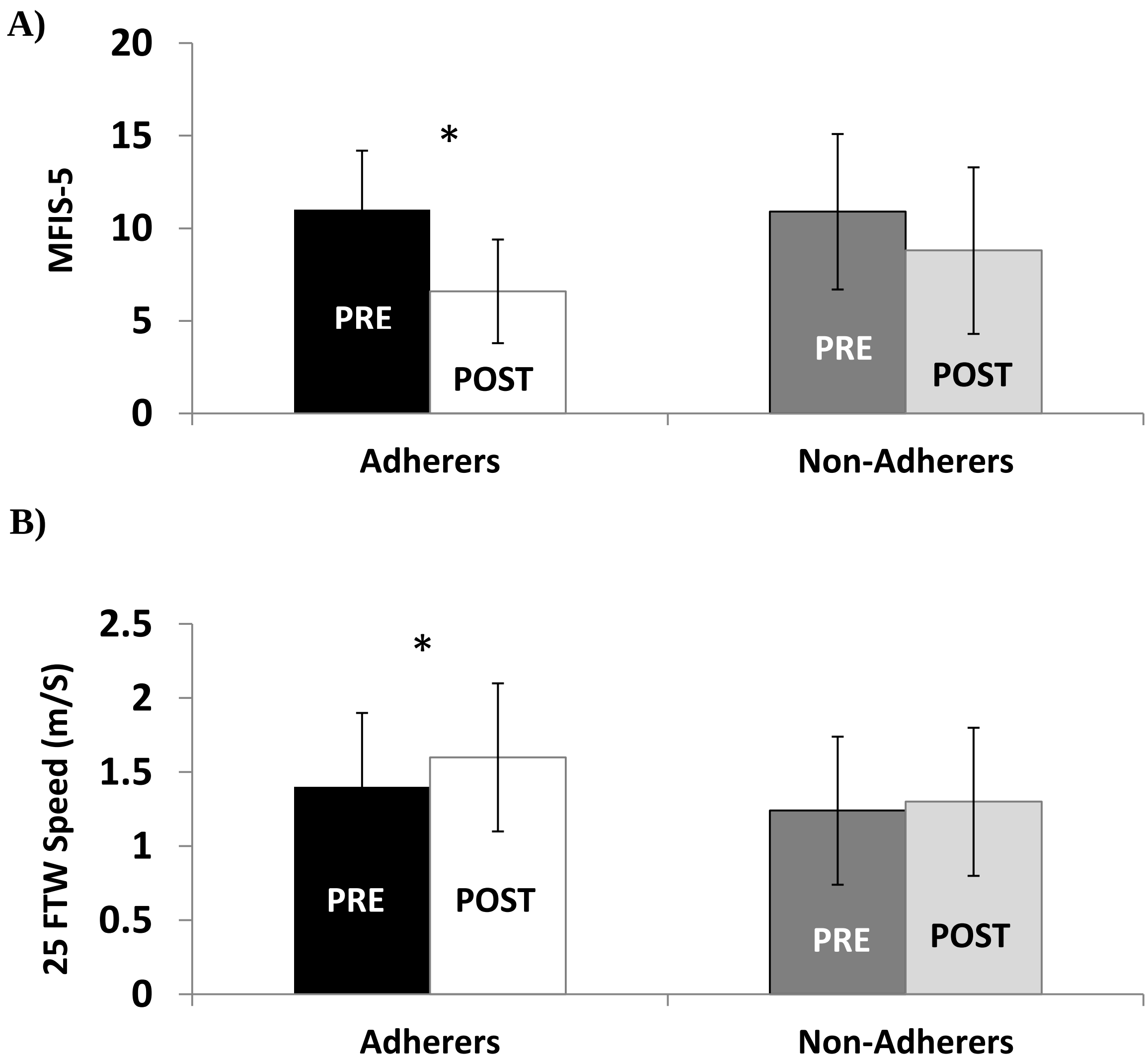


Figure 3.4. Changes in Fatigue **A)** and Changes in Mobility **B)** in Adherers versus Non-Adherers after Following PAGs for 16 Weeks.

* significant group by time interaction $p < 0.05$

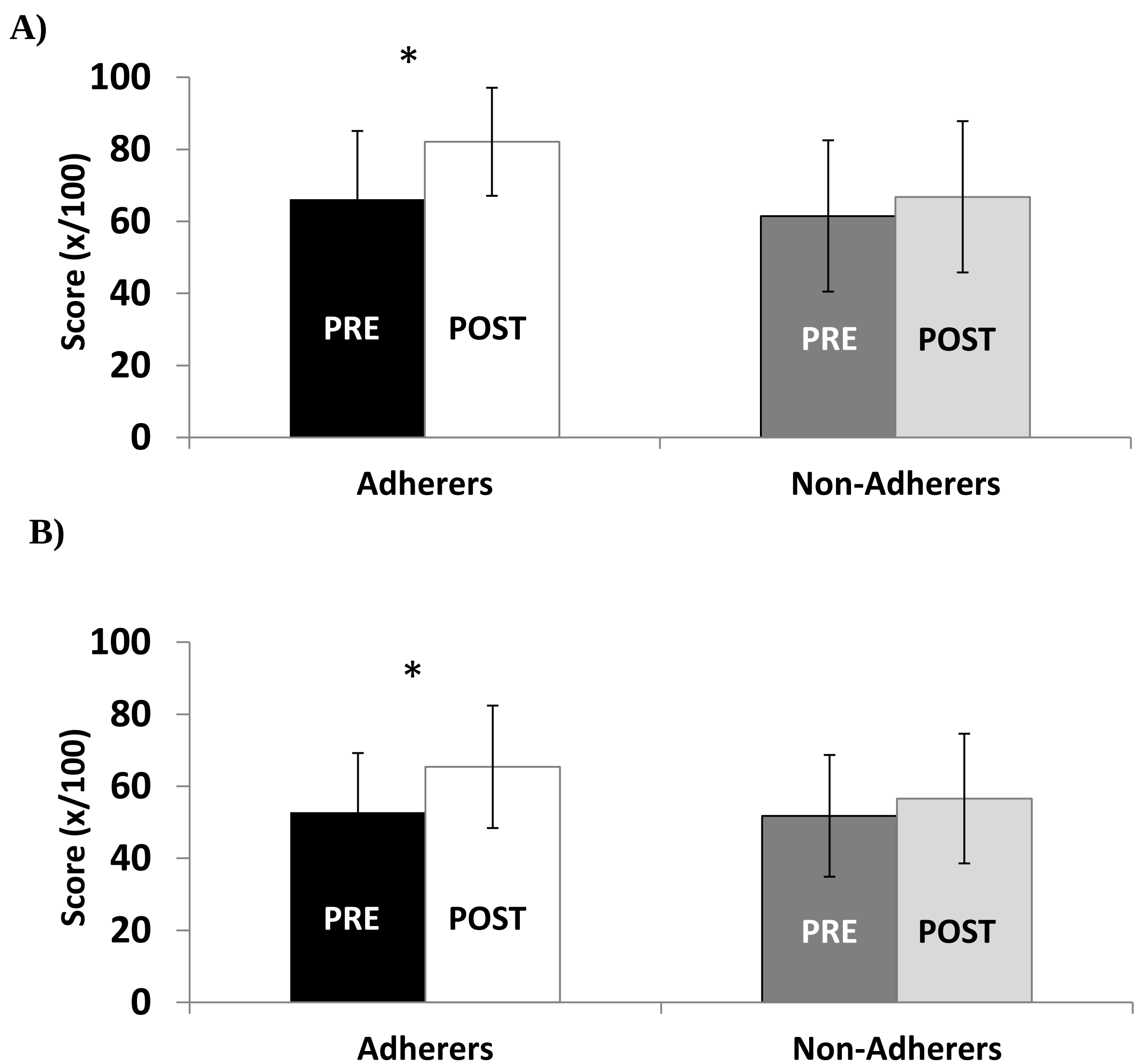


Figure 3.5. Changes in Mental **A)** and Physical **B)** Health-Related Quality of Life in Adherers versus Non-Adherers after Following PAGs for 16 Weeks.

* significant group by time interaction $p < 0.05$

Figure 3.6. Satisfaction with PAGs in 77 Adults Living with MS

CHAPTER 4:

The Effect of 16 Weeks of Exercise on Cognition in Adults with Multiple Sclerosis

Karissa L. Canning, MSc & Audrey L. Hicks, PhD

Abstract

Objectives: Cognitive dysfunction is a common and debilitating symptom in the MS population. It is currently unclear whether exercise has a role to play to improve cognition in adults with MS, but there is some evidence of its potential benefit. The purpose of this study was to determine if following the physical activity guidelines (PAGs) for people with MS for 16 weeks results in significant improvements in executive functioning, processing speed and memory.

Methods: Twenty-seven people living with MS completed the Symbol Digits Modalities Test (SDMT) and the Rey Auditory Verbal Learning Test (RAVLT) at baseline and after 16 weeks of following the PAGs. Twenty people completed the Flanker Task at baseline and post-testing. Participants were categorized as PAG "Adherers" or "Non-Adherers" based on achieving the PAGs recommendations for at least 75 % of the time over the 16 week period.

Results: Participants who adhered to PAGs significantly improved aerobic capacity, muscle strength, fatigue symptoms, and mental health-related quality of life ($p < 0.05$). Compared to Non-Adherers, Adherers significantly improved processing speed, assessed by the SDMT, after following PAGs for 16 weeks ($p = 0.013$). In addition, Adherers significantly improved memory, as measured by the number of words recalled from the RAVLT, after following PAGs for 16 weeks compared to the Non-Adherers. There were no significant differences in reaction time or accuracy for the Flanker task between the 2 groups after the 16 week period ($p > 0.05$).

Conclusion: This is the first trial to report significant, positive changes in cognition after exercise. Following the PAGs for 16 weeks significantly improves processing speed and memory in adults living with MS.

Introduction

The degenerative nature of Multiple Sclerosis (MS) is associated with a wide range of debilitating symptoms including cognitive decline (1). Cognitive function has been previously reported to be correlated with the amount of overall brain damage, including lesions in the brain and brain atrophy, as a result of the MS (2). Approximately 40-65% of people living with MS experience some degree of cognitive dysfunction affecting cognitive processing speeds, executive functioning, learning and memory (3, 4). In turn, this cognitive dysfunction is associated with poor quality of life, depression and dependant living (5). There is no treatment (e.g., pharmaceutical or other) for cognitive impairments in people living with MS, however behavioural approaches (e.g., cognitive rehabilitation) have been associated with some improvements in cognition (6).

A positive association between exercise and cognitive function has been demonstrated in both young and healthy populations (7). It is currently unclear whether exercise has a role to play in improving cognition in adults with MS but there is some evidence of its potential benefit. A pilot study on 2 individuals with MS who were randomized to either stretching or aerobic exercise revealed an increase in both hippocampal volume and brain connectivity in the person who performed 3 months of twice-weekly aerobic exercise (8). Only 3 RCTs have been completed to date evaluating the effect of exercise on cognition in people living with MS and none of these trials have provided scientific evidence to prove exercise improves cognition (1, 9, 10). However, results from these trials do seem promising as trends for beneficial effects have been demonstrated and associations between exercise and cognitive function have been made.

Though these studies were RCTs, the authors did not solely look at the effect of exercise on cognition, rather cognition was an additional secondary outcome. The effect of exercise on fitness was the primary outcome with cognition being the secondary outcome in all 3 trials. However, there are a few cross-sectional studies that have reported positive relationships between aerobic fitness and cognition. (1, 11, 12). Briken et al. (2014) concluded that aerobic training is feasible and could be beneficial in the MS population as authors reported correlations associated between improvements in aerobic fitness and measures of cognition (1) while Sandroff et al. (2017) provided novel evidence of an association between cardiorespiratory fitness and processing speed in people living with MS (11). In addition, treadmill walking has been associated with improvements in executive control (12). The literature pertaining to the effects of exercise and its effect on cognition in the MS population are primarily associative in nature and almost solely focused on aerobic exercise. To date, no RCT has been conducted evaluating the effect of both aerobic and resistance exercise on brain function and cognition in the MS population.

The purpose of this study was to determine the effect of exercise on overall brain function and cognition in a sample of adults living with MS. We wanted to determine if following the Physical Activity Guidelines (PAGs) for adults with MS for 16 weeks would result in improvements in cognitive processing speeds, executive function, learning and memory. We also wanted to determine if following only the aerobic portion of the PAGs would elicit stronger improvements in cognitive function. The results from this study will add to the limited literature available today on cognition and exercise in the

MS population and can potentially provide new evidence supporting the beneficial effect exercise on cognition in people living with MS. Further, this will be the first trial evaluating the effectiveness of the PAGs for people with MS on improving cognition.

Methods

Participants

Participants were recruited as a subset from an ongoing RCT examining implementation of the PAGS for adults with MS at McMaster University in Hamilton, ON. Participants were included in the trial if they had an EDSS between 1 and 7, between the ages of 18 to 64 years and had clearance by a physician to participate in exercise. Participants were excluded from participation if they were physically active (≥ 2 times per week) or if they had any other serious medical condition that would impair ability to participate in strength or aerobic training. All participants were ambulatory in the upper limbs and able to write. All participants provided written informed consent and all procedures were approved and conducted in accordance with the ethical guidelines of the Hamilton Integrated Research Ethics Board. Established procedures and details about the primary RCT are explained in Chapter 2 (13).

Demographics and Questionnaires

A variety of questionnaires assessing demographics, quality of life and fatigue symptoms were completed at baseline and post-testing. Quality of life was assessed using the MS Quality of Life 54 (MSQOL-54) (14). Fatigue was assessed using the Modified Fatigue Impact Scale (MFIS-5) (15).

Assessing Cognitive Function

All cognitive tests were performed at baseline and after the 16 week intervention period before cardiorespiratory and muscular fitness testing.

i) Symbol Digits Modalities Test

To measure processing speed, participants were required to complete the Symbol Digits Modalities Test (SDMT) (16). The number of correct symbols participants achieved in 90 s (raw score) were reported. Participants were provided with different versions of the test at both time points.

ii) Rey Auditory Verbal Learning Test

To measure memory, participants completed the Rey Auditory Verbal Learning Test (RAVLT) (17). Different versions of the RAVLT were given at baseline and post-testing to reduce learning effect. A list consisting of 15 words were read aloud across 5 learning trials by an examiner with the participant repeating back as many words as they remembered after each presenting trial. The 5 learning trials were followed by a second list of different words used to distract the participant from remembering the first list. The participant was then asked to recall the words from the first list, immediate recall. A half an hour later, participants were asked to recall all the words from the first list. Participants were presented with a word recognition list where they were instructed to indicate which words they thought appeared on the first list. For the purposes of this study, only the sum of trials 1-5 was used in analyses.

iii) Flanker Task

To measure executive functioning participants were required to complete the Flanker task (18) at baseline and after the 16 week training period. The Flanker task was completed on a computer and required participants to inhibit task-irrelevant information in order to correctly respond to a centrally presented target stimulus, represented by an arrow on the screen. Stimuli were presented as congruent, all arrows facing the same direction to the left or the right (e.g.., <<<<< or >>>>>) or incongruent, center arrow facing a different direction than outside arrows (e.g., <<><< or >><>>). Participants indicated the direction of the stimulus by pressing either the “<” key or the “>” key on the computer. Periods of rest were interspersed between the randomized trials. Reaction time (ms) and percent accuracy were reported for the congruent and incongruent trials separately.

Cardiorespiratory Fitness & Muscle Strength

To measure cardiorespiratory fitness, a progressive VO_2 peak test to peak oxygen consumption or volitional exhaustion on an arm cycle ergometer (Lode B.V., Groningen, Netherlands) was completed by participants. One repetition maximum (1RM) strength testing was completed on a multi-station (wheelchair accessible) weight training system (Equalizer Multi-Station, Equalizer Exercise Machines, Red Deer, AB, Canada), unilateral wall pulleys (Endorphin Pulleys, Patterson Medical Supply, Mississauga, ON, Canada) and using the HUR leg extension/flexion machine (HUR Health & Fitness

Canada INC, Canada). Established procedures for evaluating aerobic fitness and muscle strength can be found in **Chapter 3**.

Mobility

Mobility was assessed using the 25 ft walk test. Participants were instructed to walk 25 ft as quickly as possible but safely and in their usual manner and they repeated this twice. An average of the walking speeds for the 2 attempts was calculated (7.62 m divided by the time it took to complete the test (m/s).

Adherence to PAGs

Adherence to the PAG recommendations was assessed over 16 weeks by weekly physical activity logs. Participants were emailed weekly logs for aerobic and strengthening exercises. If participants were unable to access internet, hard copies of 16 weeks of logs were provided at baseline testing and participants were instructed to return the physical activity logs at post-testing. Detailed information about type, duration and intensity of exercise was provided by participants in the logs for analysis of adherence. Adherence to the PAGs was calculated as the number of weeks (calculated as a percentage) participants achieved both the aerobic and resistance exercise recommendations over the 16 week period. Participants were categorized as “Adherers” if they met the PAGs recommendations for 12 out of 16 weeks, or had a calculated adherence rate of at least 75 %. Participants who did not meet this criterion were categorized as “Non-Adherers.” Secondary analyses were conducted on participants who adhered to only the aerobic component of the PAGs versus those who did not adhere. The same cut-off of 75 % was used to classify an Aerobic PAG Adherer and Non-Adherer.

Data Analyses

Continuous variables are reported as means and standard deviations and categorical variables are presented as frequencies and prevalence values**.** Differences in baseline values and % change values were compared using independent samples t-tests. Pearson R correlational analyses were used to assess relationships between variables. Analysis of covariance (ANCOVA) was used to analyze effects of group on SDMT and RAVLT tests while adjusting for baseline measurement of respective outcome variables. Other covariates included age, sex, EDSS, education and test version number. Repeated measures ANCOVA was used to analyze Flanker task results with between subjects factor: group (Adherers vs. Non-Adherers), within subjects factor: congruency (Congruent vs. Incongruent) and pre-trial outcome scores as covariate. Covariates included in analysis consisted of age, sex, EDSS and education. Additional analyses using the above aforementioned statistics were conducted using PAG Adherers vs. Non-Adherers for the aerobic component *only*. Outliers for RT and accuracy variables were removed using the formula Q1-1.5*IQR, Q3+1.5*IQR for upper and lower bound limits. All statistical analyses were performed using IBM SPSS Statistics v24. Statistical significance was set at alpha < 0.05.

Results

Participant Characteristics

Twenty-seven participants were recruited to participate (age 48.8 ± 11.5 years, EDSS score 3.3 ± 1.6, 13.1 ± 10.4 years living with MS). Demographic and clinical characteristics are presented in **Table 4.1.** Eight people were categorized as PAG Adherers and 19 people were categorized as PAG Non-Adherers. **Table 4.2** presents pre and post fitness and health outcomes in Adherers versus Non-Adherers.

Total PAG Adherers vs. Non-Adherers

A significant, moderate correlation was observed between % change in SDMT scores and % change in RAVLT scores ($r = 0.451$, $p = 0.018$). **Table 4.3** presents the mean pre- and post-test scores for all cognitive tests in PAG Adherers versus Non-Adherers. After controlling for pre-test SDMT scores, age, sex, education, EDSS and pre- & post-test version numbers, there was a statistically significant difference ($p = 0.015$) between Adherers and Non-Adherers on post-test SDMT scores. After controlling for pre-test RAVLT scores, age, sex, education, EDSS and pre- & post-test version numbers, there was a significant difference between Adherers and Non-Adherers ($p = 0.038$) in RAVLT scores at post-testing. The Adherers significantly improved scores on the SDMT and number of words recalled on the RAVLT compared to the Non-Adherers after 16 weeks of following both the aerobic and resistance portions of the PAGs for adults with MS.

Twenty participants completed the Flanker task and were analyzed for executive function outcomes. Seven people were categorized as PAG Adherers and 13 people were categorized as PAG Non-Adherers. After removing outliers from analyses, 5 people remained in the Adherer group and 13 people in the Non-Adherer group. With respect to RT measured by the Flanker task, there was a main effect for congruency ($p = 0.024$) such that participants in both groups performed better on congruent trials compared to incongruent trials. For accuracy, the main effect for congruency closely approached significance ($p = 0.055$). There were no significant differences between PAG Adherers and Non-Adherers in RT or accuracy at post-testing ($p > 0.05$).

Aerobic Component Only PAG Adherers vs. Non-Adherers

Additional analyses categorizing Adherers versus Non-Adherers for the aerobic portion only of the PAGs were conducted. Fifteen people were categorized as PAG Adherers and 12 people were categorized as Non-Adherers of the aerobic component of PAGs. Percent change in VO_2 peak ($p = 0.002$), SDMT scores ($p = 0.041$) and RAVLT scores ($p < 0.0001$) were significantly greater in the PAG Adherers of aerobic component compared to Non-Adherers. Strong, positive correlations were observed between adherence to the aerobic portion of guidelines and % change in VO_2 peak ($r = 0.662$, $p < 0.0001$) and % change in RAVLT scores ($r = 0.463$, $p = 0.015$).

Processing Speed

Figure 4.1 depicts pre- and post-test SDMT scores in Adherers and Non-Adherers for the aerobic portion of the PAGs. After controlling for pre-test SDMT scores, age, sex, education, EDSS and pre- & post-test version numbers, there was a statistically significant difference in SDMT post-test scores between participants who adhered to the aerobic portion of the PAGs compared to those who did not adhere such that Adherers significantly improved SDMT scores after 16 weeks of aerobic training compared to Non-Adherers (p = 0.008).

Memory

Figure 4.2 depicts pre- and post-test RAVLT scores in Adherers and Non-Adherers for the aerobic portion of the PAGs. After controlling for pre-test RAVLT scores, age, sex, education, EDSS and pre- & post-test version numbers, there was a statistically significant difference between participants who adhered to the aerobic portion of the PAGs compared to those who did not adhere, such that Adherers significantly improved in the number of words for Trials 1-5 after 16 weeks of aerobic training compared to Non-Adherers (p = 0.002).

Executive Functioning

Of the twenty participants who completed the Flanker test, six people were categorized as Non-Adherers and 12 people were categorized as Adherers of the aerobic component of the PAGs.

Reaction Time

There was a main effect for congruency (p = 0.012) such that participants in both groups performed better on congruent trials compared to incongruent trials. RT was slower for the incongruent trials (pre & post) compared to the congruent trials in the Adherers and the Non-Adherers. Adherers and Non-Adherers of the aerobic component of the PAGs had similar reductions in RTs at post-testing ($p > 0.05$) **(Figure 4.3A & B).**

Accuracy

The main effect for congruency closely approached significance ($p = 0.051$). As expected, both Adherers and Non-Adherers seemed to perform with more accuracy for the congruent trials compared to the incongruent trials. No significant differences between Adherers and Non-Adherers were observed in the accuracy of hitting the correct incongruent and congruent targets after 16 weeks of adhering to the aerobic component of the PAGs ($p > 0.05$) **(Figure 4.4A & B).**

Discussion

This is the first trial to determine the effects of exercise on processing speed, memory and executive function in the MS population. The results from this study demonstrate that 16 weeks of following the PAGs for adults with MS significantly improves processing speed and memory but has no apparent effect on executive functioning in individuals living with MS. The small sample size was problematic, but perhaps the Flanker task may not be sensitive enough to capture changes in executive functioning after exercise in the MS population. Larger controlled trials are clearly warranted, but the results from this study are extremely promising.

About 40-65% of adults living with MS have decreased cognitive function compared to healthy populations which ultimately affects quality of life and independence (1). This was evident in our sample of adults living with MS, as their scores on the SDMT and RAVLT were considerably lower than what would be seen in the general population (22-24, 28, 29).   Literature suggests that regular exercise can improve cognitive function in general healthy populations as well as older adults (7). The evidence surrounding the MS population is not so robust. There have only been 3 RCTs conducted thus far determining the effect of exercise on cognition in people living with MS. Two of the 3 RCTs reported no significant of an exercise intervention on cognitive function in people living with MS (9, 10). Oken et al., 2004 conducted a 6-month parallel group, RCT where subjects were randomized to either the yoga, exercise class or wait-list control group arms. The authors concluded that participants who completed 6 months of yoga or exercise class improved fatigue however no relative improvement in cognitive function was observed (9). Romberg et al., 2005 conducted a RCT where participants exercised for 6 months following a progressive exercise program. Authors concluded that 6 months of long term exercise does not improve auditory information cognitive processing speed (10). The third RCT reported correlations of improvements in cardiorespiratory fitness and verbal memory but not processing speed or executive function (1). In this trial, participants were randomized to either arm ergometry, rowing or a bicycle ergometry exercise intervention for 8-10 weeks. Since all of the studies that have evaluated the relationship between exercise and cognition in the MS population have used aerobic exercise modalities, we felt it important to conduct our secondary analysis of categorizing participants as Adherers or Non-Adherers of only the aerobic component of PAGs to determine the specific effects of aerobic exercise on cognition. It is noteworthy that the results from analyzing those participants who adhered specifically to the aerobic portion of the PAGs were no different from those from participants who adhered to full PAG recommendations for both aerobic and resistance exercise.

Studies that have evaluated cognitive dysfunction in the MS population suggest that individuals living with MS have reduced processing speeds (3, 20). Most studies that have evaluated exercise and its effect on processing speed in adults with MS thus far have been associative in nature. Sandroff and colleagues reported a significant association between cardiorespiratory fitness and processing speed, such that higher levels of cardiorespiratory fitness were associated with faster processing speeds (11). The most common tool to assess processing speed in both research and clinical settings is the use of the SDMT, which is used as a part of the cognitive impairment screening examination

(21). The baseline scores for the SDMT in this current study were quite low compared to previous research in MS, other populations and healthy norms (22–24), suggesting that this sample of adults living with MS had impaired processing speeds. This was demonstrated by the low average SDMT scores (46) for our sample of adults with MS. For individuals with MS, an average score of ~48 is expected compared to approximately 58 for healthy controls (22-24). Approximately 52 % of our sample of adults with MS scored quite low on the SDMT which is similar to the percentage of individuals in the MS population who have cognitive impairment. To our knowledge, this is the first study to report significant improvements in information processing speed after 16 weeks of twice-weekly exercise in adults with MS. Further, this study confirms that the dose of exercise recommended in the PAGs for adults with MS is strong enough to elicit improvements in processing speed.

Difficulties with long and short-term memory are common amongst patients with MS (25). The RAVLT has been previously used in the MS population to assess working memory and learning with the sum of trials 1-5 commonly reported (25–27). Briken et al. (2014) reported that exercise was associated with better performance in verbal learning and delayed memory (1), and that the better performances were associated with greater cardiorespiratory fitness. The baseline scores for the RAVLT in this current study (37) were similar compared with previous research in MS, however lower than the average score of 42 commonly reported in healthy controls (28, 29). Similar to the SDMT results, approximately 52 % of our sample had lower than average scores on the RAVLT. This is the first study to determine the effects of both aerobic and resistance exercise on learning and memory. The results from this trial suggest that 16 weeks of following the PAGs for adults with MS (with at least 75% adherence) results in significant improvements in working memory and learning.

Executive functions consist of many different aspects of cognition such as planning, working memory, inhibition, the ability to sustain attention and problem-solving (30). Executive dysfunction, as measured by the Flanker task, has been reported in the MS population (11, 12, 28, 29). Sandroff et al. (2015) reported general improvements in pre- to post-testing RTs, but not accuracy, after exercise in a small sample of adults living with MS (12). The authors suggested that treadmill walking may be the most effective at improving executive control compared to other modalities of aerobic exercise, due to greater attentional control and efficiency in processing conflicting information in environment while walking and taxing executive control processes (12). The results from the current study did not find any significant change in performance on the Flanker task after the 16 week intervention, with no differences in performance between those who adhered or did not adhere to the PAG recommendations. It is possible, however, that despite our limited sample size, the Flanker task may not be sensitive enough to capture changes in executive function after exercise in people living with MS.

In conclusion, the results from this study provide exciting and novel evidence that following the PAGs for adults living with MS results in improvements in processing speed, memory and learning. Our results suggest that the aerobic component of the PAG recommendations is likely most important for inducing these positive changes in cognitive function, but given the positive benefits of participating in strength training exercise and the overall palatability of the PAG recommendations, there is no reason to only focus on the aerobic component when prescribing exercise to adults with MS. Larger trials are warranted to determine the potential benefits of exercise on executive function in the MS population.

References

1. Briken S, Gold SM, Patra S, et al. Effects of exercise on fitness and cognition in progressive MS: a randomized , controlled pilot trial. Mult. Scler. J. 2014;20:382–390.

2. Fisher E, Rudick RA., Simon JH, et al. Eight-year follow-up study of brain atrophy in patients with MS. Neurology 2002;59:1412–1420.

3. Guimarães J, Sá MJ. Cognitive dysfunction in Multiple Sclerosis. Front. Neurol. 2012;3:1–8.

4. Benedict RHB, Holtzer R, Motl RW, et al. Upper and Lower Extremity Motor Function and Cognitive Impairment in Multiple Sclerosis. J. Int. Neuropsychol. Soc. 2011;17:643–653.

5. Benedict RHB, Wahlig E, Bakshi R, et al. Predicting quality of life in multiple sclerosis: accounting for physical disability, fatigue, cognition, mood disorder, personality, and behavior change. J. Neurol. Sci. 2005;231:29–34.

6. Rilo O, Peña J, Ojeda N, et al. Integrative group-based cognitive rehabilitation efficacy in multiple sclerosis : a randomized clinical trial. Disabil. Rehabil. 2016:1–9.

7. Smith PJ, Blumenthal JA, Hoffman BM, et al. Aerobic exercise and neurocognitive performance: a meta-analytic review of randomized controlled trials. Psychosom. Med. 2010;72:239–52.

8. Leavitt VM, Cirnigliaro C, Cohen A, et al. Aerobic exercise increases hippocampal volume and improves memory in multiple sclerosis: Preliminary findings. Neurocase 2013;00:1–3.

9. Oken BS, Kishiyama S, Zajdel D, et al. Randomized controlled trial of yoga and exercise in multiple sclerosis. Neurology 2004;62:2058–2064.

10. Romberg A, Virtanen A, Ruutiainen J. Long-term exercise improves functional impairment but not quality of life in multiple sclerosis. J. Neurol. 2005;252:839–845.

11. Sandroff BM, Motl RW, Deluca J. The Influence of Cognitive Impairment on the Fitness – Cognition Relationship in MS. Med. Sci. Sport. Exerc. 2017.

12. Sandroff BM, Hillman CH, Benedict RHB, Motl RW. Acute effects of walking, cycling, and yoga exercise on cognition in persons with relapsing- remitting multiple sclerosis without impaired cognitive processing speed. J. Clin. Exp. Neuropsychol. 2015;37:209–219.

13. Canning KL, Hicks AL. Factors that predict adherence to physical activity guidelines for adults with Multiple Sclerosis: A randomzied controlled trial. 2017.

14. Vickrey BG, Hays RD, Harooni R, et al. A Health-Related Quality of Life Measure for Multiple Sclerosis. Qual. life Res. 1995;4:187–206.

15. Fisk JD, Ritvo PG, Ross L, et al. Measuring the Functional Impact of Fatigue : Initial Validation of the Fatigue Impact Scale. Clin. Infect. Dis. 1994;18:S79–S83.

16. Smith A. Symbol Digit Modalities Test (SDMT). Manual (Revised). Los Angeles; 1982.

17. Schmidt M. Rey Auditory Verbal Learning Test. A handbook. (Western Psychological Services, editor.). Los Angeles; 1996.

18. Eriksen BA, Eriksen CW. Effects of noise letters upon the identification of a target letter in a nonsearch task. Percept. Psychophys. 1974;16:143–149.

19. Sandroff BM, Pilutti LA, Benedict RHB, Motl RW. Association Between Physical Fitness and Cognitive Function in Multiple Sclerosis: Does Disability Status Matter ? Neurorehabil. Neural Repair 2015;29:214–223.

20. Forn C, Belenguer A, Parcet-Ibars M, Ávila C. Information-processing speed is the primary deficit underlying the poor performance of multiple sclerosis patients in the Paced Auditory Serial Addition Test (PASAT). J. Clin. Exp. Neuropsychol. 2008;30:789–796.

21. Aupperle RL, Beatty WW, Shelton F, Gontkovsky ST. Three screening batteries to detect cognitive impairment in multiple sclerosis. Mult. Scler. 2002;8:382–389.

22. Benedict RHB, Drake AS, Irwin LN, et al. Benchmarks of meaningful impairment on the MSFC and BICAMS. Mult. Scler. J. 2016:1–9.

23. Kiely KM, Butterworth P, Watson N, Wooden M. The Symbol Digit Modalities Test: Normative Data from a Large Nationally Representative Sample of Australians. Arch. Clin. Neuropsychol. 2014;29:767–775.

24. Sheridan LK, Fitzgerald HE, Adams KM, et al. Normative Symbol Digit Modalities Test performance in a Community-based Sample. Arch. Clin. Neuropsychol. 2006;21:23–28.

25. Moriarty DM, Blackshaw AJ, Talbot PR, et al. Memory Dysfunction in Multiple Sclerosis Corresponds to Juxtacortical Lesion Load on Fast Fluid-Attenuated Inversion-Recovery MR Images. Am. J. Neurodiology 1999;20:1956–1962.

26. Bodling AM, Denney DR, Lynch SG. Individual Variability in Speed of Information Processing : An Index of Cognitive Impairment in Multiple Sclerosis. Neuropsychology 2012;26:357–367.

27. Kizlaitiene R, Kaubrys G, Giedraitiene N, Ramanauskas N, Dementaviciene J. Composite Marker of Cognitive Dysfunction and Brain Atrophy is Highly Accurate in Discriminating Between Relapsing-Remitting and Secondary Progressive Multiple Sclerosis. Med. Sci. Monit. 2017;23:588–597.

28. Patanella AK, Zinno M, Quaranta D, et al. Correlations between peripheral blood mononuclear cell production of BDNF, TNF-alpha, IL-6, IL-10 and cognitive performances in Multiple Sclerosis patients. J. Neurosci. 2010;88:1106–1112.

29. Minden S, Moes E, Orav J, Kaplan E, Reich P. Memory impairment in multiple sclerosis. J. Clin. Exp. Neuropsychol. 1990;12:566–86.

30. Chan RCK, Shum D, Toulopoulou T, Chen EYH. Assessment of executive functions: Review of instruments and identification of critical issues. Arch. Clin. Neuropsychol. 2008;23:201–216.

31. Prakash R, Snook E, Lewis J, Motl R, Kramer A. Cognitive Impairments in Relapising-Remitting Multiple Sclerosis: A Meta-Analysis. Mult. Scler. 2008;14:1250–1261.

32. Sandroff BM, Balto JM, Klaren RE, Sommer SK, Deluca J, Motl RW. Systematically developed pilot randomized controlled trial of exercise and cognition in persons with multiple sclerosis. Neurocase 2016;22:443–450.

Table 4.1. Participant Characteristics of 27 Adults Living with MS Categorized by PAG Adherers (n = 8) and Non-Adherers (n = 19)

Characteristic	**Mean ± SD**	
	Adherers (n = 8)	**Non-Adherers (n = 19)**
Age (y)	49.6 ± 10.8	48.5 ± 11.7
Female (N, %)	5 (62)	11 (58)
EDSS	3.6 ± 1.5	3.2 ± 1.6
Time Since Diagnosis (y)	13.4 ± 11.4	12.3 ± 8.0
RRMS (N, %)	5 (62)	10 (53)
Education		
High school	4 (50)	6 (32)
University (or similar)	1 (12)	10 (53)
Post-Graduate (or similar)	3 (37)	3 (16)
Pre VO_2 Peak (ml/kg/min)	11.8 ± 5.3	13.7 ± 13.6
Adherence (%)	83.6 ± 9.4*	30.3 ± 23.4

PAG, Physical Activity Guidelines
REF, Referral Group
CON, Control Group
EDSS, Expanded Disability Status Score
RRMS, Relapsing-Remitting MS
* $p < 0.05$, significantly different from Non-Adherers

Table 4.2. Fitness, Fatigue, Mobility & Health-Related Quality of Life Outcomes Pre and Post 16 Weeks of Following Physical Activity Guidelines for Adults with MS

	Adherers (n = 8)			Non-Adherers (n = 19)		
	Pre	**Post**	**% Change**	**Pre**	**Post**	**% Change**
Outcome						
VO_2 (ml/kg/min)	11.82 ± 5.30	17.01 ± 6.78	43.91*	13.95 ± 3.69	13.75 ± 4.13	-1.43
Composite Muscle Strength	18.12 ± 6.19	21.04 ± 6.73	16.11*	15.91 ± 5.41	16.93 ± 6.4	6.41
25FTW (m/s)	1.27 ± 0.43	1.39 ± 0.50	9.45	1.22 ± 0.43	1.20 ± 0.55	-1.64
MFIS-5	11.63 ± 4.31	8.38 ± 4.81	-27.94*	11.47 ± 2.72	10.42 ± 3.08	-9.15
MHQOL	65.10 ± 14.03	75.23 ± 6.89	15.56*	61.58 ± 19.40	60.86 ± 19.42	-1.17
PHQOL	51.92 ± 9.92	59.61 ± 13.38	14.81	48.32 ± 10.83	53.40 ± 12.08	10.51

VO_2, Peak Oxygen Consumption
25FTW, 25 Foot Walk Test
MFIS-5, Modified Fatigue Impact Scale 5 Factor Questionnaire
MHQOL, Mental Health-Related Quality of Life
PHQOL, Physical Health-Related Quality of life
* indicates a significant group by time interaction ($p < 0.05$)

Table 4.3. Mean Values for Cognitive Outcomes at Pre- and Post-Test Across Total PAG Adherers versus Non-Adherers

	Adherers n = 8 (5)		**Non-Adherers** n = 19 (13)		**ANCOVA**
	Pre	**Post**	**Pre**	**Post**	**P-Value**
Outcome					
SDMT	41.63 ± 19.81	53.88 ± 21.50	48.11 ± 11.75	48.42 ± 12.02	p = 0.013
RAVLT	35.25 ± 2.19	49.25 ± 11.82	40.63 ± 10.79	43.68 ± 11.24	p = 0.038
Congruent RT (m/s)	614.44 ± 137.76	545.92 ± 98.34	788.89 ± 372.90	707.89 ± 351.73	* p = 0.805
Incongruent RT (m/s)	817.81 ± 269.83	670.96 ± 125.79	987.27 ± 484.25	892.69 ± 532.41	
Congruent Accuracy (%)	94.67 ± 6.70	97.75 ± 2.15	97.57 ± 2.10	98.52 ± 1.99	* p = 0.740
Incongruent Accuracy (%)	83.18 ± 19.94	83.89 ± 9.06	88.26 ± 14.12	90.30 ± 16.71	

N = ( ), Different sample size for Flanker task
PAG, Physical Activity Guidelines
ANCOVA, Analysis of Covariance
SDMT, Symbol Digits Modalities Test
RAVLT, Rey Auditory Verbal Learning Test
RT, Reaction Time
* Main effect of congruency, $p < 0.05$

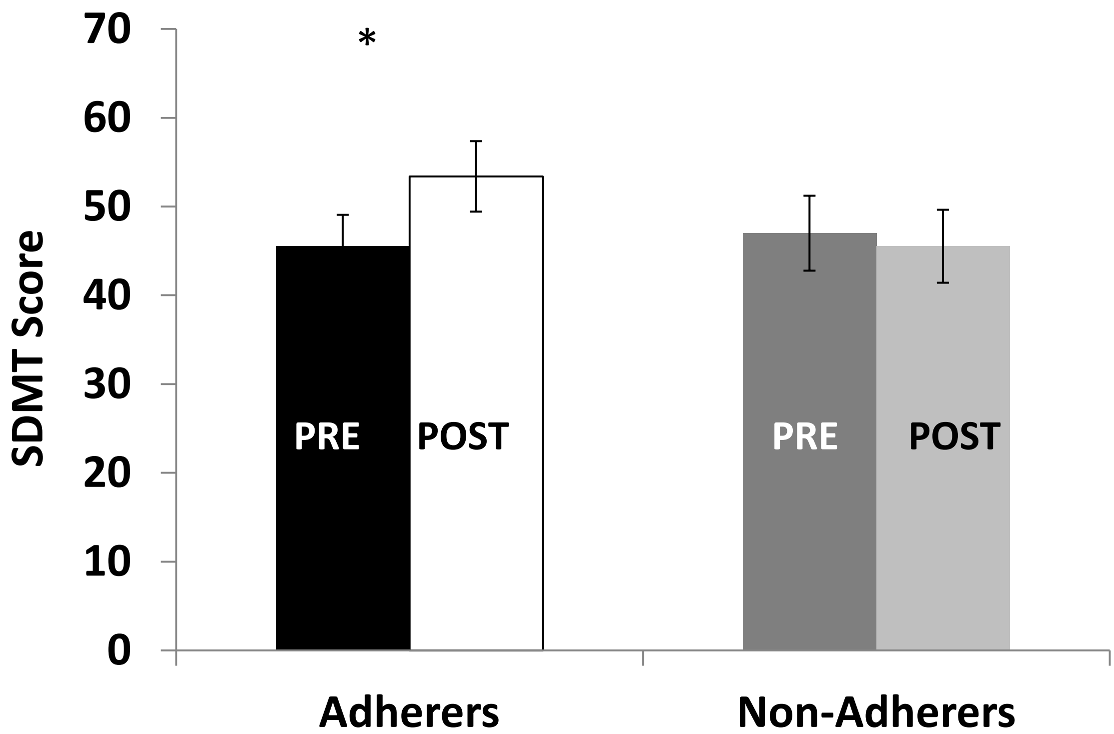


Figure 4.1. Processing speed measured by Symbol Digits Modalities Test at Pre- and Post- Test in Adherers and Non-Adherers for the Aerobic Portion of PAGs

SDMT, Symbol Digits Modalities Test

* significantly different from Non-Adherers $p < 0.05$

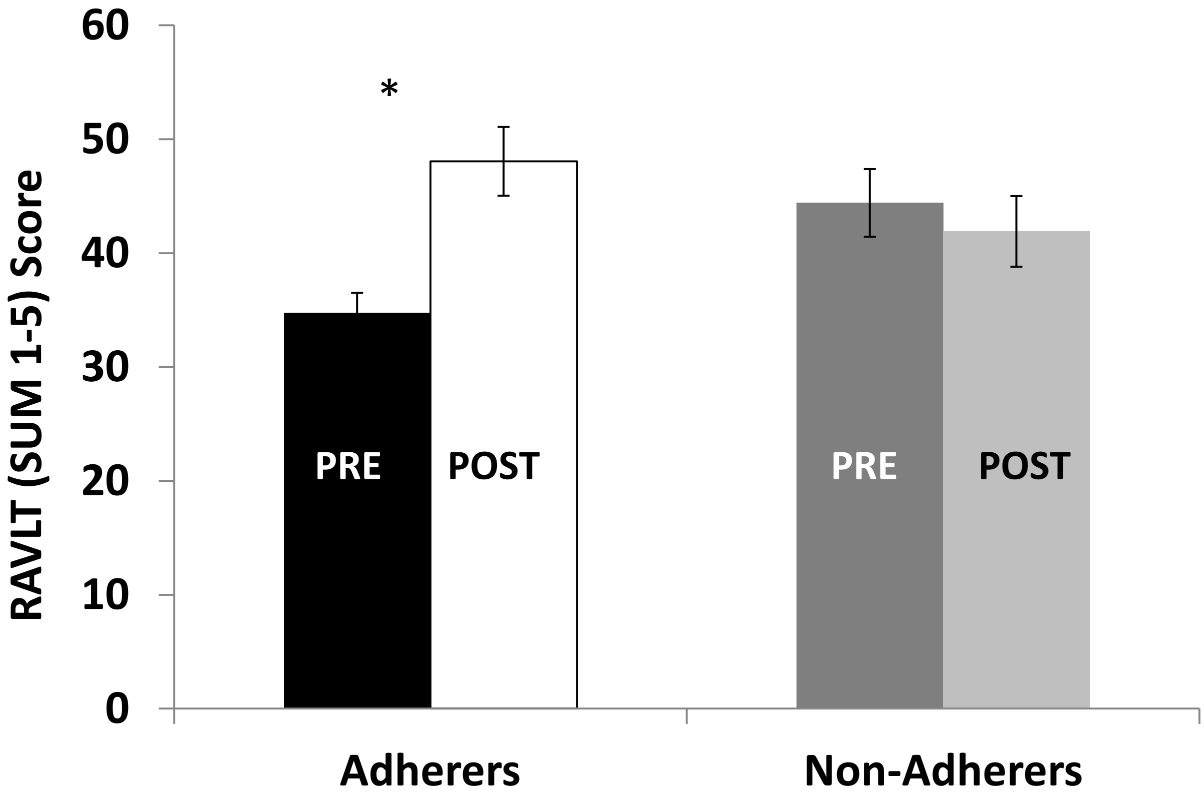


Figure 4.2. Memory measured by Rey Auditory Verbal Learning Test at Pre- and Post- Test in Adherers and Non-Adherers for the Aerobic Portion of PAGs

RAVLT, Rey Auditory Verbal Learning Test

* significantly different from Non-Adherers $p < 0.05$

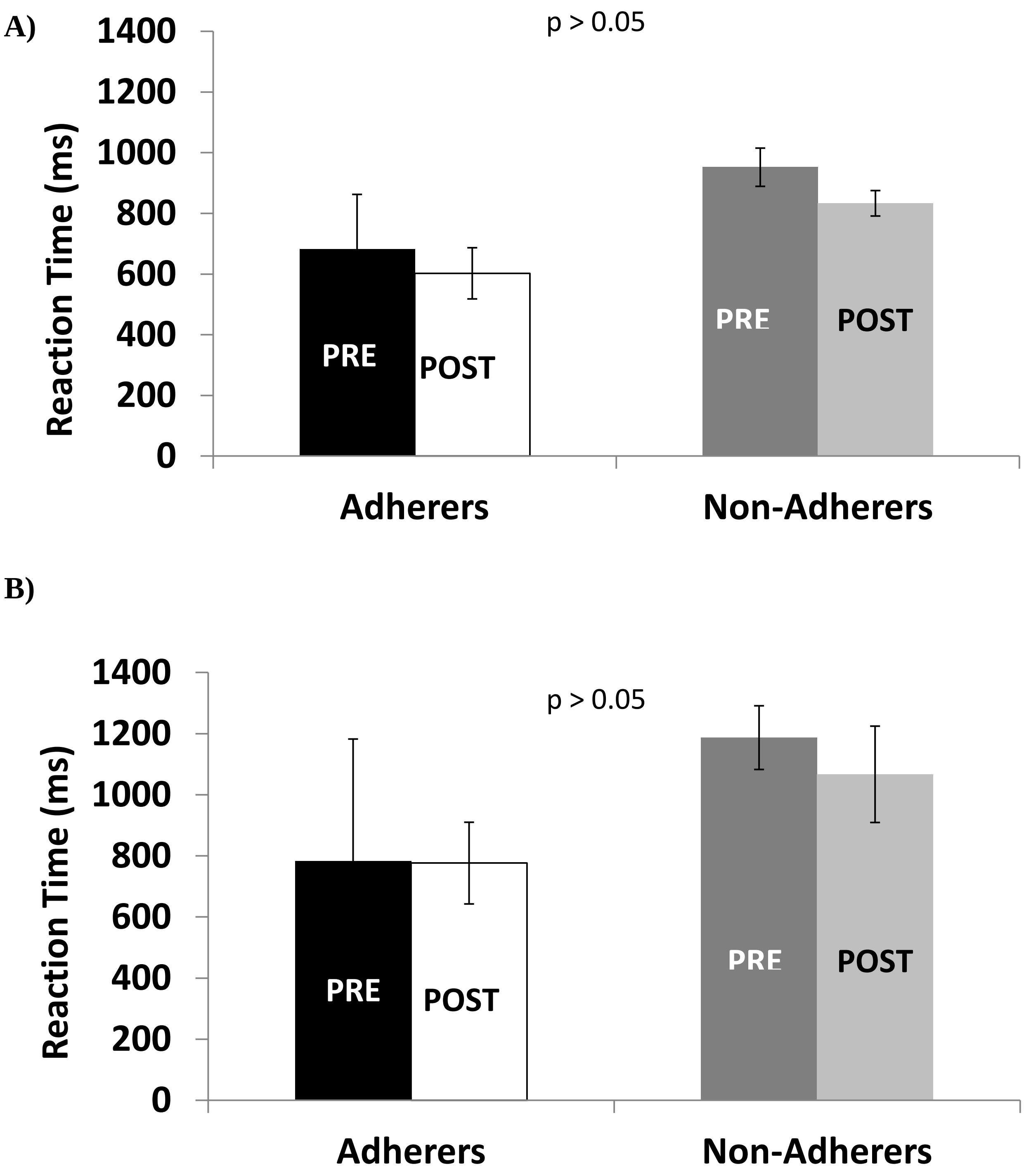
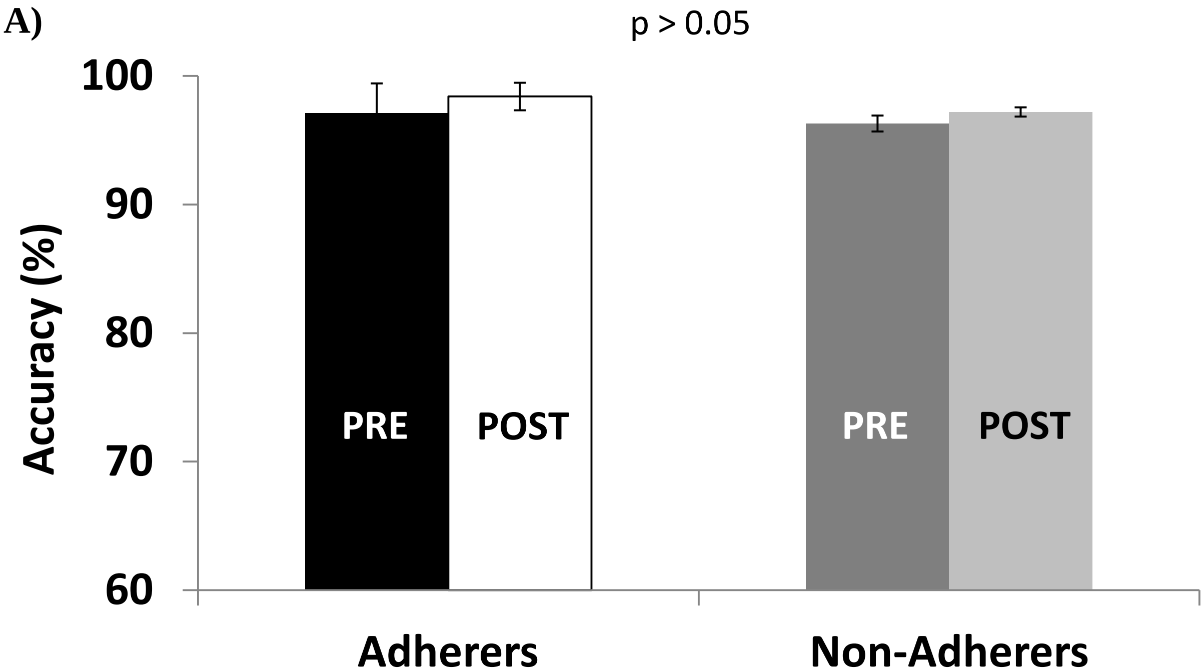


Figure 4.3. Reaction Time assessed using the Flanker Task at Pre- and Post-Test in Adherers and Non-Adherers for the Aerobic Portion of PAGs for Congruent Trials **A)** and Incongruent Trials **B)**

A)



B)

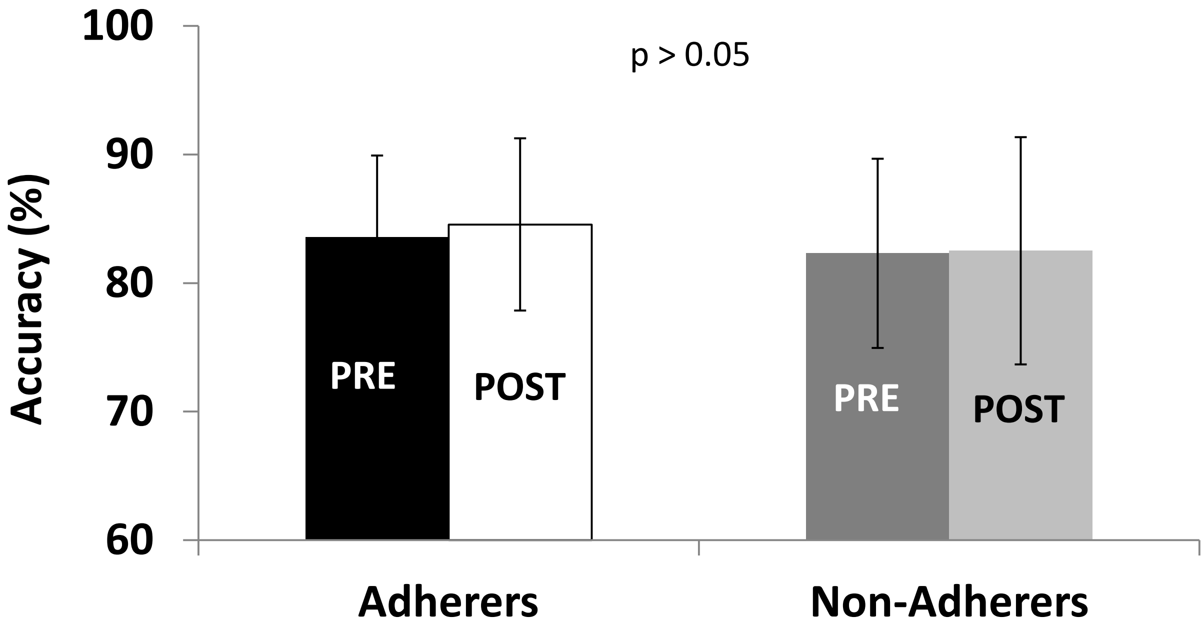


Figure 4.4. Accuracy assessed using the Flanker Task at Pre- and Post-Test in Adherers and Non-Adherers for the Aerobic Portion of PAGs for Congruent Trials **A)** and Incongruent Trials **B)**

CHAPTER 5:

DISCUSSION

The purpose of this dissertation was to explore the association between physical activity and health in the MS population. Taken together, these series of studies present convincing scientific evidence of the magnitude of benefit physical activity participation can have on overall health in the MS population. Previous literature demonstrates the importance of physical activity participation in the MS population and its potential as a disease modifying therapy (1, 2). The results from this dissertation emphasize the important role of physicians to aid with adherence to physical activity programs and have identified additional factors that may predict adherence to the guidelines. The results also confirm the validity of the physical activity guidelines (PAGs) for people living with MS (3) with respect to improving fitness, fatigue symptoms, mobility and health-related quality of life. Lastly, the results from this dissertation provide novel evidence of the beneficial effect of exercise on cognition in the MS population.

For the purposes of this dissertation, the terms *exercise* and *physical activity* were used interchangeably however it is noted that the two are related but different concepts. Physical activity is defined as *"any bodily movement produced by skeletal muscles that results in energy expenditure"* whereas exercise is *"planned, structured and repetitive and has a final or an intermediate objective- the improvement or maintenance of physical fitness"*(4). The studies in this dissertation focused on the evidence-based PAGs for adults with MS. Participants recruited to participate in all 3 studies were asked to engage in the recommended dose of physical activity in the guidelines for 16 weeks. The studies used in the systematic review by Latimer-Cheung et al. (2013) to inform guideline develop used studies that evaluated *exercise* training on outcomes of fitness, mobility, fatigue and QOL (2). Consequently, the similar use of terms exercise and physical activity was justified. One important difference to highlight in this dissertation compared to other exercise intervention trials, was that participants were not expected to complete their exercise in a lab setting. The decision to participate in our exercise program (or another one in the community) was made by the participants and the participants had to pay the standard membership fees to join the community-based exercise program at McMaster University or a different program in the community. This makes the results of these studies more ecologically valid.

The focus of the first study of this dissertation was on implementation of the PAGs; we wanted to determine the effect of physician referral on adherence in a community setting as well as identifying what other factors may also predict adherence to the PAGs. The results from this study revealed that direct referral to physical activity from a physician is twice as effective as simply providing information about physical activity with respect to adhering to the PAG recommendations in people with MS. Further, the results revealed that a high self-efficacy for exercise at baseline may be an additional predictor to PAG adherence, which supports previous work in the MS population (5–7). The strong effect of a physician referral has been demonstrated in the cardiac rehabilitation literature (8, 9), but never before in the MS population. Previous work has provided compelling evidence supporting the importance of exercise (10, 11) but has never tested the effect of physician referral on exercise adherence in the MS population. Clearly these results have demonstrated that a model of referral to a defined program is more effective than simply providing information about the PAGs to adults with MS. There is a dire need for the development of specialized community-based exercise programs for the MS population, and our results should empower physicians to start prescribing exercise to their patients as regularly as they prescribe pharmaceutical disease-modifying medications.

The PAGs for adults living with MS were released in 2012. Since then no study has been conducted evaluating the effectiveness of the guidelines on improving fitness and overall health. The purpose of the second study of this dissertation was to validate the PAGs for people with MS within a community-based intervention, and to affirm that following the PAGs for 16 weeks would result in improvements in fitness, mobility, fatigue symptoms and QOL. The first challenge faced in this second study was determining a criterion to define PAG adherence. Physical activity adherence is a grey area in the literature, as no gold standard defining what constitutes physical activity adherence exists. While most studies calculate adherence rates as the number of sessions attended over the total number of sessions for the duration of the study (12), the definition of what constitutes "adherence" to a physical activity intervention is variable. When initially designing this RCT, we fully expected that we could test the validity of the PAGs by comparing our various secondary outcomes between the referral (REF) and control (CON) groups. However, once the data started coming in we realized that although PAG adherence rates were significantly higher in the REF group as a whole, the adherence rates were quite variable in both groups (0%-100%). Determining differences in fitness and health outcomes after the 16 week study period between the REF and CON groups did not make sense as there were some individuals in the REF group who did not adhere to the PAGs and there were some individuals in the CON group who actually adhered quite well. This led to us deciding upon an adherence rate that would distinguish an “Adherer” from a “Non-Adherer”, and after reviewing the limited literature on physical activity adherence in the MS population we arrived at a threshold of 75% adherence to define an Adherer in this dissertation. The results from the second study confirm the validity of the PAGs for people with MS for improving health as significant improvements in fitness, mobility, fatigue symptoms and QOL were observed in individuals who adhered to the PAGs for at least 12 out of the 16 weeks. These results provide convincing evidence of the broad range of benefits of regular exercise in the MS population.

When determining who was an “Adherer” versus a “Non-Adherer” we were committed to the specific recommendations in the PAGs; as they are a weekly prescription, our formula for calculating adherence depended on participants attaining the precise guideline recommendations in any given week (e.g. 30 minutes of moderate intensity aerobic activity AND complete strength training for major muscle groups two days per week). There were instances where on some weeks, some individuals completed the dose of exercise in the guidelines in only one session (as opposed to two per week), they may have been just shy of completing 30min each session, or they completed just the aerobic portion or just the resistance portion of the guidelines. Based on our criterion, we couldn’t count those weeks as “adherence”, despite these individuals still experiencing positive benefits from participating in physical activity. The individual response graphs in

Chapter 3 (Figures 1B and 2B) nicely illustrate not only individual variability, but also a dose-response effect to the exercise stimulus.

An additional point to make in regards to adhering to the PAGs is the fact that it is important that people adhere to both the aerobic and resistance components of the guidelines. The literature surrounding cognitive function and exercise in MS may suggest that aerobic exercise contributes most to the benefits observed in cognition. However, it is important to understand that doing both aerobic and resistance exercise is beneficial for many reasons, and the benefits can transfer into other areas. For example, resistance training strengthens muscles in the legs which translates into improvements in mobility while aerobic exercise improves cardiorespiratory fitness which may translate into greater energy reserves leading to reductions in fatigue.

Physical activity participation is one way people living with MS can take control of aspects of their disease and improve disease related symptoms and overall QOL. All of the pharmaceutical options currently available to slow progression of the disease are available for RRMS patients only (13) except for one very recent new drug, "*Ocrelizumab*", approved by the FDA for primary progressive MS (yet to be approved in Canada) (14). Physical activity, however, is available to all, and although most exercise intervention studies have been performed on people with mild-to-moderate MS, there are also positive studies on the benefits of exercise in cases of severe MS (15–17). There is no pharmaceutical therapy to date that can lead to the multi-faceted benefits on overall health and function that exercise has been shown to elicit, so it is critical that health care professionals and neurologists start prescribing exercise to their patients with MS.

The purpose of the third study was to determine the effect of exercise on overall brain function and cognition in a sample of adults living with MS. We wanted to determine if following the PAGs for adults with MS for 16 weeks would result in improvements in cognitive processing speeds, executive function, and memory. This is the first trial to report significant, positive changes in cognition after exercise in adults with MS. Specifically, following the PAGs for 16 weeks led to significant improvements in processing speed and memory. The baseline scores for cognitive processing speed, assessed by the SDMT and memory, assessed by the RAVLT were quite low in comparison to other general populations (18–21), but were in agreement with previous research (22–24). It is important to point out that the improvement in SDMT scores in the Adherers after the 16 week period gave them a group mean that matched the scores in a healthy population (20). These results are very exciting and extremely promising, but larger controlled trials are definitely warranted.

The studies within this dissertation confirm that the PAGs for adults with MS are effective at improving fitness and other aspects of health including cognition in the MS population in a community setting. Having these disease-specific guidelines not only makes it easy for health professionals to prescribe exercise, they can also now be used to inform researchers in determining the durations, intensities and modes of exercise to use in their exercise trials. One of the limitations of the literature on exercise in the MS population has been the heterogeneity in dose, intensity and duration of exercise, making comparisons of results across studies sometimes difficult. We now have evidence to show that the PAG recommendations on the dose, type and intensity of exercise are an effective minimum threshold to produce significant benefits across a wide range of fitness and health-related outcomes.

It is important to highlight that the PAGs for adults with MS are considerably different from the PAGs for the general population. The PAGs for the general population recommend that for health benefits adults should engage in at least 150 minutes per week of moderate- to vigorous-intensity aerobic activity (25). This is in contrast to the recommendations in the PAGs for adults with MS which suggest only 60 minutes per week of moderate intensity physical activity. For those individuals living with MS who have not thought about exercise as part of their weekly regimen, the MS guidelines are far more feasible to incorporate into one's weekly routine and are certainly less daunting compared to the 150 minutes recommended for the general population.

In terms of next steps, it will be important to determine if the PAGs can aid people who are older or who have more progressed forms of MS improve aspects of fitness and health. Unfortunately, very little is known about how exercise training affects individuals with more advanced forms of MS (10). Further, future studies should explore the recommendations in the PAGs and determine if a weekly cumulative prescription of "60 minutes per week" of moderate intensity aerobic activity is better than the current recommendations in the guidelines, specifying 30 minutes of moderate aerobic activity on "two days per week." Other future directions include determining specific physiological mechanisms behind the effect of exercise and how exercise might modulate MS-related symptoms and disease progression. One proposed mechanism to explain how exercise might improve MS-related symptoms (e.g., cognitive dysfunction and fatigue) and potentially impact disease pathogenesis is related to inflammation. MS is a complex, inflammatory disease that is characterized by an overactive immune system. It is noteworthy that previous research in animal models of MS suggest that exercise can reduce the inflammatory response by inhibiting the release of proinflammatory cytokines and increasing the release of anti-inflammatory cytokines (26).

In conclusion, this dissertation has explored and evaluated the PAGs for adults with MS from a variety of perspectives, ranging from implementation to adherence to effectiveness. The data demonstrate the value of physician referral to improve PAG adherence, as well as highlighting the importance of exercise self-efficacy as an additional predictor of adherence. It has been demonstrated that following the PAGs for adults with MS for 16 weeks results in improved fitness, fatigue symptoms, mobility and health-related QOL. Lastly, it has been found that cognitive processing speed and memory are significantly improved after 16 weeks of following the PAGs for adults with MS. Overall, the results from this dissertation are extremely promising and highlight the importance of physical activity to improve aspects of health, fitness and function in this population.

References

1. Dalgas U, Stenager E, Ingemann-Hansen T. Multiple sclerosis and physical exercise: recommendations for the application of resistance-, endurance- and combined training. Mult Scler. 2008;14:35–53.

2. Latimer-Cheung AE, Pilutti LA, Hicks AL, et al. Effects of exercise training on fitness, mobility, fatigue, and health-related quality of life among adults with multiple sclerosis: a systematic review to inform guideline development. Arch Phys Med Rehabil. 2013;94:1800–1828.

3. Canadian Society for Exercise Physiology. Physical Activity Guidelines for Adults with MS. [Internet] 2012. [Cited 2017 May 4] Available from: http://www.csep.ca/CMFiles/Guidelines/specialpops/CSEP_MS_PAGuidelines_adults_en.pdf

4. Caspersen CJ, Powell KE, Christenson GM. Physical Activity, Exercise, and Physical Fitness: Definitions and Distinctions for Health-Related Research. Public Health Rep. 1985;100:126–131.

5. Motl RW, Mcauley E, Doerksen S, Hu L, Morris KS. Preliminary evidence that self-efficacy predicts physical activity in multiple sclerosis. Int J Rehabil Res. 2009;32:260–263.

6. Nickel D, Spink K, Andersen M, Knox K. Attributions and self-efficacy for physical activity in multiple sclerosis. Psychol Health Med. 2014;19:433–441.

7. Plow MA, Resnik L, Allen SM. Exploring physical activity behaviour of persons with multiple sclerosis: a qualitative pilot study. Disabil Rehabil. 2009;31:1652–65.

8. Jackson L, Leclerc J, Erskine Y, Linden W. Getting the most out of cardiac rehabilitation: a review of referral and adherence predictors. Heart 2005;91:10–15.

9. Dunn SL, Dunn LM, Buursma MP, et al. Home- and Hospital- Based Cardiac Rehabilitation Exercise: The Important Role of Physician Recommendation. West J Nurs Res. 2017;39:214–233.

10. Motl RW, Sandroff BM. Benefits of Exercise Training in Multiple Sclerosis. Curr Neurol Neurosci Rep 2015;15:1–9.

11. Mayo NE, Bayley M, Duquette P, Lapierre Y, Anderson R, Bartlett S. The role of exercise in modifying outcomes for people with multiple sclerosis: a randomized trial. BMC Neurol. 2013;13:69.

12. Heesen C, Bruce J, Gearing R, et al. Adherence to behavioural interventions in multiple sclerosis: Follow-up meeting report (AD@MS-2). Mult Scler J. 2015;1:1–4.

13. Boissy AR, Cohen JA. Multiple sclerosis symptom management. Exepert Rev Neurother. 2007;7:1213–1222.

14. MS Society of Canada. Breaking News: OCREVUS™ (ocrelizumab) is the first drug approved by the FDA for primary progressive MS. [Internet] 2017. [cited 2017 Jun15] Available at: https://mssociety.ca/research-news/article/fda-grants-breakthrough-therapy-designation-for-genentechs-experimental-therapy-ocrelizumab-in-primary-progressive-ms.

15. Pilutti LA, Lelli DA, Paulseth JE, et al. Effects of 12 weeks of supported treadmill training on functional ability and quality of life in progressive multiple sclerosis: a pilot study. Arch Phys Med Rehabil. 2011;92:31–6.

16. Briken S, Gold SM, Patra S, et al. Effects of exercise on fitness and cognition in progressive MS: a randomized , controlled pilot trial. Mult Scler J. 2014;20:382–390.

17. Pilutti LA, Paulseth JE, Dove C, Jiang S, Rathbone MP, Hicks AL. Exercise Training in Progressive Multiple Sclerosis. Int J MS Care 2016;18:221–229.

18. Benedict RHB, Drake AS, Irwin LN, et al. Benchmarks of meaningful impairment on the MSFC and BICAMS. Mult Scler J. 2016:1–9.

19. Kiely KM, Butterworth P, Watson N, Wooden M. The Symbol Digit Modalities Test: Normative Data from a Large Nationally Representative Sample of Australians. Arch Clin Neuropsychol. 2014;29:767–775.

20. Sheridan LK, Fitzgerald HE, Adams KM, et al. Normative Symbol Digit Modalities Test performance in a Community-based Sample. Arch Clin Neuropsychol. 2006;21:23–28.

21. Vakil E, Greenstein Y, Blachstein H. Normative Data for Composite Scores for Children and Adults Derived From the Rey Auditory Verbal Learning Test. Clin Neuropsychol. 2010;24:662–677.

22. Guimarães J, Sá MJ. Cognitive dysfunction in Multiple Sclerosis. Front Neurol. 2012;3:1–8.

23. Forn C, Belenguer A, Parcet-Ibars M, Ávila C. Information-processing speed is the primary deficit underlying the poor performance of multiple sclerosis patients in the Paced Auditory Serial Addition Test (PASAT). J Clin Exp Neuropsychol. 2008;30:789–796.

24. Moriarty DM, Blackshaw AJ, Talbot PR, et al. Memory Dysfunction in Multiple Sclerosis Corresponds to Juxtacortical Lesion Load on Fast Fluid-Attenuated Inversion-Recovery MR Images. Am J Neurodiology 1999;20:1956–1962.

25. Canadian Society for Exercise Physiology. Canadian Physical Activity Guidelines. [Internet] 2011. [Cited 2017 Jun 15] Available at: http://www.csep.ca/CMFiles/Guidelines/CSEP-InfoSheets-adults-ENG.pdf.

26. Souza PS, Gonçalves ED, Pedroso GS, et al. Physical Exercise Attenuates Experimental Autoimmune Encephalomyelitis by Inhibiting Peripheral Immune Response and Blood-Brain Barrier Disruption. Mol Neurobiol. 2016. DOI: 10.1007/s12035-016-0014-0

APPENDICES

A. Chapter 2

A.1 Exercise Referral Form

Exercise Referral Form

Patient's Name:______________________________
Date:________________

HEALTH CARE PROFESSIONAL'S RECOMMENDATION

Commit to improving your health by adhering to the new physical activity guidelines for people with MS. To achieve important fitness benefits, be sure to perform at least:
○ 30 minutes of moderate intensity aerobic activity twice per week
AND
○ Strength training exercises for major muscle groups twice per week

You are being referred to a community-based exercise program at McMaster University.

Signature: ________________________

For more information about the program at McMaster University please contact: Olga Skarina
E-mail: cr_pams@mcmaster.ca
Phone Number: 905-525-9140 Ext. 20527

Clearance for Participation in Physical Activity

(To be completed by health care professional)

1. Type of MS: ____________________________
2. Date of Diagnosis: __________________________
3. Medical Conditions that may affect exercise tolerance (ie. Cardiovascular, metabolic, infection, lung, CNS, blood, musculoskeletal) :
4. Medications (indicate any exercise-related precautions):
5. Based on a current review of the health status of the above pers I recommend:
   - ❑ Unrestricted Physical Activity
   - ❑ Progressive Physical Activity,

     with avoidance of__________________
     ____

     with inclusion of____________________

Health care professional's name: ____________________________
Address: ____________________________
Telephone: ____________________________
Fax: ____________________________
Signature: ____________________________

A.2 Self-Efficacy for Exercise Questionnaire

Self-efficacy for Exercise

Instructions
We are interested in your opinions about being able to follow the new physical activity guidelines for people with multiple sclerosis over the next four months.

Outcome expectations
I think that following the physical activity guidelines in the next four months will…

	Strongly Disagree						Strongly Agree
increase my mobility	1	2	3	4	5	6	7
interfere with my disease recovery	1	2	3	4	5	6	7
increase the pain I am experiencing	1	2	3	4	5	6	7
make my activities of daily living (e.g. getting dressed, housework) easier to perform	1	2	3	4	5	6	7
increase my energy level	1	2	3	4	5	6	7
prevent secondary health conditions (e.g. cardiovascular disease)	1	2	3	4	5	6	7
increase my self-esteem	1	2	3	4	5	6	7
increase my confidence in social situations	1	2	3	4	5	6	7
be very risky	1	2	3	4	5	6	7
be very dangerous	1	2	3	4	5	6	7

Self-efficacy beliefs

In the next four months, how confident are you that you can complete aerobic exercise

	Not at all confident						Completely confident
2x/week	1	2	3	4	5	6	7
20 minutes	1	2	3	4	5	6	7
At a mild intensity	1	2	3	4	5	6	7
At a moderate intensity	1	2	3	4	5	6	7

How confident are you that you can…

	Not at all confident						Completely confident
Complete the exercise sessions prescribed for you	1	2	3	4	5	6	7
Meet your target intensity during your exercise sessions	1	2	3	4	5	6	7

The next few questions ask about STRENGTHENING activities. These are activities that work your muscles, such as lifting weights and using exercise bands.

How confident are you that you can…

In the next four months, how confident are you that you can complete strengthening exercise

	Not at all confident						Completely confident
2x/week	1	2	3	4	5	6	7
3 sets	1	2	3	4	5	6	7
8-10 repetitions	1	2	3	4	5	6	7
70-80% of the maximum weight you can lift	1	2	3	4	5	6	7
Complete the exercise sessions prescribed for you	1	2	3	4	5	6	7

How confident are you that you can complete your exercise program regularly over the next…

	Not at all confident						Completely confident
1 month	1	2	3	4	5	6	7
2 months	1	2	3	4	5	6	7
4 months	1	2	3	4	5	6	7
6 months	1	2	3	4	5	6	7
1 year	1	2	3	4	5	6	7

A.3 Physical Activity Log

PHYSICAL ACTIVITY LOG

WEEK:
AEROBIC ACTIVITY

DAY	TYPE OF ACTIVITY	DURATION	INTENSITY
Example	- Arm cycle - NuStep -Walk	30 minutes 20 minutes 30 minutes	Moderate Vigorous Moderate
MONDAY			
TUESDAY			
WEDNESDAY			
THURSDAY			
FRIDAY			
SATURDAY			
SUNDAY			

Light Intensity: easy; you aren't really sweating and breathing is normal; **Moderate Intensity:** somewhat hard; you start to sweat a little, breathing becomes a little harder and you can carry on a conversation but not sing; **Vigorous Intensity:** hard; you are sweating, out of breath and you can only talk in short phrases

STRENGTH TRAINING ACTIVITY

DAY	MUSCLE GROUP	SETS	REPS	WEIGHT/ RESISTANCE	INTENSITY
Example	-Shoulders -Biceps -Chest	3 3 2	12 10 12	5 lbs 15 lbs Blue resistance band	Light Moderate Moderate
MONDAY					
TUESDAY					
WEDNESDAY					
THURSDAY					
FRIDAY					
SATURDAY					
SUNDAY					

B. Chapter 3

B.1 Satisfaction with Physical Activity Guidelines Questionnaire

Participant ID:____________ Interviewer:______________ Date:_______________

Satisfaction with Physical Activity Guidelines

Considering the exercise program you have been completing over the last 4 months, please rate the following statements:

	Strongly Disagree						Strongly Agree
The exercise program was easy to fit into my schedule	1	2	3	4	5	6	7
The exercise program was appropriate for my ability	1	2	3	4	5	6	7
I was able to complete the exercises without any additional pain or discomfort	1	2	3	4	5	6	7
I was able to complete each exercise session in a reasonable amount of time	1	2	3	4	5	6	7
Overall, I enjoyed the exercise program	1	2	3	4	5	6	7
	1	2	3	4	5	6	7

The next few questions ask about the AEROBIC exercise. This includes the exercise that you did that increased your heart rate and breathing such as arm biking, NuStep, and the vita glide.

	Strongly Disagree						Strongly Agree
The time of each exercise session was easy for me to complete	1	2	3	4	5	6	7
The intensity was appropriate	1	2	3	4	5	6	7
The types of exercise I performed were appropriate for my ability	1	2	3	4	5	6	7
I enjoyed the types of exercise that I completed	1	2	3	4	5	6	7
The exercise program improved my physical fitness	1	2	3	4	5	6	7
	1	2	3	4	5	6	7

The next few questions ask about STRENGTHENING activities. These are activities that work your muscles, such as lifting weights and using the pullies.

I enjoyed the strengthening exercises that I completed

	Strongly Disagree						Strongly Agree
The number of exercises I did was appropriate	1	2	3	4	5	6	7
The amount of weight I lifted was appropriate	1	2	3	4	5	6	7
The types of exercises I performed were appropriate for my ability	1	2	3	4	5	6	7
The number of repetitions of each exercise was suitable	1	2	3	4	5	6	7
The exercise program increased my strength	1	2	3	4	5	6	7
	1	2	3	4	5	6	7