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PHYSICAL FITNESS AND CARDIOVASCULAR FUNCTION IN MULTIPLE SCLEROSIS

BY

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THESIS

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Abstract

Multiple sclerosis (MS) is an immune-mediated neurodegenerative disease that affects the central nervous system. Cardiovascular function (CV) has been shown to be impaired in persons with MS which can lead to the development of comorbidities that can promote disability progression. Cardiorespiratory fitness (CRF) and, to a lesser extent, muscular fitness (MF) have been shown to improve CV function in healthy populations. This thesis examined the relationships between CRF, MF, and exercise presented by randomized controlled trials via meta-analysis. Then, the relationships between CRF, MF, and CV function in persons with MS was determined in order to determine targets for therapy that might improve CV function. Results suggest exercise training improved CRF and MF in RCTs of exercise training examining CRF and MF outcomes. Further, the results of this cross-sectional study indicate significant relationships exist between CRF, MF and CV function in persons with MS. These studies support the potential to improve physiological fitness through exercise training as a possible means to improve CV function in persons with MS. This might be accomplished through exercise training interventions involving aerobic and/or resistance exercise.

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Chapter 1

Review of the literature

1.1 Introduction and background

Multiple sclerosis (MS) is an immune-mediated neurodegenerative disease that affects the central nervous system (CNS) and can eventually cause disability. MS has prevalence of about 58 of every 100,000 persons in the U.S. Current estimates by the National MS Society estimate the total number of persons living in the U.S. with MS to be above 400,000.[1] MS is occurring at a rate of about 200 new cases each week in the U.S. More cases tend to be diagnosed north of the equator, especially in Europe and North America. In the U.S., a difference in diagnoses rates between those who live above the 37th parallel when compared to than those who live below it can be observed. Those who live above the 37th parallel develop MS at a higher rate, approximately 110-140 cases per 100,000 people, while those living below the 37th parallel develop MS at a lower rate, approximately 57-78 cases per 100,000 people. Underdiagnoses of MS has also been suggested, and would result in a lower estimated prevalence. This could be due to the similarities between symptoms of MS symptoms and other neurological diseases such as Alzheimer's and Parkinson's diseases.

There are genetic and environmental risk factors that influence the development of MS. Gender plays a large factor in risk of MS development with 2.3-3.5 women being diagnosed for every one male diagnoses.[2] This is thought to be caused by different expression of genes between men and women, well as differences in the response to environmental factors that could play a role in the etiology of MS. Race is another factor that influences the risk of MS and is also

genetically determined.[3] A higher prevalence for disease occurrence has be proposed to occur in North American descended whites, but this has been contested by other studies suggesting that American blacks have a higher prevalence.[4] Along with these genetic factors, an individual's environment is also largely a predictor for developing MS. Geographical latitude is related to risk of developing MS. The prevalence of the disease is higher in the more northern latitude countries, although an argument could be made that these are largely western countries and have better diagnostic procedures in place. Lower levels of vitamin D have been suggested to be related to risk for MS.[4] The theory of vitamin D's influence on risk of MS relates to exposure to sunlight which is dependent on geographical location. However, MS does not occur at the same rate in geographical areas in the southern hemisphere that receive similar amounts of sunlight as higher locations in the northern hemisphere. Along with sunlight based vitamin D, ingestion of vitamin D has also be proposed as being influential in MS development. Other prominent environmental factors include infection (Epstein barr virus) and smoking. Higher antibody levels for the Epstein-Barr virus have been correlated with increased risk of developing MS. A similar case has been made for increased risk in persons who have been infected with mononucleosis.[3] Although these theories are possible, a causal link between these infections and MS has yet to be determined. Lastly, smoking has been shown to be related to MS risk although again this a correlative relationship. Genetics and environmental factors are two key factors that determine risk of developing MS.

MS is both an inflammatory and neurodegenerative disease affecting the CNS. Although the culmination of these factors initiate a varied pattern of lesion development and subsequent symptom development, progression of the disease eventually follows a similar course toward a neurodegenerative state. Initial stages of the disease involve inflammatory attacks that target

neurons, perhaps due to the development of an anti-myelin antibody that the body has begun to genetically express. These inflammatory attacks lead to histologic trademark damage in the myelin sheath and surrounding oligodendrocytes. The myelin sheath is responsible for expediting the electrical current that travels from neuron to neuron. Oligodendrocytes are responsible for the development of myelin and its repair. The damage in these two structures prevents optimal signal propagation within the CNS. As inflammatory attacks persist, axonal damage becomes seemingly irreversible. Over time, inflammatory episodes lessen and immunoglobulins can be seen, while separated myelin continues to be surrounded and destroyed by immune cells. This state of chronic neuronal injury is seen in those that have usually had MS for a longer period of time.[5]

The pathogenesis of the disease is classified into four types/courses of MS. The most common course is relapsing remitting MS (RRMS), of which 85% are initially diagnosed with. RRMS is characterized by episodic inflammatory attacks that are known as exacerbations or relapses.[6] During these relapses, the patient can be under a great deal of disability. A relapse is defined as a new neurologic symptom lasting for more than 24 hours that has no other explanation.[7] Criteria for relapse involve: (1) Signs of inflammation and demyelination presented through testing or progression of disability; (2) The relapse lasts over 24 hours; (3) The relapse is separated by at least 30 days from a previous relapse; and (4) The relapse is not related to stress, fever or infection. The periods of relapse can have lasting damage on the structure and signaling potential of neurons, as well as functional and symptomatic implications. Remissions are periods between relapses in which symptoms can improve, sometimes completely. These relapses are commonly treated with different steroid treatments which have been shown to decrease the acute impact of relapses.[8] Over time, the course of MS can transition. Most people initially diagnosed

with RRMS will eventually transition to secondary progressive MS (SPMS).[6] SPMS is different from the RRMS because relapses and high inflammation is not as prevalent, but disease progression steadily continues. Two other types/courses of MS also exist. The Primary progressive multiple sclerosis (PPMS) course involves disease progression that is similar to SPMS, but occurs from the onset of the disease.[6] Persons with PPMS have no relapses and have lower basal inflammation that is more common in SPMS. Lesions are also more prevalent within the spinal cord of persons with PPMS as compared to those with RRMS. PPMS involves a steady and continuous increase in disease progression as opposed to the off and on progression seen with RRMS. About 10% of persons with MS have PPMS at disease onset according to the National MS Society. The fourth type of MS is also the least prevalent with only 5% of diagnoses. Progressive-relapsing MS (PRMS) involves a progression similar to PPMS in that a steady disease progression is always occurring, but there are also relapses occurring.[6] Like RRMS and PPMS, PRMS is diagnosed at disease onset.

The general measure of disability in MS is the Expanded Disability Status Scale (EDSS). The EDSS is a scale that ranges from 0 (no disability) to 10 (death) that seeks to identify disability through assessments involving visual, brainstem, pyramidal, cerebellar, sensory, bowel and bladder, and cerebral function as well as ambulation. 0 to 3.0 on the EDSS indicates minimal disability. Patients in this range do not have musculoskeletal impairments, but may have other symptomology that is prevalent. The range of 3.0 to < 6.0 is considered moderate disability. Gait impairment and ambulatory dysfunction occurs in this range, but no assistive device is necessary. The range of 6.0 to 9.5 is considered severe disability. In this range different disability scores are given largely based on the use of ambulatory devices for assistance including unilateral

assistance (6.0), bilateral assistance (6.5), or wheelchair (7.0) with scores >7.0 associated with bed rest.

1.2 Disability and Physical Activity in MS

The accumulation of disability has profound effects on the daily lives of people with MS. Impaired CNS signaling has a direct impact on musculoskeletal function and results in lower activity levels in persons with MS. A cycle of deconditioning begins with the onset of MS leading to physical inactivity and subsequently physiological deconditioning.[9] A relationship exists between deconditioning and disability that accompanies disease progression.[10] Physical inactivity is not only an issue in clinical populations like MS. According to the CDC's 2014 report on physical activity in the U.S., only about 20% of Americans are achieving the 150 minute a week recommendation for moderate aerobic exercise and muscular strengthening guidelines. The implications have been clear as lower levels of physical activity are associated with higher rates of CVD, obesity, metabolic disease, and all-cause mortality. The case is similar in MS. Historically, persons with MS have been told to refrain from too much physical activity (PA) and to be easy on themselves physically. A meta-analysis on PA in MS found that persons with MS participate much less PA than healthy people. In the same study, the authors found persons with MS do not differ in PA levels compared to other clinical populations (chronic fatigue syndrome, chronic obstructive pulmonary disease, cerebral palsy). As with increased risk of CVD and metabolically related disease in the healthy populations, persons with MS can have a similarly increased risk of developing these diseases which can impact their disease.[11,12] PA in MS is also related to type/course of MS. People with PPMS tend to have lower levels of PA when compared to those suffering from RRMS. People with PPMS tend to have more severe

symptoms, a higher disability level overall, less mobility, and are less likely to engage in PA. This can directly interfere with day to day function or participation in physical activity.[13] Even with the consistency of these findings, PA among persons with MS varies from person to person and can be affected by other lifestyle choices.

1.3 Physical Fitness

Cardiorespiratory fitness reflects the body's ability for delivering, extracting, and using oxygen for prolonged endurance exercise and is typically measured as peak aerobic capacity (VO_{2peak}), peak power output (W_p), and anaerobic or lactate threshold (l/mmol). Muscular fitness reflects the body's ability for generating and maintaining muscular force via skeletal muscle contraction and is commonly measured as muscular strength (e.g., peak force) and endurance (e.g., maximum repetitions). Higher rates of fitness have been associated with improved all-cause mortality in non-diseased populations. Specifically, improved physical fitness has been shown to associate with lower rates of death from CVD and cancer.[14] This is a clear indicator that along with regular physical activity, good physical fitness is conducive to a healthy lifestyle and better longevity. When concerning MS, a disease that is associated with low PA, low fitness, and a more sedentary lifestyles physical fitness is often ignored as a component of health, not being seen as a potential factor for improving functionality in MS.

Physical fitness has two main components for the sake of this discussion: cardiorespiratory and muscular. Cardiorespiratory fitness (CRF) reflects the body's ability for delivering, extracting, and utilizing oxygen for endurance exercise and is typically measured as peak aerobic capacity (VO_{2peak}), peak power output (W_p), and anaerobic or lactate threshold (l/mmol).[15] CRF has individually been associated with better overall mortality rates, CVD, metabolic syndrome, diabetes, and cancer in healthy people.[16,14,17,18] Because of its strong

relationship with improved health outcomes, CRF has become an integral component in a multidisciplinary approach to health in medicine. Augmentation of CRF is possible through exercise intervention involving aerobic exercise which can be conducted via many modalities such as running, biking, rowing, swimming, etc. Increases in VO_{2peak} occur even with lower intensity aerobic exercise and continue to increase in a dose-dependent manner with increasing intensity and duration of aerobic exercise.[19] These changes also can result in better insulin sensitivity, decreases in fat mass, and markers of inflammation, and plasma triglycerides.[20,21] Clearly, aerobic exercise has become a well-established medical therapy for many issues especially in chronic disease prevention and treatment.

1.4 Physical Fitness in MS: Muscular Fitness

Muscular fitness (MF) reflects the body's ability for generating and maintaining muscular force via skeletal muscle contraction and is commonly measured as muscular strength (e.g., peak force) and endurance (e.g., maximum repetitions). MF has also been associated with better health outcomes, albeit not as robustly as CRF. MF has been found to be inversely related to all-cause mortality and cancer in men after adjusting for CRF.[22,23] MF has also been shown to be associated with better risk factor analyses for metabolic syndrome, osteoporosis, diabetes, and CVD in healthy people.[24,25,26,27,28,29,30,31,32,33,34]. This means the risk factors, or physiological measures that have been known to increase risk of one of these diseases are found less in persons with improved MF. These findings illustrate the importance of MF in both healthy, older, and clinical populations. Research on the effects of improved MF in these populations through different types of resistance exercise training. Resistance training is defined as the act of repeated voluntary muscle contractions against a resistance greater than those normally encountered in activities of daily living.[35] Through this form of training three main changes affecting

performance can be observed: hypertrophy, strength, and endurance. Hypertrophy refers to changes in morphology in musculature in which muscle fibers grow in diameter. Strength changes are commonly assessed as peak torque and reflect neuromuscular adaptations involving motor recruitment as well as hypertrophy. Endurance refers to the capacity to achieve multiple repetitions of a given weight and reflects the muscles ability to delay neural and intramuscular fatigue. These changes facilitate the aforementioned metabolic, functional, and clinically relevant benefits of MF. The case has been resoundingly made for the potential of resistance training to affect MF and be of possible benefit to health outcomes involving cardiovascular and musculoskeletal function in healthy and clinical populations alike.

1.5 Physical Fitness in MS: Cardiorespiratory Fitness

When compared to healthy controls, persons with MS have been found to have worse CRF. In one study, CRF, based on VO_{2peak}, was 28% higher in a sample of 25 healthy controls compared to 25 participants with MS.[36] In another study, 32 persons with MS were found to have roughly 12% decreased relative VO_{2peak} compared to 16 healthy controls. MF shares a similar case. For example, one study of 15 participants with MS and 15 healthy controls demonstrated that persons with MS had significantly lower peak torque production in the nondominant knee extensors, dominant knee flexors, and nondominant knee flexors compared to healthy controls.[37] Another study found persons with MS to have significantly worse isokinetic strength in the knee extensors during the eccentric and concentric phases of contraction when compared to healthy controls.[38] As previously described, a cycle of deconditioning is present in persons with MS and this is only further promoted as disease progression, relapse, increases in symptomology, or complications due to comorbidity occur. The physical inactivity that is spurred on by the onset of MS is an important factor in the physiological deconditioning seen in MS. Even the light

stimulus provided by daily PA on the cardiorespiratory and muscular systems can promote maintenance of current musculature and function. Persons with MS often encounter a spiral downward in their functionality. This is due to deconditioning from MS progression that leads to less likelihood of PA and eventually a loss of function. Fortunately, exercise physiologists have been examining the effects of exercise on persons with MS and current literature suggests a potential reversal of the downward spiral caused by inactivity and physiological deconditioning. After all, the body of a person with MS is still under the same principles of physiology regarding exercise and fitness.

1.6 Exercise Training and Physical Fitness in MS

Both exercise with the intent of improving CRF and MF has been studied in MS. A recent review of 54 studies of varying quality found the current evidence to suggest that exercise training is effective for improving both CRF and MF in persons with MS. Further, this review suggested exercise may be beneficial to mobility, fatigue, and health related quality of life. Twelve studies of varying quality suggested changes in aerobic capacity following exercise training. The authors concluded that a frequency of 2-3 bouts of exercise a week at 60% or more VO_{2peak} will elicit adaptations in CRF. Further, peak power output was shown to improve following aerobic exercise in 6 studies as well. The effect of combined modality (aerobic and resistance training) has also been shown to positively affect peak power although there is less evidence regarding this.[39] There is also evidence for increases in MF following exercise training in MS. The same review examined evidence from 6 randomized controlled trials and found 8-20 weeks of supervised resistance training performed 2-3 times a week at moderate intensity increased MF. There are established benefits to improving CRF in both clinical and non-clinical populations alike. CRF in particular is important for maintaining cardiovascular health, body

composition, and physical function and in a population that can be impaired in these health qualities it is imperative to provide novel therapies to augment them. The benefits of improving MF in persons with MS are also well established. MF improvements have been associated with improved walking speed and endurance, gait outcomes, cognition, and fatigue in MS.[40] It can be concluded that, with regular exercise, fitness in persons with MS can be improved. These improvements in CRF and MF help to facilitate further secondary benefits in persons with MS that encompass each realm of disability that can be seen in MS. Through review and meta-analyses a quantifiable effect on CRF and MF can be expected suggesting exercise as a therapy in this clinical population is nothing to overlook when considering the benefits of improved fitness.

Other Benefits of Exercise Training in MS Exercise also have benefits to persons with MS that do not directly related to fitness improvements. But exercise among persons with MS is not common. A study that surveyed 2,995 veterans that had MS found only about 28% of them to self-report doing any regular exercise[41]. Even though few people with MS participate in regular exercise there are a number of studies that have looked at mental health, quality of life, mobility and gait, and components of health in MS following regular exercise. A number of randomized controlled trials have examined the effects of exercise on depressive symptoms in MS. Out of the 13 studies that did so 11 were found to have positive effects on depression symptoms. A meta-analyses of the effects of exercise on MS was conducted and quantified the effect of exercise on depression in these studies. The authors found an effect of 1/3 SD or ES = 0.36 suggesting a small magnitude change in depressive symptoms can be expected following regular exercise training for persons with MS.[42] This is supported by meta-analyses that demonstrate a favorable effect of exercise on depression in healthy and clinically depressed persons that do not have

MS.[43,44,45,46]. Depression or depressive symptoms are common in MS. An estimated 50% of patients with MS become depressed or develop depressive symptoms over the duration of their MS. Because of the complicated nature of MS disease pathology within the CNS and depression's neurological basis, treating depression in MS patients can be difficult due to drug interactions and disability affecting accessibility to therapists. These studies suggest exercise may be an alternative means to help with these depressive symptoms in MS.

The effect of exercise on quality of life has also been examined in persons with MS. Quality of life considers one's subjective interpretation of components of their life's that they deem important such as psychological, social, and physical well-being. Evidence suggests that persons with MS can have compromised quality of life.[47] This may be due to the nature of having a progressive disease of which there is not yet a cure available. A meta-analyses examined the available literature involving the effects of exercise on quality of life in persons with MS. Out of high quality studies 13 studies examined, 12 showed positive effects of exercise on quality of life in MS. Overall, the authors found an effect of approximately ¼ SD or SE=0.23 suggesting a small magnitude change in quality of life can be expected following regular exercise training in persons with MS.[48] The conclusion that exercise can help provide a small effect to quality of life is important in a clinical population like MS. Again patients are shown to be more predisposed to depression and to have a negative outlook on their own lives which can be affected by having a progression disease such as MS. Exercise is a behavior that can added to one's lifestyle and has numerous established benefits. Along with those health benefits, the possibilities of improving one's outlook on life can have real impact of further behavior and positivity which can lead to better outcomes.[49]

Mobility and gait have also been shown to improve following exercise training in persons with MS. The progression of MS is synonymous with the development of gait impairments and further disruptions to mobility. These impairments culminate disability that often results in the need for ambulatory devices such as canes, walkers, and wheelchairs. The effect loosing mobility capability can be profound as it demotes incentives to move decreasing PA. Nearly half of those diagnosed with MS with be in need of an ambulatory device within 15 to 25 years of diagnoses. Further 9 out of every 10 persons with MS with have severe disability leaving them with even larger mobility limitations. Since mobility is largely used as an identifier of disease progression it is a target for treatment either indirectly through disease-modifying medications or directly through exercise intervention. In another meta-analyses the effect of exercise interventions on mobility outcomes in MS was quantified. 22 high-quality studies were included in the analysis. All but 3 of the included studies showed a beneficial effect of exercise on walking mobility. The overall effect size indicated that walking mobility improved 1/5 SD in persons with MS following exercise training. The overall effect size (ES) was g=0.19. The effect was more pronounced when controlling for supervision of exercise training with an ES of g=0.32 suggesting more improvements can be seen regarding walking mobility when people are supervised throughout their exercise regimen. It is clear that exercise training has effects on the musculoskeletal system of clinical and non-clinical populations alike. Both aerobic and resistance training can elicits these benefits in the musculoskeletal system leading to improved mobility, gait, and function. These improvements in turn can spur motivation to be more improving PA which would in turn help maintain these functions.

1.7 Cardiovascular Function in MS

CV function involves circulatory and autonomic function related to the heart, as well their responsiveness to stimulus or return to homeostasis. This is also affected by morphological components of arteries such as arterial stiffness, compliance of the blood vessel, and heart function. Importantly, such cardiovascular dysfunction can contribute to risk of developing vascular comorbidities and CVD in MS, which are associated with MS disease progression.[10]

Arterial function has been shown to be compromised in persons with MS. Arterial function describes measures such as blood flow, arterial stiffness, arterial wave reflection, and morphological changes like intima media thickness. The collection of these measures provides a multifactorial view of arterial function and are considered subclinical indicators of atherosclerosis and a compromised cardiovascular system. One cross sectional study compared arterial function in 33 MS patients to 33 healthy controls. The authors found arterial function to be significantly different in persons with MS compared to healthy controls. Particularly, peak forearm blood flow, pulse wave velocity (a measure of arterial stiffness), and arterial compliance were all significantly lower in the MS group. The authors also measured markers of inflammation since persons with MS can have chronically elevated levels of these markers and they can be responsible for cardiovascular challenge and further dysfunction. Inflammatory markers were not found to be elevated in the MS group compared to the healthy controls; therefore, arterial dysfunction is occurring in absence of chronically elevated inflammation.[50] This supports the notion that MS is also a vascular disease due to its effects on endothelial function.

Additionally, person with MS are known to develop compromised autonomic nervous systems leading to symptoms involving cardiovascular function, bowel and bladder function, sexual dysfunction, fatigue, sleep and others. In the cardiovascular system, autonomic disruption

stemming from demyelination of the CNS in MS results in issues related to heart rate variability and blood pressure variability. Previous studies have found a raised sympathetic tone in persons with MS.[51] Further, persons with MS have decreased heart rate variability and decreased blood pressure response. These issues can be a consequence of the development of brain lesions that are occur during MS disease progression.[52] In one study examining autonomic function in MS, researchers recorded heart rate variability in deep breathing examinations and heart rate and blood pressure responses in a tilt table test. Cardiovascular response was found to correlate with MS disease disability and number of brain lesions.[52] This is supported by the progression of autonomic cardiovascular dysfunction in MS following a one year follow up.[53] The effects of disease progression on autonomic function and its subsequent cardiovascular dysfunction help to further develop the cardiovascular profile of MS patients and provide avenues for potential intervention. Since autonomic nervous system issues are commonplace in MS the effects of lesion load on autonomic nervous system functions, especially cardiovascular responses, remains a topic for research and potential intervention.

Vascular Comorbidities in MS Vascular comorbidity can include hypercholesterolemia, hypertension, heart disease, diabetes, and peripheral vascular disease. Many people have multiple vascular comorbidities in addition to MS, further exacerbating their risk profile. A review found even one vascular comorbidity can increase the rate of progression in MS disability if it is present at the onset of MS. Those with one vascular comorbidity at onset were ultimately found to have a 50% increased risk of ambulatory disability throughout the course of their MS. The same review found a dose-response relationship between the number of vascular comorbidities and the speed of disability progression in persons with MS. Persons with MS suffering from two vascular comorbidities are at 228% risk of developing gait disability.[10] With

this information in mind, treating comorbid conditions in persons with MS has the potential to diminish disability progression, particularly ambulatory function.

Persons with MS have been found to have a greater risk of CVD. In one example, a large cohort study involving 8000 participants, researchers examined the risk of myocardial infarction, heart failure, stroke, and atrial fibrillation or flutter in patients diagnosed with MS.[54] The authors found a significantly greater risk for CVD in persons with MS. Specifically, relative risk of myocardial infarction, stroke, and heart failure were 1.85, 1.71, and 1.97 times more likely in persons with MS. The authors proposed several factors contributing to this including immune dysfunction and elevated inflammation but also included suggestions that homocysteine, decreased arterial function, oxidative stress, cerebral hypoperfusion, and even therapeutic use of glucocorticoids all can affect the risk for development of CVD. The end result of these factors and the development of CVD can expectedly increase the mortality of those with MS. Therefore, addressing the components of cardiovascular health is imperative for helping persons with MS maintain function and improve mortality.

The aforementioned evidence paints a stark picture of the cardiovascular profile of person with MS. As disease progression occurs and further disability accumulates a decrease in PA can also be expected without direct intervention. A compromised cardiovascular system coupled with the effects of deconditioning are important consideration for clinicians responsible for treating MS. Neglecting cardiovascular health has obvious detrimental effects on health in non-clinical populations who have no disability issues let alone MS. MS patients and their clinicians should be fully aware of the challenges presented in cardiovascular health that can accompany MS. Interventions for increasing cardiovascular health are also of interest in MS. Aerobic exercise has extensive support as an intervention for maintaining and improving all components of one's

cardiovascular profile. The results of aerobic exercise on MS have been previously mentioned here but again provide a means to counteract the negative cardiovascular issues that can arise in MS.

1.8 Purpose and Rationale

Physiological fitness and cardiovascular health are two components that have potential to be augmented by exercise and benefit persons with MS. Exercise training is a potential intervention to augment both of these components in persons with MS (since it has a large body of evidence to support its effects on physiological fitness and cardiovascular function in healthy people). It is important to determine whether or not exercise training can be associated with improvement in physiological fitness which includes cardiorespiratory and muscular fitness in persons with MS. Current evidence from higher quality studies, randomized controlled trials, of exercise training effects on physiological fitness in MS are promising but suffer from being examined in individually resulting in conclusions drawn from smaller sample sizes and possibly failing to determine effects of exercise interventions. When examining these studies, a systematic quantification of the effects of exercise on fitness is necessary to determine an overall effect of exercise training interventions on physiological fitness. For this reason, a meta-analysis was used to quantify the effect of exercise interventions on cardiorespiratory and muscular fitness outcomes in persons with MS. The result of this analyses will provide an indication of the magnitude of effect one could expect from implementing an exercise training program in this population. The hypothesis considered was that exercise training would be associated with improvements in muscular and cardiorespiratory fitness outcomes and these improvements would be moderate in magnitude.

The relationships between MS, physiological fitness, and CV function are in need of further evidence. Although evidence suggests an impaired cardiovascular profile among persons with MS, more studies are needed to corroborate these deficits in MS. However, cardiovascular improvements have yet to be studied in this population. Since cardiovascular function is strongly related to CRF and is also associated with muscular fitness to a lesser degree in healthy populations it is important to examine the relationship between physiological fitness and cardiovascular function in MS. For this reason a cross-sectional study was used to examine these relationships among in patients with MS. It was hypothesized that physiological fitness will be associated with all components of cardiovascular function and arterial function. This study will provide insight into the relationship between fitness and cardiovascular function in MS helping identify better targets for therapy to promote better cardiovascular health and a better disease risk profile in persons with MS.

The purpose of this thesis is to provide evidence about the relationships between MS, physiological fitness, and CV function. To examine this, (1) a meta-analysis will be conducted to systematically quantify current research literature that used exercise as an intervention in MS. This will provide information regarding the magnitude of effect that can be expected if a person with MS engages in regular exercise training. Both CRF and MF will be examined to determine the effect of exercise on them individually. To examine the relationship between physiological fitness and CV function in persons with MS (2) a cross-sectional analysis will be conducted using validated measures of CV function and gold standard measures of fitness. The overall benefit of these studies will be to provide evidence for clinicians to make educated, evidence-based recommendations when developing exercise programs for persons with MS that concern fitness and CV function.

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Chapter 2

The effect of exercise training on fitness in multiple sclerosis: A meta-analysis

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2.1 Introduction

Multiple sclerosis (MS) is a neurological disease characterized by inflammatory attacks within the central nervous system that result in axonal demyelination and transection as well as neurodegeneration.[1] The pathophysiological processes associated with the disease result in impairments in various domains including walking, cognition, and symptomatic changes such as depression and fatigue. The consequences of MS further compromise participation in physical activity and this results in significant detraining (i.e., physiological deconditioning), particularly in the domains of muscular and cardiorespiratory fitness.[2] Muscular fitness reflects the body's ability for generating and maintaining muscular force via skeletal muscle contraction and is commonly measured as muscular strength (e.g., peak force) and endurance (e.g., maximum repetitions). Cardiorespiratory fitness reflects the body's ability for delivering, extracting, and using oxygen for prolonged endurance exercise and is typically measured as peak aerobic capacity (VO_{2peak}), peak power output (W_p), and anaerobic or lactate threshold (l/mmol). The maintenance of muscular and cardiorespiratory fitness is critical for preserving and restoring physical functioning and participation among persons with MS.[3]

There is evidence that both muscular and cardiorespiratory fitness are impaired in persons with MS. For example, one study of 15 participants with MS and 15 healthy controls demonstrated that persons with MS had significantly lower peak torque production in the nondominant knee extensors, dominant knee flexors, and nondominant knee flexors compared to

healthy controls.[4] This has been replicated in other studies.[5,6] Similarly, cardiorespiratory fitness, based on VO_{2peak}, was 28% higher in a sample of 25 healthy controls compared to 25 participants with MS, and such deficits have been replicated in other studies.[5,7,8] The detraining and loss of fitness in persons with MS combined with the importance of physiological fitness for functional and symptomatic outcomes underscores the importance of developing and evaluating the efficacy of interventions that target indices of muscular and cardiorespiratory fitness.

Exercise training probably reflects the intervention modality with the best likelihood and relevance for improving physiological fitness in persons with MS. There is evidence for the benefits of resistance and aerobic training for improving physiological fitness in persons with MS.[9-11] For example, one systematic review reported that 8-20 weeks of moderate intensity (i.e., 10-12 repetitions @ 70-80% 1RM) resistance training performed 2 to 3 times per week increased muscular strength in persons with MS; there were insufficient data for demonstrating a change in muscular endurance.[12] That review further reported that moderate intensity (i.e., 60-80% W_p or 60% VO_{2peak}) aerobic exercise training, 2 to 3 times a week for 30 to 60 minutes increased cardiorespiratory fitness (VO_{2peak}) in persons with MS.[12]

Those data are promising, but have important limitations that can be overcome in a meta-analysis. The studies often suffer from small sample sizes resulting in non-significant effects resulting in the possible interpretation of no consistent or definitive effect of exercise training on fitness. The studies and literature review do not provide an indication of the magnitude of improvement in fitness outcomes following exercise training that can be provided through meta-analysis. Such an indication of magnitude is important for clinical research and practice by providing an evidence-based estimate of the actual benefit that exercise training may confer on physiological fitness. It is further note that there is likely variability in the effect of exercise

training on fitness adaptations, and this can be quantified using moderator analysis in meta-analysis. This will be important for indicating the characteristics of exercise or the sample that maximize the improvement in fitness outcomes. There are further examples of the value of meta-analysis for providing additional insight into the effect of exercise training on outcomes in MS that were not possible in literature reviews.[13,14]

We undertook a meta-analysis for providing a quantitative assessment of the effect of exercise training on muscular and cardiorespiratory fitness outcomes in persons with MS. To do this, we conducted a systematic and comprehensive meta-analysis of published randomized controlled trials (RCTs) involving exercise training and MS that included outcomes of muscular and cardiorespiratory fitness. We hypothesized exercise training to be associated with improvements in muscular and cardiorespiratory fitness outcomes and these improvements would be moderate in magnitude as fitness is a more proximal outcome of exercise training than other outcomes (e.g., walking and quality of life) included in meta-analyses of exercise training in MS.[14-17]

2.2 Methods

This meta-analysis was conducted consistent with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) framework, and a visual description of these step-by-step methods is provided in Figure 1.[18] We conducted a search of the following electronic databases: PubMed, Web of Science and Google Scholar, using the keywords “exercise” OR “aerobic” OR “strength” OR “resistance training” OR “cardiorespiratory” AND “multiple sclerosis”. We included RCTs that were published up to October 2014. We initially retrieved 1501 articles of which 1439 were excluded for the following reasons: duplicates, review articles and no inclusion

of persons with MS. We further searched the bibliographies of the retrieved articles and reviewed a total of 62 articles in detail. Of these articles, there were 42 without an objective fitness outcome measure, exercise training manipulation, appropriate control group, or randomization, and these studies were excluded. If the papers did not include sufficient information for calculating effect sizes (ES), we contacted the authors for further information. We included RCTs (i.e., studies that compared exercise training vs. no-treatment control and stated assigning participants to conditions randomly) that administered measures of physical fitness (e.g., VO_{2peak}, isokinetic strength) pre-post intervention. We excluded RCTs that did not include persons with MS, an appropriate objective fitness outcome, or an appropriate exercise training intervention. This resulted in a total of 20 RCTs that were included in the meta-analysis.[7,9,11,19-36]

We computed Ess expressed as Cohen's *d*.[37] To do this, we computed the mean change from before to after exercise training and subtracted the mean change of the control condition. The resulting difference in mean change between the conditions was then divided by the baseline standard deviation (SD) pooled between conditions. The Ess were calculated so that a positive ES indicated an improvement in fitness levels after exercise training, whereas a negative ES indicated a worsening of fitness levels in the exercise condition compared with control. Separate Ess were calculated per dependent variable (i.e., some studies had multiple fitness outcomes) as well as per type of exercise (i.e., some studies had more than one type of exercise training modality or condition). The overall analysis took place using a single ES per study (i.e., an average ES when there was more than one ES computed by the software). This was necessary as multiple Ess from the same study are not independent.[38] The lack of independence can bias the

standard error (SE) for judging the significance of the overall ES and multiple Ess from one study bias the overall ES disproportionately compared with the studies that have a single ES.[38]

The Ess along with the associated standard errors (Ses) were entered into the Comprehensive Meta-analysis Software (Version 2.0, Biostat, Englewood, New Jersey). The analyses were conducted separately for the muscular and cardiorespiratory fitness outcomes. We used a random-effects model for computing the overall or mean ES (for each fitness outcome) as this model assumes that the samples come from populations with different Ess and that the true effect differs between studies.[38] We further computed a 95% confidence interval (CI) around the mean ES. An overall Q value and I^2 value were calculated to test for homogeneity of variance among Ess. The Q value is a measure of variance among the Ess and a statistically significant ($p < .05$) sum of the squares of each ES about the weighted mean (Q) indicates heterogeneity. The I^2 value represents the magnitude of the heterogeneity where a larger number indicates larger heterogeneity.

We further performed separate post-hoc, exploratory moderator analyses using a random-effects model to partition any possible homogeneity within the 2 overall Ess for muscular and cardiorespiratory outcomes. Under the random-effects model, it is assumed that the ES heterogeneity is due to unobserved, random sources and is recommended as the preferred strategy due to the generality of this model.[39] We sought to apply this model as it is a more robust approach and to avoid potentially underestimating the variation between studies. The moderator analyses for muscular outcomes were based on the categorical variables of type of outcome measure (muscular strength vs. endurance), type of measurement device (isokinetic vs. other), training progression (progression over time vs. no progression), sample size (40 or fewer vs. more than 40 participants) and supervision (supervised training vs. partially or unsupervised

training). The moderator analyses for cardiorespiratory outcomes were based on the categorical variables of type of cardiorespiratory outcome measure (VO_{2peak} vs. W_p vs. other), type of exercise training (aerobic vs. other), exercise modality (cycle ergometer vs. other), exercise intensity (moderate vs. high based on the American College of Sport Medicine Guidelines for Exercise Testing and Prescription), sample size (fewer than 25 vs. 25 or more participants), and supervision (supervised training vs. partially or unsupervised training).[40] The selected moderators were categorized, in part, based on the number of studies available within each category (at least 3 studies per category) and upon initial reactions regarding possible effect moderators. Each study was used as the unit of analysis (averaging the Ess within each study in the case of multiple subgroups per study) when conducting the moderator analyses, except where noted (See Tables 2 and 3). The Ess per subgroup were coded separately (i.e., without averaging all subgroup Ess per study) in two cases to allow for comparisons of the categories within the moderator variable. This occurred with respect to the moderator variables type of muscular outcome measure in studies by Medina-Perez et al and Broekmann et al and, and the moderator variable of supervision in the study by Cakit et al.[21,26,27]

The quality of the studies included in the meta-analysis was established using the 11-item Physiotherapy Evidence Database (PEDro) scale for RCTs.[41,42] This scale has previously been used in reviews of exercise training in MS.[12,43] As recommended by the PEDro scoring guidelines, item 1 was not included when computing the overall score; therefore, total scores on the PEDro ranged between 0 and 10.[41] Higher scores on the PEDro indicate better methodological quality.

2.3 Results

Table 1 provides the sample and exercise characteristics per study, along with the PEDro scores. Overall, 62 Ess were retrieved from the 20 published RCTs that included a total of 722 persons with MS. Figures 2 and 3 provide visual descriptions of the average ES per study for muscular and cardiorespiratory fitness outcomes, respectively.

The distribution of Ess for muscular outcomes had slight positive skewness (g1=1.05, SE=.60) and kurtosis (g2=.88, SE=1.15). Eleven of the 14 Ess from the studies were greater than zero (i.e., 79%). The funnel plot of the average Ess from the 14 studies suggested against publication bias. The overall weighted mean ES was 0.27 (SE=0.05, 95% CI=0.17-0.38, z=5.05, p<.001). This reflects a statistically significant and small effect in favor of exercise training for improving muscular fitness compared with the control condition. The weighted mean ES was not heterogeneous (Q=11.09, df=13, p=.60, I^2=0.00). This indicates that the variation among studies was not greater than expected due to random chance.

The distribution of Ess for cardiorespiratory fitness had slight negative skewness (g1=-1.46, SE=.69) and significant positive kurtosis (g2=3.023, SE=1.33). Nine of the 10 Ess from the studies were greater than zero (i.e., 90%). The funnel plot of the average Ess from the 10 studies suggested against publication bias. The overall weighted mean ES was 0.47 (SE=0.09, 95% CI=0.30-0.65, z=5.40, p<.001). This reflects a statistically significant and moderate effect in favor of exercise training for improving cardiorespiratory fitness compared with the control condition. The weighted mean ES was not heterogeneous (Q=7.83, df=9, p=0.55, I^2=0.00). This indicates that the variation among studies was not greater than expected due to random chance.

Moderator analyses

The lack of heterogeneity in the overall analyses indicated minimal variation in Ess across the RCTs, yet we still conducted exploratory, post-hoc analyses using categorical moderator variables for possibly informing future research. Point estimates, Ses and significance values for the Q_b statistic are provided in Tables 2 and 3 for muscular and cardiorespiratory fitness outcomes, respectively. For muscular fitness outcomes, the additional analyses identified the type of muscular outcome measure as a possible moderator variable (p=.05) (see Table 2), indicating an effect in favor of muscular compared to cardiorespiratory outcomes. In the cardiorespiratory fitness analysis, the moderator variable of supervision approached statistical significance (p=0.06). The presence of exercise supervision was associated with greater improvements in cardiorespiratory fitness outcomes than conditions that had no or minimal supervision. However, the results of this moderator analyses should be interpreted with caution due to the uneven and small number of Ess per category.

Clinical meaningfulness

We estimated the possible clinical meaningfulness of the overall Ess by determining the degree of improvement in fitness outcomes using mean scores and SDs from a recent publication of persons with MS.[44] We first estimated the amount of change in fitness outcomes by multiplying the overall Ess with the SDs for VO_{2peak}, (SD = 7.25) and peak knee extensor and flexor torque (Nm, SDs = 52.41 and 24.75, respectively). This indicated that aerobic exercise training resulted in an increase in VO_{2peak} of 3.41 ml/kg/min, whereas resistance exercise resulted in an increase of peak extensor and flexor torque of 14.15 and 6.69 Nms, respectively. We then determined the percent change in fitness outcomes by dividing the amount of change in fitness

outcomes by the respective mean values for VO_{2peak} (M = 19.26) and peak knee extensor and flexor torque (M = 149.15 and 57.50, respectively). This resulted in a 17.7% change in VO_{2peak} as a consequence of exercise training, and a 9.5% change in extensor strength and 11.6% change in knee flexor strength as a result of exercise training. The calculated percent change for cardiorespiratory fitness clearly exceeded the threshold value of a 10% change in VO_{2peak} that has been deemed clinically relevant.[45]

2.4 Discussion

We conducted a meta-analysis quantifying the effect of exercise training on muscular and cardiorespiratory fitness outcomes in RCTs of persons with MS. Overall, exercise training improved muscular fitness by 0.27 standard deviations, whereas it improved cardiorespiratory fitness by 0.47 standard deviations. The mean effect for muscular strength translated into increases of 14.15 and 6.69 Nm for knee extensor and flexor peak torque, respectively, or approximately a 10% improvement in strength. The mean effect for cardiorespiratory fitness translated into an improvement of 3.41 ml/kg/min or 18% in VO_{2peak}. These findings extend previous data from systematic reviews on the benefits of exercise training in persons with MS by providing estimates of the magnitude of improvement in muscular and cardiorespiratory fitness outcomes following exercise training.[12] Such data are important for informing future research and clinical practice by providing an estimate of the actual benefit of exercise training on physical fitness in persons with MS. The Ess, for example, can inform power analyses for designing future RCTs, and provide clinicians with an evidence-based estimate of the expected improvement in fitness with exercise training in MS patients.

Muscular Fitness

Muscular fitness is critical in MS for maintaining functional mobility and independence, and persons with MS demonstrate relative muscle weakness compared with controls and across the range of disability status.[5,6] This supports interest in quantifying the effect of exercise training on muscular fitness outcomes in MS. Overall, the effect of exercise training on muscular fitness was statistically significant, but small in magnitude. Eleven of the fourteen studies (i.e., 78%) had Ess that were greater than zero, suggesting a generally positive effect of exercise training on muscular fitness. We examined the clinical meaningfulness of the effect of exercise training on muscular fitness by determining the percent change using previously published data in MS. The Ess translated into changes for muscular fitness outcomes involving the knee extensors and flexors of 9.5% and 11.6%, respectively. Such changes might reflect clinically meaningful improvements that translate into secondary benefits for persons with MS. Indeed, muscular fitness has been associated with walking speed and endurance, gait outcomes, cognitive processing speed, and fatigue in persons with MS.[44] Further, exercise-training interventions that improve muscular fitness in those with MS have also resulted in improved mobility, quality of life, and fatigue.[46] We identified type of outcome measure as a significant moderator of the effect of exercise training on muscular fitness outcomes, where muscular strength outcomes yielded a larger effect than muscular endurance outcomes. Overall, exercise training is beneficial for improving muscular fitness in persons with MS, and researchers and clinicians can expect an average change of approximately ⅓ SD.

Cardiorespiratory Fitness

Cardiorespiratory fitness is important for maintaining physical function, body composition, and cardiovascular health and it has been reported that persons with MS have lower

levels of cardiorespiratory fitness compared to healthy, age-matched controls.[5,8] This supports interest in quantifying the effect of exercise training on cardiorespiratory fitness in MS. The overall effect of exercise training on cardiorespiratory fitness was statistically significant and moderate in magnitude. Importantly, nine of the ten studies (i.e., 90%) had Ess that were greater than zero suggesting a consistent, positive effect of exercise training on cardiorespiratory fitness in MS. The average percent change for cardiorespiratory fitness was 17.7%, and this achieves a clinically meaningful change according to previously established criteria that suggest an increase of 10% in VO_{2peak} or more to be meaningful.[45] There are important potential secondary benefits of improving cardiorespiratory capacity for persons with MS. Cardiorespiratory fitness has been associated with cortical plasticity, grey and white matter integrity, walking performance, cognition, and fatigue in MS samples.[5,44,47-49] Improvements in cardiorespiratory fitness might further reduce the risk of cardiovascular comorbidities, as higher levels of subclinical atherosclerosis have been reported in persons with MS.[50] There were no statistically significant moderators of the effect of exercise training on cardiorespiratory fitness; however, the presence of exercise supervision approached statistical significance (p=0.06) as a moderator variable. This might reflect the high number of studies that involved supervised exercise training (i.e., 80%) and included cardiorespiratory fitness outcomes. Exercise training interventions that are supervised likely enhance adherence with the exercise prescription, and this would increase the likelihood for positive training adaptations. Overall, we determined that exercise training is beneficial for improving cardiorespiratory fitness in persons with MS, and researchers and clinicians can expect an average change of approximately ½ SD or 18% following exercise training.

Muscular vs. Cardiorespiratory Fitness Effect

The effect of exercise training on muscular fitness was approximately 0.20 SD units smaller than the effect on cardiorespiratory fitness and there was no overlap of point-estimates and 95% Cis for Ess. Such results suggest a considerably stronger effect of exercise training on cardiorespiratory fitness than muscular outcomes. Importantly, this information is novel in that we provide a direct comparison of the effect of exercise training on fitness outcomes through meta-analytic procedures. One potential reason for differential effects of exercise training on fitness outcomes might be related to the assessment of physical fitness. There was considerable variability in the type and quality of measures used to assess muscular fitness (e.g., peak force, peak torque, manual muscle test, maximum number of repetitions, etc.), compared to cardiorespiratory fitness (i.e., primarily VO_{2peak} and W_p). These measurement issues might have contributed to greater inconsistencies in the assessment of muscular strength, and therefore, a smaller overall effect of exercise training. Another factor that might have contributed to different effects of exercise training on muscular and cardiorespiratory fitness was the prescription of exercise training. Aerobic exercise was prescribed either independently or in combination with other modalities in the majority of studies reviewed (n = 15). Based on the specificity principle of exercise training we would expect greater adaptations in cardiorespiratory fitness since most studies involved an aerobic training component.

Comparison with Meta-analyses of Other Outcomes

There are several meta-analyses that have quantified the effect of exercise training on other outcomes that are important for persons with MS. Previous meta-analyses have reported

positive effects of exercise training on quality of life (g = 0.23), mobility (g = 0.19), depressive symptoms (g = 0.36), and fatigue (g = 0.45).[14-17] The effect of exercise training on muscular fitness (g = 0.27) was within the mid-range of previously reported effects on other outcomes, whereas the effect on cardiorespiratory fitness (g = 0.47) was larger than all of the previously reported effects. It was expected that exercise training would have a positive effect on physiological fitness outcomes, considering previous research on exercise training in MS, and fitness representing a direct consequence of exercise training. Collectively, the evidence from previous and current meta-analysis supports the beneficial effects of exercise training from fitness through participatory outcomes for people with MS.

2.5 Study Limitations

There are several limitations of the current literature involving exercise training in persons with MS. A primary limitation was that not all studies included an assessment of physical fitness, and therefore, these studies could not be included in this review. We believe that fitness measures should become a standard outcome of exercise training studies for quantifying fitness benefits as well as understanding the importance of fitness adaptations for other outcomes. There was some variability in the quality of tools used to quantify physical fitness (e.g., manual muscle testing using a hand-held dynamometer vs. isokinetic dynamometer machine), and this might have influenced the precision and accuracy of the overall point-estimates. Future researchers might consider optimizing the measurement of fitness outcomes in future RCTs by using gold standard assessments. Another limitation of the literature is that most studies of exercise training have not included individuals with MS with more severe mobility

impairment. This limits the generalizability of these findings to persons with mild to moderate disability.

The 20 studies included in this meta-analysis were scored for quality using the Physiotherapy Evidence Database (PEDro) scale which ranges between 0 (lowest possible quality) and 10 (highest possible quality). A score of 6 on the PEDro scale has previously been established as the cut point for high-quality studies. All 20 studies scored 6 points or higher on the PEDro scale indicating good overall quality of the RCTs reviewed. Reasons for missing points on the PEDro scale commonly included failure to conceal allocation, failure to blind subjects or assessors, failure to retain participants, and failure to complete intention-to-treat analyses. These shortcomings should be addressed in future studies of exercise training in persons with MS to improve the quality of current research in this field.

Limitations of the Meta Analysis

There are several limitations that should be considered when interpreting the results of this meta-analysis. The primary limitation of this study was that we only included RCTs. The inclusion of only RCTs resulted in high quality data, however, we might have failed to include valuable information from non-RCTs. This meta-analysis did not examine variability in exercise training modalities and other characteristics such as frequency, intensity, and duration of training. This was challenging based on the limited number of RCTs that have examined exercise training in persons with MS. It is also possible that this analysis is missing other important moderator variables that could influence the magnitude of the effect of exercise training on physical fitness.

2.6 Conclusion

We conducted a meta-analysis of RCTs involving persons with MS that examined the effect of exercise training on muscular and cardiorespiratory fitness outcomes. Exercise training was associated with changes in muscular (small in magnitude) and cardiorespiratory (moderate in magnitude) fitness outcomes that approximated a 10% and 18% improvement, respectively. Subsequent research might examine the effect of improvements in muscular and cardiorespiratory fitness on brain structure, functions such as walking and cognition, and symptoms such as depression and fatigue in MS. Researchers can rely on the point estimates provided in this paper when designing clinical trials involving exercise training, and clinicians can provide a better estimate of actual improvements in fitness when developing exercise prescriptions for patients with MS.

Conflict of Interest

None declared. The results of the present study do not constitute an endorsement by the ACSM.

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Chapter 3

Physical fitness is associated with improved arterial function in persons with MS

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3.1 Introduction

Multiple sclerosis (MS) is an immune-mediated disease characterized by inflammation, demyelination, and axonal loss within the central nervous system (CNS).[1] MS is one of the most prevalent neurological diseases affecting 1 out of 1,000 adults in the United States.[2] Progressive inflammatory attacks within the CNS cause structural damage and transection of axons. Further, neurodegenerative processes result in axo-neuronal loss over the later course of the disease. This damage results in life-altering functional consequences which can be accompanied by cardiovascular comorbidity.

There is evidence for cardiovascular dysfunction in persons with MS. Previous research indicates decreased arterial function and increased markers of subclinical atherosclerosis in persons with MS compared to healthy controls[3]. For instance, one study reported decreased carotid arterial compliance and pulse wave velocity in 33 persons with MS compared to 33 healthy adults.[3] Autonomic dysfunction, as it affects the heart and circulatory function, can accompany cardiovascular dysfunction in persons with MS as well leading to impaired blood pressure variability and heart rate variability[4]. Cardiovascular comorbidities such as diabetes, hypertension, hypercholesterolemia, peripheral vascular disease are common in persons with MS and significantly increase the risk of disability progression.

Cardiorespiratory fitness (CRF) is one of the largest influencers of CV function in healthy people and when increased, can improve cardiovascular risk factors like insulin

sensitivity, decreases in fat mass, decreased markers of inflammation, and lower plasma triglycerides.[5,6] CRF refers to the body's ability to deliver, extract, and utilize oxygen for endurance exercise and is usually measured as peak aerobic capacity (VO_{2peak}) and peak power output (W_p). Muscular fitness (MF) which refers to the body's ability to generate and maintain muscular force via skeletal muscle contraction and is usually measured as muscular strength (e.g., peak force) and endurance (e.g., maximum repetitions) and has also been related to an improved risk factor profile. CRF and MF are impaired in persons with MS. In a study comparing CRF in 37 MS patients and 26 healthy controls VO_{2peak} was demonstrated to be 28% lower in the MS sample.[7] Another study comparing MF in 15 MS patients and 15 healthy controls demonstrated lower peak torque production in knee flexors and extensors in persons with MS compared to healthy controls.[8]

In MS, deconditioning that accompanies disease progression, is associated with a loss of physiological fitness involving both CRF and MF. This loss of fitness in turn can further demote cardiovascular function and may contribute to both disability progression and increased risk of CVD[9]. The relationship between CV function and fitness has been well examined in healthy people. CRF has been inversely related with arterial stiffness measures in a sample of 405 young men and women.[10] Further, CRF is commonly associated with reductions in blood pressure, and improvements in cardiac output and circulatory vasodilation.[11,12,13] MF has been inversely related to arterial stiffness, positively related to compliance, and has been shown to modestly improve blood pressure.[14] CRF and MF have also been associated with a decreased risk for comorbidities such as metabolic syndrome, obesity and CVD in healthy populations.[15,16] Although evidence exists for CRF and MF having a positive relationship with CV function in healthy people, the relationships between CRF, MF and CV function in MS have not been determined. [15,17]

We examined the cross-sectional association between physiological fitness (CRF and MF) and CV function in a cohort of patients with MS. We hypothesized that both CRF and MF will be associated with CV function similar to research conducted in healthy people. This study will provide insight into the relationship between fitness and cardiovascular function in this clinical population and help identify targets for therapeutic intervention to promote cardiovascular function and a reduce comorbid disease risk in persons with MS.

3.2 Methods

Participants

Participants were recruited from the North American Research Committee on Multiple Sclerosis registry and from a database of participants from previous studies in our laboratory. Healthy controls were recruited from the local community. Criteria for inclusion were: 18-64 years old; relapse free for the last 30 days; Expanded Disability Status Scale (EDSS) <8.0; able to visit our laboratory for testing; minimal risk for engaging in physical activity based on the Physical Activity Readiness Questionnaire; physician's approval for participation and physician confirmation of MS diagnosis.[18] We made contact with 128 persons of which 86 were screen for inclusion. 25 individuals qualified, but were uninterested in participation and 4 individuals did not meet inclusion criteria. The final sample included 57 participants with MS.

EDSS

Disability status was determined by EDSS (28 from main paper)* examination by Neurostatus-certified assessors.

Brachial blood pressure

Following 10 minutes of quiet rest in a supine position, participants' resting systolic (SBP) and diastolic (DBP) blood pressures were taken at the brachial artery with an automated oscillometric cuff (HEM-907XL; Omron Corporation, Kyoto, Japan). Blood pressure measurements were taken in duplicate and averaged. When the recordings were not within 5 mmHg an additional measurement was taken.

Cardiovascular function

Measures of cardiovascular function was collected in the supine position following 10 minutes of quiet rest. Applanation tonometry was performed using a high-fidelity strain gauge transducer (SphygmoCor, AtCor Medical, Sydney, Australia) on the right radial artery to obtain pressure waveforms. A central aortic pressure waveform was reconstructed from the radial artery pressure waveform using a generalized validated transfer function.[59] Aortic pulse pressure will be calculated by subtracting the aortic diastolic blood pressure (DBP) from the aortic systolic blood pressure (SBP). Central pulse wave velocity (cPWV) was calculated from the waveform at the right common carotid artery and right femoral artery using the same strain gauge transducer. HR was obtained simultaneously using a three-lead CM5 configuration. The distance in millimeters from the carotid artery to the suprasternal notch, and the suprasternal notch to the femoral artery was measured with a measuring tape. The carotid-suprasternal distance was subtracted from the suprasternal-femoral distance to account for differences in the direction of pulse wave propagation. cPWV will be calculated from the distances between measurement sites and the measured time delay between the proximal and distal waveforms.

Cardiorespiratory Fitness

We determined cardiorespiratory fitness ($VO_{2peak)}$ using an incremental exercise test on a recumbent stepper (Nustep $T5^{XR}$ recumbent stepper, Nustep Inc., Ann Arbor, MI). Expired gases were collected using a two-way non rebreathable valve (Hans Rudolph Inc., Shawnee, KS) and oxygen consumption was measured using an open circuit spirometry system (TrueOne 2400, Parvo Medics, Sandy, UT). Participants performed a one minute warm-up at 15W . The resistance on the stepper was then gradually increased until the participant reached volitional fatigue. The intensity was increased by 10W/minute for participants with mild-to-moderate MS (EDSS 1.0-5.5) and 5W/minute for participants with severe MS (EDSS 6.0). Heart rate (Polar Electro Oy, Kempele, Finland) and rating of perceived exertion (RPE) were recorded each minute of the test. VO_{2peak} was expressed as ml/kg/min, with 20 second averaging. Criteria for VO_{2peak} involved at least one of the following: (1) respiratory exchange ratio ≥1.10; (2) heart rate within 10 beats/minute of age-predicted maximum; or (3) RPE ≥17.

Muscular Fitness

Muscular strength was assessed bilaterally as peak torque of the knee extensors (KE) and flexors (KF) using an isokinetic muscle dynamometer (Biodex System 3 Dynamometer, Biodex Medical Systems, Inc., Shirley, NY). Participants performed three, 5 second maximal KE and one 5 second maximal KF at 60° and 90° flexed. A rest period of 5s was given between each attempt. Peak isometric strength was expressed in N·m and determined as the highest recorded value for each muscle group.

Data analysis

Data were analyzed using SPSS Version 22.0 (SPSS Inc., Chicago, IL). Values in the text are presented as mean (SD), unless otherwise noted. Participant characteristics were summarized

using descriptive statistics. We examined the relationship between CRF or MF and CV function measures using bivariate Pearson correlations (*r*). Statistical significance was set at $p < .05$.

3.3 Results

CRF

Participant characteristics are presented in Table 4. Correlation coefficients are presented in table 5. Aortic pulse pressure (mmHg) was significantly correlated with relative VO_2 peak (r = -.288, p = .033) and peak power (r = -.268, p = .046). Augmentation pressure (mmHg) was significantly correlated with relative VO_2 peak (r = -.393, p = .003) and peak power (r = -.375, p = .004). Aortic transit time (msec) was significantly correlated with relative VO_2 peak (r = .545, p < .001) and peak power output (r = .537, p < .001). Aix (%) was significantly correlated with relative VO_2 peak (r = -.502, p = .002) and peak power (r = -.447, p = .001). Aix at 75 bpm (%) was significantly correlated with relative VO_2 peak (r = -.624, p < .001) and peak power (r = .561, p < .001). SEVR was significantly correlated with relative VO_2 peak (r = .290, p = 0.32) but not peak power. End systolic pressure (mmHg) was significantly correlated with relative VO_2 peak (r = -.312, p = .021) but not peak power. Pulse wave velocity was not related to relative VO_2 peak or peak power.

MF

Aortic pulse pressure (mmHg) was significantly correlated with extensor (r = -.346, p = .008) and flexor (r = -.347, p = .008) strength (Nm). Augmentation pressure (mmHg) was significantly correlated to extensor (r = -.346, p < .001) and flexor (r = -.464, p < .001) strength. Aortic transit time (msec) was significantly correlated with extensor (r = .601, p < .001) and flexor (r = .591, p < .001) strength. Aix (%) was significantly correlated with extensor (r = -.497, p < .001) and flexor (r = -.529, p < .001) strength. Aix at 75 bpm (%) was significantly correlated with

extensor ($r = -.556$, $p < .001$) and flexor ($r = -.575$, $p < .001$) strength. Pulse wave velocity ($m \cdot s^{-1}$) was significantly correlated with flexor ($r = .297$, $p = .040$) but not extensor strength.

3.4 Discussion

We conducted a cross sectional analysis examining the relationships between fitness (CRF and MF) and arterial function in persons with MS of varying disability level. The main findings indicate that CRF and MF maintain significant relationships with CV function in persons with MS, including measures of arterial function and cardiac function. These findings are consistent with the previously mentioned hypothesis that CRF and MF are associative of better arterial function in persons with MS. Further, these relationships provide therapeutic targets to promote better cardiovascular health in MS by improving CRF and MF.

CRF

VO_2 peak and peak power were significantly correlated with aortic PP, augmentation pressure, aortic transit time, and augmentation index. These findings indicate CRF is significantly associated with cardiovascular function in MS. Specifically, arterial stiffness and pressure aspects of the aortic waveform were found inversely related to CRF. This supports previous research on the relationship between CRF, arterial function, and cardiovascular morbidities in heathy people.[19] SEVR and EDP were significantly correlated with relative VO_2 peak, but not with PPO suggesting VO_2 peak is more strongly related to cardiac perfusion and aortic waveform pressures at the of systole than PPO. VO_2 peak is the gold standard measure of CRF and is a direct indicator of cardiovascular function which would explain its stronger correlations with arterial function outcomes.[20] PWV, the primary measure of arterial stiffness was not related to CRF or PPO. This is contrary to previous evidence on the relationship between VO_2 peak and

arterial stiffness in healthy populations[10]. Previous research has found young persons with MS to have compromised arterial stiffness. The relationship between MS and artieral stiffness may be less moderated by physical fitness than we have presumed do to disease symptoms such as inflammation and progression of MS.[21]

Improvements in CRF have long been associated with improved function within the cardiovascular system. In MS, increasing disability and lower levels of physical activity are responsible for decreasing fitness, which in turn, can affect arterial function and increase the likelihood of disease progression, comorbidity, and subsequently further disability. By augmenting CRF, this cycle of degenerating function and disability may be altered. In summary, CRF has a significant relationships to arterial and cardiac function. Through augmentations to CRF via exercise interventions, persons with MS may be able to improve their CV health and CV risk profile.

MF

Peak extensor torque (Nm) and flexor torque (Nm) were significantly correlated with aortic PP, augmentation pressure, aortic transit time, and augmentation index. These findings indicate MF to be significantly associated with cardiovascular function in MS. Similar to CRF, an inverse relationship exists between pressure aspects of the waveform, arterial stiffness, and MF. Along with this, PWV, the best marker for arterial stiffness, was positively correlated with flexor peak torque supporting previous evidence that MF is negatively associated with arterial stiffness.[17] Neither SEVR nor EDP were significantly associated with MF outcomes suggesting MF is not strongly related to cardiac perfusion or end systolic pressure in persons with MS.

Conflicting evidence exists regarding the relationship between MF and CV function. More recent evidence suggests a positive relationship exists between MF and CV function.[10,17] Resistance training (RT) has also been suggested for metabolic, blood pressure, and musculoskeletal improvements.[14] RT has also been shown to improve muscular fitness (citations from Rob/Lara review), balance, ambulation, and fatigue in persons with MS. These additional benefits along with improvements in muscular fitness suggest RT to have a potential effect on cardiovascular health in MS albeit less than aerobic exercise. Future research should continue to determine the effects of RT on cardiovascular function in MS persons in order to further clarify this.

3.5 Study Limitations

Limitations of this cross sectional study involving fitness and CV function in MS also exist. First, this study is a cross sectional study and fails to establish cause and effect relationships between fitness and CV function in MS. Therefore, it is recommend that future research should examine the effect of exercise training on fitness and CV function using a RCT design to establish cause and effect. Second, this sample involved persons with varying levels of disability of MS. The difference in disability level can influence fitness and CV function and makes generalizability of this study more difficult. Another limitation involves this CV measures taking recordings as a result of mathematical algorithms instead of direct measurement of fluid dynamics within the cardiovascular system. This CV measurements have been well validated in healthy people but may suffer precision as opposed to more invasive measurements of CV function.[22,23] Although participants were asked to control their diet via fasting there have no guarantee that CV outcomes were not influenced by nutrition or ingestion of drugs such as caffeine and nicotine prior to assessments. Lastly, since CV measures for men were taken by a

male researcher and women were taken by a female researcher, inter-tester reliability may be a limitation.

3.6 Conclusion

In this study, the relationship between fitness and CV function in persons with MS of varying disability was examined. It can be concluded that both CRF and MF are correlated with better CV function in persons with MS. Relative to CRF, this result is not surprising, and supports to the concept that improving CRF might improve CV function in persons with MS. The best way to achieve these adaptations are through aerobic exercise training which has numerous established benefits for persons with MS. Further research, including intervention studies, should be conducted in order to determine the effects of aerobic training on CV function in persons with MS. MF was also positively correlated with both pressure outcomes and arterial stiffness. With more recent evidence confirming better CV function to be related to better MF, further research should be conducted to determine the effect of resistance training on CV function in persons with MS. In summary, CRF and MF are associated with better CV function in persons with MS and augmenting fitness with aerobic and/or resistance training may be a viable therapy to improve CV function and comorbidity in persons with MS.

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Chapter 4

Discussion

This thesis describes the relationships between multiple sclerosis (MS), physiological fitness, cardiovascular (CV) function, and exercise. First a meta-analyses was used to determine the magnitude of effect of exercise training on cardiorespiratory fitness (CRF) and muscular fitness (MF). The purpose of this meta-analyses was help clarify the efficacy of exercise training programs on CRF and MF in persons with MS. Without this systematic quantification of studies using exercise as an intervention effects, it would be difficult to determine whether or not benefits of exercise that have been shown to occur with training in MS are resultant of the physiological adaptations to fitness that come with aerobic and resistance training. It is important to determine if fitness adaptations can be expected to accompany MS related benefits following exercise training. Secondly, a cross sectional design was used to examine the relationship between CRF, MF and CV function in persons with MS. Arterial function in MS is not thoroughly examined and its relationship with physiological fitness has not been described in this clinical population. It is important for determining the potential efficacy that improving CRF and MF, through exercise intervention, can have on persons with MS. Overall, the results of these two studies have provided clinically relevant information that can help the development of future research protocols and applied exercise programming involving persons with MS.

The meta-analyses examined 20 randomized controlled trials (RCTS) of which 63 effects sizes (ES) were calculated. These 20 studies were rated for quality according to the Physiotherapy Evidence Database Scale (PEDro) scale involves a checklist of 10 scale allowing for assessment of low quality (1) and high quality (10) criteria within each study. Failure to conceal allocation, failure to blind subjects or assessors, failure to retain participants, and failure

to complete intention-to-treat analyses are common methodological failures for which points are deducted from RCTs. A score of 6 has been previously established as the cut point for high quality RCT's of which all 20 RCT's in this meta-analyses achieved.[1] Therefore, the results of this analysis are drawn from studies of higher methodical quality.

Of the fourteen studies with MF measures, eleven showed a positive effect of exercise training on MF. For MF outcomes, the overall mean ES was 0.27 (SE=0.05, 95% CI=0.17-0.38, z=5.05, p<.001) suggesting a small but significant effect of exercise training on MF outcomes. Of the ten studies with CRF measures, nine showed a positive effect of exercise training on CRF. For CRF outcomes, the overall mean ES was 0.47 (SE=0.09, 95% CI=0.30-0.65, z=5.40, p<.001) suggesting a moderate and significant effect of exercise training on CRF.

The results were quantified into a clinically meaningful metric for both CRF and MF. The ESs for VO_{2peak}, (SD = 7.25), peak knee extensor, and flexor torque (Nm, SDs = 52.41 and 24.75, respectively) were multiplied by their SDs resulting an average increase in VO_{2peak} of 3.41 ml/kg/min or 17.7% change. The improvements for extensor and flexor strength were 14.15 and 6.69 Nms and their percent changes were 9.5% and 11.6% respectively. Overall, the improvements calculated are not substantial nor minimal. CRF improvements above 10% change in VO_{2peak} have been deemed clinically relevant previously.[2] Participants analyzed achieved an average improvement to CRF well above this threshold indicating aerobic exercise training to be a clinically relevant intervention for achieving improvements in CRF in MS. Improvements to muscular fitness were approximately 10% for both extensors and flexors. Even small improvements in muscular fitness can have clinically relevant effects on mobility and stability in MS and these improvements indicate the efficacy of resistance training for improving MF in MS.

In this study, a cross sectional examination of the relationships between cardiovascular function, physiological fitness and MS in 57 participants with MS was conducted. Blood pressure, arterial function, and arterial stiffness, and cardiac perfusion were measured. Fitness measures included a VO_{2peak} test on a recumbent stepper and max strength test on an isokinetic dynamometer. The main finding of this cross sectional analysis indicate the CRF and MF are positively correlated with better arterial function in persons with MS. These relationships have not been thoroughly examined in MS and are novel since they provide a potential therapeutic target to promote cardiovascular health in MS. Since aerobic and resistance training have each been shown to benefit persons with MS it would further highlight them as possible interventions for another important health factor such as cardiovascular health.

Cardiorespiratory fitness measures including relative VO_{2peak} and peak power output (PPO) were significantly correlated with aortic pulse pressure, augmentation pressure, aortic transit time, and augmentation index. According to the finding that CRF is related to better arterial functioning it can be concluded that CRF is a predictor of these outcomes. Both arterial stiffness and pressure aspects of the aortic waveform were found to be better in MS patients with better CRF. Further, Subendocardial viability ratio (SEVR) and end diastolic pressure (EDP) were significantly correlated with relative VO_{2peak} but not PPO suggesting VO_{2peak} is a better predictor of cardiac perfusion and aortic pressures than PPO. This is understandable since VO_{2peak} is known as the gold standard for CRF assessment and is a direct indicator of CV function. While significantly correlations occurred between CRF and many CV outcomes, the gold standard for arterial stiffness, pulse wave analysis (PWV) was not found to be significantly related to CRF. The explanation for this is lacking as a previous cross sectional examination of CV function in healthy populations showed an indirect relationship between VO_{2peak} and arterial

stiffness.[3] As mentioned, CRF is a well-established indicator of CV function in healthy people. MS diagnosis is eventually accompanied by increasing disability and decreasing PA along with physiological deconditioning which further decrease CRF. These effects on CRF then can in turn affect CV function, promoting a more chronically stressed CV system and may lead to increases in disease progression and comorbidity or even CVD. This research illustrates the importance of CRF in preventing this downward progression involving MS and CV health.

MF was also found to be related to CV function in MS. Specifically, extensor peak torque and flexor peak torque were each significantly correlated with aortic pulse pressure, augmentation pressure, aortic transit time, and augmentation index. These results suggest MF is also a predictor of CV function in persons with MS. However, MF was also significantly correlated with arterial stiffness in the PWV measures indicating MF is negatively associated predictor of arterial stiffness in MS. In contrast to CRF, MF was not found to have positive correlations with SEVR or EDP suggesting MF is not a good predictor of cardiac perfusion or pressures at the end of diastole in persons with MS. The relationship between MF and CV function has been difficult as there is conflicting evidence available. More recent research has suggested no relationship or a positive relationship exists between MF and CV function.[4,5,6,7] Better MF may be responsible for lessening the cardiovascular burden by affecting risk factors (such as BP, HDL, body fat, inflammation, insulin sensitivity, and lean tissue) and therefore may reduce risk of CVD.

These results provide evidence for the strength of the relationships between CRF, MF and CV function in persons with MS. These results also support the potential for exercise to improve CV function in MS through exercise adaptations. Such adaptations will likely lead to adaptations in CV function that have been long established by research done with healthy people following

regular exercise training. Such improvements include better insulin sensitivity, decreases in fat mass, decreased markers of inflammation, and lower plasma triglycerides [8,9]. These can be highly influential to overall cardiovascular health and influential to one's disposition to CVD. Improvements to MF that accompany regular resistance training can also have beneficial effects on these risk factors as previously mentioned. Further, benefits to cardiovascular health are common following regular exercise training in healthy populations but have not been tested in persons with MS.

These two studies provide evidence of an inherent relationship between fitness and CV function in MS. This relationship has been previously established in healthy people and other clinical populations but had not been thoroughly examined in persons with MS. Persons with MS have been shown to have more CV dysfunction than healthy people and are more prone to developing vascular comorbidity also. This results show that physiological fitness (CRF and MF) in persons with MS is 1. Augmentable via exercise and 2. A mediator of CV function. This is important because exercise has a large body of literature to draw from when attempting to determine exercise's effects on CV function in healthy population. If this evidence is also relative to MS in terms of the anticipated adaptations that can be expected from regular exercise training then CV function can be improved by adoption of regular exercise in persons with MS. The implications of improving CV function can be of great benefit to longevity and maintenance of MS and to the prevention of MS disease progression.

Although the results of this meta-analysis and cross sectional study are pertinent to developing options for therapy there remain limitations within this research. When developing a meta-analysis a primary limitation found in the literature is the failure by researchers to effectively measure physiological fitness or not measure it at all. This makes assessing the

effects of exercise on fitness impossible for those studies even though they may have used exercise as an intervention. These articles are unusable for this analysis. For this reason, it is suggested physical fitness measures be implemented in any study that involves an exercise training intervention in MS. Standardizing these measures in exercise training studies would provide knowledge of exercise training effects on fitness which is directly related to different outcomes in MS. Another limitation to the meta-analysis involved the variability of the quality of tools used to assess fitness adaptations which may have influenced the precision and accuracy of the effects of exercise on CRF and MF. For example, muscle testing assessed via hand held dynamometer is not as accurate in comparison to muscle testing assessed via an isokinetic dynamometer. For this reason, it is suggested that optimizing measurements of fitness outcomes in future studies should be done by using gold standard assessments for determining fitness changes following exercise in MS. Another limitations comes from a lack of diversity of severity among participants recruited for research. The majority of research has been done with participants who have more severe impairment and therefore it's more difficult to generalize this findings across all people with MS. The meta-analysis was also limited by a low number of RCTs available for analysis. The 20 studies were considered high quality according to PEDro scoring but a larger sample for analysis would strengthen analysis and support overall ES calculations. Another limitation was that this meta-analysis did not examine variability in exercise training modalities and other characteristics such as frequency, intensity, and duration of training. Lastly, it is possible that this analysis failed to determine certain moderator variables that could influence the magnitude of the ES that exercise had on fitness.

4.1 Limitations

Limitations of this cross sectional study involving fitness and CV function in MS also exist. First, this study is a cross sectional study and fails to establish cause and effect relationships between fitness and CV function in MS. Therefore, it is recommended that future research should examine the effect of exercise training on fitness and CV function using a RCT design to establish cause and effect. Second, this sample involved persons with varying levels of disability of MS. The difference in disability level can influence fitness and CV function and makes generalizability of this study more difficult. Another limitation involves this CV measures taking recordings as a result of mathematical algorithms instead of direct measurement of fluid dynamics within the cardiovascular system. This CV measurements have been well validated in healthy people but may suffer precision as opposed to more invasive measurements of CV function.[10,11] Although participants were asked to control their diet via fasting there is no guarantee that CV outcomes were not influenced by nutrition or ingestion of drugs such as caffeine and nicotine prior to assessments. Lastly, since CV measures for men were taken by a male researcher and women were taken by a female researcher, inter-tester reliability may be a limitation.

4.2 Future Directions

Future research is needed to continue to elucidate the relationships between MS, physiological fitness and CV function and exercise. Differences in MS functionality that manifest externally become quite clear with disease progression but less obvious changes to other internal body system functions and their potential impairment, such as CV impairment, are equally important to address. CV function is addressed clinically and through research in healthy

populations and other clinical populations consistently but has received less attention in those with MS. In order to address and adequately treat physiological changes that occur with MS, is it important to determine the relationships between CV function and physiological fitness in MS and how this relationship impacts CV outcomes among other health outcomes followed regular exercise training. Future RCTs could aim to determine this with a carefully designed study utilizing aerobic exercise and taking CV function measures such as arterial stiffness, arterial wave reflection, and measuring morphological change like intima media thickness. Evidence provided by this meta-analyses and cross sectional examination is the foundation for developing these future protocols. With further evidence corroborating these relationships researchers and clinicians can be confident in designing exercise programming that benefits persons with MS in order to achieve the previously established benefits exercise has on MS as well as potential CV benefits.

4.3 Conclusion

The extent of this literature review and discussion provide an analysis of evidence regarding the relationships between MS, physiological fitness, CV function, and exercise. Overall, this research suggests exercise training interventions have an effect on CRF and MF in persons with MS. Further, it is determined that significant relationships exist between both CRF and MF and CV function in persons with MS. These relationships indicate an inverse relationship exists between fitness and CV function and provides insight to physiological fitness being a potential target of therapy that could result in CV benefits and improved cardiovascular risk profiles in persons with MS. This conclusion supports previous evidence on the efficacy of exercise training for functional benefits in MS. However, a little evidence exists on the topic of

fitness and CV function in persons with MS it is important that future researchers examine cause and effect relationships that may exist between exercise training and CV function in MS patients. This can be achieved via RCTs using this cross sectional study as a foundation for protocol development.

4.4 References

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Chapter 5

Figures and Tables

Figure 1. Flow diagram of study selection.

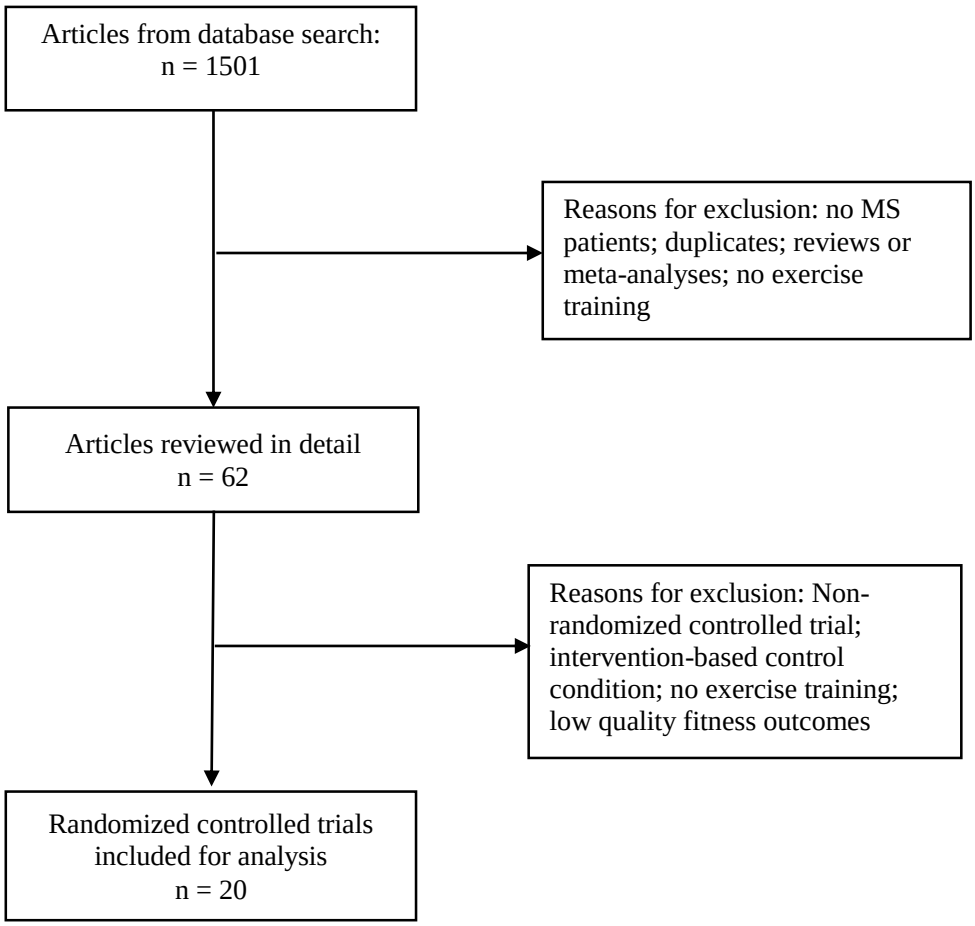


Figure 2. Average effect size, standard errors, and upper and lower limit of effects from 14 studies included in the muscular fitness outcomes meta-analyses. CI = confidence interval.

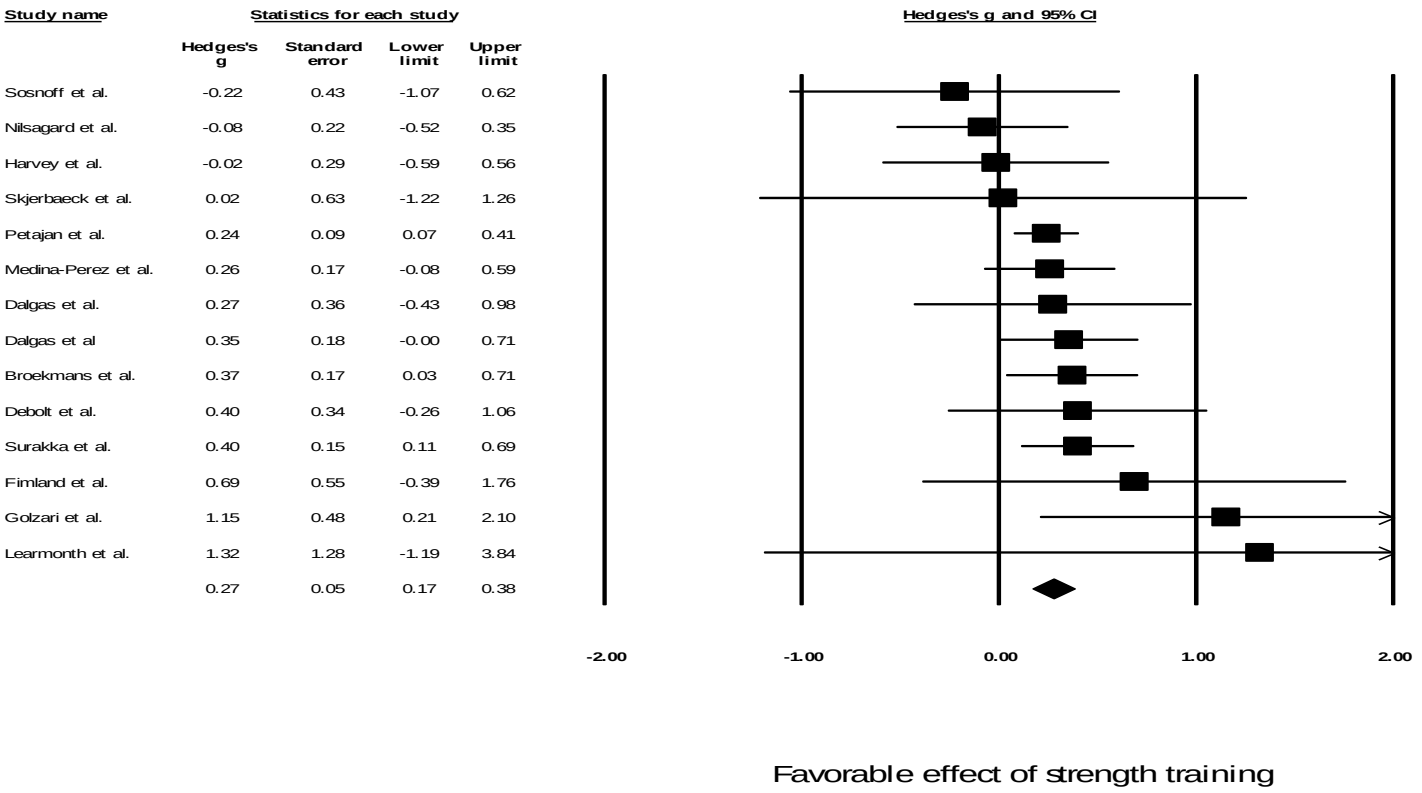
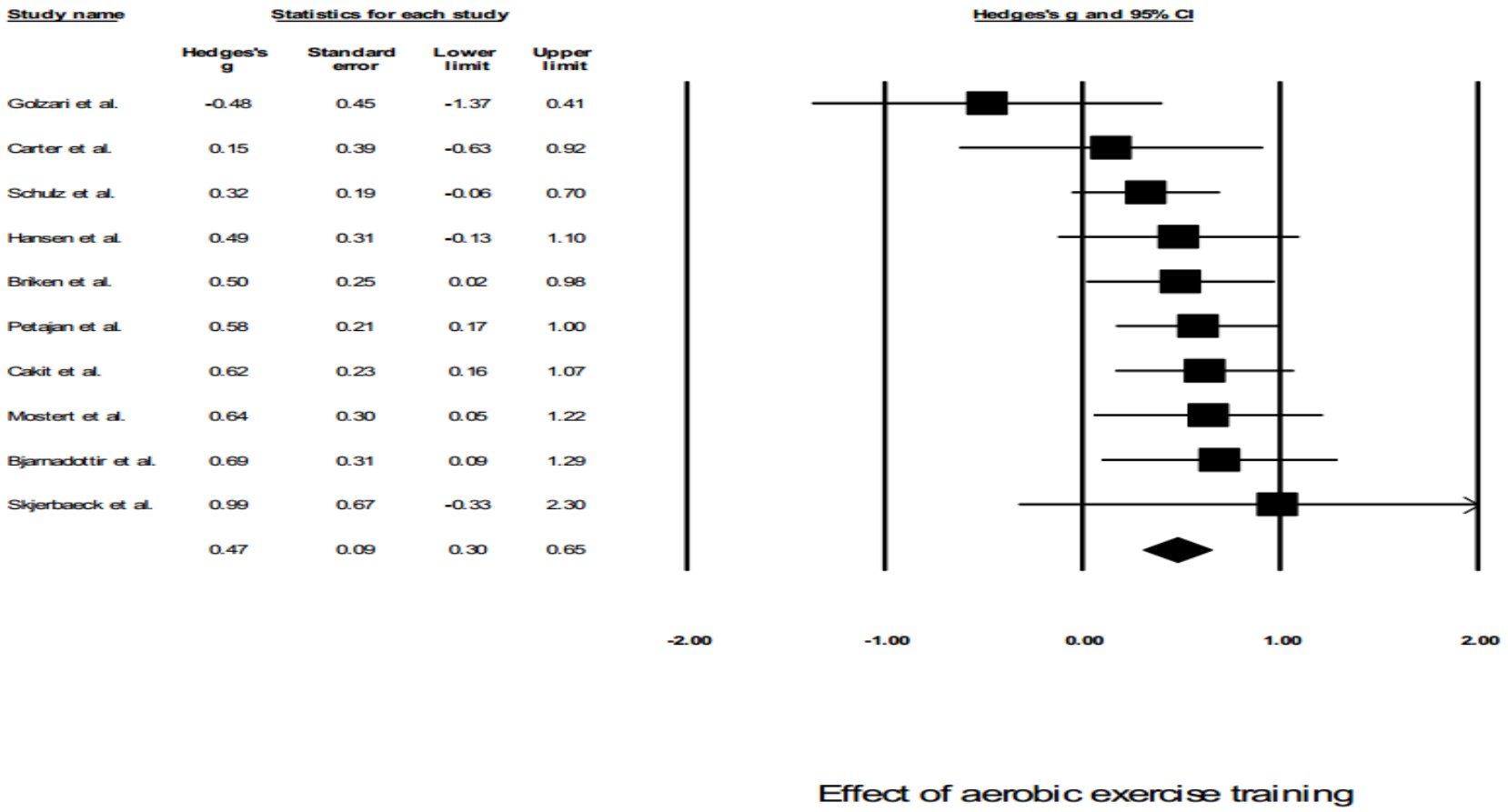


Figure 3. Average effect size, standard errors, and upper and lower limit of effects from 10 studies included in the cardiorespiratory fitness outcomes meta-analyses. CI = confidence interval.



TABLES

TABLE 1. Study quality, sample size, number, average and range of effect sizes for muscular and cardiorespiratory fitness, and training mode for the 20 studies included in the meta-analysis.

			Muscular		Cardiorespiratory					
Ref #	PEDro Score	n	# of Effects	Average Effect (range)	# of Effects	Average Effect (range)	Mode	Time (Min)	Frequency (x/Wk)	Duration (Wks)
2	6	16	0	N/A	3	0.69 (0.65 - 0.77)	Combined	60	3	5
4	7	42	0	N/A	3	0.48 (0.33 - 0.72)	Aerobic	14-45	2-3	8-10
6	7	33	0	N/A	4	0.61 (-0.33 - 1.41)	Combined	60	5	20
8	7	30	0	N/A	1	1.41	Combined	60	3	10
17	6	20	1	1.10	1	-0.46	Combined	60	3	8
29	6	25	0	N/A	2	0.61 (0.61)	Aerobic	30	5	3-4
35	7	46	12	0.24 (0.04 – 0.57)	2	0.59 (0.55 - 0.62)	Aerobic	40-50	3	15
45	9	10	0	N/A	1	0.89	Aerobic	NR	2-3	4
44	8	28	0	N/A	1	-0.04	Aerobic	30	2	8
18	7	23	0	N/A	2	-0.61 (-1.12 - -0.10)	Mixed	NR	2-3	24
28	6	42	4	0.25 (0 – 0.43)	0	N/A	Resistance	NR	2	12
5	7	23	6	0.36 (-0.01 – 0.49)	0	N/A	Resistance	60	2-3	20

10	8	31	4	0.35 (0.10 – 0.56)	0	N/A	Resistance	NR	2	12

Table 1 (cont.)

11	7	31	1	0.27	0	N/A	Resistance	NR	2	12
12	7	36	1	0.39	0	N/A	Resistance	NR	3	8
15	6	14	1	0.64	0	N/A				
19	6	19	4	-0.01 (-0.34 – 0.39)	0	N/A	Resistance; other	40	2	6
25	7	28	1	1.28	0	N/A	Combined	60	2	12
34	7	80	1	-0.08	0	N/A	Combined	30	2	6-7
49	6	95	4	-0.31 (-0.54 - -0.74)	0	N/A	Mixed	NR	3-5	26
47	6	22	1	-0.22	0	N/A	Aerobic	30	2	8

NR = not reported.

TABLE 2. Muscular outcomes random–effects moderator analysis.* p<.05, **p<.001.

Moderator	Type (# of studies)	Point estimate (SE)	Z –value (p)	Q_b (df)
Program type	Resistance only (3)	0.32 (0.15)	2.14*	0.10 (1)
	Combined (11)	0.27 (0.06)	4.34**	
Type of outcome measure	Strength (13)	0.31 (0.06)	5.42**	3.96* (1)
	Endurance (3)	-0.05 (0.17)	-0.29	
Type of measurement device	Isokinetic (10)	0.28 (0.06)	5.03**	0.07 (1)
	Other (4)	0.39 (0.38)	1.03	
Progression	Progression (10)	0.33 (0.07)	4.47**	1.33 (1)
	No progression (4)	0.21 (0.08)	2.62*	
Sample size	40 or less (10)	0.33 (0.10)	3.42**	0.48 (1)
	< 40 participants (4)	0.25 (0.07)	3.50**	
Supervision	Completely supervised (10)	0.27 (0.06)	4.44**	0.00 (1)
	Partially or unsupervised (4)	0.28 (0.13)	2.19*	

TABLE 3. Cardiorespirtory outcomes random-effects moderator analysis.* p<.05, **p<.001.[+]subgroup as unit of analysis was used.

Moderator	Type (# of studies)	Point estimate (SE)	Z –value (p)	Q_b (df)
Type of cardiorespiratory outcome measure[+]	VO_2 (10)	0.37 (0.14)	2.72*	1.08 (2)
	Work (7)	0.50 (0.16)	3.11*	
	Other (6)	0.65 (0.26)	2.49*	
Exercise type	Aerobic (7)	0.50 (0.10)	5.04**	0.32 (1)
	Other (3)	0.31 (0.31)	0.99	
Exercise modality	Cycle (5)	0.53 (0.11)	5.02**	1.27 (1)
	Other (3)	0.10 (0.37)	0.28	
Exercise intensity	Moderate (4)	0.60 (0.14)	4.40**	0.50 (1)
	High (4)	0.48 (0.13)	3.80**	
Sample size	< 25 participant (7)	0.49 (0.21)	2.38*	0.04 (1)
	25 or more (4)	0.44 (0.12)	3.62**	
Supervision	Supervised (9)	0.55 (0.13)	4.43**	3.2 (1) (p=0.06)
	Partially or unsupervised (2)	0.03 (0.25)	0.10	

Table 4. Participant Characteristics

	MS (n = 57)
Age (yr)	51.58 (7.99)
Sex (F/M)	39/18
Disease type (relapsing/progressive)	43/13
Height (cm)	170.41 (10.26)
Weight (kg)	78.74 (20.03)
Years diagnosed (yr)	13.55 (8.93)
SBP (mmHg)	121.40 (23.79)
DBP (mmHg)	75.68 (10.46)
HR (bpm)	65.07 (10.43)

Table 5.

Correlation coefficients between aerobic capacity and muscular strength in the overall MS sample.				
CV outcome	Relative VO_2 peak (ml/kg/min)	Peak power output (W)	Extensors 60° (Nm)	Flexors 60° (Nm)
Aortic PP (mmHg)	-.288 (p = .033)	-.268 (p = .046)	-.346 (p = .008)	-.347 (p = .008)
Augmentation Pressure (mmHg)	-.393 (p = .003)	-.375 (p = .004)	-.455 (p < .001)	-.464 (p <.001)
Aortic T1 (msec)	.376 (p = .005)	.376 (p = .005)	.364 (p = .008)	.448 (p < .001)
Aortic Tr (msec)	.545 (p < .001)	.537 (p < .001)	.601 (p < .001)	.591 (p < .001)
Aix (%)	-.502 (p = .002)	-.447 (p = .001)	-.497 (p < .001)	-.529 (p < .001)
Aix 75 bpm (%)	-.624 (p < .001)	-.561 (p <.001)	-.556 (p < .001)	-.575 (p < .001)
SEVR	.290 (p = .032)	.223 (p = .099)	.079 (p = .558)	.117 (p = .385)
End systolic pressure (mmHg)	-.312 (p = .021)	-.194 (p = .153)	-.237 (p = .076)	-.247 (p = .064)
Pulse wave velocity ($m \cdot s^{-1}$)	.057 (p = .707)	.172 (p = .247)	.226 (p = .123)	.297 (p = .040)