The Independent Contribution of Muscle Strength or Cardiorespiratory Fitness to Cognitive Health in Aging Adults

by

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Abstract

As the world's population ages, the number of people affected by dementia and the overall burden of the disease continues to grow. Research dedicated to refining strategies to reduce the risk of cognitive decline and dementia are of vital importance to promote cognitive health. Exercise can play a neuroprotective role by mitigating the consequences of physical inactivity such as low muscle strength and cardiorespiratory fitness. However, limited studies have focused on examining the contribution of muscle strength and cardiorespiratory fitness for maintaining cognitive function in mid-to-late life.

In this thesis, I conducted a secondary analysis using the Canadian Space Agency (CSA) Inactivity Study, a randomized controlled trial (RCT) of either: 1) 14 days 6° head-down tilt bed rest (HDBR); or 2) HDBR with daily resistance training (RT) and aerobic training (AT) to examine the independent and relative contribution of change in muscle strength and change in cardiorespiratory fitness on cognitive function in adults aged over 55 years. Results from multiple linear regressions showed that change in muscle strength, but not cardiorespiratory fitness was significantly associated with improved executive function following 14 days of HDBR. This finding prompted the inclusion of the Reshaping the Path of Vascular Cognitive Impairment (RVCI) trial, a RCT of 12-month, twice-weekly RT vs. active control in community-dwelling adults with vascular cognitive impairment to further examine the relationship between change muscle strength and cognitive function.

Using data from RVCI, results from multiple linear regressions showed that muscle strength was positively associated with processing speed and working memory. The RVCI dataset addresses the limitations of the CSA study by providing a larger sample size, a non-HDBR sample, and a greater RT stimulus.

This thesis provides preliminary evidence that maintaining muscle strength may be critical for preserving cognitive function in aging adults who experience bed rest or have cerebral small vessel disease. Importantly, this thesis prompts future research to examine: 1) the effect of exercise modality; and 2) the mediating factors between exercise and cognitive health. A better understanding will inform public health policies to help provide more precise exercise recommendations that focus on promoting healthy cognitive aging.

Lay Summary

The number of people living with dementia is expected to triple by 2050. Maintaining a physically active lifestyle is key to reducing the risk of cognitive decline and dementia in late-life. Despite this, physical activity levels decrease with age, leading to consequences such as low muscle strength and physical fitness, which are shown to increase the risk of cognitive impairment. The goal of this thesis was to determine the contribution of muscle strength or fitness to cognitive function. This thesis demonstrates that maintaining muscle strength may be critical for preserving cognitive function in adults over 55 years of age. The preliminary finding suggests that the type of exercise (e.g., running or weightlifting) may have different effects on cognitive health. Thus, future studies should investigate the effect of exercise type on cognitive health which can better inform public health policies to refine exercise guidelines.

Preface

This thesis consists of materials written and compiled by Jammy Zou. The content of this thesis was reviewed by Professors Teresa Liu-Ambrose, Jennifer Davis, Todd Handy, Kenneth Madden, and Bill Sheel. Feedback provided by my MSc Committee was taken into consideration for the final version of the thesis.

All of the work presented henceforth was conducted in the Aging, Mobility, and Cognitive Health Laboratory at the Research Pavilion of the Vancouver General Hospital, the Centre for Aging SMART, and the Djavad Mowafaghian Centre for Brain Health at the University of British Columbia. Jammy Zou was responsible for concept formation, data analysis and interpretation, and manuscript composition. Dr. Teresa Liu-Ambrose was the supervisory author and was involved in concept formation, data analysis and interpretation, and manuscript revision.

Chapter 2. A version of this chapter will be submitted for publication as: Zou, J., Falck, S. R., Balbim, G. M., Davis, J. C., Madden, K., Handy, T. C., Liu-Ambrose, T. (2024). Putting the Brain to Bed: The Importance of Preserved Muscle Strength vs. Cardiorespiratory Fitness for Cognitive Function During Bed Rest. *Applied Physiology, Nutrition, and Metabolism.* Ethical approval for this randomized controlled trial (ClinicalTrials.gov identifier: NCT04964999) was obtained from University of British Columbia Office of Research Ethics (H20-00528 and V20-00528) and the Research Ethics Board of the McGill University Health Center (study no. 2021–7170). The MUHC staff were involved in the study's delivery and assessments. Dr. Ryan S. Falck contributed to the data analysis plan and Dr. Guilherme M. Balbim provided guidance throughout the project and provided a critical revision of the manuscript.

Chapter 3. Ethical approval for this randomized controlled trial (ClinicalTrials.gov identifier: NCT02669394) was obtained from University of British Columbia Clinical Research

Ethics Board (H15-00972) and Vancouver Coastal Health Research Institute (V15-00972). Dr. Teresa Liu-Ambrose, Dr. Elizabeth Dao, Dr. Rachel A. Crockett, and Dr. Cindy K. Barha jointly developed the protocol. Research staff and graduate students within the Aging, Mobility, and Cognitive Health Laboratory were responsible for the study's delivery, assessments, and data processing.

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List of Abbreviations

AD – Alzheimer's disease

ADAS-Cog – Alzheimer Disease Assessment Scale

AT – Aerobic training

BDNF – Brain-derived neurotrophic factor

CSA – Canadian Space Agency

CSVD – Cerebral small vessel disease

DCCS – Dimensional Change Card Sort test

DSST – Digit Symbol Substitution Test

HDBR – 6° head-down tilt bed rest

IGF-1 – Insulin-like growth factor-1

MCI – Mild cognitive impairment

MMSE – Mini-Mental State Examination

MoCA – Montreal Cognitive Assessment

NIH – The National Institutes of Health

PA – Physical activity

PCPS – Pattern Comparison Processing Speed test

RCT – Randomized controlled trial

RT – Resistance training

RVCI – Reshaping the Path of Vascular Cognitive Impairment

TMT – Trail Making Test

VCI – Vascular cognitive impairment

WMH – White matter hyperintensities

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The work I present in this thesis would not be possible without the endless mentorship and support of my supervisor, committee members, and colleagues over the course of my MSc. I would like to express my deepest appreciation to Dr. Teresa Liu-Ambrose. Thank you so much for encouraging my curious nature, trusting my abilities, and guiding my development as an early researcher. You have built an incredible research community that inspires and helps each other to achieve the highest quality of research. Most of all, thank you for your unwavering support of my personal and professional aspirations. I would also like to thank my supervisory committee, Dr. Jennifer Davis, Dr. Todd Handy, and Dr. Kenneth Madden for their advice and feedback that have been critical to the development of my thesis.

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I would like to thank the Canadian Institute of Health Research for funding my MSc research through the Canadian Graduate Scholarship – master's program. This contribution has made it financially possible for me to pursue my MSc.

Finally, to my family and friends, I would like to express my heartfelt gratitude for your endless support through all the celebrations and challenges I faced over the last two years.

Dedication

I dedicate this thesis to my family.

To my Mom and Dad who have prioritized my health and happiness above all else.

To my Brother, for always putting my best interests above your own.

To Sophia, my loving partner. You are the one I look forward to seeing every day, the one I wish to celebrate my greatest achievements with, and the one I rely on for comfort in times of trouble.

Chapter 1: Background

1.1 Introduction

Worldwide, the proportion of the population over 60 years of age is expected to double from 12% in 2015 to 22% by 2050 (1). In Canada, over 18% of the population (7 million people) are over 65 years of age (2). As the population ages, the number of people living with age-related neurodegenerative diseases such as dementia is expected to increase. According to the World Health Organization, around 55 million people have dementia worldwide, with numbers expected to triple by 2050 (3). Canada follows a similar trend; around 597,000 Canadians are living with dementia, with numbers estimated to reach 1 million by 2030 and 1.7 million by 2050 (4). In 2020 alone, 124,000 new cases of dementia were diagnosed in Canada which equates to 15 new cases of dementia every hour (4). Thus, research dedicated to understanding and developing strategies to prevent or delay the onset of cognitive impairment and dementia are of vital importance to maintain the health and quality of life of older adults.

Changes in cognitive function can occur with normal aging. However, accelerated rates of decline that are greater than that expected for an individual's age and education level is an indicator of cognitive impairment with further decline that disrupts an individual's ability to perform daily activities as a sign of dementia. Physical activity (PA) and exercise are promising lifestyle and behavior change strategies that can preserve late-life cognition and prevent dementia by targeting modifiable risk factors including: 1) physical inactivity and 2) cardiometabolic comorbidities (e.g., diabetes mellitus, obesity, and hypertension) (5).

PA is defined as all voluntary bodily movements produced by skeletal muscles that result in energy expenditure (6). Exercise is a subset of PA and is defined as bodily movements that are

planned, structured, and repetitive with an objective of maintaining or improving components of physical health (6). The two main types of exercise are aerobic training (AT) and resistance training (RT); each has its own distinct physiology and benefits. Currently, most evidence supporting the benefits of exercise for healthy cognitive aging stem from AT interventions whereby the mitigation of cardiometabolic risk factors for cognitive impairment are primarily targeted.

Higher cardiorespiratory fitness, a key benefit of AT, is associated with lower cardiometabolic risk factors (e.g., serum lipid and insulin sensitivity) later in life (7). AT-induced improvements in cognitive function are often described by a positive association between cardiorespiratory fitness and cognitive function (8). Evidence highlighting the efficacy of RT for improving cognitive functions in older adults suggests that RT can elicit both cardiometabolic and skeletal muscle health benefits (9). Notably, skeletal muscles can exert neuroprotective effects through endocrine signaling to the brain (10). Thus, changes in skeletal muscle parameters have been described in relation to cognitive health in the contexts of: 1) exercise-induced adaptations (i.e., muscle mass and strength); 2) inactivity (e.g., bed rest); and 3) disease (e.g., sarcopenia).

Despite the utility of exercise as an intervention to promote healthy cognitive aging, differences in exercise modality-dependent benefits and mechanisms prompts the question of the independent and relative contributions of muscle health or cardiorespiratory fitness to cognitive health in aging adults. A better understanding of the relationship between exercise-induced physiological changes and cognitive health can inform public health guidelines to refine and personalize exercise recommendations.

In this chapter, I will provide an overview of neurocognitive changes with age and the role of PA and exercise training for healthy cognitive aging with an emphasis on relevant literature

including: 1) the independent contributions of muscle health parameters (i.e., muscle mass and strength) vs. cardiorespiratory fitness on cognitive function; 2) the effect of AT vs. RT on cognitive health; and 3) the underlying molecular mechanisms. I will conclude with a brief summary of the evidence and the gaps in the literature, before introducing the two research studies that aim to address these gaps.

1.2 Aging and Cognitive Function

Broadly, cognition can be categorized as fluid or crystallized intelligence (11). Observational studies show measurable declines in some but not all cognitive domains with normal aging (12). For example, fluid intelligence, which refers to the ability to process and manipulate new information for reasoning and problem-solving, tends to steadily decline starting in the third decade of life (11,13). Whereas, crystallized intelligence, which refers to the cumulative knowledge that is learned and practiced over time (e.g., vocabulary), can be preserved until around 80 years of age (11,13). The diagnostic and statistical manual of mental disorders (DSM-5) provides six principal domains of cognitive function (Fig. 1) to better classify cognitive deficits associated to neurocognitive disorders; these cognitive domains include: 1) executive functions, 2) learning and memory, 3) language, 4) complex attention, 5) psychomotor function, and 6) social cognition (14,15). Processing speed, executive function, memory, and psychomotor abilities are considered fluid cognitive domains and are important for living independently and with quality (11). Notably, processing speed declines in early adulthood and may be a significant contributor to age-related declines in all cognitive domains (11,12). Even in the absence of disease, strategies that preserve late-life cognitive function would be crucial for one's functional independence and quality of life.

This thesis will focus on executive functions as the main cognitive outcomes. Executive function is an umbrella term that describes a set of mental processes that allow a person to successfully engage in independent, appropriate, and purposive behavior (11,13). Specific processes of executive functions include: 1) response inhibition; 2) set-shifting; and 3) working memory. Response inhibition refers to the ability to suppress actions that can interfere with the goal of a task (16). Set-shifting, or cognitive flexibility, is the ability to alternate between mental sets quickly and efficiently (17). Working memory refers to the ability to temporarily retain information that can be used to complete a task (18). The Stroop Color-Word test, Trail Making Test, and Digit Symbol Substitution test are commonly used to assess response inhibition, set-shifting, and working memory, respectively (19). The National Institutes of Health (NIH) Toolbox Cognition Battery includes measures that are sensitive to age-related changes in response inhibition and set-shifting, which are measured by the Flanker Inhibitory Control and Attention Test and the Dimensional Change Card Sort test, respectively (20).

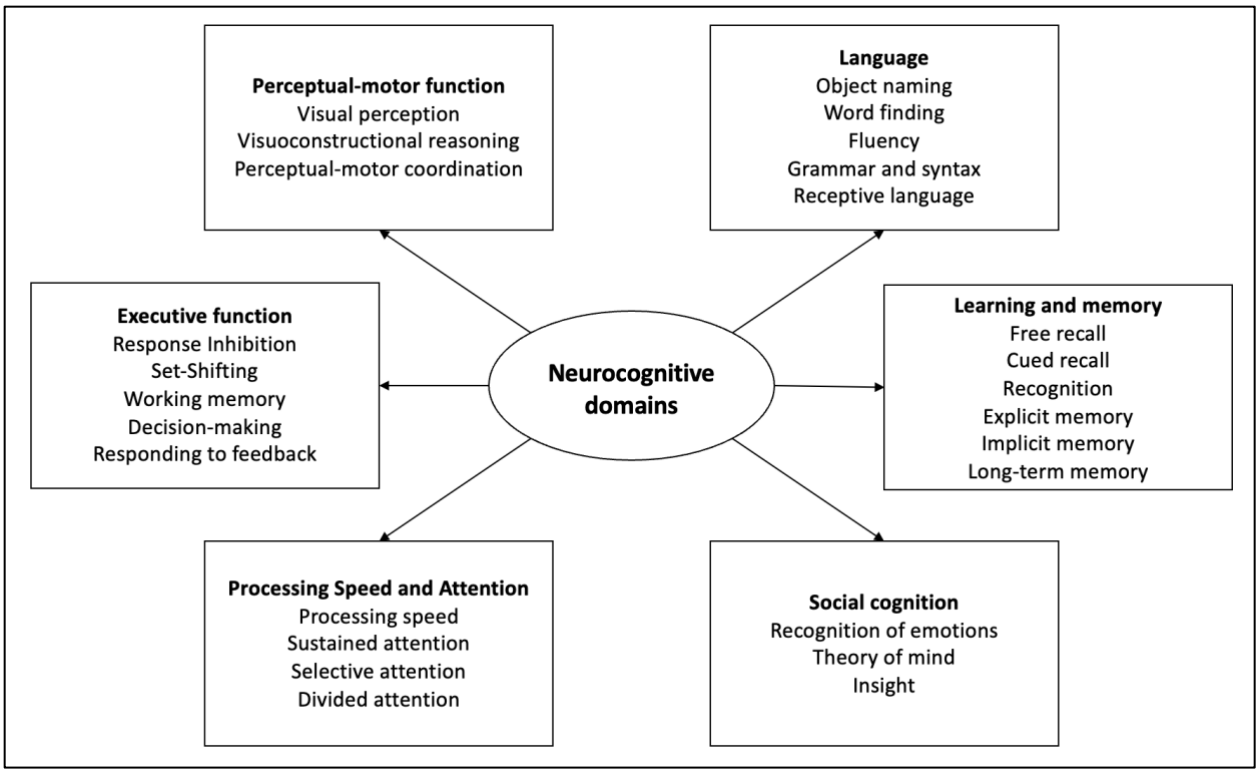

Figure 1: The six neurocognitive cognitive domains defined by the DSM-5 and the corresponding sub-domains used to establish severity of neurocognitive disorders; adapted from Sachdev and colleagues (14).

1.3 Neurocognitive Disorders

Non-normal age-related cognitive decline can be attributed to neuropathological changes in the brain. Cognitive decline that occurs at a greater rate than that expected for an individual's age and education level but does not impair an individual's ability to perform activities of daily living is defined as mild cognitive impairment (MCI) (21). MCI has two clinical subtypes: 1) amnestic, defined by isolated memory deficits and 2) non-amnestic, defined by deficits in non-memory cognitive domains. Petersen and Morris (22) suggest that by combining the clinical subtypes of MCI with presumed etiology, a probable prognosis for the type of dementia can be deduced (Fig. 2). For example, amnestic MCI combined with a suspected neurodegenerative

etiology (e.g., presence of amyloid β) would likely lead to Alzheimer's Disease (AD). In contrast, non-amnestic MCI combined with a suspected vascular etiology (e.g., cerebrovascular damage) would potentially predict vascular cognitive impairment (VCI). The rate of progression from MCI to AD is estimated to be 18% per year in clinical research settings (21). The progression of VCI can be attributed to numerous vascular problems which complicates disease progression (23,24).

The two most common types of dementia are AD which accounts for over 50% of cases, and VCI which accounts for 25-30% of cases (23). The hallmarks of AD include the presence of amyloid β and phosphorylated tau; abnormal accumulation of amyloid β is thought to induce the spread tau pathology via unknown mechanisms, ultimately leading to neurodegeneration (25). VCI is defined as having any level of cognitive impairment (i.e., MCI or dementia) that is caused by overt or covert cerebrovascular disease (23). The leading cause of VCI is cerebral small vessel disease (CSVD), in which the integrity of the brain's small blood vessels is compromised causing inadequate cerebral blood flow and chronic ischemia (23,24). Importantly, an estimated 75% of people with dementia show evidence of vascular neuropathology at autopsy (24).

Given the diverse neuropathology of dementia, the neurocognitive symptoms observed between individuals and different types of dementia are often heterogenous. A longitudinal cohort study investigating the trajectories of cognitive decline in different types of dementia (AD, n=199; VCI, n=10; Other, n=61) found that 1) global cognition declined faster in AD compared with VCI; 2) memory and language declined in AD but was preserved in VCI; and 3) attention and executive functioning declined in all types (26). Findings are consistent with the DSM-5 in which impairments in attention and executive functions are clinical features of vascular neurocognitive disorders whereas declines in memory and learning are clinical features of AD (15).

			Etiology		
			Degenerative	Vascular	Psychiatric
Clinical Classification	Amnestic MCI	Single domain	Alzheimer's Disease	-	Depression
		Multiple domain	Alzheimer's Disease	Vascular Cognitive Impairment	Depression
	Non-amnestic MCI	Single domain	Frontotemporal Dementia	-	-
		Multiple domain	Dementia with Lewy Bodies	Vascular Cognitive Impairment	-

Figure 2: Scheme of combining clinical subtypes with presumed etiology; adapted from Petersen & Morris (22).

1.4 Modifiable Risk Factors for Cognitive Decline and Dementia

Modifiable risk factors for cognitive decline and dementia include: 1) low education; 2) traumatic brain injury; 3) smoking; 4) excessive alcohol consumption; 5) social isolation; 6) physical inactivity; and 7) cardiometabolic comorbidities (5,27). Cardiometabolic risk factors such as diabetes mellitus, hypertension, and obesity are key risk factors for VCI and are highly modifiable by regular PA (23). The following sections will focus on the role of PA and exercise in 1) promoting late-life cognitive health and 2) mitigating the consequences of physical inactivity and cardiometabolic risk factors.

1.5 Physical Activity and Cognitive Function

Regular PA is associated with healthy cognitive aging and a decreased risk of late-life cognitive impairment and dementia (28,29). A meta-analysis of 37 prospective cohort studies that combined relevant studies from two previous meta-analyses with an updated search showed that

higher self-reported PA reduced the risk of cognitive decline by 35% (Relative Risk (RR): 0.65; 95% CI: 0.55 to 0.76) and dementia by 14% (RR: 0.86; 95% CI: 0.76 to 0.97) (30). These significant negative associations survived sensitivity analyses that included higher quality studies, ≥ 10 adjustments, effect sizes reported as odds ratios (OR), and ≥ 10-year follow-up time, albeit with more conservative estimates (30). In a RCT including 170 participants with subjective memory complaint, a 24-week home-based physical activity intervention (i.e., instructions to perform ≥ 150 minutes of moderate-to-vigorous PA per week) resulted in a significant improvement in the Alzheimer Disease Assessment Scale (ADAS-Cog) by 0.26 points compared with the usual care group that deteriorated by 1.04 points ($p = 0.04$) (31). Evidence suggests that engaging in regular PA can promote healthy cognitive aging independent of cognitive status.

Engaging in PA throughout life is important; however, regular PA may be particularly important in mid-to-late life. A cross sectional study by Hillman and colleagues (32) which included participants between the ages of 15-71 years reported that higher PA was significantly correlated with faster reaction time and greater response accuracy on the congruent and incongruent trials of the Flanker test, a measure of executive functions. Further regression analyses showed a stronger positive association between PA and response accuracy in trials with greater interference that require greater executive control (i.e., incongruent trials). Notably, greater PA levels was associated with greater response accuracy in the middle-aged cohort (mean age = 49.6 years), but not in the younger cohort (mean age = 25.5 years). Thus, data from this cross-sectional study indicates that PA in mid-to-late life may exert a greater influence on maintaining executive functions. Further examining the relationship between PA and specific cognitive domains, a systematic review of 23 observational studies showed that higher intensity PA in midlife (>35 years of age) to late-life was associated with better global cognition, executive functions, and

memory during old age (33). There is strong evidence to support that PA not only decreases the risk of late life cognitive impairment and dementia, but engaging in PA, particularly in mid-to-late life, can preserve cognitive function.

1.6 Physical and Cognitive Health Consequences due to Physical Inactivity

Physical inactivity is defined as not meeting the current PA recommendations of ≥ 150 minutes of moderate-to-vigorous PA per day (34). Despite the benefits of PA on cognitive health, PA levels tend to decrease with age; around 60% of Canadians over 65 years are physically inactive according to self-reported PA levels (35). Broadly, PA levels are highest in early adulthood and maintained until around 50 years of age where PA levels begin to gradually decline towards a predominantly inactive lifestyle by 80 years of age (36). Physical inactivity is associated with a host of negative health outcomes (37), many of which are thought to mediate the relationship between physical inactivity and increased risk of cognitive decline and dementia. Of relevance to my thesis, cognitive impairment and dementia risk will be examined in relation to inactivity-induced deterioration in 1) cardiorespiratory fitness and 2) skeletal muscle strength.

The two main factors contributing to decreases in cardiorespiratory fitness are biological aging and physical inactivity which accelerates the decline at any given age (37). In a longitudinal cohort study, Barnes and colleagues (38) showed that cardiorespiratory fitness, represented by VO_{2peak} (ml/kg/min), was positively associated to preserved global cognition and executive function in adults ≥ 55 years of age over a 6-year follow-up period; worse cardiorespiratory fitness at baseline was related to worse performance on all neurocognitive tests 6 years later. These findings were replicated by the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) trial whereby VO_{2peak} was associated with better performance on the neuropsychological test battery ($\beta = 0.12$, $p = 0.01$) over a two-year follow-up

period (39). More specifically, VO_{2peak} was positively associated with executive functions (β = 0.16, p = 0.01) and processing speed (β = 0.25, p < 0.001), but not with memory (β = 0.11, p = 0.12). Evidence also supports measures of cardiorespiratory fitness as health predictors of dementia risk. A prospective cohort study showed that healthy adults who either maintained a high estimated VO_{2peak} (i.e., stayed fit) or improved their estimated VO_{2peak} (i.e., unfit to fit) had a 40-50% reduced risk of incident dementia over a median follow-up period of 7 years and 30-40% reduced risk of dementia-related mortality over a median follow-up period of 19 years when compared with people who maintained low estimated VO_{2peak} (i.e., stayed unfit) (40). Thus, poor cardiorespiratory health due to persistent physical inactivity can increase the risk of cognitive decline and dementia.

Engaging in PA plays a key role in maintaining skeletal muscle health and function. Accelerometer-measured PA duration and intensity show an independent, dose-response relationship with lean mass and lower limb strength in community dwelling older adults (41). Another muscular consequence of prolonged physical inactivity is an increased risk of sarcopenia, which is defined as a progressive and generalized skeletal muscle disorder characterized by low muscle strength and mass (42). A meta-analysis found that PA levels are inversely associated with risk of sarcopenia both cross-sectionally (OR = 0.49, 95% CI: 0.37 to 0.62) and longitudinally (OR = 0.51, 95% CI: 0.27 to 0.94) (43). Several studies have reported that muscle mass and strength are associated with cognitive function (44–46). While increased muscle strength has been repeatedly shown to be associated with improved overall cognition (44,45), contradictory findings emerge in the association between muscle mass and cognition (46,47). Furthermore, sarcopenia is associated with increased risk of cognitive impairment and dementia (48–51). A longitudinal analysis by Berri and colleagues (52) showed that sarcopenia is associated with incident cognitive

decline, MCI, and AD. Notably, muscle strength rather than muscle mass was the primary driver of this association. Thus, maintenance of skeletal muscle strength through regular PA can mitigate the associated consequences to cognitive health.

A review by Le Roux and colleagues (53) suggests a different method to examine the relationship between the adverse consequences of physical inactivity and its effects on cognitive function; strict bed rest can be a unique model of extreme physical inactivity. Kehler and colleagues (54) reviewing the effects of bed rest on the skeletal muscle and cardiorespiratory system describe: 1) a reduction of 1.4 kg fat free mass with a preferential decrease in lower body skeletal muscle by 3.3% within 7 days of bed rest; 2) a decrease in quadriceps maximal voluntary contraction by 13.2% and power by 12.3% following 14 days of bed rest; and 3) a linear decline in cardiorespiratory fitness of up to 1% per day. Fortunately, AT and RT (see definitions in 1.6.1 and 1.6.2, respectively) protected skeletal muscle mass and strength, and cardiorespiratory fitness against bed rest; however, exercise training did not fully mitigate the metabolic consequences of bed rest (53). To date, limited studies have investigated exercise can counteract the negative effects of physical inactivity on cognitive health.

1.7 Exercise and Cognitive Health

Exercise is a promising strategy to: 1) reduce the risk of cognitive decline and late-life dementia (55,56); or 2) promote cognitive health by acting as a countermeasure to the detrimental changes caused by prolonged physical inactivity, previously described (53). A seminal meta-analysis by Colcombe & Kramer (55) found that executive functions were most sensitive to exercise-induced improvements compared with other cognitive domains. The following sections will summarize the evidence from RCTs on the independent effects of AT and RT on cognitive function and dementia risk in older adults.

1.7.1 Aerobic Training and Cognitive Function

AT is defined by physical activity that involves the rhythmic and repetitive use of large muscle groups resulting in an elevated heart and respiratory rate that requires aerobic metabolism to sustain the activity (e.g., running or cycling) (57). AT is generally performed with an objective to improve cardiorespiratory fitness or the capacity at which the circulatory and respiratory systems can supply oxygen to skeletal muscle mitochondria necessary for sustained physical activity (6). Thus, maintenance of cardiorespiratory fitness via AT can help preserve cognitive function in older adults (58). To date, the effects of AT on cognition in older adults have been studied more extensively (56).

According to a meta-analysis by Colcombe and Kramer (55), exercise modalities that aim to increase VO_{2Peak} (AT or AT+RT) are shown to significantly improve cognition in older adults with the greatest effects being on executive functions. Moreover, multimodal exercise (AT+RT) resulted in a greater degree of improvement in all cognitive tasks compared with AT alone (ES = 0.59 vs. 0.41, $p < 0.05$) (55). Another systematic review using objective measures of cardiorespiratory fitness extended these findings; AT interventions that resulted in approximately 14% increased VO_{2Peak} coincided with improvements in processing speed, visual attention, auditory attention, and motor function in healthy older adults (8). More recently, a meta-analysis of nine studies demonstrated that AT alone had a large effect size on memory (Hedges' $g = 0.80$, 95% CI: 0.14 to 1.47; $p = 0.02$) and a small effect size on executive functions (Hedges' $g = 0.37$, 95% CI: 0.04 to 0.69; $p = 0.03$) in healthy adults over 50 years of age (59).

A quasi-experimental study by Guadagni and colleagues (60) explored changes in cognition, cardiorespiratory fitness, and cerebrovascular function following a 6-month AT intervention; cardiorespiratory fitness and executive functions improved following the AT

intervention. This study also showed exploratory evidence that AT-induced improvements in some executive functions are related to AT-induced improvements in cerebrovascular function. An RCT investigating the effect of a 16-week AT intervention on cerebrovascular and cognitive function in physically inactive adults found that cerebrovascular responsiveness to both physiological (hypercapnia) and cognitive stimuli (Trail Making Task and Spatial Span Test) increased following AT compared with the control group (61). This study measured cerebrovascular responsiveness via transcranial doppler ultrasonography which reflects the ability for the brain's microvasculature to maintain cerebral dynamics and autoregulation (61,62). Thus, evidence suggests that AT can elicit improvements in cognitive function through changing cerebrovascular processes.

The effects of AT on cognitive function also apply to older adults with cognitive impairments. A meta-analysis of 11 RCTs examining the effect of moderate-intensity (40-60% heart rate reserve) AT on cognitive function in older adults with MCI report an improvement in global cognition with a modest improvement in memory and no significant effects on attention, executive functions, verbal fluency, and visuospatial function (63). Interestingly, institutionalized older adults with dementia randomized to an AT intervention of ≥ 15 minutes of daily cycling for 15 months showed improvements in functional mobility (measured by Timed "Up and Go" test), global cognition (measured by Mini-Mental State Examination; MMSE) and immediate memory (measured by Fluid Object Memory Evaluation), while those who did no exercise showed a significant decline in the same measures (64). Moreover, when participants' level of cognitive impairment was categorized using MMSE cut-off points (a: 24 > MMSE > 18; b: 18 > MMSE > 14; c: MMSE < 14), AT exerted greater benefits to those with worse levels of cognitive impairment.

1.7.2 Resistance Training and Cognitive Function

RT is defined by performing skeletal muscle contractions against an external resistance with the objective of improving one or more components of muscle health – muscle mass, strength, endurance, and power (e.g., weight-lifting) (57,65). Numerous studies report the benefits of RT on executive functions regardless of cognitive status; however, the effect of RT on memory functions is heterogenous and may depend on cognitive status. A seminal RCT by Liu-Ambrose and colleagues (66) found that 12-months of once and twice-weekly RT improved selective attention and response inhibition (measured by Stroop test) by 12.6% and 10.9%, respectively, compared with the active control group that deteriorated by 0.5%. A meta-analysis by Northey et al. (56) of 36 RCTs that included adults over 50 with no neuropsychiatric conditions showed that exercise improved cognitive function; a moderator analysis revealed a significant effect of RT on executive functions (SMD = 0.49, 95% CI: 0.20 to 0.78), memory (SMD = 0.54, 95% CI: 0.23 to 0.85), and working memory (SMD = 0.49, 95% CI: 0.16 to 0.82). More recently, a meta-analysis aiming to show benefits of RT on cognitive function in older adults with different cognitive statuses found that RT improved global cognitive function in both cognitively healthy and cognitively impaired (i.e., MCI or subjective memory complaints) older adults. However, short-term memory only significantly improved in cognitively healthy older adults following RT (67). No significant RT-induced improvements were found for attention, long-term memory, set-shifting, spatial awareness, reaction time, and verbal fluency, but these null results may be due to small, heterogenous samples that investigated these cognitive domains (67). A network meta-analysis of 73 studies including adults diagnosed with MCI or dementia examined the comparative efficacy of AT, RT, multimodal exercise, and mind-body exercise interventions on global cognition, executive functions, and memory (68). Results indicated that RT had the highest probability of

being the most efficacious exercise intervention to improve global cognition, executive functions, and memory function in adults with dementia; multimodal exercise which includes at least two types of exercise such as RT was most efficacious in improving global cognition and executive functions in adults with MCI (68). Gomez and colleagues (69) examining the dose-response relationship between exercise and cognition found that lower doses of RT elicited clinically important differences in cognition compared to AT: 135 min/week of RT vs. 175 min/week of AT.

To my knowledge, limited number of studies have examined the associations between changes in skeletal muscle parameters and cognitive functions in response to RT. One RCT of a 12-week RT intervention that included 29 older females showed a significant improvement in global cognition following RT and was positively associated with increased lower limb strength (70). Thus, future research should examine whether skeletal muscle parameters mediate the relationship between RT and cognitive function in older adults.

Based on the current literature, AT and RT are both viable options for improving and maintaining cognitive function and reducing the risk factors associated with dementia. Furthermore, the respective exercise-induced improvements in VO_{2Peak} and muscle strength may mediate cognitive improvement. Thus, the question remains of whether exercise-induced changes in muscle strength or cardiorespiratory fitness is more important for mid-to-late life cognitive health.

1.8 Proposed Mechanisms of Exercise-Induced Changes in Cognitive Function

While evidence supports the benefits of exercise on cognitive health in older adults, less is known about the neurobiological mechanisms of exercise-induced improvements in cognitive function. Currently, the Muscle-Brain Crosstalk theory is at the forefront of explaining these exercise-induced benefits in cognition (10). This theory proposes the existence of a muscle-brain

endocrine loop in which skeletal muscle contractions cause a release of central and/or peripheral factors, known as myokines, that can elicit neuroprotective effects (10,71–73). The list of potential myokines is extensive; the most studied are neurotrophic factors include brain-derived neurotrophic factor (BDNF) and insulin-like growth factor 1 (IGF-1). Presently, BDNF cascades are known to be the central mechanism mediating exercise-dependent proliferation of hippocampal neurons and synaptic plasticity (10,73,74). Notably, Erickson and colleagues (74) demonstrated that greater serum BDNF levels are associated with increased hippocampal volume in older adults following one year of AT. Additionally, hippocampal volume was positively associated with spatial memory. IGF-1 can also increase hippocampal neurogenesis and decrease neuroinflammation but is commonly considered an upstream regulator of BDNF (71,72). It is unclear whether IGF-1 can elicit direct neuroprotective effects independent of the BDNF signaling pathway.

The impact of exercise modality (i.e., AT vs. RT) on serum BDNF and IGF-1 concentrations is not well examined or understood. Preliminary evidence from an animal study suggest that exercise modality may elicit divergent molecular mechanisms to elicit changes in cognitive function and brain health. Cassilhas and colleagues (75) show that RT preferentially increases serum IGF-1 levels while AT preferentially increases BDNF levels in rats. In humans, a meta-analysis of 29 studies including exercise programs over two weeks in length showed that resting peripheral BDNF concentrations increased following exercise (Standardized mean difference (SMD) = 0.39, 95% CI: 0.17 to 0.60; $p < 0.001$) and subgroup analyses suggested a significant effect in AT (SMD = 0.66, 95% CI: 0.33 to 0.99, $p < 0.001$), but not RT (SMD = 0.07, 95% CI: -0.15 to 0.30, $p = 0.52$) (76). A meta-analysis of 33 RCTs examining the effect of RT on IGF-1 showed that IGF-1 significantly increased following RT compared with the control group

(weighted mean difference (WMD) = 10.34 ng/ml, 95% CI: 4.93 to 15.74; $p < 0.001$) (77). Interestingly, subgroup analyses showed that the effect of RT on IGF-1 concentrations was only significant in: 1) treatment durations ≤ 16 weeks; 2) participants older than 60 years; and 3) females compared with males. Overall evidence suggests that exercise modality can play a role in preferential myokine release; however, future studies are required to verify these preliminary findings.

Exercise-induced physiological changes in muscle health and cardiovascular health may also play a role in myokine release and delivery. It is hypothesized that the association between sarcopenia and cognitive impairment is due to compromised muscle-brain crosstalk such that muscle atrophy leads to an imbalance in the secretion of myokines (47). Thus, resistance training may maintain or restore the muscle-brain crosstalk and in-turn preserve or improve cognitive function with age. Stimpson and colleagues (78) suggest that improvements in cardiovascular health has more significant benefits on cognitive function and brain health; improved cardiovascular health leads to: 1) increased cerebral angiogenesis and circulation; 2) increased cerebral perfusion; and 3) increased neurotrophin delivery. These cerebrovascular benefits may be particularly important for reducing the risk factors associated with VCI.

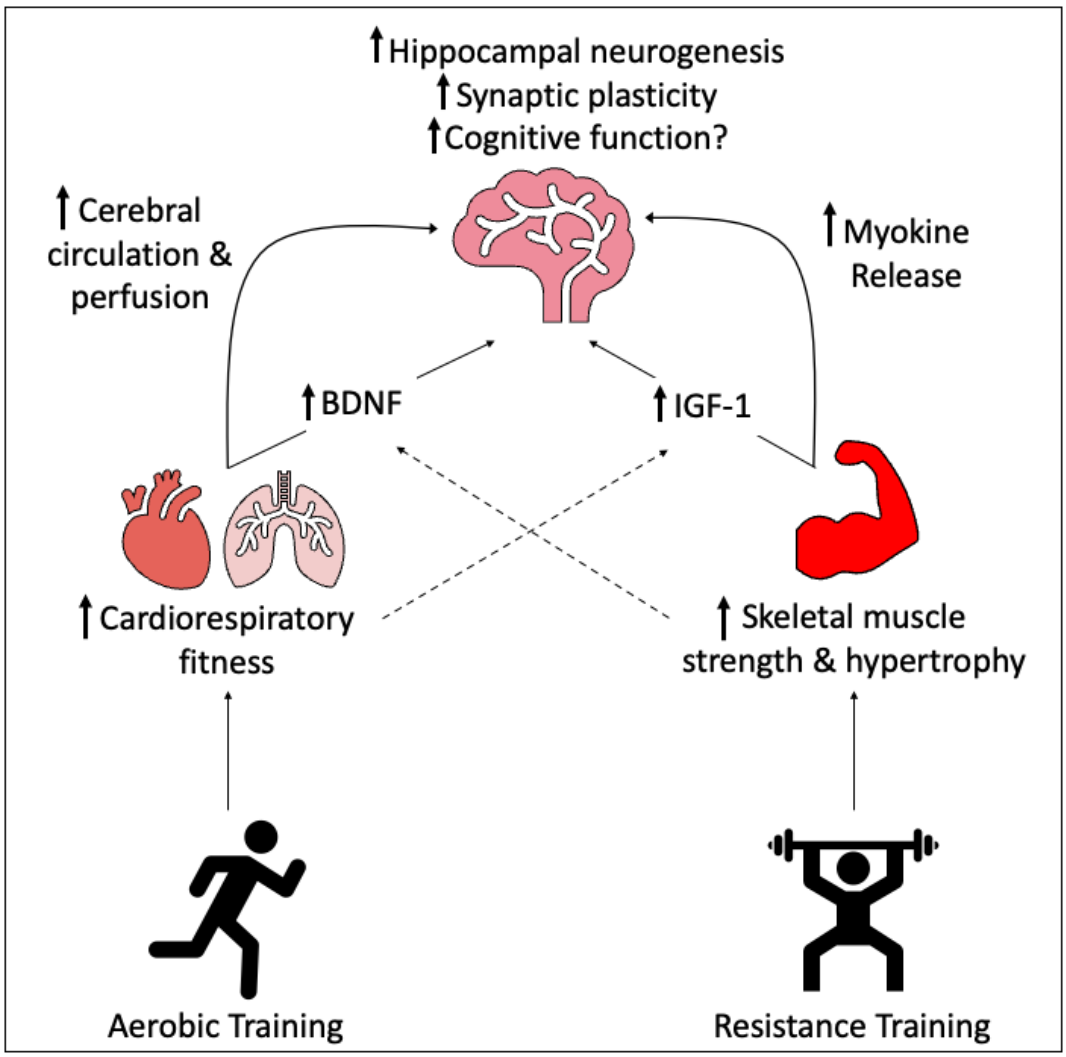

Figure 3: The proposed mechanisms of exercise-induced benefits in brain health and cognitive function via myokines, BDNF and IGF-1; adapted from Kim and colleagues (72).

1.9 Thesis Objectives and Hypotheses

1.9.1 Knowledge Gaps

What is known:

1. Persistent physical inactivity in mid-to-late life can lead to deterioration in muscle strength and cardiorespiratory fitness; these consequences are independently associated with increased risk of cognitive decline and dementia in late-life.

2. AT and RT are promising strategies to improve cognitive function and reduce risk factors associated with cognitive impairment and dementia in middle aged and older adults of varying cognitive status.

What is unknown:

1. The contribution of changes in muscle strength vs. changes in cardiorespiratory fitness to changes in cognitive function in middle age to older adults.
2. The role of peripheral neurotrophic factors (e.g., IGF-1) as an underlying mechanism driving the relationship between exercise training and cognitive function.

1.9.2 Thesis Objectives

Primary Objective: To determine the independent and relative contribution of changes in muscle strength and changes in cardiorespiratory fitness to changes in cognitive function.

Secondary Objective: To determine whether changes in peripheral neurotrophic factors are associated with changes in cognitive function.

1.9.3 Hypotheses

1. I hypothesize that changes in muscle strength and changes in cardiorespiratory fitness will be independently predict changes in cognitive function with greater variation explained by changes in cardiorespiratory fitness.
2. I hypothesize that changes in peripheral neurotrophic factors will be associated with changes in cognitive function.

Chapter 2

A version of this chapter will be submitted for publication as: Zou, J., Falck, S. R., Balbim, G. M., Davis, J. C., Madden, K., Handy, T. C., Liu-Ambrose, T. (2024). Putting the Brain to Bed: The Importance of Preserved Muscle Strength vs. Cardiorespiratory Fitness for Cognitive Function During Bed Rest. *Applied Physiology, Nutrition, and Metabolism.*

2.1 Introduction

Despite evidence highlighting the physical and neurocognitive benefits of a physically active lifestyle (33,79), PA levels tend to decrease with age (36). The gradual decrease in PA in the older population can occur secondary to chronic conditions, or acutely, due to bed rest as a result of injury, surgery, or hospitalization. Even a brief period of bed rest in older adults can initiate a downward spiral in muscle strength (80), cardiorespiratory fitness (81), and cognitive function (82).

Current evidence show that bed rest can lead to deleterious consequences to physical and cognitive health. A systematic review including adults aged < 50 years showed that muscle mass and strength in the knee extensors (i.e., quadriceps) declined at nonuniform rates with rates of decline in muscle strength exceeding that of muscle mass in the first two weeks of bed rest (83). These declines in muscle parameters due to experimental bed rest have also been shown by a meta-analysis of healthy older adults, over 60 years; knee extension power (N/s) significantly decreased (ES = -1.06, 95% CI: -1.37 to -0.75, $p < 0.001$) and leg muscle mass significantly decreased (ES = -0.68, 95% CI: -0.96 to -0.40, $p < 0.001$) following bed rest interventions (84). A seminal bed rest study including five 20-year-old males showed that three weeks of bed rest resulted in greater deterioration in cardiorespiratory capacity than did 30 years of aging (85). A systematic review

reported that cardiorespiratory fitness declines linearly with bed rest duration; participants who had higher VO_{2peak} pre-bed rest also experienced greater declines (86). To my knowledge, no studies have investigated whether bed rest-induced declines in muscle strength and cardiorespiratory fitness are associated with cognitive decline and increased risk of dementia. Thus, the relationship can only be speculated based on studies examining the associations in non-bed rest contexts (38,40,43,52).

Despite the putative relationship between bed rest-induced physical consequences and cognitive decline, a review summarizing the effects of clinical and experimental bed rest on cognitive function showed variable findings (87). Reasons that explain the mixed results could include: 1) repeated cognitive task exposure leading to practice effects; and 2) the use of traditional summary scores that fail to account for within-person variability in performance (87,88). Clinically, critical and non-critical hospitalizations were significantly associated with greater declines in global cognition while non-critical hospitalizations were also significantly associated with incident dementia in older adults over 65 years of age (82). Given the positive relationship between PA and cognitive function (30), it is plausible that the effects of physical inactivity due to bed rest is detrimental to cognitive health.

Experimental bed rest represents an extreme model of physical inactivity (37,53). The 6-degree head-down tilt bed rest (HDBR) approach has been predominantly used in experimental bed rest studies to examine the effects of microgravity experienced by astronauts in spaceflight contexts. However, the physical maladaptation in the skeletal muscle and cardiovascular systems due to HDBR are comparable to that of horizontal bed rest experienced during hospitalization (53,54). Thus, HDBR approaches can inform how to care for adults who undergo bed rest or

experience prolonged inactivity during acute hospitalization or long-term care due to injury or chronic illness.

Exercise training can be a countermeasure to the consequences of physical inactivity (89). Meta-analyses of RCTs suggest that exercise training improves older adults' cognitive function, particularly in executive functions (55,56,90). Few studies have investigated the effects of an exercise intervention as a countermeasure to preserve cognitive function during bed rest. Some evidence suggests that the neuroprotective effects of exercise hold true in bed rests contexts despite a markedly shorter duration of the exercise intervention (91,92). Notably, an analysis using the same data from the CSA Inactivity Study showed that the exercise group maintained performance in the Flanker test, measuring response inhibition whereas, the non-exercise control group had worse performance following 14 days of HDBR (91). Another RCT of a 60-day HDBR intervention including 22 healthy males support the benefits of exercise training to modulate the effect of bed rest on brain health and cognitive function (93). It remains unclear whether exercise-induced changes in muscle strength and VO_{2Peak} are associated with changes in cognitive function following bed rest.

The neurobiological mechanisms driving exercise-induced improvements in cognitive function are unclear. One theory, the Muscle-Brain Crosstalk, suggests that skeletal muscle contractions cause secretions of peripheral neurotrophic factors, BDNF and IGF-1, which can lead to downstream neuroprotective effects (10,71). Data from the CSA Inactivity Study examining the effects of 14-day HDBR with and without exercise on serum BDNF and IGF-1 concentrations found no changes in BDNF from pre- to post-bed rest, by group, nor by sex; however, IGF-1 significantly reduced at HDBR-completion in females only, regardless of group ($p = 0.018$) (94).

Hence, one of the objectives of this study was to determine whether changes in IGF-1 concentrations are associated to changes in cognitive function.

This study aims to address the knowledge gap regarding whether exercise-induced changes in muscle strength, measured by isokinetic knee extension peak torque (Nm), and cardiorespiratory fitness, measured by VO_{2Peak} (ml/kg/min), independently contribute to the maintenance of cognitive function in adults confined to 14 days of HDBR. We also aimed to examine whether changes in serum IGF-1 levels are associated to changes in cognitive function to explore underlying neurobiological mechanisms. We hypothesize that: 1) both change in muscle strength and $VO2_{peak}$ will be significantly associated with changes in executive functions with greater variation in executive functions explained by change in $VO2_{peak}$; and 2) changes in IGF-1 levels will be associated with changes in executive functions.

2.2 Materials and Methods

This CSA Inactivity Study was supported by a consortium comprising the Canadian Space Agency (CSA), Canadian Institutes of Health Research (CIHR), and Canadian Frailty Network (CFN) and developed in collaboration with the McGill University Health Center (MUHC). The study details are described in depth published protocol (95) and the trial was registered with the US National Institutes of Health (ClinicalTrials.gov, NCT04964999). Study protocols were developed with reference to the "Guidelines for Standardization of Bed Rest Studies in the Spaceflight Context" (96). The study protocol and consent form are written in accordance with the Declaration of Helsinki. Ethical approval was granted from the Research Ethics Board of the MUHC, and the University of British Columbia's Clinical Research Ethics Board. All participants provided written informed consent after receiving a thorough explanation of the study procedures

by study staff. Participants were permitted to withdraw from the study at any time or were prematurely withdrawn if they experienced an adverse event.

2.2.1 Study Design

A secondary analysis of an open-label, non-blinded, parallel-group, proof-of-concept RCT in which 23 healthy older adults (12 males and 11 females) aged 55-65 years were randomized to either: 1) 14 days of HDBR (CON); or 2) HDBR with daily combined resistance and aerobic exercise training (EX). The experimental period spanned 26 days and included 1) an adaptation phase (days 1-5); 2) an intervention phase (day 6-19); and 3) a recovery phase (day 20-26).

2.2.2 Recruitment and Eligibility

Participants were recruited from the greater Montreal area from April 16, 2021, to July 12, 2021, via print and electronic media advertisements. Interested individuals were first screened for basic eligibility criteria and consent via telephone then proceeded through a second stage of screening with medical and psychological assessments. Detailed procedures of the recruitment process are available in the published protocol (95).

Individuals were included if they were: a) between 55 and 65 years of age; b) community dwelling; c) able to participate in at least 2.5 hours of aerobic exercise per week at a moderate to vigorous intensity; d) if female, postmenopausal (no menses for ≥ 1 year) or with documented ovariectomy and serum follicle-stimulating hormone above 30 IU/l; e) cognitively healthy, as determined by a Montreal Cognitive Assessment score ≥ 26/30 and a Mini-Mental State Examination score ≥ 27 (97,98); f) completed high school education; g) between 158 and 190 cm in height; h) body mass index (BMI) from 20 to 30 kg/m^2; and i) read, write, and speak English. Additional inclusion criteria are outlined in the “Guidelines for Standardization of Bed Rest”.

The exclusion criteria were: a) history of heart attacks, thrombosis risk, severe allergies, hypocalcemia, uric acidemia, orthostatic intolerance, vestibular disorders, considerable musculoskeletal issues, chronic back pain, head trauma, seizures, ulcers, renal stones, gastro-esophageal reflux disease or renal function disorder, hiatus hernia, migraines, or diagnosed psychiatric conditions; b) electrocardiogram abnormalities; c) diagnosis of AIDS, hepatitis B, or C; d) anemia, defined as ferritin lower than 10 or >154 ng/ml (females) and lower than 20 or >245 ng/ml (males); e) family history of thrombosis; f) bone mineral density lower than 2 standard deviation of T-score; g) claustrophobia; h) special dietary requests (e.g., vegetarian, vegan); i) contraindications to undergoing magnetic resonance imaging; j) donated blood in the past three months; k) smoked (tobacco and/or marijuana) within six months prior to the start of the study; l) abused drugs, medicine, or alcohol (i.e., >10 drinks a week, with >2 drinks a day most days) within up to 30 days prior to the start of the study; m) participated in another study within 2 months before study onset; or n) positive COVID-19 test within one week to 24 h before study start date.

2.2.3 Randomization and Blinding

The randomization sequence was generated using Microsoft Excel at a 1:1 ratio stratified by biological sex. Group allocation was not concealed to the study coordinator. Randomization was performed after baseline assessments and participants were allocated to their assigned groups on day 6. Blinding of group allocation from participants and staff carrying out the intervention was not possible. Outcome assessors were also not blinded to group allocation.

2.2.4 Experimental Groups

Participants in both the EX and CON groups remained in the 6° HDBR position for 24/day during the 14-day intervention period (days 6-19). All activities were performed in the HDBR position.

There were no restrictions on electronic use and participants were permitted to move and stretch in bed. Participants from different groups did not interact with each other.

CON: Participants in the control group stayed in a 6° HDBR position. Daily physiotherapy sessions lasting 15 to 20 minutes included stretching, motion therapy, and massages.

EX: Participants in the experimental group engaged in daily combined aerobic and resistance exercise training while in the 6° HDBR position. Exercise training was split into three sessions consisting of a combination of high-intensity interval training (HIIT), continuous aerobic, progressive aerobic, and lower and upper body strength training exercises for a total daily exercise duration of 60 to 72 minutes (Table 2.1). A detailed description of exercise type, intensity, and duration are provided in (Table 2.2). All exercise sessions occurred between 06:00 and 18:00, with a 4-hour break between sessions. Trained exercise instructors delivered all exercise sessions with a 1:1 supervisor-to-participant ratio.

2.2.5 Measurements

All measurements were acquired by highly trained staff at the Research Institute of the MUHC, Centre for Innovative Medicine, Lindsay Gingras Rehabilitation Centre, and the Douglas Mental Health University Institute in Montreal, Canada. Outcome measures were taken at baseline (day 1-5) and at HDBR completion (day 20-26).

2.2.5.1 Descriptive Measures

Demographic data collected at baseline included: a) age; b) biological sex; c) years of education; d) occupation; e) height (cm); f) weight (kg) using a standing scale (Rice Lake Medical Scale, model: 250-10-2); g) and body mass index (BMI) (kg/m^2).

2.2.5.2 Cognitive Measures

Executive functions and processing speed were assessed using the National Institutes of Health (NIH) Toolbox Cognition Battery (99). All assessments were completed in the HDBR position using a portable 9.7-inch Apple iPad. The NIH Toolbox Cognition Battery included the Flanker Inhibitory Control and Attention Test (congruent and incongruent), the Dimensional Change Card Sort Test (DCCS), and the Pattern Comparison Processing Speed Test (PCPS).

The Flanker Test measures response inhibition. Response inhibition is an executive function that refers to the ability to control automatic response tendencies that may interfere with achieving a goal (16). The Flanker test includes two types of trials, congruent and incongruent. In congruent trials, participants indicate the direction (left or right) of a target arrow presented in a line of other arrows (flanker arrows) pointed in the same direction. In incongruent trials, the target arrow is pointed in the opposite direction of flanker arrows (100). Participants were instructed to indicate the direction of the target arrow as fast as possible without making a mistake. A total of 20 trials were conducted, with 12 congruent and eight incongruent.

The Dimensional Change Card Sort Test assessed set-shifting. Set shifting is an executive function that refers to the capacity to switch between multiple tasks or mental sets (17). In this test, participants were presented with cards containing a pattern of a color and shape; participants were instructed to switch between sorting the cards by color and by shape as fast as possible without making a mistake (100). A total of 30 trials were conducted.

The Pattern Comparison Processing Speed Test assessed processing speed. Processing speed is a measure of mental efficiency and is necessary for many cognitive domains; it refers to the amount of time it takes to process a set amount of information (101). Participants were presented with two images side-by-side and instructed to indicate whether the images are the same

or different as fast as possible without making a mistake (100). This test lasted 85 seconds with a maximum of 130 trials.

Fully corrected T-scores which corrected for age, education, gender, and race/ethnicity were derived for all three tests of the NIH Toolbox Cognition Battery. Higher scores indicated better performance. The Flanker t-score was the main cognitive outcome variable of interest to extend the findings of the primary analysis (91). The DCCS and PCPS scores were the secondary cognitive outcome variables of interest.

2.2.5.3 Physical Measures

Quadriceps (i.e., knee extension) isokinetic strength was used to index changes in skeletal muscle health and measured using a quantitative multi-joint muscle dynamometer (Biodex-system 3, Biodex Medical Systems, NY, USA). Standardized verbal encouragement was provided during the test. Muscle strength was represented by peak torque (N/m), unadjusted by weight. Two muscle strength outcomes were collected: 1) isokinetic 3 repetition extension and 2) isokinetic 20 repetition extension. Only knee extension measures will be used for data analyses because findings from an ancillary study reported significant reductions in knee extension measures following HDBR but not in knee flexion measures (102).

Maximal aerobic capacity (VO_{2Peak}) was used to index changes in cardiorespiratory fitness and measured using incremental bicycle ergometry test to exhaustion on an electronically braked cycle ergometer (Lode Corival CPET, Lode B.V., Groningen, NL, the Netherlands). Briefly, participants cycled at around 70 RPM starting at 15W for 3-min followed by incremental increases in work rate by 15W each minute until exhaustion (i.e., RPM <65 despite verbal encouragement). Oxygen uptake was measured using either: 1) a metabolic cart (Quark CPET, COSMED, Rome,

IT, Italy) or 2) a portable metabolic system (MetaMax 3B-R2®). VO_{2peak} was normalized to participants' body mass at the time of assessment.

2.2.5.4 Biomarkers

Fasting blood samples were collected via venipuncture by a trained phlebotomist and transported to the MUHC Clinical Laboratory. Blood was centrifuged, and serum and plasma were frozen at −80°C until analysis. Serum IGF-1 concentrations (nmol/L) were analyzed by enzyme-linked immunosorbent assay (ELISA) (R&D Systems). Serum BDNF data was not available.

2.2.6 Sample Size and Data Analysis

The sample size is predetermined by the consortium for a comparison test at a 0.05 two-sided significance level, with a power of 80% to detect an effect of bed rest and between group differences in maximal aerobic power, muscle-pump baroreflex, muscle and marrow adiposity, cortical bone porosity, neuromotor drive, muscle protein turnover, and heat shock protein expression. Thus, findings generated in this secondary analysis are hypothesis generating and should be interpreted with caution.

Analyses were performed in IBM SPSS Statistics software version 29.0.1.0 for MacOS (IBM Inc., Chicago, IL, USA) including only participants with complete data at baseline and trial completion. For all tests, significance was set at $p < 0.05$. I performed an one-way Analysis of Covariance (ANCOVA) to assess between-group differences in change in: 1) knee isokinetic extension peak torque; 2) VO_{2Peak}; and 3) IGF-1 concentration, including baseline measures as covariates. To examine within-group differences in: 1) knee isokinetic extension peak torque; 2) VO_{2Peak}; and 3) IGF-1 concentration from baseline to trial completion, I performed paired samples t-tests for each group (two-sided p). The independent contribution of: 1) change in isokinetic knee extension peak torque; and 2) change in VO_{2peak} to changes in executive functions and processing

speed was evaluated using multiple linear regressions. We performed two separate multiple linear regressions for each cognitive outcome to determine whether: 1) change in VO_{2Peak} was associated with change in cognitive function, after accounting for change in isokinetic knee extension and covariates; and 2) change in isokinetic knee extension was associated with change cognitive function, after accounting for change in VO2max and covariates. Covariates included: 1) baseline cognitive performance; 2) baseline VO_{2peak}; 3) and baseline isokinetic knee extension peak torque.

Partial Pearson correlations were performed to assess associations between change in serum IGF-1 and change in cognitive functions after accounting for biological sex and baseline measures of interest. Additionally, data was split by biological sex to include only a sample of females (n=6) and partial correlations were performed to examine associations between change in IGF-1 and change in cognitive functions, adjusting for baseline outcome measures.

Table 2.1: Weekly and daily exercise protocol – 3 sessions per day.

Week 1						
Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
RT – UE	AT – Cont. 1	AT – Prog.	AT – Cont. 1	AT – HIIT	AT – Cont. 1	AT – HIIT
AT – Prog.	RT – LE	AT – Cont. 2	RT – UE	AT – Prog.	RT – UE	AT – Cont. 2
AT – HIIT	AT – Prog.	AT – HIIT	AT – Prog.	RT – LE	AT – Prog.	AT – Prog.
Week 2						
Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
AT – Cont. 2	AT – HIIT	AT – Cont. 1	AT – HIIT	AT – Cont. 1	AT – HIIT	AT – Cont. 2
RT – LE	AT – Cont. 2	RT – LE	AT – Cont. 2	RT – LE	AT – Prog.	AT – Cont. 1
AT – Prog.	AT – Prog.	AT – Prog.	AT – Prog.	AT – Prog.	RT – UE	AT – Prog.

Abbreviations: AT = Aerobic training; RT = resistance training; UE = upper extremity; LE = lower extremity; Cont. 1 = continuous (30 minutes); Cont. 2 = continuous (15 minutes); Prog. = progressive; HIIT = high intensity interval training.

Table 2.2: Exercise protocol descriptions.

Exercise type	**Duration (min)**	**Descriptions**
HIIT	32	High-intensity interval training (32 min) on a cycle ergometer: 5 min warm-up (40% HRR), 11 intervals (30s on 80%-90% HRR, 1.5 min relaxed cycling), 5 min cooldown
Aerobic (continuous)	30	Aerobic cycle exercise (30 min): 5 min warm-up (40-50% HRR**), 20 min at 60-70% HRR, 5 min cooldown (40-50% HRR).
Aerobic (continuous)	15	Aerobic cycle exercise (15 min): 3 min at HRR 40%, 9 min at 60-70%, 3 min at HRR 40%.
Aerobic (progressive)	15	Aerobic cycle exercise (15 min): 3 min stages at the following HRR: 30%, 40%, 50%, 60%, 40%.
Strength training (lower body)	25	Strength exercise with cables, resistance bands, and Swiss ball. Three sets (1 warm-up) of 10-12 repetitions: hip raise, leg press unilateral supine lying on the cable, ankle pump, and leg curl. The first set was a warm-up at low load (5-6 at 10-point RPE Borg scale) and sets 2 and 3 at targeted load (7-8 at 10-point RPE Borg scale).
Strength training (upper body)	25	Strength exercise with cable, resistance bands, and Swiss ball. Three sets (1 warm-up) of 10-12 repetitions: external shoulder rotation, chest fly, dead bug, and lateral pull down. The first set was a warm-up at low load (5-6 at 10-point RPE Borg scale) and sets 2 and 3 at targeted load (7-8 at 10-point RPE Borg scale).

Abbreviations: HIIT = High-Intensity Interval Training. RPE = Rate of Perceived Exertion.
**HRR: Heart Rate Reserve = Heart Rat max–Resting Heart Rate.

2.3 Results

2.3.1 Participant Characteristics

Twenty-four participants were eligible for the study. Twenty-three participants were randomized following completion of baseline assessments. One participant was excluded before randomization due to unforeseen logistical reasons and one participant's outcome measures were not made available at the time of analysis (Fig. 1: CONSORT diagram). The analytic sample was N=22. Baseline characteristics are described in Table 2.3. Participant's mean age was 58.77 (SD=2.96), mean years of education was 22.55 (SD=4.00), and 50% were females (n=11).

Table 2.3: Baseline demographics and clinical characteristics of study participants.

Variables[a]	**Overall (n=22) M (SD)**	**Exercise (n=11) M (SD)**	**Control (n=11) M (SD)**
Age	58.77 (2.96)	59.09 (2.77)	58.45 (3.24)
Females (n, %)	11 (50.00)	0.45 (0.52)	0.55 (0.52)
Education (years)	22.55 (4.00)	21.45 (4.44)	23.64 (3.35)
Cognitive function[b]			
Flanker	47.09 (6.41)	47.09 (5.11)	47.09 (7.75)
DCCS	59 (12.84)	66.18 (8.52)	51.82 (12.66)
PCPS	52.82 (14.92)	54.64 (14.25)	51 (16.04)
Physical characteristics			
BMI (kg/m^2)	24.88 (2.91)	25.73 (2.91)	24.03 (2.78)
Knee extension–3 rep (Nm)	91.83 (32.24)	96.62 (34.03)	87.05 (31.22)
Knee extension–20 rep (Nm)	62.9 (21.48)	64.39 (19.37)	61.42 (24.27)
VO_{2peak} (ml/min/kg)	31.11 (6.46)	32.03 (6.98)	30.19 (6.10)
IGF-1 (nmol/L)	20.77 (5.59)	22.43 (6.82)	19.44 (4.29)

Abbreviations: DCCS = Dimensional Change Card Sorting Test; PCPS = Pattern Comparisons Processing Speed Test; BMI = Body mass index; VO_{2peak} = maximal aerobic capacity; rep = repetition.

[a] Data presented as mean (standard deviation) or count (%) where applicable.

[b] Fully corrected t-score; higher scores indicate better performance (corrected for age, education, biological sex, and race/ethnicity).

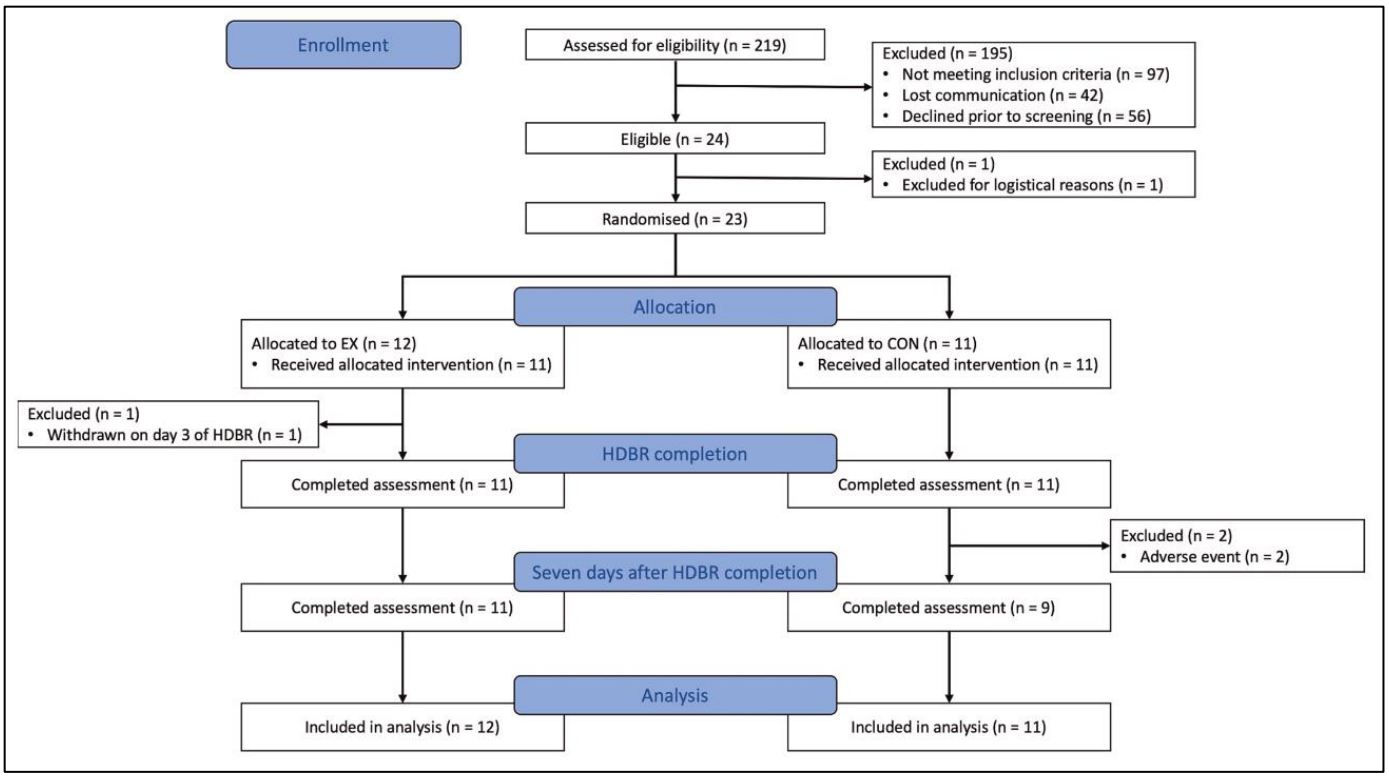

Figure 4: CONSORT diagram. Abbreviations: EX = exercise group; CON = control group (91).

2.3.2 Between-Group and Within-Group Differences

Results from the one-way ANCOVA show that change in VO_{2Peak} was significantly different between groups ($F(1,16) = 7.258$, $p = 0.016$). The mean change showed that the control group ($M = -4.21$, $SE = 1.01$; 95% CI: -6.36 to -2.06) had a greater decline in VO_{2Peak} compared with the exercise group ($M = -0.43$, $SE = 0.96$; 95% CI: -2.47 to 1.61). There were no other significant between-group differences in changes in: 1) knee isokinetic (3 rep & 20 rep) peak torque; and 2) IGF-1 concentrations (all ps > 0.05).

Results from the paired samples t-tests indicate that there was a significant reduction in VO_{2Peak} from baseline ($M = 31.61$, $SD = 5.82$) to trial completion ($M = 27.45$, $SD = 5.81$) in the CON group ($t(8) = 3.20$, $p = 0.013$). However, there was no significant change in VO_{2Peak} from baseline ($M = 32.96$, $SD = 6.60$) to trial completion ($M = 32.47$, $SD = 7.03$) in the EX group ($t(9)$

= 0.84, p = 0.422). Isokinetic knee extension (3 rep) peak torque significantly reduced in both groups (CON: t(9) = 2.59, p = 0.029; EX: t(10) = 2.98, p = 0.014) from baseline (CON: M = 87.99, SD = 32.74; EX: M = 96.62, SD = 34.03) to trial completion (CON: M = 79.14, SD = 30.91; EX: M = 81.30, SD = 29.57). Similarly, isokinetic knee extension (20 rep) peak torque significantly reduced in both groups (CON: t(9) = 2.50, p = 0.034; EX: t(10) = 3.91, p = 0.03) from baseline (CON: M = 62.70, SD = 25.19; EX: M = 64.39, SD = 19.37) to trial completion (CON: M = 57.01, SD = 24.67; EX: M = 57.26, SD = 21.12). There were no significant within-group differences in IGF-1 concentrations in both groups (CON: t(9) = -0.17, p = 0.868; EX: t(6) = -0.66, p = 0.535) from baseline (CON: M = 19.44, SD = 4.29; EX: M = 21.11, SD = 6.18) to trial completion (CON: M = 19.61, SD = 6.70; EX: M = 22.11, SD = 7.78).

2.3.3 Main Analyses

The results of the multiple linear regression model analyses are reported in Table 2.4 and Table 2.5. Change in VO_{2peak} after adjusting for change in isokinetic 3-rep knee extension peak torque and covariates was not significantly associated with change in Flanker performance following HDBR, β = -0.01; t(13) = -0.01; p = 0.990. Whereas change in isokinetic 3-rep knee extension peak torque was significantly associated with change in Flanker t-score after adjusting for change in VO_{2Peak} and covariates following HDBR, β = 0.63; t(13) = 2.19; p = 0.040. Change in VO_{2peak} after adjusting for change in isokinetic 20-rep knee extension peak torque and covariates was not significantly associated with change in Flanker performance following HDBR, β = 0.19; t(13) = 0.883; p = 0.394. Change in isokinetic 20-rep knee extension peak torque was not significantly associated with change in Flanker t-score after adjusting for change in VO_{2Peak} and covariates following HDBR, β = 0.50; t(13) = 2.17; p = 0.051. There were no significant

independent associations between changes in VO_{2Peak} and isokinetic knee extension peak torque (3 and 20 repetition) with changes in DCCS or PCPS performance following HDBR (all $p > 0.05$).

2.3.4 IGF-1 Analyses

Complete data for IGF-1 was available for 17 participants (6 females and 11 males). There were no significant correlations between changes in IGF-1 concentrations and changes in Flanker ($r(12) = -0.46$; $p = 0.099$), DCCS ($r(12) = -0.14$; $p = 0.639$), or PCPS ($r(12) = -0.30$; $p = 0.302$) performance, after adjusting for baseline measures and biological sex. Since a previous study using the same dataset only observed a significant decrease in IGF-1 with time in females (94), data was split by biological sex (females $n = 6$; males $n = 11$) to examine correlations between change in IGF-1 and changes in cognitive function. There were no significant correlations between change in IGF-1 and changes in cognitive function in female- and male-only samples (all $p > 0.05$).

Table 2.4: Multiple linear regression with knee isokinetic 3 repetition extension and VO_{2Peak} as the main predictor variables (Complete-case; N=18).

NIH Toolbox tasks	Block	Variables	B (SE)	β	p-value	R^2	Adjusted R^2	p-value
ΔFlanker[a]				Model 1				
		BL Flanker	0.07 (0.30)	0.06	0.813			
	1	BL isokinetic (3 rep)	0.19 (0.06)	0.91	0.009*	0.26	0.10	0.232
		BL VO_{2peak}	-0.07 (0.29)	-0.06	0.806			
	2	ΔVO_{2peak}[b]	-0.01 (0.55)	0.00	0.990	0.26	0.03	0.868
	3	Δ isokinetic (3 rep)[b]	0.35 (0.16)	0.63	0.049*	0.47	0.25	0.049*
				Model 2				
		BL Flanker	0.07 (0.30)	0.06	0.813			
	1	BL isokinetic (3 rep)	0.19 (0.06)	0.91	0.009*	0.26	0.10	0.231
		BL VO_{2peak}	-0.07 (0.29)	-0.06	0.806			
	2	Δ isokinetic (3 rep)[b]	0.35 (0.16)	0.63	0.049*	0.47	0.31	0.040*
	3	ΔVO_{2peak}[b]	-0.01 (0.55)	0.00	0.990	0.47	0.25	0.990
ΔDCCS[a]				Model 1				
		BL DCCS	-0.32 (0.21)	-0.37	0.154			
	1	BL isokinetic (3 rep)	0.12 (0.08)	0.49	0.137	0.41	0.28	0.055
		BL VO_{2peak}	-0.47 (0.32)	-0.34	0.161			
	2	ΔVO_{2peak}[b]	-0.9 (0.69)	-0.31	0.220	0.47	0.31	0.237
	3	Δ isokinetic (3 rep)[b]	0.18 (0.18)	0.28	0.339	0.51	0.31	0.339
				Model 2				
		BL DCCS	-0.32 (0.21)	-0.37	0.154			
	1	BL isokinetic (3 rep)	0.12 (0.08)	0.49	0.137	0.41	0.28	0.055
		BL VO_{2peak}	-0.47 (0.32)	-0.34	0.161			
	2	Δ isokinetic (3 rep)[b]	0.18 (0.18)	0.28	0.339	0.44	0.27	0.384
	3	ΔVO_{2peak}[b]	-0.9 (0.69)	-0.31	0.220	0.51	0.31	0.220
ΔPCPS[a]				Model 1				
	1	BL PCPS	-0.46 (0.16)	-0.70	0.012*	0.58	0.49	0.006*
		BL isokinetic (3 rep)	0.02 (0.09)	0.05	0.853			

		BL VO_{2peak}	0.09 (0.38)	0.06	0.807			
	2	ΔVO_{2peak}[b]	-0.36 (0.84)	-0.10	0.679	0.59	0.46	0.663
	3	Δ isokinetic (3 rep)[b]	-0.03 (0.2)	-0.04	0.878	0.59	0.42	0.878
				Model 2				
		BL PCPS	-0.46 (0.16)	-0.70	0.012*			
	1	BL isokinetic (3 rep)	0.02 (0.09)	0.05	0.853	0.58	0.49	0.006*
		BL VO_{2peak}	0.09 (0.38)	0.06	0.807			
	2	Δ isokinetic (3 rep)[b]	-0.03 (0.2)	-0.04	0.878	0.58	0.45	0.862
	3	ΔVO_{2peak}[b]	-0.36 (0.84)	-0.10	0.679	0.59	0.42	0.679

Abbreviations: B = Unstandardized B coefficient; SE = Standard error; DCCS = Dimensional Change Card Sort test; PCSP = Pattern Comparison Processing Speed test; BL = Baseline; Δ = Change in; VO_{2peak} = Maximal aerobic capacity.
[a] Fully corrected t-score (corrected for age, education, biological sex, and race/ethnicity); higher scores = better.
[b] Change score calculated by final – baseline.
[*] Statistically significant ($p < 0.05$)

Table 2.5: Multiple linear regression using isokinetic 20 repetition extension and VO_{2Peak} as the main predictor variables (Complete-case; N=18).

NIH Toolbox tasks	Block	Variables	B (SE)	β	p-value	R^2	Adjusted R^2	p-value
				Model 1				
		BL Flanker	-0.28 (0.28)	-0.22	0.336			
	1	BL isokinetic (20 rep)	0.25 (0.07)	0.79	0.005	0.34	0.20	0.109
		BL VO_{2peak}	-0.08 (0.26)	-0.07	0.766			
	2	ΔVO_{2peak}[b]	0.47 (0.53)	0.19	0.394	0.34	0.14	0.885
	3	Δ isokinetic (20 rep)[b]	0.88 (0.40)	0.50	0.051	0.53	0.33	0.051
ΔFlanker[a]				Model 2				
		BL Flanker	-0.28 (0.28)	-0.22	0.336			
	1	BL isokinetic (20 rep)	0.25 (0.07)	0.79	0.005	0.34	0.20	0.109
		BL VO_{2peak}	-0.08 (0.26)	-0.07	0.766			
	2	Δ isokinetic (20 rep)[b]	0.88 (0.40)	0.50	0.051	0.50	0.34	0.066
	3	ΔVO_{2peak}[b]	0.47 (0.53)	0.19	0.394	0.53	0.33	0.394

ΔDCCS[a]				Model 1				
		BL DCCS	-0.39 (0.21)	-0.46	0.081			
	1	BL isokinetic (20 rep)	0.11 (0.09)	0.29	0.256	0.41	0.29	0.053
		BL VO_{2peak}	-0.39 (0.32)	-0.28	0.244			
	2	ΔVO_{2peak}[b]	-0.59 (0.71)	-0.21	0.425	0.46	0.29	0.314
	3	Δ isokinetic (20 rep)[b]	0.28 (0.47)	0.14	0.563	0.47	0.25	0.563
				Model 2				
		BL DCCS	-0.39 (0.21)	-0.46	0.081			
	1	BL isokinetic (20 rep)	0.11 (0.09)	0.29	0.256	0.41	0.29	0.053
		BL VO_{2peak}	-0.39 (0.32)	-0.28	0.244			
	2	Δ isokinetic (20 rep)[b]	0.28 (0.47)	0.14	0.563	0.44	0.27	0.407
	3	ΔVO_{2peak}[b]	-0.59 (0.71)	-0.21	0.425	0.47	0.25	0.425
ΔPCPS[a]				Model 1				
		BL PCPS	0.11 (0.29)	0.10	0.723			
	1	BL isokinetic (20 rep)	0.19 (0.12)	0.42	0.146	0.13	-0.06	0.570
		BL VO_{2peak}	-0.32 (0.44)	-0.19	0.478			
	2	ΔVO_{2peak}[b]	-1.79 (1.00)	-0.50	0.099	0.32	0.12	0.076
	3	Δ isokinetic (20 rep)[b]	0.00 (0.66)	0.00	0.998	0.32	0.04	0.998
				Model 2				
		BL PCPS	0.11 (0.29)	0.10	0.723			
	1	BL isokinetic (20 rep)	0.19 (0.12)	0.42	0.146	0.13	-0.06	0.570
		BL VO_{2peak}	-0.32 (0.44)	-0.19	0.478			
	2	Δ isokinetic (20 rep)[b]	0.00 (0.66)	0.00	0.998	0.14	-0.12	0.655
	3	ΔVO_{2peak}[b]	-1.79 (1.00)	-0.50	0.099	0.32	0.04	0.099

Abbreviations: B = Unstandardized B coefficient; SE = Standard error; DCCS = Dimensional Change Card Sort test; PCSP = Pattern Comparison Processing Speed test; BL = Baseline; Δ = Change in; VO_{2peak} = Maximal aerobic capacity.

[a] Fully corrected t-score (corrected for age, education, biological sex, and race/ethnicity); higher scores = better.

[b] Change score calculated by final – baseline.

[*] Statistically significant ($p < 0.05$).

2.4 Adverse events

Twenty-seven adverse events were recorded and addressed. Complete details are reported in the primary analysis (91). Briefly, two participants withdrew due to development of atrial fibrillation on day 3 of recovery. Some participants reported nausea and experienced presyncope during the first day of recovery which could have affected performance of cycle ergometry to exhaustion and maximal voluntary contraction tests performed on day 1 and 2, respectively. Exercise training sessions did not cause adverse events.

2.5 Discussion

This secondary analysis suggests that preservation of muscle strength during HDBR is critical for the maintenance of response inhibition in healthy adults aged 55-65 years. Specifically, change in knee extension strength was positively associated with performance in cognitive tests measuring response inhibition, but not set-shifting or processing speed. Moreover, change in serum IGF-1 concentration was not associated with change in cognitive function in males and females.

The main finding of this study extends the results of the parent study by Balbim et al., 2024, in which cognitive function, measured by intraindividual variability (IIV) in the Flanker task, was maintained in the exercise group compared with the control group following HDBR completion. Briefly, IIV is a measure of consistency in cognitive performance across multiple time points such that lower IIV indicates better cognitive performance. We provide exploratory evidence that maintenance of muscle strength contributes to the maintenance of response inhibition during HDBR. Corroborating results were reported in a previous RCT of multicomponent exercise intervention (i.e., combined progressive resistance exercises, balance training, and walking) in acutely hospitalized older adults ≥75 years of age; global cognition, verbal fluency, and executive function showed significant improvements in the intervention group compared with the control

group at discharge; no measures of muscle strength or cardiorespiratory fitness were conducted in this RCT (92). This study, however, includes numerous differences such as: 1) a horizontal bed rest model; 2) older participants with comorbidities; and 3) a variable exercise intervention length corresponding to length of hospital stay. Outside of bed rest contexts, executive functions were also shown to be particularly responsive to RT interventions (56) that aim to improve parameters of muscle health (56). Thus, this study provides preliminary evidence that maintenance of muscle strength through RT can promote healthy cognitive aging, and future studies should examine whether RT-induced benefits to cognitive function are mediated by improvements in skeletal muscle health parameters (e.g., mass and strength).

Maintenance of muscle health parameters may be particularly important for cognitive function because: 1) skeletal muscle disorders (e.g., sarcopenia) are associated with worse cognitive function (48,49) and 2) skeletal muscles are a major endocrine organ can secrete neurotrophic factors (e.g., IGF-1) (10,71).

Sarcopenia is a progressive and generalized skeletal muscle disorder characterized by low muscle strength, muscle mass, and physical performance (42). A meta-analysis of 15 cross-sectional studies showed that sarcopenia approximately doubled the risk of mild cognitive impairment and dementia, odds ratio of 2.25 (49). A longitudinal analysis showed that sarcopenia is associated with incident cognitive decline, MCI, and AD. Notably, muscle strength and function rather than muscle mass was the primary driver of this association (52). Thus, further highlighting RT as a promising strategy to maintain cognitive function by mitigating the development of sarcopenia in older adults.

Although this thesis did not demonstrate a link between IGF-1 and cognitive function, other studies have shown that IGF-1 concentrations may have a U-shaped dose-response relationship

with risk of dementia, such that higher and lower IGF-1 concentrations increased the risk of cognitive decline and dementia (103,104). Our findings can be explained by: 1) small sample size; 2) lack of group differences in muscle strength; and 3) disproportionate AT to RT ratio in the exercise intervention. Specifically, Haj-Boutros and colleagues (102), an ancillary team using data from the CSA Inactivity Study, reported a significant decrease in isokinetic knee extension strength following HDBR with no group differences (time effect, $p \leq 0.05$; group*time, $p > 0.05$), such that the exercise group decreased by 14% and the control group decreased by 9%. This reported reduction in muscle strength across time is expected when considering the proportion of total time spent performing aerobic vs. resistance exercises; only 225 total minutes of RT was performed whereas, 700 minutes of AT was performed in 14-days (Table 2.1 and Table 2.2). Moreover, a recent meta-analysis of 30 RCTs examining the effect of RT on neuroprotective factors showed that RT significantly increased IGF-1 levels (SMD: 0.48; 95% CI: 0.27 to 0.69; $p = 0.001$) with greater effects when RT was performed ≥ 3 times per week (SMD: 0.55; 95% CI: 0.31 to 0.79) (105). Future studies that wish to study the associations between muscle parameters and peripheral IGF-1 concentrations and its subsequent relationship to cognitive functioning are warranted to include an appropriate RT stimulus to allow for muscle adaptations.

2.5.1 Strengths and Limitations

To my knowledge, this is the first study to examine the independent contribution of muscle strength and cardiorespiratory fitness as a function of exercise training on cognitive function in older adults confined to HDBR. This study has several limitations, and thus, findings are hypothesis generating and should be interpreted with caution. First, the small sample size ($N = 22$) likely limited our ability to detect: 1) the independent association of isokinetic 20 repetition knee extension peak torque on flanker performance ($p = 0.051$); and 2) the association between change

in IGF-1 concentration and change in cognitive function. Despite having a sex-balance sample, the small sample size also limited our statistical power and prevented an examination of sex differences in the main analysis. Participants included in the study were generally healthy, highly educated, and physically active which: 1) limits the generalizability of our results to other populations; and 2) may underestimate the effect of exercise on physical outcomes due to ceiling effects. Furthermore, HDBR models aim to represent microgravity which lead to additional physiological changes such as altered fluid dynamics that are not observed in horizontal bed rest during hospitalization (106). Finally, the exercise intervention favoured AT over RT and changes in muscle strength and cardiorespiratory fitness reflected the greater AT stimulus (102,107).

2.6 Conclusion

Maintenance of muscle strength through daily bouts of moderate-to-vigorous AT and RT may be critical for the preservation of executive functions in adults aged 55-65 years that are confined to 14 days of HDBR. Future studies that include: 1) a larger sample size; 2) a horizontal bed rest model; and 3) a balanced AT and RT stimulus are needed to verify the proof-of-concept findings.

Chapter 3

3.1 Introduction

VCI may be the most treatable type of dementia in older adults because its key risk factors, which include cardiometabolic and vascular disorders, are highly modifiable by regular PA and exercise. Currently, research examining the neuroprotective effects of exercise on VCI focuses on modifying the aforementioned risk factors through AT interventions (108,109). However, emerging evidence suggests that RT may also play a protective role for people with VCI because it provides similar cardiometabolic adaptations as AT with added benefits to skeletal muscle health (9). In addition to the cognitive benefits associated with maintaining skeletal muscle health parameters (i.e., mass and strength) (44–46,52), the skeletal muscle system is also a highly active endocrine organ that can communicate with the brain, termed muscle-brain crosstalk (10). It is posited that enhancing or preserving its endocrine properties via RT can lead to downstream benefits on cognitive health (10,71). Therefore, more research examining the effects of RT on cognitive health in VCI is necessary to determine which type of exercise optimizes the therapeutic outcomes on VCI.

The presence of white matter hyperintensities (WMH) on neuroimaging is a hallmark of cerebrovascular damage (i.e., myelin loss due to chronic ischemia) caused by CSVD and a key clinical characteristic of VCI (24). A systematic review and meta-analysis conducted by Debette and colleagues (110) showed that WMH is associated with incident dementia (HR = 1.9; 95% CI: 1.3 to 2.8) and increased risk of global cognitive decline with domain-specific declines in processing speed and executive functions. To date, clinical trials examining the efficacy of exercise for preventing or managing VCI often use change in volume of WMH as a clinical outcome

measure. The following sections will summarize the effects of RT on the risk factors and clinical outcomes related to VCI.

Hypertension is the most significant vascular driver for WMH progression and subsequent VCI (24). A recent prospective cohort study using data from the UK Biobank found that higher systolic blood pressure (SBP) and diastolic blood pressure (DBP) was associated with greater WMH; more specifically, high DBP at midlife and high SBP at late life was more strongly associated with greater WMH (111). Therefore, managing blood pressure during mid-to-late life via exercise may be a promising strategy to prevent WMH and VCI. A meta-analysis of 28 RCTs showed that RT significantly reduced SBP and DBP in normotensive (SBP < 120 mm Hg and DBP < 80 mm Hg) and prehypertensive (120 ≤ SBP ≤ 139 mm Hg or 80 ≤ DBP ≤ 89 mm Hg) groups, whereas hypertensive (SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg) groups did not show significant reductions in blood pressure (112). Data from a RCT (Brain Power Study) subset of 54 community-dwelling older women with evidence of WMH on baseline MRI showed that participants in the 12 months of twice-weekly RT had significantly lower WMH compared with the active control group ($p = 0.03$). However, change in WMH volume was not significantly associated with executive function performance ($r = 0.30$, $p = 0.06$) (113). One other RCT (SMART trial) of 100 older adults with MCI showed corroborating results; WMH volumes in specific brain regions regressed by 3.5% in groups that performed RT while in non-RT groups, WMH volumes progressed by 3.0%. Again, change in WMH volume was not associated with change in either global cognition or memory (114). Despite evidence showing that RT can independently decrease blood pressure and slow WMH progression, the association between RT-induced changes in blood pressure and clinical outcomes of VCI has yet to be examined.

RT may provide additional benefits for VCI by: 1) mitigating the negative effects of sarcopenia on WMH progression (115) and 2) promoting muscle-brain crosstalk (10,103). Both cross-sectional and prospective cohort studies found that indices of sarcopenia such as muscle strength measured by hand grip dynamometry were associated with greater WMH (115–117). Notably, data from the UK biobank showed that a 5-kg loss in hand grip strength was associated with greater WMH volume, poorer cognitive performance, and incident dementia for both men and women (117). A cross-sectional analysis including 57 people with dementia and 22 cognitively normal controls examined the association between sarcopenia parameters (appendicular skeletal muscle mass, grip strength, 5-time sit-to-stand time, and gait speed) and WMH volume (115). This study found that WMH volumes were not correlated to any sarcopenic parameters in the cognitively normal group; whereas greater WMH volume was associated with lower appendicular lean mass, slower gait speed, and worse sit-to-stand performance in the dementia group. Moreover, greater WMH volume is related to declines in executive functions (115). Given the observational design of the available evidence, causal inferences between sarcopenia and WMH progression cannot be drawn.

IGF-1 is one of the most studied myokines facilitating muscle-brain crosstalk and is secreted during skeletal muscle contractions particularly following RT (10,75). A systematic review and meta-analysis of 33 trials reported that serum IGF-1 significantly increased following RT compared with the control groups (WMD = 10.34 ng/ml, 95% CI: 4.93 to 15.74; p = 0.000) (77). A more recent meta-analysis showed comparable results and also reported pooled estimates for change in upper and lower body muscle strength; RT significantly increased IGF-1 (MD: 17.34 ng/ml; 95% CI: 7.23 to 27.46; p = 0.000), muscle strength in leg press (MD: 0.82 kg; 95% CI: 0.30 to 1.34; p = 0.002), and muscle strength in bench press (MD: 0.82 kg; 95% CI: 0.42 to 1.23; p =

0.000) (118). Interestingly, subgroups analyses performed by both studies showed that increase in IGF-1 levels following RT was only statistically significant in women compared with men or both sexes (77,118). Data from the UK Biobank including 369,711 cognitively normal participants reported a U-shaped dose-response relationship between IGF-1 concentrations and risk of dementia (103). Notably, IGF-1 concentrations were positively associated with white matter volume and negatively associated with WMH volume which suggests that IGF-1 may play a protective role against cerebrovascular damage and WMH (103). In summary, there is growing evidence to suggest that RT may be particularly protective for people with VCI because it can provide a dual role in mitigating the cardiometabolic and sarcopenic risk factors for VCI.

To my knowledge, no studies have examined the effects of RT-induced changes in muscle strength and peripheral IGF-1 concentration in relation to changes in cognitive function in a sample of participants diagnosed with VCI. Thus, using data from a single-blind, proof-of-concept RCT of a 12-month, twice-weekly RT vs. active control in community-dwelling adults with VCI, I explored whether changes in muscle strength and serum IGF-1 concentrations are associated with changes in cognitive function. We hypothesized that muscle strength and IGF-1 concentrations would be positively associated with better cognitive function.

3.2 Methods

3.2.1 Study Design

A secondary analysis of a 12-month, parallel group, proof-of-concept, RCT in which 91 community-dwelling older adults (61 females and 30 males) with subcortical ischemic vascular cognitive impairment (SIVCI) will be randomized to either: 1) twice-weekly progressive RT or 2) twice-weekly balance and tone training (BAT; active control). The complete details of the trial are available in the published protocol (119).

3.2.2 Recruitment and Eligibility

Participants were recruited through newspaper advertisement and from four clinics: 1) University of British Columbia (UBC) Hospital Clinic for Alzheimer Disease and Related Disorders; 2) Vancouver General Hospital (VGH) Stroke Clinic; 3) VGH Falls Prevention Clinic; and 4) VGH Geriatric Internal Medicine Teaching Clinic. Interested individuals were provided with a consent form and screened through 1) the Physical Activity Readiness Questionnaire to assess capability to begin exercise; and 2) the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) to assess cognitive function. Health status and suitability to start exercise were further verified with participants' family physician when relevant health concerns were reported.

We included community-dwelling older adults aged 55 years or older who fulfill the criteria for SIVCI, defined as the presence of both cognitive impairment (MoCA score < 26) combined with CSVD verified by white matter hyperintensities (WMH) and/or lacunes on computed tomography (CT) or magnetic resonance imaging (MRI). Additional inclusion criteria are as follows: 1) MMSE score ≥ 20; 2) be able to comply with scheduled visits, treatment plan, and other trial procedures; 3) read, write, and speak English; 4) be on a fixed dose of cognitive medications that are not expected to change during the 12-month study period; 5) provide informed consent; 6) be able to walk independently; and 7) be in sufficient health to participate in the RT program.

Individuals are excluded for the following reasons: 1) absence of CSVD on a brain CT or MRI; 2) are diagnosed with a genetic cause of SIVCI; 3) diagnoses with any neurodegenerative condition (e.g., Alzheimer's disease and Parkinson's disease); 4) insufficient health to participate in RT intervention; 5) participated in regular RT in the last 6 months; 6) significant impairments

in motor ability due to peripheral neuropathy or musculoskeletal or joint diseases; 7) started taking medication that affects cognitive function < 3 months prior to the study; 8) are enrolled in other exercise or drug trials; or 9) are unable to meet MRI scanning requirements, as specified by the UBC 3T MRI Research Center.

3.2.3 Randomization and Blinding

The randomization scheme was generated with permuted blocks on May 26, 2016, and stored by randomization.com (http://www.randomization.com). The sequence was held independently and remotely by an investigator not involved in running the trial. Participants were enrolled and randomized (1:1) to either RT or BAT. Allocation was concealed. Assessors were blinded to group allocation. It was not possible to blind staff that delivered the RT or BAT programs. Research personnel and participants were instructed to not discuss treatment allocation to remain blinded.

3.2.4 Experimental Groups

All classes were led by certified instructors with a participant to instructor ratio of 4:1. Exercise classes were 60 minutes and included a 10-minute warm-up (i.e., stretching major muscles and walking on the spot), 40-minutes of progressive RT, and a 10-minute cool down (i.e., stretching and relaxation). Classes were audited on a monthly basis to ensure consistent protocol delivery. Home-based training was delivered for both groups through instructional videos to meet public health mandates during COVID-19. Participants were called on a weekly basis to monitor progress and adherence.

The BAT program was an active control group and included basic exercises that targeted flexibility, range of motion, balance, agility, core/postural control, and breathing/relaxation. All exercises were done with body weight with no additional loading. This type of training has not

been shown to improve cognitive function and thus served as an active control for confounding variables such as changes in physical activity levels due to travel, social interaction, changes to lifestyle secondary to study participation, and attention from research staff.

The progressive RT program consisted of a combination of free weight exercises including mini-squats, mini-lunges, and lunge walks and pressurized air system exercises including biceps curls, seated row, latissimus dorsi pull downs, triceps extension, leg press, hamstring curls, and calf raises. The intensity of training will begin at 50–60% of their 1 repetition maximum (1RM) and progress to 2 sets of 6–8 repetitions at 75–85% 1RM by week 4. The 7RM method will be used to increase the training load when 2 sets of 6–8 repetitions are completed with the correct form. The number of sets completed, and the load lifted will be recorded for each participant at each class.

3.2.5 Measurements

All measurements were acquired by a highly trained research team that will implement standardized protocols. Measurements were taken at baseline and trial completion (12 months). No personal identifiers will be acquired during data collection. All data will be deidentified and stored on secured server hosted by University of British Columbia.

3.2.5.1 Descriptive Measures

Demographic data collected at baseline include: a) age; b) sex; c) weight (kg) using a calibrated digital scale; d) standing height (cm) using a wall-mounted stadiometer; e) BMI (kg/m^2); and f) MoCA (97) to assess cognitive function at baseline.

3.2.5.2 Cognitive Measures

Executive functions and processing speed were of particular interest because Debette and colleagues (110) reported that WMH progression was significantly associated with greater declines

in these cognitive domains. Moreover, executive functions may be particularly sensitive to RT (56). Three key executive processes were assessed: 1) set-shifting; 2) inhibitory control; and 3) working memory.

We measured set-shifting using the Trail Making Test (TMT) parts A and B (120). In part A, participants are instructed to connect a series 24 encircled numbers in numerical order. In part B, participants must connect 25 encircled numbers and letters in alphanumerical order alternating between numbers then letters (e.g., 1-A-2-B-3-C…). The total time of completion is recorded for each part. We calculated the difference between part B and A (i.e., TMTB – TMTA) as an index of the level of interference between the two parts. Lower scores indicate better performance.

Inhibitory control was assessed using the Stroop Color-Word Test which includes three conditions: two congruent conditions and one incongruent condition (121). The congruent conditions required participants to: 1) read the name of colors printed in black ink (W); and 2) name color patches (C) as quickly as possible. The incongruent condition included mismatched coloured words (e.g., the word "green" printed in blue ink) and participants were instructed to name the color of the ink rather than read the printed word (CW). The total time to complete the list of words was recorded. An interference score was calculated by taking the difference between the time taken to complete the incongruent and congruent conditions (i.e., CW – C). Lower scores indicated better performance.

The Digit Symbol Substitution Test (DSST) was used to measure processing speed and working memory (122). The test contains a legend with numbers that correspond to different symbols and a list of numbers in random order with an empty space below each number. Participants are instructed to match symbols to numbers according to the legend. The number of correct symbols within the allowed time is reported; higher scores indicate better performance.

The DSST was later added on August 15, 2017, with the start of the second cohort of participants. This resulted in 18 participants for whom DSST data were not collected.

3.2.5.3 Physical Measures

Maximal knee isometric extension force (kg) was assessed as part of the Physiological Profile Approach (PPA) to falls risk assessment (123). Tests were performed using an anchored spring gauge that is attached about 10 cm above the participant's ankle joint using a Velcro strap. Participants are seated in a tall chair with hips and knee joints positioned at 90 degrees. Three trials were performed for the dominant leg and each trial lasted around 2-3 seconds to allow maximal force generation. The highest measure of the three trials were taken at both baseline and trial completion. Higher scores indicated greater knee isometric extension strength.

We assessed resting systolic and diastolic blood pressure in the supine position using an automatic blood pressure monitor. Assessors placed the blood pressure cuff on the left arm (unless contraindications) and asked participants to relax in the supine position for five minutes to obtain a resting blood pressure.

3.2.5.4 Blood Biomarkers

Fasting blood samples were collected in the morning by standard venipuncture at baseline and 12 months. Blood was processed and stored at -80 °C as plasma, serum, and whole blood until analysis. Serum IGF-1 concentrations (pg/ml) were analyzed by enzyme-linked immunosorbent assay (ELISA) (R&D Systems).

3.2.6 Statistical Analysis

Analyses were performed in IBM SPSS Statistics software version 29.0.1.0 for MacOS (IBM Inc., Chicago, IL, USA) following the intention-to-treat principle. Power analyses were conducted in G*Power 3.1 to determine sample size. The trial is sized for the primary analysis

which aims to examine the effects of RT on Alzheimer's Disease Assessment Scale-Cognitive-Plus (ADAS-Cog-Plus) (124) and WMH progression at trial completion, assuming alpha of 0.05 (two-tailed). 35 participants per group will provide a power of 0.80. We recruited a total of 93 participants which accommodated for a conservative drop-out rate of 20%. Findings from this secondary analysis are hypothesis generating and should be interpreted with caution.

A complete-case analysis including only participants with complete data at baseline and trial completion will be included for analysis. I performed a one-way Analysis of Covariance (ANCOVA) to assess between-group differences in change in: 1) knee isometric extension strength; 2) systolic blood pressure; and 3) IGF-1 concentration, including baseline measures as covariates. To examine within-group differences in: 1) knee isometric extension strength; 2) systolic blood pressure; and 3) IGF-1 concentration from baseline to trial completion, I performed paired samples t-tests for each group (two-sided p). I conducted three separate multiple linear regressions for each cognitive measure as the outcome variable to determine whether following 12 months of twice-weekly RT knee isometric extension strength and serum IGF-1 concentrations are associated with performance in the: 1) TMT; 2) Stroop Color-Word Test; and 3) DSST. Each model was also adjusted for group, change in systolic blood pressure, the respective baseline cognitive score, baseline physical measures of interest, and baseline serum IGF-1 concentrations.

3.3 Results

3.3.1 Participant Characteristics

Ninety-three participants were eligible for the study. Two participants withdrew from the study prior to randomization. 91 participants were randomized following the completion of baseline assessments; 45 (32 females and 13 males) were in the RT group and 46 (29 females and 17 males) were in the control group (Fig. 5: CONSORT diagram). Baseline characteristics are

described in Table 3.1. Participants' mean age was 74.58 (SD = 5.62), mean MoCA score was 21.18 (SD = 3.30), and 67.03% were females (n = 61).

Table 3.1: Baseline demographics and clinical characteristics of study participants.

Variables[a]	**Overall (n=91) M (SD)**	**Control (n=46) M (SD)**	**RT (n=45) M (SD)**
Age	74.57 (5.65)	74.96 (5.45)	74.18 (5.87)
Females (n, %)	61 (67.03)	32 (71.11)	29 (63.04)
Cognitive function			
MoCA (/30 pts)	21.18 (3.3)	20.87 (3.39)	21.49 (3.22)
TMT (B-A)	88.65 (117.92)	109.27 (156.23)	67.57 (50.8)
Stroop (CW-C)	57.25 (32.81)	58.53 (36.56)	55.93 (28.82)
DSST[b]	42.22 (10.33)	42.24 (10.01)	42.19 (10.79)
Physical characteristics			
BMI (kg/m^2)	27.52 (5.45)	27.75 (5.22)	27.28 (5.71)
Systolic BP (mm Hg)	131.89 (18.38)	131.37 (19.19)	132.43 (17.69)
Diastolic BP (mm Hg)	77.78 (10.22)	77.15 (10.81)	78.43 (9.63)
Knee Isometric Extension Strength (kg)	29.22 (12.90)	30.93 (12.38)	27.47 (12.33)
IGF-1 (pg/ml)	3353.54 (3222.43)	3725.30 (4094.09)	2946.94 (1843.27)

Abbreviations: MoCA = Montreal Cognitive Assessment; TMT = Trail Making Test; DSST = Digit Symbol Substitution Test; BMI = Body mass index; BP = Blood pressure.
[a] Data presented as mean (standard deviation) or count (%) where applicable.
[b] DSST scored by the number of correct answers in 120 seconds; higher scores are better.

3.3.2 Exercise Class Progression

Participants in RT significantly improved from baseline in estimated 1RM leg press strength at both 6-months (estimated difference from baseline: -213.04 N; 95% CI: -375.19 to -50.89; $p = 0.012$) and 12-months (estimated difference from baseline: -512.55 N; 95% CI: -750.57 to -274.53; $p < 0.001$). Similarly, participants in RT significantly improved in estimated 1RM strength for latissimus pulldown at both 6-months (estimated difference from baseline: -47.21 N; 95% CI: -75.86 to -18.56; $p = 0.002$) and 12-months (estimated difference from baseline: -71.24 N; 95% CI: -104.63 to -37.85; $p < 0.001$).

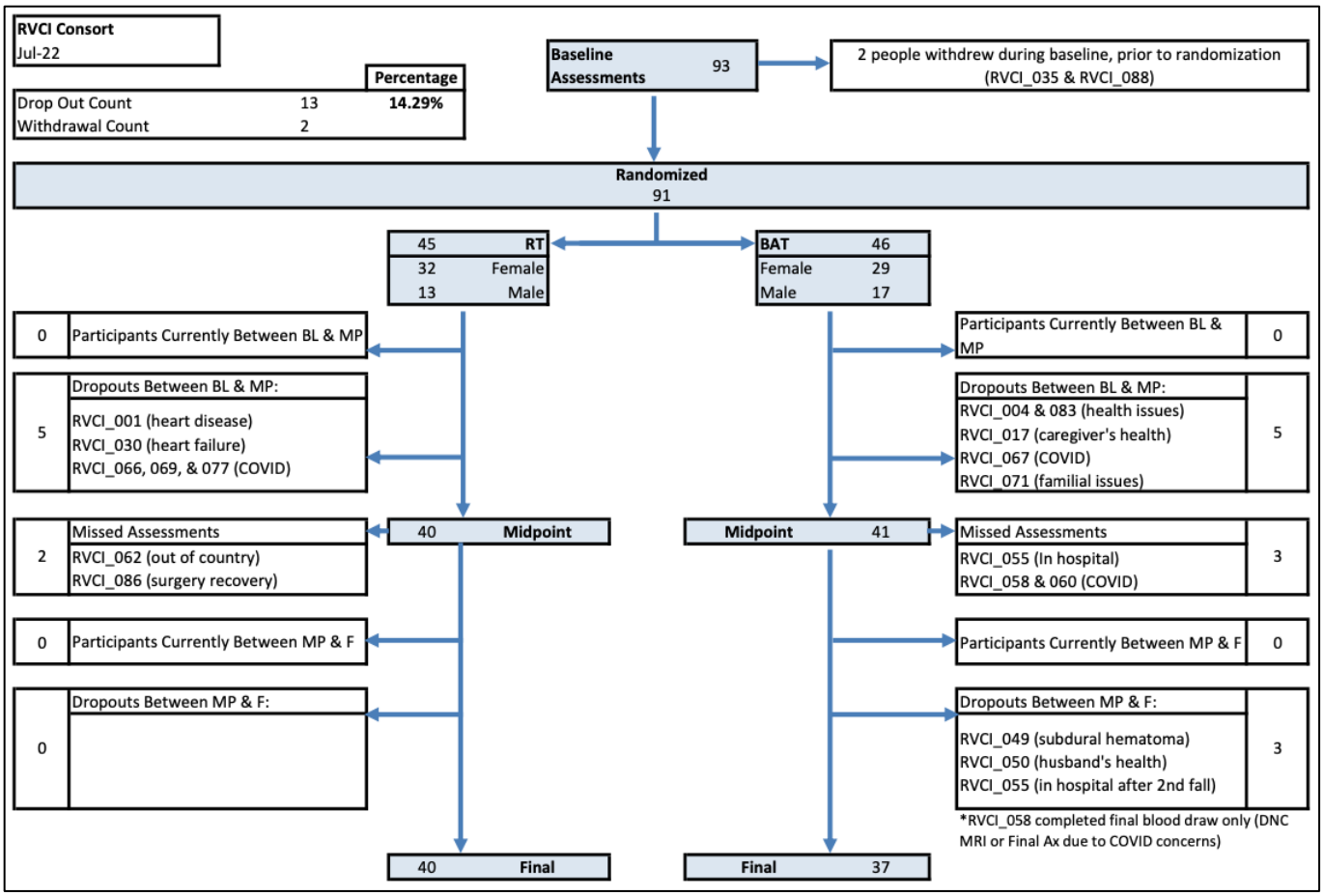

Figure 5: CONSORT diagram. Abbreviations: BAT = Balance and Tone active control (119).

3.3.3 Adherence

Overall adherence to exercise training was 77.5% for the RT group and 77.1% for the BAT group. Adherence was affected by the public health mandates of COVID-19 and participants were called on a weekly basis to monitor progress and adherence. Adherence before COVID-19 was 74.4% for the RT group and 77.1% for the BAT group. During COVID-19, from March 24 to September 29, 2020, adherence was 73.3% for the RT group and 59.7% for the BAT group. Due to COVID-19, adherence was monitored via phone calls vs. tracked attendance per session as we would in person.

3.3.4 Between-Group and Within-Group Differences

Results from the one-way ANCOVA show that changes in: 1) systolic blood pressure; 2) knee isometric extension strength; and 3) IGF-1 concentrations were not significantly different between groups (all ps > 0.05), after adjusting for baseline measures of interest. Change in knee isometric extension strength was not significantly different between groups ($F(1,69) = 1.57$, $p = 0.215$). The mean change showed that knee isometric extension strength decreased in the control group (M = -0.41, SE = 1.24; 95% CI: -2.88 to 2.06) and increased in the RT group (M = 1.79, SE = 1.20; 95% CI: -0.61 to 4.19). Systolic blood pressure decreased in both groups (CON: M = -2.15, SE = 2.36; 95% CI: -6.86 to 2.56; RT: M = -0.85, SE = 2.32; 95% CI: -5.49 to 3.78), but changes in systolic blood pressure were not significantly difference between groups ($F(1,66) = 0.153$), $p = 0.697$). Change in IGF-1 concentration was not significantly different between groups ($F(1,63) = 0.84$, $p = 0.364$). The mean change showed that IGF-1 concentrations decreased in both groups (CON: M = -125.87, SE = 180.46; 95% CI: -486.38 to 234.64; RT: M = 365.69, SE = 188.79; 95% CI: -742.84 to 11.47).

Results from the paired samples t-test showed that there were no significant within-group differences in: 1) knee isometric extension strength; 2) systolic blood pressure; or 3) IGF-1 concentration from baseline to trial completion (all ps > 0.05). There were no significant within-group differences in knee isometric extension strength in both groups (CON: $t(34) = 0.819$, $p = 0.418$; RT: $t(36) = -1.60$, $p = 0.119$) from baseline (CON: M = 32.94, SD = 12.85; RT: M = 26.16, SD = 12.05) to trial completion (CON: M = 32.11, SD = 14.37; RT: M = 28.35, SD = 11.68). Systolic blood pressure was not significantly different within-groups (CON: $t(33) = 0.82$, $p = 0.419$; RT: $t(34) = 0.48$, $p = 0.635$) from baseline (CON: M = 129.82, SD = 20.98; RT: M = 133.94, SD = 14.21) to trial completion (CON: M =128.09, SD = 20.03; RT: M = 132.69, SD = 19.46).

There were no significant within-group differences in IGF-1 concentrations in both groups (CON: $t(34) = 0.995$, $p = 0.327$; RT: $t(31) = 1.42$, $p = 0.167$) from baseline (CON: $M = 3725.30$, $SD = 4094.09$; RT: $M = 2946.94$, $SD = 1843.27$) to trial completion (CON: $M = 3548.57$, $SD = 3874.05$; RT: $M = 2636.88$, $SD = 1450.94$).

3.3.5 Main Analyses

The results of the multiple linear regression analyses are reported in Table 3.2. In the DSST model: change in knee isometric extension strength ($\beta = 0.30$; $t(43) = 2.07$; $p = 0.044$) was significantly associated with change in DSST scores, after adjusting for group, change in SBP, and baseline measures of interest. The Stroop and TMT model including the same predictor variables and respective covariates did not significantly explain the variance in change in Stroop or TMT scores (all $p > 0.05$).

Table 3.2: Multiple linear regression (Complete-case).

Cognitive Tests	Block	Variables	B (SE)	β	p-value	R^2	Adjusted R^2	p-value
			DSST Model					
Δ DSST[a]	1	Group	-3.72 (1.87)	-0.30	0.053	0.17	0.08	0.124
		BL DSST	-0.22 (0.09)	-0.33	0.018			
		Δ Systolic Blood Pressure	0.04 (0.04)	0.12	0.378			
		BL Knee Isometric Extension	-0.08 (0.08)	-0.15	0.336			
		BL IGF-1	0.00 (0.00)	0.03	0.829			
	2	Δ Knee Isometric Extension	0.23 (0.11)	0.30	0.044*	0.24	0.12	0.128
		Δ IGF-1	0.00 (0.00)	-0.01	0.944			
			Stroop Model					
Δ Stroop[b]	1	Group	-0.46 (4.65)	-0.01	0.921	0.30	0.24	p<0.001
		BL Stroop	-0.44 (0.09)	-0.56	0.000			
		Δ Systolic Blood Pressure	-0.03 (0.12)	-0.03	0.821			
		BL Knee Isometric Extension	0.15 (0.2)	0.09	0.454			
		BL IGF-1	0.00 (0.00)	0.06	0.635			
	2	Δ Knee Isometric Extension	0.19 (0.31)	0.07	0.544	0.31	0.23	0.507
		Δ IGF-1	0.00 (0.00)	0.12	0.326			
			TMT Model					
Δ TMT[b]	1	Group	11.84 (30.31)	0.05	0.697	0.21	0.14	0.015
		BL TMT	-0.57 (0.17)	-0.43	0.001			
		Δ Systolic Blood Pressure	-0.01 (0.76)	0.00	0.992			
		BL Knee Isometric Extension	-0.35 (1.31)	-0.04	0.790			
		BL IGF-1	0.00 (0.01)	0.00	0.993			
	2	Δ Knee Isometric Extension	-0.07 (1.93)	0.00	0.972	0.21	0.11	0.982
		Δ IGF-1	0.00 (0.01)	0.02	0.854			

* Statistically significant ($p < 0.05$)

[a] DSST was added in Cohort 2; complete-case analysis (n = 51); higher scores = better performance.

[b] Stroop and TMT complete-case analysis (n = 65); lower scores = better performance.

3.4 Discussion

This secondary analysis provides preliminary results that suggest change in muscle strength is positively associated with change in performance on a working memory and processing speed task following 12-months, twice-weekly RT in adults aged over 55 with VCI. Change in IGF-1 was not significantly associated with changes in performance in cognitive function.

There are limited studies that investigate the effect of RT on cognitive function in people with VCI. Although this study provides preliminary evidence that RT-induced improvement in muscle strength is associated with better working memory, the Brain Power study including cognitively normal older females (66,113) showed equivocal results, albeit in different sample populations. 12-months of once- and twice-weekly RT significantly improved response inhibition, but not working memory compared with the control group. Furthermore, twice-weekly RT significantly decreased WMH volume, but change in WMH volume was not significantly associated with change in response inhibition ($p = 0.06$). Forthcoming data from the primary analysis (119) will investigate the effect of RT on cognitive function and WMH progression in adults with VCI.

In the context of VCI, IGF-1 plays a role in stimulating oligodendrocytes to initiate myelination (i.e., production of myelin or white matter) which may reduce WMH progression (125,126). Moreover, mouse model of reduced IGF-1 showed cerebrovascular disfunction and altered blood flow to active brain tissue which likely contributes to cognitive impairment (127). A review by Frater and colleagues (104) describes the role of IGF-1 in the aging adult brain; broadly, central and peripheral IGF-1 are involved in signaling pathways that affect numerous neurophysiological processes (e.g., synapse morphology, neurogenesis, angiogenesis, beta-amyloid clearance, and metabolic function) that are critical for cognitive function and brain health.

Despite the potential mechanisms by which IGF-1 can contribute to cognitive health, this study did not find an association between changes in IGF-1 concentration and changes in cognitive function.

3.4.1 Strengths and Limitations

This study has limitations. The COVID-19 pandemic affected: 1) the delivery of the intended RT protocol; and 2) the timing of assessments and data collection following trial completion. A total of six out of 13 participants dropped out due to COVID-19 related reasons. Although the adherence of the RT group before and during the pandemic was fairly similar at 74.4% and 73.3%, respectively, the differences between the home-based vs. supervised RT protocol may have reduced the intended effects of RT. Furthermore, adherence of home-based training was self-reported via weekly phone calls rather than attendance of in-person sessions. The home-based RT programs were unsupervised and used household objects and resistance bands instead of free weights and pressurized air system exercise machines. Due to public health mandates, closures resulted in delayed assessments or missing data at trial completion. Overall, 45 out of the 91 randomized participants had documented changes to the delivery of the intended study protocol due to the COVID-19 pandemic. The trial was sized for the primary analysis; the analytic sample size of this secondary analysis likely affected our ability to detect statistical significance in the statistical tests we performed. Thus, findings are hypothesis generating and should be interpreted with caution. Furthermore, the study included only adults with VCI verified by presence of WMH and lacunes on neuroimaging which limits the generalizability of the findings to samples with different characteristics. Finally, the Stroop was scored by completion time alone and did not account for the number of uncorrected errors. Faster response times alone may not be indicative of better response inhibition if more errors are made during the task. Notably,

a review by Scarpina and Tagini (128) state that error rate rather than response speed is an index of response inhibition, but both response accuracy and speed should be used to compute a performance score for the Stroop Color-Word test. This review also summarizes numerous scoring methods that can account for both response speed and accuracy. For example, interference score can be calculated by the following: CW – [(W*C)/(W+C)] where CW is the number of correct responses in 45 seconds in the incongruent trial and W, C the number of correct responses in 45 seconds in the two congruent trials (128).

3.5 Conclusions

To my knowledge, this is the first study to show that changes in muscle strength are positively associated with processing speed and working memory in adults aged over 55 years with VCI. The results from this study provide preliminary insight on a potential mediating factor between exercise and cognitive function in adults with VCI and contribute to research aiming to understand the role of RT to reduce the risk of factors associated with VCI.

Chapter 4: General Discussions and Conclusion

4.1 Summary of Chapters

My literature review shows that the consequences of physical inactivity including reduced muscle strength and cardiorespiratory fitness are associated with increased risk of cognitive decline and risk for dementia (38,40,43,52). Engaging in both exercise modalities (i.e., AT and RT) play a neuroprotective role (55,56) and that skeletal muscle and cardiorespiratory health are independently associated with better cognitive function and risk reduction for dementia (38,40,43,52). However, limited studies have focused on examining whether exercise-induced improvements in muscle strength or cardiorespiratory fitness is more important for maintaining cognitive function in mid-to-late life. This thesis used a novel bed rest approach as a model of extreme physical inactivity to more tightly examine how exercise can act as a countermeasure to the adverse effects of physical inactivity on cognitive function (Chapter 2).

In chapter 2, it was hypothesized that both change in muscle strength and VO_{2Peak} would be significantly associated with changes in executive functions following bed rest and that VO_{2Peak} would better explain the variation in executive functions compared with muscle strength. In contrast, we found that changes muscle strength and not cardiorespiratory fitness was critical for maintenance of executive functions following 14-days of HDBR. However, there were key limitations in this study: 1) small sample size; 2) participants were healthy, highly educated, and physically active which limited generalizability and may underestimate the effect of exercise due to ceiling effects; and 3) insufficient RT stimulus.

Thus, chapter 3 aimed to address the limitations of chapter 2 and further explore the relationships between RT-induced physiological changes and cognitive function in extension to

the main finding of chapter 2. The RVCI dataset addresses the limitations of the CSA study by providing me with a larger sample size, a sample population that will likely not be susceptible to ceiling effects, and an exercise intervention of RT only. Results from chapter 3 provide preliminary evidence that muscle strength is positively associated with working memory and processing speed following a 12-month, twice-weekly RT program.

4.2 Overall Limitations Future Directions

Given the study design of the CSA Inactivity study and the RVCI study, I was not able to directly examine the effect of exercise modality on cognitive function. Instead, I used physical outcomes as indices of each modality (i.e., muscle strength as an index of RT and VO_{2Peak} as an index of AT). This method is imperfect because RT can improve VO_{2Peak} (129) and AT can improve parameters of skeletal muscle health (130); thus, the effect of AT and RT alone could not be examined. Thus, future studies should include a factorial design such that each arm of the intervention is one type of exercise allowing for comparisons between the effect of exercise type of cognitive function.

4.3 Final Conclusions

Maintenance of muscle strength rather than cardiorespiratory fitness may be more important for preserving executive functions in mid-to-late life by: 1) mitigating the associations between skeletal muscle disorders (e.g., sarcopenia) and poorer cognitive health; and 2) enhancing the endocrine properties of the skeletal muscle system. The role and exercise-dependent signaling pathways by which peripheral IGF-1 may act on cognitive function requires further investigation. Importantly, this thesis provides preliminary evidence for the need to examine the effect of exercise modality on cognitive function and further investigate the mediating factors between exercise and cognitive health. A better understanding will help better inform public health policies

to develop more precise exercise recommendations to reduce the risk of cognitive decline and dementia.

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