MOBILITY IN AGING: CLINICAL AND NEUROIMAGING STUDIES

by

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Abstract

Introduction: The world’s population is aging at an unprecedented rate. By 2050, the number of adults older than 60 years will double from 10% to 20%. This trend has immense implications, due to the prevalence of impaired physical and cognitive functions among older adults. Therefore, it is important to understand the underlying mechanisms for these impairments and identify effective prevention strategies.

White matter hyperintensities (WMHs) are common findings on MRI scans of older adults, and are associated with both physical and cognitive decline. Key risk factors for WMHs are related to metabolic and cardiovascular health. Thus, due to the established and significant benefit of targeted exercise training on metabolic and cardiovascular health in older adults, we hypothesized that one mechanism by which exercise, and specifically resistance training (RT), promotes physical and cognitive functions is by reducing WMH progression among older adults.

Methods: We explored the associations between WMHs and physical and cognitive functions in Chapters 2 to 4. In Chapter 5, we presented a randomized controlled trial of 52-week RT. Participants were randomized to either once-weekly RT, twice-weekly RT, or twice-weekly balance and tone. We investigated the effect of RT on WMH progression.

Results: Results from Chapters 2 and 3 suggest that reduced WMH progression may translate to maintained, or improved, physical and cognitive functions. Chapter 4 demonstrated that physical function is important for cognitive health. Chapter 5 provided proof-of-concept evidence that RT has beneficial effects on WMH progression, which may translate to improved physical and cognitive function. Specifically, we found that reduced WMH progression was significantly
associated with improved gait speed. Moreover, our results suggest this effect may be dose-dependent, as the significant reduction in WMH progression was only observed among those in the twice-weekly RT group, and not in the once-weekly RT group.

**Conclusion:** We provided converging evidence from four separate studies leading to the conclusion that RT has beneficial effects on WMH progression. Since WMHs are demonstrated to have significant associations with physical and cognitive dysfunctions, we believe that exercise-induced reductions of WMHs progression might translate to improvements in physical and cognitive functions in older adults.
Preface

All the research presented in Chapters 2 to 5 was primarily conducted in the Aging, Mobility, and Cognitive Neuroscience laboratory at the University of British Columbia, and have been published, accepted, or submitted for publication. Studies pertaining to Chapters 3 to 5 were approved by the University of British Columbia’s Research Ethics Board. Publication details and ethics approvals are presented below.

A version of Chapter 2 has been published in BMC Neurology [Niousha Bolandzadeh, Jennifer C Davis, Roger Tam, Todd C Handy, and Teresa Liu-Ambrose. The Association between Cognitive Function and White Matter Lesion Location in Older Adults: A Systematic Review, BMC Neurology, 2012;12:126]. I was responsible for study conception, search strategy design, study selection, data extraction and quality assessment, interpretation, and manuscript composition. JCD contributed to search strategy design, study selection, data extraction and quality assessment, and critical review of the manuscript. RT and TCH were responsible for critical review of the manuscript. TLA was responsible for study conception, search strategy design, study selection, data extraction and quality assessment, interpretation, and critical review of the manuscript.

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<tr>
<td>1x AT</td>
<td>Once-Weekly Aerobic Training</td>
</tr>
<tr>
<td>1x RT</td>
<td>Once-Weekly Resistance Training</td>
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<tr>
<td>3MS</td>
<td>Modified Mini-Mental State Examination</td>
</tr>
<tr>
<td>6-MWT</td>
<td>Six-Minute Walk Test</td>
</tr>
<tr>
<td>Aβ</td>
<td>Beta Amyloid</td>
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<tr>
<td>ABC</td>
<td>Activities-Specific Balance Confidence</td>
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<tr>
<td>ACSM</td>
<td>American College of Sports Medicine</td>
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<tr>
<td>AD</td>
<td>Alzheimer’s Disease</td>
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<tr>
<td>AHA</td>
<td>American Heart Association</td>
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<td>ALP</td>
<td>Automated Labeling Pathway</td>
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<td>AT</td>
<td>Aerobic Training</td>
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<td>ATP</td>
<td>Adenosine Triphosphate</td>
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<tr>
<td>ATRR</td>
<td>Right Anterior Thalamic Radiation</td>
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<tr>
<td>BAT</td>
<td>Balance and Tone Training</td>
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<td>BET</td>
<td>Brain Extraction Tool</td>
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<td>BDNF</td>
<td>Brain-Derived Neurotrophic Factor</td>
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<tr>
<td>BMI</td>
<td>Body Mass Index</td>
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<tr>
<td>CCF</td>
<td>Frontal Corpus Callosum</td>
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<tr>
<td>CDR</td>
<td>Clinical Dementia Rating</td>
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<tr>
<td>CONSORT</td>
<td>Consolidated Standards of Reporting Trial</td>
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<td>DSST</td>
<td>Digit Symbol Substitution Test</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>ES</td>
<td>Effect Size</td>
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<tr>
<td>FCI</td>
<td>Functional Comorbidity Index</td>
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<tr>
<td>FLAIR</td>
<td>Fluid Attenuated Inversion Recovery</td>
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<tr>
<td>fMRI</td>
<td>Functional Magnetic Resonance Imaging</td>
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<tr>
<td>GDS</td>
<td>Geriatric Depression Scale</td>
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<td>HBP</td>
<td>Healthy Brain Project</td>
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<td>Health ABC</td>
<td>Health Aging and Body Composition</td>
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<td>IGF-1</td>
<td>Insulin-Like Growth Factors 1</td>
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<td>IMT</td>
<td>Intima-Media Thickness</td>
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<td>LOOCV</td>
<td>Leave-One-Out Cross-Validation</td>
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<td>MMSE</td>
<td>Mini-Mental State Examination</td>
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<td>MoCA</td>
<td>Montreal Cognitive Assessment</td>
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<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<td>MS</td>
<td>Multiple Sclerosis</td>
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<td>N3</td>
<td>Nonparametric Non-Uniform Intensity Normalization</td>
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<td>PASE</td>
<td>Physical Activity Scale for the Elderly</td>
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<td>PD</td>
<td>Proton Density</td>
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<tr>
<td>PPA</td>
<td>Physiological Profile Assessment</td>
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<tr>
<td>PRISMA</td>
<td>Preferred Reporting Items for Systematic Reviews and Meta-Analysis</td>
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<td>RCT</td>
<td>Randomized Controlled Trial</td>
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<td>RT</td>
<td>Resistance Training</td>
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<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>SD</td>
<td>Standard Deviation</td>
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<tr>
<td>SPPB</td>
<td>Short Physical Performance Battery</td>
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<tr>
<td>TBI</td>
<td>Traumatic Brain Injuries</td>
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<tr>
<td>TE</td>
<td>Echo Time</td>
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<tr>
<td>TR</td>
<td>Reaction Time</td>
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<tr>
<td>TUG</td>
<td>Timed Up and Go</td>
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<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>VCI</td>
<td>Vascular Cognitive Impairment</td>
</tr>
<tr>
<td>VEGF</td>
<td>Vascular Endothelial Growth Factor</td>
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<td>WHO</td>
<td>World Health Organization</td>
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<td>WMHs</td>
<td>White Matter Hyperintensities</td>
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Health Research (CIHR) Post-Doctoral Fellow. CLH is an Alzheimer’s Society Research Program Doctoral trainee. JCD is an MSFHR and a CIHR Post-Doctoral Fellow. ED is a CIHR Doctoral Trainee.
To My Family

May this thesis be a partial compensation for all these years away from them.
Chapter 1: Introduction

This thesis aims to examine the impact of white matter hyperintensities (WMHs) on physical and cognitive functions in older adults, and the beneficial effect of targeted exercise training on the progression of WMHs in this population. In this regard, this chapter (Chapter 1) is focused on a review of literature. In Section 1.1, we will discuss the role of age-related physical and cognitive decline on mobility impairment. In Section 1.2, we will focus on WMHs as an important risk factor for both physical and cognitive functions in older adults. In Section 1.3, we will present exercise as a potential strategy to reduce the progression of WMHs, and ultimately improve physical and cognitive functions in older adults. Lastly in Section 1.4, we will provide an overview of the studies included in this thesis.

1.1 Mobility in Aging

The world’s population is aging at an unprecedented rate. By 2050, the number of adults older than 60 years will double from 10% to 20% \(^1\). This trend has immense implications, due to the prevalence of impaired mobility and subsequent functional dependence among older adults.

Mobility refers to the ability of planning, navigating, and moving independently and safely from one place to another \(^2\). With advancing age, physiological and sensory impairments, environmental barriers, and genetic vulnerabilities increase the risk for mobility decline \(^2\). In community-dwelling older adults, mobility impairment is represented as a pre-clinical transitional stage to disability, which will lead to activity limitation and participation restriction \(^1\). Mobility impairment is associated with both impaired physical and cognitive functions (Figure 1.1) \(^1\). Therefore, to improve mobility, and thereby maintain independent functioning
and quality of life in older adults, it is important to understand the underlying mechanisms and risk factors for both physical and cognitive decline and identify strategies to promote them in this population\textsuperscript{2}. In this regard, we have devoted the following two sections to the impact of physical decline (Section 1.1.1) and cognitive decline (Section 1.1.2) on mobility in older adults.

![Diagram of Mobility Association with Both Physical and Cognitive Functions in Older Adults]

Figure 1.1 Mobility Association with Both Physical and Cognitive Functions in Older Adults.

Common physical disorders in older adults include gait impairment, falls, and sarcopenia. Cognitive functions also comprise of global cognition and executive functions. The integrity of both factors is necessary in order for older adults to have intact mobility function.

1.1.1 Aging and Physical Decline

1.1.1.1 Epidemiology of Physical Decline in Older Adults

Mobility is a complex task that relies on the musculoskeletal, cardio-respiratory, sensory, and neural systems\textsuperscript{3}. The first signs of mobility decline appear during more demanding physical
tasks such as walking or running. Gait impairment, falls, and sarcopenia are among the most common physical geriatric syndromes and are considered as major causes of disability in older adults (Figure 1.1).

Gait impairment, based on definition from the world health organization (WHO), includes “spastic gait, hemiplegic gait, paraplegic gait, asymmetric gait, limping, and stiff gait patterns”, and has been shown to be predictive of mobility decline and mortality in older adults. Verghese and colleagues showed that a prevalence of 35% gait abnormality was present in a sample of 468 community-dwelling adults of 70 years and older. Moreover, they reported the incidence as 168.6 per 1000 person-years. Among the components of gait, gait speed has been specifically demonstrated to reflect health and functional status, and was associated with survival in older adults.

In addition to gait impairment, falls is a common geriatric syndrome defined as coming to rest on the ground unexpectedly, and is considered as the third leading cause of chronic disability. About 30% of community-dwelling adults of 65 years and older experience one or more falls, 5% of which result in fractures. Shumway-Cook and colleagues believe that impaired balance greatly increase the probability of falls, fractures, and functional dependency among older adults.

The third common physical geriatric syndrome is sarcopenia, which is the age-related reduction of muscle mass and strength, and is considered as one of the main causes of frailty and disability in older adults. This disease is highly prevalent in older adults and increases with aging. Fielding and colleagues in 2011 conducted a review on the prevalence of sarcopenia in older adults.
adults. From the studies they reviewed with sample sizes of over 2000 participants, they found a prevalence of 7 to 17% for individuals older than 60 years \cite{13,14}.

1.1.1.2 Risk Factors for Physical Decline

All the three above-mentioned physical syndromes – impaired gait, falls, and sarcopenia – are associated with poor mobility (Figure 1.1) and elevate the risk of disability in older adults \cite{15}. In order to develop clinical approaches and target for prevention, we need to understand the risk factors contributing to these physical syndromes. Older age and female gender are considered as important risk factors which are not modifiable \cite{15}. In contrast, chronic diseases such as diabetes, hypertension, and low bone density are known risk factors that can be modified \cite{15,17}. Obesity, which is mainly the result of age-related decrease in total energy expenditure, is another factor significantly associated with physical decline \cite{18}. Among health and physical measures, impaired vision and poor physical fitness including poor balance and low muscle strength are important predictors of physical decline in older adults \cite{15}. All these modifiable factors could be targets for interventions to promote physical function among older adults \cite{19}.

In addition, cognitive impairment and specifically deficits in executive functions have been suggested as independent risk factors for physical and mobility decline, leading to loss of independence and low quality of life in older adults \cite{20}. This effect occurs mainly through the reductions in attentional capacity, impaired central processing, decreased judgment and self-regulation, and loss of motivation and initiation \cite{9}. In addition, older adults with cognitive decline are at great risk for developing dementia, especially Alzheimer’s Disease (AD) \cite{21}. Therefore, to prevent mobility impairment and dementia in older adults, there is a great need to understand the
underlying mechanisms for cognitive decline in this population and ultimately develop strategies
to slow down this process. In the next subsection (Section 1.1.2), we will discuss the
epidemiology of cognitive decline and dementia (Section 1.1.2.1) and their risk factors (Section
1.1.2.2).

1.1.2 Aging and Cognitive Decline

1.1.2.1 Epidemiology of Cognitive Decline and Dementia in Older Adults

Dementia is one of the most pressing health care issues of the 21st century. Dementia is a generic
term describing “chronic or progressive dysfunction of cortical and subcortical function that
result in complex cognitive decline” 22. Alzheimer’s Disease is the most common type of
dementia 23. The cholinergic hypothesis proposes that AD is caused by reduced synthesis of the
neurotransmitter acetylcholine 24. The lower amount of this neurotransmitter was shown to be
associated with memory and learning deficits. However, the medications intended to treat
acetylcholine deficiency have not been significantly effective in clinical trials, and this
hypothesis did not receive further support 22, 25. Amyloid hypothesis was proposed in 1991,
suggesting extra beta-amyloid (Aβ) deposits outside neurons as the main cause of AD 26. The
accumulation of Aβ interferes with neuron to neuron communication at synapse level and
contributes to neuron death. Another hypothesis – tau hypothesis – supports the idea that tau
protein abnormalities initiate the disease cascade, by forming tangles inside nerve cell bodies 27.
Tau tangles block the transport of nutrients in the neuron and ultimately contribute to neuron
death. Another hypothesis states that age-related myelin breakdown is the main cause of AD 28.
Myelin repair processes contribute to the development of deposits such as Aβ and tau. Currently,
it is believed that AD happens when multiple impairing mechanisms (including Aβ accumulation,
tau tangles, and myelin breakdown) occur on the brain and overwhelm brain’s self-repair system. All these mechanisms will lead to the disconnection between neuronal connections and death of neurons.

The second most common type of dementia is vascular dementia (VaD), which is defined as vascular cognitive impairment (VCI) of sufficient severity to meet the criteria for dementia. One sub-type of VaD occurs as a post-stroke syndrome, in which lacunar infarcts in strategic locations cause cognitive dysfunctions. The infarct volume, degree of pre-existing subcortical white matter disorder, and cerebral atrophy have been considered as determinants of post-stroke VaD. The second sub-type of VaD is caused by subcortical small vessel ischemic disease, diagnosed by the WMHs and lacunar infarcts related to small vessel or microvascular ischemic disease. Although AD and VaD are considered to affect different domains of cognitive functions (i.e., AD mainly affects memory function versus VaD affects executive functions), they have common vascular pathologies. Evidence from recent studies have shown that vascular pathology and specially atherosclerosis and WMHs are evident in both types of AD and VCI, and that co-occurrence of multiple risk factors increases the risk beyond the additive effect of each factor. Due to the coexistence of AD and VaD pathologies in older adults and the difficulty of differentiating between the two dementia types, the term “mixed dementia” is recently being used.

Cognitive impairment, AD, VaD, and mixed dementia are extremely prevalent in older adults. In 2014, the Alzheimer’s Association published a report on the prevalence of AD in the US, using the latest data from 2010 US Census and the Chicago Health and Aging Project. It showed that 5.2 million Americans of all ages have AD in 2014, 5 million of which are over 65 years old and
200,000 of which are below 65 years old. This report also included a national estimate of the prevalence of all forms of dementia, based on Aging, Demographics and Memory Study, as being 13.9 percent of people older than 71 in US.  

In addition to the prevalence of dementia in US, Ferri and colleagues conducted a study to estimate the global prevalence of dementia. Twelve international experts worked on the estimation of the prevalence of dementia for people living in different WHO regions in 2001, 2020, and 2040. The incidence rates were estimated from prevalence, remission, and mortality. 24.3 million people were estimated to suffer from dementia in 2001, and they will double every 20 year, to 81.1 million by 2040, assuming no effective change for the cure or mortality rate. In addition, the Framingham study showed that 65 year old women without dementia have 20% chance of developing dementia during the remainder of their lives. The same estimate is 17% for men without dementia. All these estimates present the growing number of older adults in the world who are at risk for cognitive impairment and dementia.

1.1.2.2 Risk Factors for Cognitive Decline and Dementia in Older Adults

As discussed in the previous section, the number of older adults with cognitive impairment and dementia is growing substantially. To improve cognitive functions in this population, it is important to learn the risk factors for this process. It is currently well-known that age is the greatest risk factor for cognitive decline and dementia. Normal aging is accompanied by progressive deterioration of cerebral structure (including distributed synaptic loss and degeneration of myelinated axons in prefrontal cortex), which is associated with functional decline.
Genetics is another risk factor for cognitive decline and dementia. Among the genes affecting AD, ApoE4 is the most important genetic risk factor for AD\textsuperscript{36}. It is believed that ApoE4 promotes the production of $\beta$ and tangles, and adversely affects mitochondrial functions and synaptic mechanisms. Moreover, Post-menopausal state has been known to be associated with cognitive decline\textsuperscript{37}. Estrogen, which is known to be a neuroactive hormone upregulating acetylcholine neurotransmitter\textsuperscript{37} highly drops in post-menopausal state.

In addition to age, genetics, and post-menopausal state, cardiovascular disorders are considered as significant contributors to cognitive decline and dementia, particularly VaD\textsuperscript{38}, and are believed to be treatable if diagnosed in a timely manner. Diabetes is recognized as a cardiovascular risk factor for cognitive decline and dementia\textsuperscript{39,40}. It has been shown that in people with dementia, cerebral glucose cannot be used properly\textsuperscript{41}. This might be because the cells are dead, or the cells refrain from utilizing insulin to use glucose (i.e., insulin resistance - resembling Type 2), or the production of insulin is reduced (i.e., resembling Type 1). Also, insulin level has been shown to be associated with memory function in this population\textsuperscript{39}. In addition to diabetes, both hypertension and hypotension are cardiovascular contributors to cognitive decline and dementia\textsuperscript{40}. Hypertension contributes to vascular damages and also damages to the blood brain barrier, which leads to overproduction of $\beta$\textsuperscript{40}. Hypotension is also believed to be associated with cognitive decline and dementia\textsuperscript{42} as it leads to deprivation of oxygen and glucose to neurons.

In addition to cardiovascular disorders, chronic disorders such as chronic inflammation and chronic stress are suggested as potential risk factors for cognitive decline and dementia. Inflammation, which is a common feature in cardiovascular disorders, is believed to modify the
increased risk of cognitive decline associated with cardiovascular disorders \(^{43}\). Moreover, neuroinflammatory processes are derived by pro-inflammatory cytokines that are up-regulated in neurodegenerative disorders and are neurotoxic. Chronic stress and high levels of cortisol have also been shown to be associated with hippocampal atrophy and decline in memory and learning \(^{44}\).

In addition, lifestyle status, including inadequate cognitive activity, lower levels of education, lack of physical activity, type of diet, and obesity have been shown to contribute to cognitive decline and dementia in later stages of life \(^{42}\). Both cognitive and physical activities seem to promote the production of growth factors in the brain, and can be a preventive factor for cognitive decline and dementia. Higher education levels are shown to be associated with lower risk of AD and related dementia, which might be partly related to the compensatory strategies that delay the detection of disease \(^{22}\). In addition, low levels of omega 3 and vitamins D, B6, and B12 are associated with overproduction of \(A_\beta\) and higher risk for dementia \(^{42}\). Saturated dietary fat also damages the blood brain barrier and allows \(A_\beta\) to enter the brain. In addition, obesity has been shown to be related to diabetes Type 2, which is considered a great risk factor for cognitive decline and dementia.

Lastly, structural changes in the brain can be a risk factor for cognitive decline and dementia. Importantly, one consequence of traumatic brain injuries (TBI) is the breakdown of the blood brain barrier, which allows blood plasma containing toxic agents (e.g., \(A_\beta\)) to enter the brain and facilitate the onset of various neurodegenerative diseases \(^{45}\). Another theory supporting the association between TBI and exacerbated cognitive decline is that less age-related neuronal loss would be needed to exceed the threshold for dementia in older adults with previous TBI \(^{45}\). In
addition, WMHs are important cerebral structural changes that have been shown to be significantly associated with cognitive decline and dementia, particularly VaD. O’Sullivan and colleagues\(^4\) presented evidence for age-related white matter disconnection hypothesis in older adults and suggested WMHs as the biological basis for age-related cognitive decline. They reported a significant reduction in diffusional anisotropy, which is a marker of white matter integrity, in older adults. Moreover, this measure fell linearly with increasing age in the older group. These changes were maximal in the anterior white matter and were correlated with higher level cognitive functions. In addition to their association with cognitive decline, WMHs are shown to be significantly associated with impaired gait and balance in older adults\(^5\).

Due to the importance of WMHs as potential risk factor for both physical and cognitive decline, we will devote the next section (Section 1.2) to WMHs, their epidemiology among older adults (Section 1.2.1), etiology (Section 1.2.2), detection (Section 1.2.3), and common prevention strategies for their growth (Section 1.2.4).

1.2 White Matter Hyperintensities

1.2.1 Epidemiology of WMHs in Older Adults

White matter hyperintensities are highly prevalent findings visible on magnetic resonance images (MRI) of normal older adults with or without dementia\(^5\). De Leeuw and colleagues selected a random sample of 1077 individuals between the ages of 60 and 90, and showed that only 5% of the sample was free from WMHs. This study confirmed findings of the Cardiovascular Health Study\(^5\), which demonstrated that only 4.4% of their large sample of 3301
individuals older than 65 years were free of WMHs. Both studies found a high volume of WMHs in the frontal regions affecting cognitive functions in this population.

1.2.2 Etiology of WMHs

The basic components of age-related white matter pathology are damage to the brain parenchyma (ranging from demyelination to complete axonal disruptions), increase in glial cells (gliosis), vascular changes, and necrosis. It is believed that the severity of WMHs increase with lesion size and their pathologies might differ in regards to their structural locations. Based on their shapes, sizes and locations, Galluzzi and colleagues categorized WMHs into three groups of confluent, punctate, or periventricular.

Confluent WMHs (also known as diffuse or patchy WMHs) are caused by small vessel disease, usually due to hypertension or diabetes. Small vessel disease affects small arteries of 150 micrometer in diameter, and results in progressive thickening of small vessel walls (i.e., arteriolosclerosis) and alterations in tissue surrounding the damaged vessels. The degree of tissue alterations can range from demyelination with preservation of axonal integrity to gliosis and complete axonal disruption. Confluent WMHs are usually larger than 5 mm in diameter, have irregular shape and boundaries, seem to be built by the confluence of smaller lesions, are shown to progress over time, and parallel cognitive decline.

The second type of WMHs are known as punctate WMHs (also known as focal or punctuate WMHs), which are round lesions with a boundary, usually smaller than 5 mm in diameter. These lesions correlate to mild perivascular demyelination or edema, and are suggested to be less
clearly related to cerebrovascular pathology, compared to confluent WMHs. Punctate WMHs have negligible rate of progression over time.

The third type of WMHs are periventricular caps and halos, which might be due to the chronic edema of white matter immediately adjacent to the ventricles, and might not represent axonal damage. These lesions are believed to be caused by disruption of blood brain barrier and chronic leakage of cerebrospinal fluid in the white matter.

In addition to the three types of WMHs, lacunar infarcts and lacunes look similar to regular WMHs on MR images. Lacunar infarcts are lesions associated with a clinical lacunar syndrome, and are considered ischemic and not hemorrhagic. Lacunes are cerebrospinal fluid filled cavities developed from the occlusion of arteries larger than 400 micrometer.

In summary, different pathologies (e.g., axonal disruption, demyelination, and gliosis) can be seen as WMHs in MR images. Therefore, it is important to use the right MRI sequence to detect them more accurately. The next section (Section 1.2.3) is dedicated to the detection and assessment of WMHs using MRI scans.

### 1.2.3 Detection and Assessment of WMHs

White matter hyperintensities are usually detected on MRI scans, using T2-weighted, T2-weighted Fluid Attenuated Inversion Recovery (FLAIR), Proton Density (PD), or T1-weighted sequences. Normal myelin contains of more lipids and less water than gray matter, and is shown hypointense to gray matter on T2-weighted, FLAIR and PD images, and hyperintense to gray matter on T1-weighted images. If a disease causes a reduction in myelin content of white
matter, the white matter becomes less hydrophobic and takes more water. This less myelin and more water content, as well as gliosis and dilated perivascular spaces, are shown as hyperintensities on T2-weighted, T2-weighted FLAIR and PD images, as hypointensities in case of lacunar infarcts and black holes, and as mild hypointensities in case of regular WMHs on T1-weighted images. Out of different MRI sequences, WMHs are more conspicuous on FLAIR images as the cerebrospinal fluid looks dark while WMHs look bright. This will specifically result in a more clear detection of periventricular WMHs. Moreover, T1-weighted images are not used as a sole sequence for detection of WMHs. This is because the lesions detected on T1-weighted images are a subset of the lesions detected on other sequences. In this regard, Garcia-Lorenzo and colleagues discussed that although some lesions are obvious in one sequence, the lesions should be confirmed in other sequences to avoid false positives. Therefore, they concluded that multi-modal images are necessary to detect WMHs.

After selecting the right MRI sequence for detection of WMHs, one needs to assess WMH burden using one of the following two methods; 1) volume measurement, or 2) visual scoring. The volume measurement method consists of three steps. The first step is pre-processing, which minimizes the effect of imaging artefacts and aligns multiple modalities in the same space. Pre-processing can include registration, brain extraction, intensity inhomogeneity correction, noise reduction, and intensity normalization. Registration is the process of aligning different modalities into a common space, or aligning an atlas to the brain to provide initial estimates of the tissues. In brain extraction step, the brain is extracted from the image, and the remaining processes are performed on the segmented brain. Intensity inhomogeneity correction is required on same tissues across an image, to reduce the variation of intensity of tissues. Noise reduction
algorithms reduce the negative effect of noise in the image. Lastly, intensity normalization methods modify the intensity range of image to make them similar to the intensity of training images. After pre-processing methods are applied on an image, the second step would be identifying lesions. This step can be done either manually by placing a seed by an expert radiologist to localize the lesion, or automatically. Since intensity range of WMHs overlap with those of healthy tissue, automatic methods of lesion identification produces more false positives, compared with manual identifications done by an expert radiologist \(^6^0\). Moreover, although manual methods done by expert radiologists are very time-consuming, they make it possible to differentiate between WMHs due to different pathologies (e.g., lesions due to Multiple Sclerosis (MS) or lesions with vascular origin, by investigating the location, shape, growth rate, etc.). In addition, automatic methods might bias lesion identification against certain pathologies \(^6^0\). For example, exclusion of WMHs located between the lateral ventricles by some automatic methods might reduce the effectiveness of the method for detection of MS lesions which are prevalent in corpus callosum. After the WMHs are identified manually or automatically, one can proceed to the third step, which is measuring WMH volumes. This step is complicated as lesion borders might differ according to MRI protocol used, and consistency is hard to achieve with manual methods \(^5^9\). Therefore, semi-automatic methods have been proposed, which consist of manual lesion identification process as the second step, and automated volume measurement process (e.g., based on region growing or fuzzy connectedness) as the third step \(^5^9\).

Visual scoring methods are another way of assessing WMH burden. These methods are performed manually and show a higher accuracy for selection of subtle WMHs, compared to automatic volumetric methods \(^6^1\). However, they vary significantly in terms of lesion
classification and severity scoring, which have resulted in inconsistencies between studies. Moreover, these methods are less sensitive to detect small group differences and show decreased correlations with clinical data, compared to automatic volumetric methods. In addition, each scoring method has its own specific limitations. Fazekas scoring method, which is the most commonly used scoring method for WMH quantification, provides poor information regarding the anatomical distribution and the severity of the hyperintensities. Wahlund scoring method is a more complicated scoring system which evaluates WMHs in five anatomical regions of frontal, parieto-occipital, temporal, infratentorial, and basal ganglia. However, this method grades lesions according to a 0 to 3 scale, which has less sensitivity to detect clinical correlations than continuous scales in volume measurements.

Overall, Gouw and colleagues showed that both volumetric and scoring measures are reliable for assessment of WMHs cross-sectionally. However, volumetric measurements were more reliable than scoring measures for assessment of WMH progression over time.

1.2.4 Risk Factors for WMHs and Common Prevention or Treatment Strategies for their Progression

Since WMHs are associated with clinical measures of physical and cognitive functions, it is important to understand their risk factors in order to find strategies for their prevention or treatments. Bronge and colleagues believe that in addition to aging, hypertension is a major risk factor for development of WMHs. Verhaaren and colleagues demonstrated that both systolic and diastolic blood pressures are significantly associated with annual WMH progression in older adults. They suggested that hypertension treatments could reduce WMH progression.
Confirming these results, Dufouil and colleagues\textsuperscript{67} conducted a 3-year randomized controlled trial (RCT) of blood pressure lowering therapy using perindopril or perindopril plus indapamide on 192 participants, and demonstrated that the mean total volume of new WMHs was significantly lower in the active treatment group than in the placebo group.

In this regard, due to the possible vascular origin of WMHs\textsuperscript{66} and the association between WMHs and cardiovascular risk factors, one might believe that strategies to overcome cardiovascular risk factors might as well be beneficial for WMHs progression. In a recent cross-sectional study, Burzynska and colleagues\textsuperscript{68} demonstrated that greater physical activity measured by accelerometers was associated with lower volume of WMHs, in 86 community-dwelling older adults between the ages of 60 to 78 years. Although this study suggested that engaging in physical activities and avoiding sedentariness are key factors in maintaining white matter health in older adults, it did not show the effect of physical activity on the progression of WMHs due to its cross-sectional nature. Moreover, physical activity was measured using accelerometers, in contrast to investigating the effect of targeted exercise training on the progression of WMHs. To our knowledge, no study to date has demonstrated the benefit of exercise on the progression of WMHs, in a prospective analysis. To understand the underlying mechanisms by which targeted exercise training may affect WMHs and physical and cognitive functions, we have devoted the next section (Section 1.2) to the effect of exercise on mobility as a possible strategy to reduce the rate of WMH progression and improve both physical and cognitive functions.
1.3 Effect of Exercise on Mobility in Aging

1.3.1 Exercise Definition and Types

Exercise is defined as repeated physical activity that is planned, structured, and purposive to improve physical fitness. Generally, there are two types of exercise which are demonstrated to benefit both physical and cognitive functions in older adults: 1) Aerobic Training (AT), which is primarily affecting VO\(_2\)max (maximal Oxygen consumption); and 2) Resistance Training (RT), which is primarily affecting muscle mass and strength. There is a third type (i.e., anaerobic training) that its effect on brain functions and structure has not been studied much in the literature.

Aerobic training is believed to improve aerobic capacity, which refers to the ability of body to transport and use oxygen and is traditionally measured using VO\(_2\)max. VO\(_2\)max declines at a rate of 10% per decade. Since lower levels of VO\(_2\)max contributes to limitations in activities of daily living, increases the risk of disability, and reduces the quality of life in older adults, tremendous interest has been directed towards strategies to change age-related VO\(_2\)max. In 2003, Hawkins and colleagues discussed that age-related reductions in maximal heart rate may serve as the primary reason for VO\(_2\)max decline. Moreover, less oxygen utilization by skeletal muscles, either due to age-related reductions in lean body mass and increases in fat mass or age-related inability of muscles to utilize oxygen, is suggested as a second reason for VO\(_2\)max decline. In this regard, they suggested AT for improving cardiovascular health and aerobic capacity, and RT to enhance muscle strength and lean body mass. Following the suggested strategies by Hawkins and colleagues, interventional studies of AT further confirmed the beneficial effects of this exercise on VO\(_2\)max. Renaud and colleagues conducted a RCT trial of
AT for 12 weeks on sedentary older adults with mean age of 67.8 years, and demonstrated a significant improvement in cardiorespiratory capacity measured by VO\(_2\)max estimate in the experimental group. Moreover, in a meta-analysis of 41 interventional studies of AT with sedentary adults of older than 60 years, Huang and colleagues\(^7\) found a significant effect of AT on VO\(_2\)max. They presented two important findings. First, the greatest benefits of AT was observed when practiced at 60-65% of VO\(_2\)max. Second, longer training was associated with greater VO\(_2\)max benefits.

In addition to AT, evidence shows that RT or weight training has beneficial effects on older adults. With age, the structure and function of skeletal muscles and skeletal system deteriorates\(^7\). Resistance training has been shown to increase muscular mass and strength in older adults\(^7\). Cassilhas and colleagues\(^7\) conducted a 24-week RCT of RT at two intensity levels, on 62 sedentary adults aged 65 to 75 years. They demonstrated that both groups of high and moderate intensity programs had muscle strength gains after intervention. Moreover, the lean muscle mass was increased in high intensity group compared to the control group. Confirming these results, Peterson and colleagues\(^7\) conducted a meta-analysis on 47 randomized and non-randomized controlled studies to investigate the effect of RT on muscle strength in adults older than 50 years. Their results showed that RT is an effective strategy for improving both upper and lower muscle strength among older adults, and higher intensity training was associated with greater strength improvements.

The American College of Sports Medicine (ACSM) and the American Heart Association (AHA)\(^7\) recommend an AT intensity of 55 to 90 percent of maximum heart rate, accumulating 20-60 minutes three to five days a week, to achieve improvements in cardiovascular fitness in older
adults. The recommendation for RT includes eight to ten exercises involving major muscle groups with 10-15 repetitions, at least two days per week but no more than four, to improve overall health and fitness capacity.

In summary, both AT and RT have beneficial effects for older adults. In addition to primary improvements in VO$_2$max and muscle mass and strength, both types extensively enhance physical and cognitive function. In the next sections (Sections 1.3.2 and 1.3.3), we will review the effects of AT and RT on age-related physical and cognitive decline in older adults.

### 1.3.2 Effect of Exercise on Age-Related Physical Decline

Both AT and RT have been demonstrated to improve physical function, specifically gait speed, falls risk, and sarcopenia in older adults$^{10,74,77}$. Lopopolo and colleagues$^{78}$ conducted a meta-analysis on 24 studies of adults older than 60 years and concluded that high-intensity AT and RT has significant effects on gait speed in older adults. They discussed that exercise-induced improvements in lower-extremity muscle force and flexibility along with improvements in aerobic fitness and balance are the main underlying mechanisms for the beneficial effects of exercise on gait speed. Moreover, Bolandzadeh and colleagues$^{47}$ demonstrated that the underlying pathways affecting gait speed in older adults can be either direct, or indirect through cognitive functions. They suggested exercise training as a possible intervention to promote gait speed both directly, and indirectly through improvements in cognitive functions in older adults.

In addition to improving gait speed, AT and RT have been shown to reduce falls risk among older adults. Sherrington and colleagues$^{79}$ conducted a meta-analysis on 44 RCTs to determine the effect of exercise on falls prevention in older adults. Their study concluded that exercise,
including AT and RT, reduced the rate of falls by 17%. The effect of exercise on falls prevention was greater in presence of balance training, and with higher intensity. In addition to impaired mobility and balance as leading causes of falls, impaired cognitive function, and specifically dual-task are major risk factors for falls in older adults. Liu-Ambrose and colleagues suggested cognitive functions improvement as an important yet underappreciated mechanism by which exercise reduces falls in older adults.

Thirdly, exercise has been shown to be an effective strategy for prevention of sarcopenia. Landi and colleagues in a review for the effect of physical activity and exercise on frailty discussed that a sedentary lifestyle is a risk factor for muscle weakness and could result in loss of muscle mass and strength. They suggested that a balance program of both AT and RT performed on a regular schedule would be of benefit to this problem in older adults. Confirming the benefits of exercise, Waters and colleagues argued in a review that the most compelling evidence to combat sarcopenia is RT. They believed that muscular power declines at a faster rate than strength, and power has a greater impact on physical function than strength. Therefore, in order for skeletal muscles to achieve and maintain both strength and power, RT programs need to have progressively increasing load.

1.3.3 Effect of Exercise on Age-Related Cognitive Decline

In addition to their beneficial effects on physical functions, it has been shown that both AT and RT also enhance mobility through improvements in cognitive functions in older adults. Colcombe and colleagues demonstrated that AT has selective benefits on cognitive functions, with the largest improvements on executive control processes. Stuss in 1992 explained
executive control functions as a set of higher level supervisory processes that enable us in goal selection, plan formulation, evaluation, and monitoring cognitive operations. West and Colleagues 85 discussed in 1996 that cognitive processes do not degrade uniformly with age, and executive control functions show large degradation with aging. Due to the importance of executive control functions, a substantial body of research has been conducted to investigate the effects of AT and RT on these cognitive processes. Kramer and colleagues 86 in 1999 demonstrated that a six-month AT program of walking substantially improved executive control functions of task switching, response compatibility, and stopping, in older adults of 60 to 75 years old. In addition, in 2010, Liu-Ambrose and colleagues 87 in a RCT of RT demonstrated that twelve months of once- or twice-weekly RT benefited executive functions of selective attention and conflict resolution in older adults.

Following the beneficial effects of both types of exercise on executive control functions in older adults and due to the fact that these processes are subserved by the frontal lobe, great amount of research were conducted on the effect of exercise in this cerebral region, using functional and structural magnetic resonance imaging techniques (fMRI and MRI). In 2004, Colcombe and colleagues 88 showed in a cross-sectional study that higher cardiovascular fitness was associated with greater activations in several cortical regions associated with attentional control, in addition to greater behavioral measures of executive functions. The same group also conducted a RCT of 6-month AT, and demonstrated greater levels of task-related activation in attentional control areas, increase in the cardiovascular fitness levels, and improved executive functions in the aerobic group. In 2006, Colcombe and colleagues 89 in a RCT of AT showed that participants of the exercise program had significantly increased brain volume, with the largest change in their
frontal lobe, as well as a significant increase in VO$_2$ as a result of exercise. In addition, in 2012, Weinstein and colleagues $^{90}$ demonstrated that higher fitness levels are associated with both greater gray matter volume and greater executive functions. Moreover, they showed that the effect of AT on executive functions is mediated by greater gray matter volume in the prefrontal cortex.

In addition to the great benefits of AT and RT on executive functions and frontal lobe, Colcombe and colleagues $^{83}$ highlighted that the greatest effect of AT on cognitive function was observed when it was paired with RT. Moreover, although RT improves the ability of participants to perform AT more efficiently, it has individual effects independently of AT. As an example, in a six month RCT of AT and RT, Nagamatsu and colleagues $^{91}$ demonstrated that AT had a great impact on verbal memory, while RT had a great impact on spatial memory. According to an animal study by Cassilhas and colleagues $^{92}$, the different effects of AT and RT might be due to divergent molecular pathways and different growth factor signaling. More specifically, their study showed an increase in hippocampal brain-derived neurotrophic factors (BDNF) and insulin-like growth factor 1 (IGF-1) in AT group, while the RT group showed an increase in peripheral and hippocampal IGF-1 levels.

In summary, both AT and RT have significant effects on executive cognitive functions. Studies by Cotman and colleagues $^{93}$ in 2007, Hillman and colleagues $^{94}$ in 2008, Bherer and colleagues $^{69}$ in 2013, and Kirk-Sanchez and colleague $^{95}$ in 2014 suggest two mechanisms through which exercise affects cognitive functions: 1) central benefits, by functional, structural, and metabolic changes in the brain; and 2) systemic benefits, by modifying cardiovascular risk factors.
associated with cognitive impairment and reducing stress and depression. In the following sections, we will discuss these two mechanisms in more details.

1.3.3.1 Central Benefits

The underlying benefits of exercise training on cognitive functions are believed to be a result of exercise-induced changes in brain structure and function, which is confirmed by early animal studies of adult rats. Black and colleagues \(^96\) in 1990 demonstrated that adult exercise rats had a greater density of blood vessels in the molecular layer than did the inactive rats. Following this study in 1995, Fordyce and colleagues \(^97\) demonstrated that AT increased BDNF in rats. Moreover, although most human studies have been conducted on executive functions which are related to frontal lobe, rodent studies have assessed functions associated with hippocampus. In 1999, van Praag and colleagues \(^98\) showed that hippocampal neurogenesis might be the key mechanism by which exercise affects learning and memory. Moreover, in a more recent study, they demonstrated that exercise can facilitate both acquisition and retention in various tasks related to hippocampus, in young and aged rodents \(^99\). Supporting these results, Cassilhas and colleagues \(^100\) in 2012 conducted the first study of RT on rats and demonstrated the beneficial effects of this type of exercise on peripheral and hippocampal IGF-1.

Similar to animal studies, evidence from human studies have shown great benefits of exercise on cerebral structure and function, including increased levels of growth factors, increased number of synapses, increased cerebral perfusion, improved metabolism, and improved brain connectivity. Exercise, and specifically AT \(^101\), is believed to induce higher levels of growth factors such as BDNF, which is believed to be supporting neuroplasticity and neuroprotection and stimulating
neurogenesis. In addition, exercise, and specifically RT \textsuperscript{75}, has been shown to induce IGF-1, which is believed to be stimulating neurogenesis and angiogenesis. Exercise is also shown to induce vascular endothelial growth factor (VEGF), which helps stimulating neurogenesis and vasculogenesis \textsuperscript{93, 102}. These enhancements in growth factors are either done directly, or by reducing pro-inflammatory conditions which impair growth factor signaling \textsuperscript{88, 93}. Moreover, AT might be involved in increasing the number of interconnections (synapses) in frontal and parietal gray matter \textsuperscript{88}, which are known to be responsible for executive cognitive functions.

In addition to increased levels of growth factors and number of synapses, exercise and specifically AT increases cerebral perfusion and oxygen uptake, which leads to improved nutrient supply to the brain \textsuperscript{103, 104}. The underlying mechanisms include increasing the cerebral blood flow \textsuperscript{105}, sustaining cerebral blood flow by decreasing blood pressure \textsuperscript{103} specifically in people with hypertension \textsuperscript{104}, and decreasing blood viscosity \textsuperscript{75}. These mechanisms are in accordance with the cognitive reserve hypothesis by Fratiglioni and colleagues \textsuperscript{106}, stating that increased cerebral perfusion leads to larger cognitive reserve.

Moreover, the aging process is accompanied by a decline in the number and function of the mitochondria that generate most of the cell's supply of adenosine triphosphate (ATP), which is used as a source of chemical energy. Exercise is shown to have beneficial effects on mitochondria and ATP production \textsuperscript{107}. Moreover, AT is known to benefit insulin resistance and glucose intolerance in older adults \textsuperscript{108}.

In addition, recent functional connectivity studies have provided further support for the beneficial effects of exercise on brain structure and function. In this regard, Voss and colleagues
demonstrated that a 12-month AT program leads to increased connectivity in brain circuitries involved in frontal executive network and default-mode network.

1.3.3.2 Systemic Benefits

In addition to central benefits, exercise affects cognitive functions indirectly by decreasing the cardiovascular risk factors, stress, and depression in older adults. Metabolic and cardiovascular risk factors such as hypertension, diabetes, and dyslipidemia are modifiable risk factors associated with increased risk of cognitive impairment ⁹⁵, and converge to cause brain dysfunction and neurodegeneration ⁹³. More specifically, cardiovascular risk factors and disorders have been consistently shown to be associated with executive dysfunctions ¹¹⁰. The vascular hypothesis by Fratiglioni and colleagues ¹⁰⁶ states that one mechanism through which exercise affects executive functions is by reducing the risk of cardiovascular diseases ⁹³. In search for the underlying neural correlates for this mechanism, a recent study by Chuang and colleagues ¹¹⁰ demonstrated that aggregate cardiovascular risk was associated with hyperactivations in task-related (left parietal) regions under conditions requiring high executive demand. These increased activations were also associated with poorer task performance. They showed that these hyperactivations might be indicative of the dysfunctional neural pathways that could serve as early marker of cognitive decline associated with high cardiovascular risk. Moreover, most metabolic and cardiovascular risk factors are shown to have inflammation as their common feature, which associates to cognitive decline ⁴³, ⁹³. Exercise is believed to reduce pro-inflammatory conditions and prevent the impairment of growth factor signaling ⁹³. It can also benefit the overall immune condition of the brain, by reducing brain inflammation in response to
stroke or reducing pro-inflammatory cytokines associated with increased levels of Aβ in people with AD.

In addition, exercise has great benefits for stress. Stress is the response of body to physiologically adapt organisms to deal with challenges. During a stress response, hypothalamus releases corticotropin hormone that stimulates pituitary gland to release adrenocorticotropin hormone. This hormone stimulates adrenal gland, causing it to release cortisol. After the stressful situation is finished, the excessive amount of cortisol circulates back to hypothalamus and pituitary gland. It is in chronic stress that an excessive amounts of cortisol is produced, which is harmful for the body and suppresses immune system. Cortisol prevents the production of anti-inflammatory cytokines. When cortisol is overproduced, there are less receptors on immune cells, so that inflammation cannot be ended. However, acute stress associated with exercise leads to a decrease in chronic inflammation, by enhancing organism’s ability to adapt. These mechanisms are in accordance with the stress hypothesis by Fratiglioni and colleagues, stating that exercise decreases stress which is a two-fold risk factor for dementia.

In addition to stress, depression has been shown to be associated with cognitive decline. Moreover, depressed older adults have shown significant impairment in executive functions. The beneficial therapeutic and preventive effects of exercise on depression are well-established in cross-sectional human studies and RCTs. Although the underlying mechanisms are poorly understood, it is believed that stress reduction and exercise-induced neurogenesis, specifically through increased levels of BDNF, and neuroprotection are the potential mediators of the effect of exercise on depression.
In summary, both AT and RT have great benefits for physical and cognitive functions in older adults, either directly by affecting physical and cerebral structure and function, or indirectly by reducing cardiovascular risk factors, stress, and depression.

1.4 Overview of Thesis

1.4.1 Main Research Hypotheses

In the previous sections, we discussed that aging is associated with both physical and cognitive decline. One important risk factor for these age-associated impairments is cerebral WMHs, which is demonstrated to be associated with cardiovascular risk factors. Exercise is one strategy that reduces cardiovascular risk factors and thereby, may reduce the rate of WMH progression. Both AT and RT have also been shown to benefit physical and cognitive functions in older adults. Therefore, we hypothesize that one mechanism through which exercise might benefit physical and cognitive functions in older adults is exercise-induced reductions in the rate of WMH progression. To investigate whether the effect of exercise on physical and cognitive functions is through a reduction in WMH progression, we answered the following questions:

1. Are WMHs associated with cognitive decline in older adults? Specifically, is the anatomical location of WMHs a moderator to this association?

2. Are WMHs associated with physical decline in older adults? Is this a direct association, or is it modified by cognitive functions?

3. Is physical function associated with cognitive functions? Specifically, which components of physical function and health status are predictive of cognitive decline?
4. Can exercise reduce WMH progression? What is the association between reduced WMH progression and change in a) executive functions, and b) physical function?

1.4.2 Overview of Studies

To address the above questions, this thesis is comprised of four studies. Each of these studies is presented in a separate chapter (Figure 1.2). The following is a summary of each chapter.

Figure 1.2 Overview of the Studies Included in this Thesis.

The association between WMHs and cognitive impairment is systematically reviewed in Chapter 2. The association between WMHs and physical impairment is investigated in Chapter 3. The associations between cognitive and physical impairment are explored in Chapters 3 and 4. Finally, the beneficial effect of exercise training on the progression of WMHs is demonstrated in Chapter 5.

In Chapter 2, we conducted a systematic review to evaluate peer-reviewed evidence on the role of anatomical location in the association between WMHs and cognitive functions. Of the 14
studies included, seven compared the association of subcortical versus periventricular WMHs with cognitive functions. Seven other studies investigated the association between WMHs in specific brain regions (e.g., frontal, parietal lobes) and cognitive functions. Overall, the results suggested that periventricular WMHs may have a greater impact on executive function/processing speed than subcortical WMHs. However, whether WMHs in different brain regions have a differential effect on cognitive functions remains unclear.

In Chapter 3, we explored the association between WMHs and physical function. Specifically, we investigated whether WMHs impair mobility directly, by disrupting mobility-related circuits, or indirectly, by disrupting circuits responsible for executive functions. In this regard, we identified regional WMHs most related to slower gait and examined whether these regional WMHs directly impact mobility, or indirectly through executive functions. Twenty-one WMH variables (i.e., total WMH volume and WMHs in 20 tracts), gait speed, global cognition (Modified Mini-Mental State Examination; 3MS), and executive functions and processing speed (Digit-Symbol Substitution Test; DSST) were assessed. A L1-L2 regularized regression (elastic net) identified WMH variables most related to slower gait. Multivariable linear regression models quantified the association between these WMH variables and gait speed. Formal tests of mediation were also conducted. Our results showed that, the impact, direct or indirect, of WMHs on gait speed depended on their location and was mediated by executive function. Thus, we suggested multi-faceted interventions targeting executive control functions as well as motor functions, such as balance and strength training, as candidates to the maintenance of mobility across the lifespan.
In Chapter 4, we aimed to identify measures of physical function and health status that are predictive of cognitive decline and can be easily assessed within the clinical setting. We included 89 community-dwelling adults aged 70 years and older in our study, and collected 32 measures of physical function, health status and cognitive function at baseline. We utilized a L1-L2 regularized regression model (elastic net) to identify which of the 32 baseline measures were significantly predictive of cognitive function after one year. Six measures of physical function and health status, broadly of falls risk, muscle strength, cardiovascular risk, and physical activity were significantly predictive of cognitive function after one year.

Following the suggestions in Chapters 2, 3, and 4 regarding the beneficial effects of targeted exercise training in older adults, in Chapter 5 we assessed whether RT slows down the progression of WMHs in older women. In this planned exploratory analysis of a 52-week RCT, we randomized 54 participants to either once-weekly resistance training (1x RT), twice-weekly resistance training (2x RT), or twice-weekly balance and tone (BAT). Our results showed that at trial completion, the 2x RT group had significantly lower WMH volume compared with the BAT group. There was no significant difference between the BAT group and the 1x RT group at trial completion. Among participants in the two resistance training groups, reduced WMH progression over 12-month was significantly associated with improved gait speed, but not with executive functions.

This thesis concludes with an integrated discussion on the associations between physical function, cognitive function, and WMHs, and how targeted exercise training can reduce the rate of WMH progression, and improve physical and cognitive functions in older adults. Following this discussion are the limitations and future directions for this research.
Chapter 2: WMHs and Cognitive Decline in Older Adults

2.1 Introduction

The world’s population is aging at a rate that is unprecedented in human history \(^{116}\). Maintaining cognitive function is essential for healthy aging and to function autonomously within society.

With age, the brain undergoes both structural and functional changes \(^{117-120}\). Specifically, cerebral white matter hyperintensities (WMHs) are prevalent among adults aged 60 years or older \(^{121}, 122\). These lesions are due to damage to the brain parenchyma \(^{52}\), ranging from demyelination to complete axonal disruptions \(^{53}, 123\). Although their pathogenesis is unknown, there is a growing recognition that WMHs are most likely the result of cerebrovascular disorders and cerebral ischemia \(^{52}, 124-126\). The current gold standard for diagnosis of WMHs includes various MRI sequences, such as T1, T2, proton density (PD), or fluid attenuated inversion recovery (FLAIR).

Impairing the speed or integrity of signal transmission, WMHs are associated with both impaired mobility and reduced cognitive performance as measured by standard neuropsychological testing \(^{127}, 128\). Specially, WMH load has a negative impact on multiple domains of cognitive function such as memory, processing speed, attention, and executive function \(^{52}, 129\). Pantoni et al. \(^{129}\) summarized the results of 16 studies focusing on the effect of WMHs on different cognitive domains. Their results showed that, despite the fact that the probability of finding a positive association between WMH load and cognitive decline may be affected by the cognitive domains assessed, an effect of WMH on cognition was present invariably. However, emerging evidence suggests that WMH distribution, as well as load, may also be a predictor of reduced cognitive
performance\textsuperscript{130,131}. In a study by Kim et al.\textsuperscript{130}, it is suggested that a specific distribution of fiber tract damage is more associated with cognitive and motor impairment, compared with the total WMH load. Thus, we conducted a systematic review to ascertain the role of anatomical location in the association between WMHs and cognitive function in older adults.

2.2 Materials and Methods

2.2.1 Search Strategy

In accordance with the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement\textsuperscript{132}, we [NB, JCD and TLA] conducted a search of EMBASE, MEDLINE, PUBMED, and CINAHL supplemented by manual search of included articles’ reference lists. The search strategy (Figure 2.1 (A)) was developed by April 19\textsuperscript{th} 2011, and includes studies from 2000 to 2011. We limited our search results to adults aged 60 years and older, and studies published in the English language.

2.2.2 Study Selection

We excluded case-studies, reviews, and articles lacking WMH quantification or measurements of cognitive function, based on their titles and abstracts (Figure 2.1 (B)). Also, any study with the primary focus on psychiatric conditions (e.g., depression) or progressive neurodegenerative diseases (except for Alzheimer’s disease (AD) and cerebrovascular disorders due to the high prevalence of WMHs) was excluded. Based on full text review, we excluded studies that: 1) used computed tomography (as it is less sensitive than MRI in detection of WMHs\textsuperscript{133}), or used MRI device with a magnet strength of less than 1.5T and; 2) assessed only global cognition (measured
by mini-mental state examination (MMSE)) as it may not be sensitive to the differential effects of WMH location; and 3) did not detail WMH location.

![Figure 2.1](image)

**Figure 2.1** (A) Searching Strategy Retrieved from Ovid; (B) Flowchart of Study Selection.

### 2.2.3 Data Extraction and Quality Assessment

We [NB and TLA] developed a list of extraction items including: 1) study characteristics; 2) WMH outcomes; and 3) cognitive function outcomes. One study\(^\text{134}\) did not report the strength of MRI magnet and NB contacted the author.
Two authors [NB, TLA] independently evaluated each study based on four quality assessments questions (see Table 2.1), and all the discrepancies were reviewed by JCD and RT. Assessing the validity of WMH quantification was influenced by the difficulty in the differential diagnosis of WMHs, which requires expert radiological knowledge to be done accurately \(^{135}\). In addition, the intensity range of lesions typically overlaps with those of healthy tissues, so automatic identification methods tend to produce more false positives as compared with manual identification by a radiologist \(^{136}\). Therefore, our assessment favors quantification methods that use radiologist/physician identification of WMHs. We used dichotomized answers (+: yes, -: no) for the quality assessment questions.

### 2.3 Results

#### 2.3.1 Overview of Studies

The initial number of articles identified was 490 (Figure 2.1 (B)). After duplicate removal, 156 papers were further excluded using their title and abstract. We conducted a full text review of the remaining 48 articles. In total, 14 articles met the inclusion criteria (see Table 2.2-Table 2.5). These articles were further categorized into two groups based on the cognitive status of their study samples: 1) studies that did not compare subjects based on cognitive status (i.e., normal, cognitively impaired but not demented, and demented); and 2) studies that classified and compared subjects based on cognitive status. Table 2.6 shows the most commonly-used cognitive tests in the 14 included studies.
2.3.2 Studies that did not Compare Subjects based on Cognitive Status

2.3.2.1 Subcortical vs. Periventricular WMHs

Five studies $^{58, 137-140}$ – four cross-sectional studies and one prospective study – compared the association of subcortical versus periventricular WMHs with cognitive function. In the first cross-sectional study of 1077 older adults $^{137}$, WMHs were defined as T2 and PD hyperintensities that were not T1 hypointensities. Four lobes of frontal, parietal, occipital, and temporal were considered for subcortical WMH scoring. Three regions adjacent to frontal horns, lateral ventricles wall, and occipital horns were selected for periventricular WMH scoring. The neuropsychological battery evaluated two domains of memory and executive function/processing speed. The results showed that when controlled for subcortical WMH severity, increased periventricular WMH severity in all the three regions was associated with reduced performance in both cognitive domains (p<0.01). However, when controlled for periventricular WMHs, no such association was found for subcortical WMHs.

In the second cross-sectional study of 105 older adults $^{138}$, WMHs were identified using T2 and FLAIR scans. Results showed that higher periventricular and subcortical WMH scores were not significantly associated with reduced memory and executive function/processing speed.

In a sample of 268 older adults $^{58}$, WMHs were categorized into three groups of: 1) large subcortical WMHs defined as PD and T2 hyperintensities that were not T1 hypointensities; 2) infarction lesions defined as lesions of ≥2 mm that were either T2 hyperintensities, or PD and T1 hypointensities; and 3) periventricular WMHs. The results indicated that large subcortical WMHs were significantly associated with memory, and infarction lesions were significantly
associated with executive function/processing speed (p<0.05). Contrary to the results of two previously mentioned studies, this study found no significant relationship between periventricular WMHs and cognitive performance.

In the last cross-sectional study, Kim et al.\textsuperscript{140} defined WMHs as T2 and FLAIR hyperintensities. Over the 84 older adults, only periventricular WMH was significantly correlated with memory and executive function/processing speed, when both the periventricular and subcortical WMHs were entered simultaneously into the regression model (p<0.05).

The one longitudinal study\textsuperscript{139} used a sample of 104 subjects to investigate the impact of WMH volume progression on the rate of cognitive decline. White matter hyperintensities were defined as PD and T2 hyperintensities. Infarction lesions – detected by their clean or sharp edges, and if they were relatively dark on PD scans – were excluded from WMH analysis. The neuropsychological battery assessed only memory. Higher rate of subcortical (but not periventricular) WMH volume change was associated with increased rate of decline in memory scores (p<0.001).

2.3.2.2 Regional WMHs

Six cross-sectional studies\textsuperscript{127, 134, 141-144} examined the association between WMHs in specific brain regions (e.g., frontal, parietal, etc.) and cognitive performance. McClelland et al.\textsuperscript{134} defined WMHs as PD and T2 hyperintensities that were T1 hypointensity. The results in 3647 older adults suggested that WMHs located in cerebellar and cerebral white matter and basal ganglia were significantly associated with reduced processing speed performance (p<0.05).
Among 656 older adults, Wright et al. differentiated subclinical infarction lesions from the rest of WMHs based on the size, location, and imaging characteristics obtained from PD, T2, and FLAIR scans. They were grouped by location into frontal, deep and occipital-temporal-parietal networks. The neuropsychological battery assessed only executive function/processing speed. The results demonstrated that individuals with infarction lesions in frontal and deep locations had significantly worse cognitive performance (p<0.05).

Kaplan et al. studied a sample of 95 older adults. White matter hyperintensities were defined as FLAIR and T2 hyperintensities, and were categorized into frontal and posterior regions. The results showed that frontal WMHs were associated with memory (p<0.05) and executive function/processing speed (p<0.001).

Furthermore, Wakefield et al. detected WMHs based on FLAIR and T1 scans in a sample of 99 community-dwelling older adults. The following regions of interest were segmented for WMHs: anterior, superior, and posterior corona radiata; cingulate gyrus, genu, body, and splenium of corpus callosum; anterior and posterior limb of internal capsule; and superior longitudinal fasciculus. The neuropsychological battery assessed only executive function/processing speed. In regions of posterior corona radiata and splenium of corpus callosum, the total amount of WMHs was significantly associated with executive function/processing speed (p<0.05).

O’Brien et al. detected WMHs based on FLAIR and T2 scans, in 149 older adults. The focus of their analysis was on the distribution of WMHs in the internal and external capsule. They
found that WMHs from both regions were significantly associated with cognitive performance of speed of memory retrieval and executive function/processing speed (p<0.05).

Smith et al. 127 analyzed WMH distribution using PD, T2, and T1 scans in the whole brain of 147 older adults. The total volume of WMHs was associated with the cognitive performance of memory (p<0.01) and executive function (p=0.05). In the following locations, WMHs were significantly associated with memory: right inferior temporal-occipital, left temporal-occipital periventricular, and right parietal periventricular; and anterior limb of internal capsule. Also, WMHs in the following regions were significantly associated with executive function: the bilateral inferior frontal, temporal-occipital periventricular, right parietal periventricular, and prefrontal white matter; and the anterior limb of the internal capsule bilaterally.

2.3.3 Studies that Classified and Compared Subjects based on Cognitive Status

2.3.3.1 Subcortical vs. Periventricular WMHs

Among the studies that classified participants based on their cognitive status, two cross-sectional studies 145, 146 compared the effects of subcortical and periventricular WMHs. Burns et al. 145 included 88 non-demented participants (clinical dementia rating (CDR) score=0), 68 with early-stage AD (48 with very mild AD (CDR=0.5), and 20 with mild AD (CDR=1)). White matter hyperintensities were defined as T2 hyperintensities that were T1 hypointensities. Subcortical WMHs were rated in regions of frontal, parietal, temporal, and occipital lobes. Periventricular WMHs were rated in right and left frontal horns, posterior horns, and ventricular bodies. For non-demented participants, only associate memory was associated with periventricular WMHs.
(p<0.01). For participants with early-stage AD, memory and executive function/processing speed were associated with both periventricular and subcortical WMHs (p<0.05).

Ishii et al. \textsuperscript{146} detected WMHs based on T2 hyperintensities. Sample of 453 older adults were categorized into two groups of CDR=0 and CDR=0.5. Anterior and posterior periventricular WMHs, as well as left and right subcortical WMHs were segmented. The results suggested that, for CDR=0 group, anterior periventricular WMHs and a test of executive function/processing speed were significantly correlated (p=0.001).

\subsection{Regional WMHs}

The last study \textsuperscript{147} detected WMHs based on T1 and T2 scans. They categorized 78 older adults into three cognitive groups: normal (CDR=0), cognitively impaired but not demented (CDR=0.5), and demented (CDR≥1), either by AD or vascular dementia. WMHs were analyzed in regions of orbitofrontal, prefrontal, dorsolateral frontal, parietal, and occipitotemporal. In non-demented individuals, increased volumes of frontal (specifically, prefrontal and dorsolateral), parietal, and occipital WMH were separately associated with lower executive function/processing speed scores (p<0.05). Frontal WMHs were also associated with reduced memory function in non-demented group (p<0.05). No association was found for individuals with dementia.

\subsection{Quality Assessment}

The quality assessment results for each of the four questions are presented in Table 2.1: 1) in seven studies, WMH identification is done by a radiologist/physician, while the remaining used
automatic methods; 2) all the articles employed standard methods for cognitive assessment; 3) none of the studies provided sample size calculation; and 4) the statistical analyses of twelve studies included age or education as confounders.

2.4 Discussion

2.4.1 Subcortical vs. Periventricular WMHs

Based on their proximity to ventricles, WMHs were classified as subcortical or periventricular in seven studies. The results suggest that periventricular WMHs may be more associated with the cognitive domain of executive function, than subcortical WMHs.

Subcortical WMHs are believed to primarily disrupt short connections, and thus impairing cognitive performance supported by the specific brain region. For example, dexterous hand and arm movements are generally thought to be primarily supported by the motor cortex. Therefore, subcortical WMHs in this specific region can result in reduced performance in hand and arm dextrous movements. In contrast, periventricular WMHs disrupt longer connections to spatially distant cortical areas, and thus can cause cognitive performance decline in multiple domains. For example, executive function tasks typically used in research experiments depend on multiple brain regions (i.e., frontal and non-frontal) which are not necessarily located spatially close to each other. Therefore, any disruption in long white matter tracts traversing from periventricular areas may initially reduce the axonal transmission speed, and later cause impaired executive function. In summary, cognitive function depends on intact connections within subcortical areas and between cortical and subcortical structures, and any disruption in these connections may impair cognitive function.
We categorized all included studies into two major cognitive domains which are sensitive to aging: 1) memory; or 2) executive function/processing speed. The latter category was a combination of two cognitive domains based on the idea that they are not mutually exclusive, and one needs to control for their mutual relationship before examining their unique effects. 

For memory, out of seven studies, three studies found a significant association between periventricular WMHs and memory performance, two studies found a significant association between subcortical WMHs and memory performance, and two studies did not find any association.

For executive function/processing speed, out of six studies, three studies found a significant association between periventricular WMHs and executive function/processing speed, while only one study found a significant association between subcortical WMHs and executive function/processing speed. Two studies did not find any association.

Thus, our overall results suggest that, compared with subcortical WMHs, people with periventricular WMHs may have a higher chance of impairment in cognitive performances of memory and executive function. Moreover, people with periventricular WMHs may have a greater chance of impairment in the domain of executive function/processing speed, than people with subcortical WMHs.

As highlighted earlier, periventricular WMHs may impact multiple domains of cognition because they disrupt distant connections. Hence, our findings concur with the general knowledge that the domain of executive function/processing speed may depend on multiple brain regions and spatially distant connections.
2.4.2 Regional WMHs

Seven studies \cite{127, 134, 141-144, 147} investigated regional WMHs. No common pattern was evident secondary to the heterogeneity of regions studied.

The following regions demonstrated significant associations between WMHs and cognitive function: cerebral white matter, cerebellar white matter, and basal ganglia \cite{134}; frontal (dorsolateral frontal and prefrontal) \cite{141-143}, parietal, occipital, and temporal lobes \cite{141, 143, 147}; internal and external capsule \cite{144}; posterior corona radiata, and splenium corpus callosum \cite{143}. This systematic review provides researchers with a summary set of brain regions in which an association have been found between WMHs and cognitive performance. To better understand the role of anatomical location in the association between WMH and cognitive function, future studies should examine the spatial distribution of WMHs on the whole brain, or specific set of brain regions identified in this review as being highly associated with cognitive dysfunction.

2.4.3 Limitations

The discrepancies between the results may be due to the heterogeneous study methodologies and the quality of included studies.

2.4.3.1 Different MRI Sequences, WMH Quantification Methods, and Neuropsychological Batteries

The included studies were heterogeneous in MRI sequences for WMH detection (i.e., PD, T1, T2, or FLAIR), WMH quantification method (i.e., scoring or volume measurements), and components of neuropsychological batteries. This likely contributed to variability in our results.
Moreover, two different methods were used for WMH quantification: 1) scoring \(^{137, 138, 145, 146}\); and 2) volume measurement \(^{58, 139, 140}\). Scoring measures are usually done manually, and show a higher accuracy for selection of subtle WMHs, compared to automatic volumetric methods. However, these methods vary significantly in terms of lesion classification and severity scoring. Moreover, each scoring method have its own specific limitations.

For WMH volume measurement, there are two steps. The first step is identifying lesions, which can be done either manually by an expert radiologist or automatically. After the WMHs are identified manually or automatically, one can proceed to the second step, which is measuring WMH volumes automatically. It has been shown that both scoring and volumetric quantification methods are reliable for measuring WMH load \(^{152, 153}\). However, periventricular and subcortical WMHs quantified by these two quantification methods are differently associated with cognitive function \(^{153}\). Out of three studies which used volume measurement, two studies \(^{58, 139}\) showed a significant association between the subcortical WMHs and cognitive performance. Out of four the studies which used scoring, three \(^{137, 145, 146}\) showed a significant association between periventricular WMHs and cognitive performance. These results suggest that scoring might have biased the results toward periventricular WMHs. Conversely, volume measurement might be problematic for periventricular WMHs due to their similar appearance to CSF on some MRI sequences (e.g., T2 or T1) \(^{154}\).

### 2.4.3.2 Modifying Effect of Cardiovascular Risk Factors

There is a growing recognition that WMHs are associated with age and cardiovascular risk factors \(^{52, 155}\). However, all but one included study \(^{134}\) considered the modifying effect of
cardiovascular risk factors in the statistical analysis. We recommend that future studies consider including cardiovascular risk factors in their analysis.

2.4.3.3 Quality of Studies and Lack of Sample Size Calculation

One study did not demonstrate a significant association between any type of WMHs and any of the cognitive tasks. Based on our quality assessment, this study is the only study categorizing WMHs locations as subcortical and periventricular that did not consider age or education as potential confounders. Therefore, we concluded that this study did not provide strong evidence for the lack of correlation between WMHs and cognitive function.

Moreover, the lack of sample size calculations in all of the included studies might have resulted in possible type II errors. However, we do recognize that the lack of sample size calculations may be due to the dearth of data in this research area.

2.5 Conclusion

This study provides an in depth analysis of brain regions where an association between WMH location and cognitive decline has been found in older adults. Specifically, studies that considered periventricular versus subcortical WMHs suggest that, compared with subcortical WMHs, periventricular WMHs may have a greater negative impact on cognitive performance. Moreover, periventricular WMHs appear to be more associated to the domain of executive function/processing speed, than to the domain of memory. To further clarify the association of cognitive function with WMH locations, we suggest that future studies consider spatial distribution of WMHs on the whole brain.
We avoided conducting a meta-analysis, primarily because of the small number of studies systematically found on this topic. Moreover, the neuropsychological batteries used for assessing cognitive status, the WMH quantification method, and MRI sequences used for WMH detection varied vastly between studies, and made it hard to conduct a meta-analysis.
Table 2.1 Quality Assessment Results for Studies Included in Systematic Review.

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<th>Q2. Was the cognitive performance measured using a standardized method?</th>
<th>Q3. Was there a sample size calculation?</th>
<th>Q4. Were age or education considered as confounders?</th>
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<td>Reference</td>
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<td>Q2. Was the cognitive performance measured using a standardized method?</td>
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<td>Q4. Were age or education considered as confounders?</td>
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<td>+</td>
</tr>
<tr>
<td>Smith et al. 127</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Burns et al. 145</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Ishii et al. 146</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Tullberg et al. 147</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Reference</td>
<td>Sample Size</td>
<td>Sample Characteristics</td>
<td>Study Design</td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
<td>-------------</td>
<td>-------------------------------------------------------------</td>
<td>----------------</td>
<td></td>
</tr>
<tr>
<td>Groot et al. 137</td>
<td>1077</td>
<td>Subsample of Rotterdam and Zeotemeer Studies</td>
<td>Cross-Sectional</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shenkin et al. 138</td>
<td>105</td>
<td>Random Sample of Community-Dwelling Participants</td>
<td>Cross-Sectional</td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baune et al. 38</td>
<td>268</td>
<td>Subsample of MEMO Study</td>
<td>Cross-Sectional</td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kim et al. 140</td>
<td>84</td>
<td>Random Sample of Normals/Recruited from Memory Clinic</td>
<td>Cross-Sectional</td>
<td></td>
</tr>
<tr>
<td>2011</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silbert et al. 139</td>
<td>104</td>
<td>Subsample of Oregon Brain Aging Study</td>
<td>Longitudinal</td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McClleland et al. 134</td>
<td>3647</td>
<td>Subsample of CHS Cohort</td>
<td>Cross-Sectional</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wright et al. 141</td>
<td>656</td>
<td></td>
<td>Cross-Sectional</td>
<td></td>
</tr>
</tbody>
</table>

Table 2.2 Characteristics of Studies Included in Systematic Review.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Sample Size</th>
<th>Study Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Publishing Year</td>
<td>Sample Characteristics</td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>Subsample of NOMAS Cohort study</td>
<td></td>
</tr>
<tr>
<td>Kaplan et al.\textsuperscript{142}</td>
<td>95</td>
<td>Cross-Sectional</td>
</tr>
<tr>
<td></td>
<td>Random Sample of Participants</td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td>95</td>
<td>Cross-Sectional</td>
</tr>
<tr>
<td>Wakefield et al.\textsuperscript{133}</td>
<td>99</td>
<td>Cross-Sectional</td>
</tr>
<tr>
<td></td>
<td>Sample Selected for a Longitudinal Study</td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td>149</td>
<td>Cross-Sectional</td>
</tr>
<tr>
<td>O’Brien et al.\textsuperscript{144}</td>
<td>Sample of SCOPE Study</td>
<td>Cross-Sectional</td>
</tr>
<tr>
<td></td>
<td>149</td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>145</td>
<td>Cross-Sectional</td>
</tr>
<tr>
<td>Smith et al.\textsuperscript{127}</td>
<td>145</td>
<td>Cross-Sectional</td>
</tr>
<tr>
<td></td>
<td>Subsample of Prospective Study</td>
<td></td>
</tr>
<tr>
<td>2011</td>
<td>156</td>
<td>Cross-Sectional</td>
</tr>
<tr>
<td>Burns et al.\textsuperscript{145}</td>
<td>88 Normal (CDR=0), 68 Early-Stage AD (CDR=0.5,1)</td>
<td>Cross-Sectional</td>
</tr>
<tr>
<td></td>
<td>453</td>
<td>Cross-Sectional</td>
</tr>
<tr>
<td>Ishii et al.\textsuperscript{146}</td>
<td>453</td>
<td></td>
</tr>
<tr>
<td></td>
<td>340 (CDR=0), 113 (CDR=0.5)</td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>78</td>
<td>Cross-Sectional</td>
</tr>
<tr>
<td>Tullberg et al.\textsuperscript{147}</td>
<td>22 Normal (CDR=0), 30 CIND (CDR=0.5), 26</td>
<td>Cross-Sectional</td>
</tr>
<tr>
<td>Reference</td>
<td>Sample Size</td>
<td>Sample Characteristics</td>
</tr>
<tr>
<td>--------------------</td>
<td>-------------</td>
<td>------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Demented (CDR≥1)</td>
</tr>
</tbody>
</table>

Abbreviations: MEMO = Memory and Morbidity in Augsburg Elderly; CDR = Clinical Dementia Rating Scale; CHS = Cardiovascular Health Study; NOMAS = Northern Manhattan Study; SCOPE = Study on Cognition and Prognosis in Elderly; CIND = Cognitively Impaired not Demented.
Table 2.3 Outcome Measure: White Matter Hyperintensity Quantification.

<table>
<thead>
<tr>
<th>Reference WMH Type</th>
<th>Sequence WMH Quantification</th>
<th>WMH Location</th>
<th>MRI Magnet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Groot et al. 137</td>
<td>PD, T1, T2 Scoring</td>
<td>S: Four lobes of Frontal, Parietal, Occipital, and Temporal&lt;br&gt;P: Adjacent frontal horns, lateral ventricles wall, and occipital horns</td>
<td>1.5 T</td>
</tr>
<tr>
<td>P, S, Regions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shenkin et al. 138</td>
<td>T2, FLAIR Scoring</td>
<td>-</td>
<td>1.5 T</td>
</tr>
<tr>
<td>S, P</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baune et al. 58</td>
<td>PD, T1, T2 Scoring</td>
<td>-</td>
<td>1.5 T</td>
</tr>
<tr>
<td>S, P</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kim et al. 140</td>
<td>T2, FLAIR Volum</td>
<td>-</td>
<td>1.5 T</td>
</tr>
<tr>
<td>S, P</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silberg et al. 139</td>
<td>PD, T2 Volume</td>
<td>-</td>
<td>1.5 T</td>
</tr>
<tr>
<td>S, P</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McClleland et</td>
<td>PD, T1, T2</td>
<td>Cerebral White Matter, Cerebellar White Matter, Basal Ganglia</td>
<td>1.5 T</td>
</tr>
<tr>
<td>Reference</td>
<td>WMH Type</td>
<td>Sequence</td>
<td>WMH Location</td>
</tr>
<tr>
<td>-----------</td>
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<td>----------</td>
<td>--------------</td>
</tr>
<tr>
<td>al. 134</td>
<td></td>
<td>Scoring</td>
<td></td>
</tr>
<tr>
<td>Wright et al. 141</td>
<td>Regions</td>
<td>PD, T2, FLAIR Volume</td>
<td>Frontal, Deep, and Occipital-Temporal-Parietal</td>
</tr>
<tr>
<td>Kaplan et al. 142</td>
<td>Regions</td>
<td>T2, FLAIR Volume</td>
<td>Frontal and Posterior Regions</td>
</tr>
<tr>
<td>Wakefield et al. 143</td>
<td>Regions</td>
<td>T1, FLAIR Volume</td>
<td>Anterior, Superior, Posterior Corona Radiata Cingulate Gyrus, Genu, Body, Splenium of Corpus Callusum Anterior and Posterior Limb of Internal Capsule Superior Longitudinal Fasciculus</td>
</tr>
<tr>
<td>O'Brien et al. 144</td>
<td>Regions</td>
<td>T2, FLAIR Scoring</td>
<td>Internal and External Capsule</td>
</tr>
<tr>
<td>Reference</td>
<td>WMH Type</td>
<td>Sequence</td>
<td>WMH Location</td>
</tr>
<tr>
<td>--------------------</td>
<td>----------</td>
<td>------------</td>
<td>------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Smith et al.</td>
<td></td>
<td>PD, T1, T2</td>
<td>Whole Brain</td>
</tr>
<tr>
<td>Regions</td>
<td></td>
<td>Volume</td>
<td></td>
</tr>
<tr>
<td>Burns et al.</td>
<td></td>
<td>T1, T2</td>
<td>S: Frontal, Parietal, Temporal, and Occipital Lobes</td>
</tr>
<tr>
<td>S, P, Regions</td>
<td></td>
<td>Scoring</td>
<td>P: Right and Left Frontal Horns, Posterior Horns, and Ventricular Bodies</td>
</tr>
<tr>
<td>Ishii et al.</td>
<td></td>
<td>T2</td>
<td>S: Left and Right</td>
</tr>
<tr>
<td>P, S, Regions</td>
<td></td>
<td>Scoring</td>
<td>P: Anterior and Posterior</td>
</tr>
<tr>
<td>Tullberg et al.</td>
<td></td>
<td>T1, T2</td>
<td>Orbitofrontal, Prefrontal, Dorsolateral Frontal, Parietal, and Occipitotemporal</td>
</tr>
<tr>
<td>Regions</td>
<td></td>
<td>Volume</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: PD = Proton Density; FLAIR = Fluid Attenuated Inversion Recovery.
Table 2.4 Outcome Measure: Cognitive Tests.

Cognitive Tests Used for Two Cognitive Domains of Memory and Executive Function/Processing Speed.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Executive Function / Processing Speed</th>
<th>Memory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Groot et al. et al.</td>
<td>Stroop, Letter-Digit Substitution Task, Verbal Fluency</td>
<td>Rey’s Auditory, Memory Scanning Task</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wechsler Memory Scale</td>
</tr>
<tr>
<td>Shenkin et al.</td>
<td>Verbal Fluency, Controlled Word Association, Moray House Test, Raven’s Progressive Matrices</td>
<td>3-Word Recall</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Seoul Verbal Learning Test, Ray Complex Figure Test, Delayed Recall and Recognition, Digit Span Tests</td>
</tr>
<tr>
<td>Baune et al.</td>
<td>Stroop, Letter-Digit Substitution Task</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Delayed Story Recall</td>
</tr>
<tr>
<td>Kim et al.</td>
<td>Boston Naming, Buccofacial Praxis Test, Semantic Controlled Oral Word Association Test, Stroop Color, Word Test</td>
<td>-</td>
</tr>
<tr>
<td>Silbert et al.</td>
<td>-</td>
<td>Delayed Story Recall</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>McClleland et al.</td>
<td>Digit-Symbol Substitution Task</td>
<td>-</td>
</tr>
<tr>
<td>Wright et al.</td>
<td>Color Trail 1 &amp; 2</td>
<td>-</td>
</tr>
<tr>
<td>Kaplan et al.</td>
<td>Stroop, Trail Making, CalCap</td>
<td>Repeated Battery for</td>
</tr>
<tr>
<td>Reference</td>
<td>Executive Function / Processing Speed</td>
<td>Memory Component of CDR</td>
</tr>
<tr>
<td>-----------------</td>
<td>--------------------------------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>Wakefield et al.</td>
<td>Stroop, Trail Making 1 &amp; 2, CalCap</td>
<td>-</td>
</tr>
<tr>
<td>O’Brien et al.</td>
<td>Verbal Fluency, Trail Making 1 &amp; 2</td>
<td>Memory Component of CDR</td>
</tr>
<tr>
<td>Smith et al.</td>
<td>Letter Fluency, Trail Making 2</td>
<td>Episodic Memory, Alpha Span Test</td>
</tr>
<tr>
<td>Burns et al.</td>
<td>Trail Making 1 &amp; 2, Short Blessing Test, Boston Naming</td>
<td>Wechsler Memory Scale, Wechsler Adult Intelligence Scale</td>
</tr>
<tr>
<td>Ishii et al.</td>
<td>Verbal Fluency, Trail Making Test, Benton’s Visual Form Test</td>
<td>ADAS-Cog, 10 Word Recall, Digit Span Forward</td>
</tr>
<tr>
<td>Tullberg et al.</td>
<td>Verbal Fluency</td>
<td>Wechsler Memory Scale, Word List Learning, Digit Span Backward</td>
</tr>
</tbody>
</table>

Abbreviations: CalCap = California Computerized Assessment Package; CDR = Clinical Dementia Rating Scale; ADAS-Cog = Alzheimer’s Disease Assessment Scale-Cognitive.
### Table 2.5 Association between WMHs Location and Cognitive Function.

This table presents the association between structural location of white matter hyperintensities (i.e., Subcortical, Periventricular, or Regional) with two domains of cognitive function (i.e., memory and executive function/processing speed).

<table>
<thead>
<tr>
<th>Reference</th>
<th>Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Groot et al. et al. (^{137})</td>
<td>Controlled for subcortical, periventricular WMHs were associated with memory and executive function/processing speed.</td>
</tr>
<tr>
<td>Shenkin et al. (^{138})</td>
<td>Subcortical and periventricular WMHs were not associated with any of the cognitive measurements.</td>
</tr>
<tr>
<td>Baune et al. (^{58})</td>
<td>Subcortical WMHs were associated with memory.</td>
</tr>
<tr>
<td></td>
<td>As a subgroup of subcortical WMHs, infarction lesions were associated with executive function/processing speed.</td>
</tr>
<tr>
<td></td>
<td>Periventricular WMHs were not associated with any of the cognitive functions.</td>
</tr>
<tr>
<td>Kim et al. (^{140})</td>
<td>Only periventricular WMH was significantly correlated with memory and executive function/processing speed, when both the periventricular and subcortical WMHs were entered simultaneously into the regression model.</td>
</tr>
<tr>
<td>Silbert et al. (^{139})</td>
<td>Change in subcortical WMHs (excluding infarction lesions) was associated with memory decline. This association was not true for periventricular WMHs.</td>
</tr>
<tr>
<td>McCleland et al. (^{134})</td>
<td>White matter hyperintensities were associated with executive function/processing speed, in all white matter regions of cerebrum, cerebellum, and basal ganglia.</td>
</tr>
<tr>
<td>Wright et al. (^{141})</td>
<td>Subcortical WMHs (including infarction lesions) were associated with executive function/processing speed, in regions of frontal and deep white matter.</td>
</tr>
<tr>
<td>Reference</td>
<td>Association</td>
</tr>
<tr>
<td>------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Kaplan et al.</td>
<td>White matter hyperintensities were associated with memory and executive function/processing speed, in frontal regions.</td>
</tr>
<tr>
<td>Wakefield et al.</td>
<td>White matter hyperintensities were associated with executive function/processing speed in white matter regions of posterior corona radiata and splenium of corpus callosum.</td>
</tr>
<tr>
<td>O’Brien et al.</td>
<td>White matter hyperintensities were associated with speed of memory retrieval and executive function/processing speed.</td>
</tr>
<tr>
<td>Smith et al.</td>
<td>White matter hyperintensities were associated with memory and executive function/processing speed. White matter hyperintensities in the following locations were significantly associated with memory: right inferior temporal-occipital, left temporal-occipital periventricular, and right parietal periventricular white matter; and anterior limb of internal capsule. Also, WMHs in the following regions were significantly associated with executive function: the bilateral inferior frontal, temporal-occipital periventricular, right parietal periventricular, and prefrontal white matter; and the anterior limb of the internal capsule bilaterally.</td>
</tr>
<tr>
<td>Burns et al.</td>
<td>For non-demented participants, only associate memory was associated with periventricular WMHs. For participants with early-stage Alzheimer’s Disease (AD), memory and executive function/processing speed were associated with both periventricular and subcortical WMHs.</td>
</tr>
<tr>
<td>Ishii et al.</td>
<td>For CDR=0 group, anterior periventricular WMH and a test of executive function were associated with memory, executive function/processing speed, and a test of executive function.</td>
</tr>
</tbody>
</table>
function/processing speed were significantly correlated.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tullberg et al. 147</td>
<td>In non-demented individuals, increased volumes of frontal (specifically prefrontal and dorsolateral), parietal, and occipital WMH were separately associated with lower executive function/processing speed scores. Frontal WMHs were also associated with reduced memory function in non-demented group. No association was found for individuals with dementia.</td>
</tr>
</tbody>
</table>

Abbreviations: WMH = White Matter Hyperintensities; CDR = Clinical Dementia Rating Scale.
Table 2.6 The Most Commonly-Used Neuropsychological Tests in the Included Studies.

<table>
<thead>
<tr>
<th>Executive Function</th>
<th>Trail-Making Test, Stroop Test, Verbal Fluency Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory</td>
<td>Wechseler Memory Scale, Word Recall Test</td>
</tr>
</tbody>
</table>
Chapter 3: WMHs and Physical Decline in Older Adults

3.1 Introduction

Impaired mobility in older adults is a significant public health concern. The prevalence of impaired mobility is 35% for community-dwelling older adults of age 70 years and older. Reducing both the incidence and progression of impaired mobility could preserve functional independence, reduce health-care resource utilization, and sustain health-related quality of life in older adults. However, we must first gain a better understanding of the mechanisms underlying physical disability in late life to increase our capacity to develop valid screening strategies and effective interventions.

Neuroepidemiological studies highlight white matter hyperintensities (WMHs) in the evolution of impaired mobility in older adults. White matter hyperintensities are common magnetic resonance imaging (MRI) findings among otherwise healthy older adults. These abnormalities are due to damage to the brain parenchyma, ranging from demyelination to complete axonal disruptions. Both regional and total WMH volume are independently associated with impaired mobility, specifically, gait speed.

White matter hyperintensities are also associated with impaired cognitive function, in particular, executive functions. Specifically, the prefrontal subcortical networks contain neural circuits responsible for executive functions. These circuits are located in the watershed areas and are vulnerable to lower perfusion, and are thus at high risk for WMH formation. Therefore, WMHs in prefrontal subcortical regions may further affect the tracts important for executive functions.
Executive functions include the ability to concentrate, to attend selectively, and to plan and to strategize.

Of particular relevance to our current study, lower executive functions are associated with impaired mobility. It is now widely recognized that gait depends on both higher-level cognitive function (i.e., executive functions) as well as sensorimotor processes. For example, Rosano et al. demonstrated that both global cognitive function, as measured by the Modified Mini-Mental State Examination (3MS), and executive functions and information processing speed, as measured by Digit Symbol Substitution Test (DSST), are associated with impaired gait in otherwise healthy older adults.

Given the established association between WMHs, mobility, and executive functions, we hypothesize that WMHs negatively impact mobility through two central pathways: 1) directly, by disrupting mobility-related circuits (i.e., direct pathway; Figure 3.1); and 2) indirectly, by disrupting circuits responsible for executive functions (i.e., indirect pathway; Figure 3.1). It is also possible that WMH in the sensorimotor cortex is related to the executive functions performance. Therefore, we are exploring the mediating effects of cognition on both pathways.
Figure 3.1 Two Hypothesized Pathways for the Negative Impact of WMHs on Mobility.

1. Direct pathway -- WMHs impair mobility by directly disrupting mobility-related circuits; 2. Indirect pathway – WMHs disrupt circuits responsible for cognitive function leading to impaired mobility.

If we demonstrate that the negative impact of WMHs in EF circuits on gait speed is mediated by cognitive function, then interventions targeting these networks, such as cognitive and aerobic and resistance training, should be key components in the management of older adults with impaired mobility. Both cognitive and aerobic and resistance training have been shown to be effective in promoting executive functions among older adults.

Thus, in this cross-sectional study, we examined whether WMHs directly impact mobility, or indirectly by executive functions (Figure 3.1). Specifically, we seek to extend our current understanding of the relationship between WMHs and mobility by: a) identifying specific tracts in which WMH volumes are most strongly associated with gait speed, using an automated state of the art statistical method; and b) examining whether the association between WMHs and gait speed in the selected tracts are mediated by DSST or 3MS. Moreover, due to a possible effect of age, sex, body mass index (BMI), quadriceps strength, chronic pain, and hypertension on the association between WMH, cognitive function and gait speed, we are adjusting our
models for these covariates. Identifying mechanisms underlying the association between WMHs and mobility will refine the focus in future research. This, in turn, will increase our capacity to identify and develop effective interventions to combat impaired mobility in older adults.

3.2 Methods

3.2.1 The Healthy Brain Project and Participants

Our study participants were enrolled in the Healthy Brain Project (HBP). The HBP is an ancillary study on Health Aging and Body Composition (Health ABC) cohort to examine the association of structural white matter and gray matter abnormalities with age-related mobility impairment.

Among the 803 Health ABC participants alive in 2006 to 2008, 339 were eligible for inclusion in the HBP study: they walked without an assistive device, had completed the six-meter walking test, and were eligible for MRI scanning. Three hundred and nineteen Health ABC participants were ineligible for inclusion in the HBP and 145 refused to participate. Among the 339 eligible for the HBP study, 13 changed their mind after consent, one person died prior to scanning, and 10 were not eligible for 3 Tesla (T) scanning (i.e., 315 were included and assessed). After removal of missing data across all variables of interest, the final sample size was 253.

3.2.2 Independent Variables: Total and Focal WMH Volume

Brain MRIs were acquired at the MRI Research Center, University of Pittsburgh Medical Center, with a 3T scanner. Two sequences of T1-MPRAGE and T2-FLAIR were captured. An Automated Labeling Pathway (ALP) was used to quantify volumes and localization of focal WMHs. The ALP method adapts a fuzzy connected algorithm to automatically segment the
WMHs. Using Johns Hopkins University White Matter Atlas that includes 20 white matter tracts, ALP then employs a demons-based image registration technique to automate the anatomical localization of the hyperintensities. The 21 anatomical WMH variables for this study are presented in Appendix A. The total and focal WMHs are adjusted for total brain volumes.

3.2.3 Dependent Variable: Gait Speed

Gait speed is a reliable biomarker of overall health and functional status in older adults. Slower gait in older adults is a significant predictor of disability and mortality.

The GaitMat II velocity (EQ Inc., Chalfonte, PA) measured baseline gait speed. The GaitMat II is a four-meter long walkway with embedded pressure sensors that facilitate gait analysis. In case of missing data from GaitMat II, gait speed was obtained from walking over three, four or six meters.

3.2.4 Mediators: Cognitive Function

We assessed global cognitive function, executive functions, and information processing speed. Global cognitive function was assessed using the 3MS. This test comprehensively evaluates cognitive domains of orientation, attention, calculation, language and short-term memory. Scores for the 3MS range from 0 to 100. Compared with the Mini-Mental State Examination, the 3MS assesses a broader range of cognitive processes.

Executive functions and information processing speed were indexed using the Digit Symbol Substitution Test (DSST). For this task, participants were first presented with a series of numbers (1 to 9) and their corresponding symbols. They were then asked to draw the correct
symbol for any digit - placed randomly in pre-defined series - in 90 seconds. A higher number of correct answers in this time period indicated a better executive functions and processing speed.

3.2.5 Covariates: Age, Body Mass Index, Quadriceps Strength, Years of Education, Standing Height, Prevalent Hypertension, Chronic Pain

Age measured in years, sex, BMI calculated as kg/m², years of education, and standing height in mm were added to our models. Quadriceps strength modifies the association between WMHs and gait speed \(^{159, 180}\). Thus, quadriceps strength was measured by the Kin-Com isometric dynamometer (Kin-Com Chattanooga, TN). We evaluated the average torque generated by the quadriceps (i.e., knee extensors) at 60 degrees per second. The mean of three trials and was used in our analysis.

Moreover, Rosano and colleagues \(^{181}\) have shown that chronic pain might be a contributor in the association between white matter hyperintensities and disability. Therefore, chronic pain in knee, back, or leg was documented as a binary variable and added to the models as a covariate.

Prevalent hypertension for participants with average sitting systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg concurrently or before the year of MRI, was also documented as a binary variable, and was added to the models as a covariate. This variable has been shown to be associated with both WMHs and gait speed in older adults \(^{182}\).

3.2.6 Statistical Analysis

Our statistical analyses consisted of three phases: 1) data reduction to identify WMH tracts most associated with gait speed; 2) multivariable regression models to quantify the association
between the variables of interests; and 3) formal tests of mediation analysis. The multivariable regressions as well as the mediation models were adjusted for age, BMI, and quadriceps strength.

For data reduction, we used Elastic Net \(^{173}\) to identify which of the 21 WMH variables were most associated (i.e., minimal regularized regression error using cross-validation) with gait speed. Elastic Net is an automated shrinkage and penalized statistical method. It is a preferred alternative to conventional variable selection methods, such as stepwise regression, that have been criticized for their bias, over-fitting, and exaggerated p values \(^{183}\). In Elastic Net, both L1 (i.e., the positive weighting parameter which promotes shrinkage in the regularized regression coefficients) and L2 (i.e., the weighting parameter which promotes stability on regularization) regularizations are introduced into the standard multiple linear regression model to shrink the coefficients to zero. For a given lambda (i.e., the L1 parameter) and an alpha between 0 and 1 (i.e., the L2 parameter), Elastic Net minimizes the error as presented below.

\[
\text{Min} \frac{1}{2N} \left[ ||Y - \beta_0 - X \beta||^2 + \lambda||\beta_1|| + \frac{(1-\alpha)}{2} \lambda||\beta_2||^2 \right].
\]

where \( ||\beta_1|| = \sum_{j=1}^{p} \beta_j \) and \( ||\beta_2||^2 = \sum_{j=1}^{p} \beta_j^2 \).

Here, Y represents gait speed for our 253 participants, and X is a 253*21 matrix of WMH volumes for 21 WMH variables. \( \lambda \) was set to the default value of 100, and \( \alpha \) was set to 0.5. This analysis was performed in Matlab (R2011b, Natick, Massachusetts, The Mathworks Inc.). The process of variable selection using the Elastic Net method is illustrated in Figure 3.2 (A) and explained in greater detail in Appendix B.  

66
Figure 3.2 (A) Variable Selection Using Elastic Net.

Step 1 shows the n*p data where n is the sample size and p is the size of the independent variables. Step 2 employs jackknifing technique to assign one participant to the test set and the rest to the training set. This loop is required to prevent from overfitting. In Step 3, the optimized model (i.e., minimal error using cross validation) is estimated for the training set using Elastic Net. The whole process is repeated over all the participants to avoid any bias. (B) The mediation model of cognitive function for the impact of WMH volume on gait speed. The path coefficient A represents the direct effect of WMH volume on gait speed, adjusted for
age, BMI, and quadriceps strength. The product of path coefficients B and C represents the indirect effect of WMH volume on gait speed through cognitive function. The total effect is the sum of the direct effect and the indirect effect (A+B*C).

For the second phase, multivariable linear regression models adjusted for age, sex, BMI, quadriceps strength, chronic pain, and prevalent hypertension were built with gait speed as the dependent variable and WMHs from specific tracts identified in phase one as independent variables. Each WMH tract was entered in a separate linear regression model, with and without adjustment for the putative mediators (e.g., DSST and MMSE).

For the third phase, mediation analyses was performed using PROCESS, a computational macro developed for SPSS. For each WMH variable selected in phase one (i.e., data reduction) we constructed two mediation models – one for each cognitive mediating variable (i.e., 3MS and DSST). Each selected WMH variable was entered as the independent variable and gait speed as the dependent variable, while adjusting for age, BMI, and quadriceps strength. The general mediation model is illustrated in Figure 3.2 (B).

We calculated the direct effect, indirect effect and total effect for each mediation model. The direct effect refers to the change in gait speed when WMH variable changes while the cognitive function mediators are maintained fixed (Figure 3.2 (B): path coefficient A; the association between WMHs and gait speed adjusted for covariates and all cognitive function variables). The indirect effect refers to the change in gait speed when the independent WMH Variable is maintained fixed and the cognitive mediator changes to the level it would have attained if the independent gait speed variable increased by one unit (Figure 3.2 (B): product of path coefficients B and C). We used bootstrapping (n = 10,000) to obtain a 95% confidence interval
for the indirect effect. The total effect in our linear system is the sum of direct and indirect
effects of WMH volume on gait speed (i.e., the association of WMHs and gait speed adjusted for
covariates; A+BC).

For each standardized model, we reported percentages of direct and indirect effect out of the total
effect (i.e., direct effect*100/total effect and indirect effect*100/total effect), to compare the size
of direct and indirect effects in each mediation model. A larger percentage for the direct or the
indirect effect indicates a greater effect of the independent or the mediator variable on gait speed,
respectively.

3.3 Results

3.3.1 Data Reduction

Elastic Net selected three WMH variables that were most associated with gait speed. In addition
to total WMH volume, WMHs located in right anterior thalamic radiation (ATRR) and frontal
corpus callosum (CCF) were selected. Table 3.1 provides the descriptive statistics for all the
variables of interest.

3.3.2 Multivariable Regression Analyses

The effects of total, ATRR and CCF WMHs on gait speed were -0.146, -0.152, and 0.114 in
models adjusted for age, sex, BMI, quadriceps strength, education, and standing height
(Table 3.2, Model 1). Since prevalent hypertension and chronic pain were also associated with
slower gait (-0.240 and -0.244, p<0.001 respectively) models were further adjusted for these
variables (Table 3.2, Model 2). The association between WMHs and gait speed remained similar,
and did not significantly modify previous results (change < 10%). By contrast, the association
between WMHs and gait speed substantially decreased when 3MS or DSST were added to the models (Table 3.2, Model 3 and 4; 15% and 25% for Total WMHs, 6% and 19% for ATR WMHs, and 21% and 35% for CCF WMHs). Results remained similar in men compared to women.

3.3.3 Mediation Analyses

We constructed six mediation models in total; two per selected WMH variable. Overall, executive functions and information processing speed, as measured by DSST, mediated the association between WMH volume and gait speed, after adjusting for age, sex, BMI, quadriceps strength, years of education, standing height, and prevalent hypertension. Global cognitive function, as measured by 3MS, was not a significant mediator (Table 3.3).

Table 3.3 provides the total, direct and indirect (both unstandardized and standardized beta) effects for each of the three WMH variables on gait speed, adjusted for age, sex, BMI, quadriceps strength, education, height, and prevalent hypertension. The total effect of WMH volume on gait speed was significant and negative for all three WMH variables of total brain, ATRR and CCF (standardized beta in m/sec [p value]: -0.15, -0.16, -0.11 [p<0.05], respectively). The direct effect of WMH volume on gait speed was significant and negative for total brain and ATRR (standardized beta in m/sec [p value]: -0.10 and -0.12 [p<0.05], respectively), but not significant for CCF (standardized beta in m/sec [p value]: -0.06 [p=0.16]). The indirect effect of WMH volume on gait speed through executive functions and information processing speed was significant and negative for all the three WMH variables of total brain, ATRR and CCF (standardized beta in m/sec [Significant based on 95% CI]: -0.02, -0.02, -0.03, respectively). Moreover, for total WMH volume, the direct effect was 72% of its total effect and the indirect
effect was 19% of its total effect. For ATRR, the direct effect was 78% of its total effect and the indirect effect was 14% of its total effect. For CCF, the direct effect was not significant and the indirect effect was 27% of its total effect.

3.4 Discussion

In this cohort of community-dwelling old adults free from overt neurological conditions, total volume of WMHs, as well as WMHs in CCF and ATRR, were most strongly associated with slower gait speed. While previous studies have consistently found an association between total WMH volume and slower gait, few studies to date have looked at focal WMHs in selected tracts. These associations were robust and independent of age, sex, body mass index, quadriceps strength, education, height, prevalent hypertension, and chronic pain.

Compared to previous studies examining the effect of focal WMHs on physical function, our current study had several new aspects; our subjects had higher average age 167, 185, 186, and our statistical analysis were adjusted for relevant covariates 185. Our study applied imaging with a high level of spatial resolution to quantify WMHs in individual white matter tracts. Other studies applied lower resolution methods and limited their analyses to overall volumes of lobar WMHs 167 or distributed in deep versus periventricular WMHs 185, 186 187. Importantly, our study provides novel insight into potential mechanistic pathways by which WMHs impact gait speed in older adults. Our results concur with previous studies that suggest WMHs in cortical regions containing projection fibers (e.g. anterior thalamic radiation) 21,37, commissural fibers (e.g. corpus callosum) 167, 185, 186 and association fibers (e.g. superior longitudinal fasciculus) 167 play an important role in mobility.
Lower DSST performance, an indicator of executive dysfunction and impaired processing speed, but not global cognitive function, was a significant mediator of associations between WMH volumes and gait speed, after accounting for age, BMI, and quadriceps strength, education, and height. However, the degree by which DSST mediated the association between WMHs and gait speed depended on WMH location. Specifically, it was strongest for CCF than for ATRR or total brain WMH.

The corpus callosum is the largest white matter tract and plays a primary role in cognitive function. The CCF, or corpus callosum genu and rostrum, connects the prefrontal cortex between the two hemispheres of the brain and hence, plays a role in executive functions. Of particular relevance to DSST performance, Jokinen et al. demonstrated that overall corpus callosum atrophy was associated with impaired processing speed, and that anterior corpus callosum (genu and rostrum) atrophy was associated with impaired attention and executive functions in community-dwelling older adults with WMHs. Therefore, WMHs localized in this portion of the Corpus callosum may impair mobility indirectly, because they impair executive control function.

While the association between CCF WMHs and gait was not significant after adjustment for DSST (i.e., the direct effect was not significant), the association between WMHs in the ATRR and slower gait was significant and independent of DSST (i.e., the direct effect was significant). In fact, it had a large significant direct effect (i.e., 78%) on gait speed. This finding concurs with the neuroanatomy of the ATRR. The ATRR contains fibers from superior fronto-occipital fasciculus that connects pre-motor areas with the parietal lobe. Thus, any disruption of these fibers may impair the somatosensory feedback required for gait and thus, directly impair gait. We also found a significant indirect effect (i.e., 14%) of ATRR WMHs on gait speed through
DSST performance. Duering et al. 190 previously found that WMHs in the ATR was independently associated with executive functions and processing speed. Therefore, WMHs in ATRR may negatively impact mobility through two central pathways: 1) directly, by disrupting mobility-related circuits 165-167; and 2) indirectly, by impairing circuits responsible for executive functions and subsequently impairing motor control 48, 168.

Overall, our findings highlight the importance of a multisystem assessment of slowing gait, which should include both executive functions and processing speed as well as motor pathways and the negative impact of WMHs on these processes. Interventions targeting these networks, for example cognitive interventions and aerobic and resistance training, may be particularly effective in promoting mobility among older adults 83, 169, 171, 172. Future studies should also examine whether interventions aimed at reducing vascular risk factors (e.g., hypertension, diabetes type II, hypercholesterolemia, etc.) also improve mobility and the underlying CNS mechanisms. Although we found an association between cardiovascular factors and gait, this association did not seem to modify the relationship between WMHs and gait speed. It is possible that cardiovascular factors may impact mobility through pathways that do not include WMHs.

We highlight two key strengths of our study. First, we applied automated WMH segmentation and volume quantification method in order to localize WMHs; majority of studies only examine total WMH volume. Specifically, our WMH localization method enabled us to identify WMHs located in different white matter tracts and hence, allowed us to investigate the impact of WMH location on gait speed. Second, we applied state-of-the-art reliable statistical methods for both
data reduction and mediation analysis to extend our current understanding of how WMHs impact gait speed in older adults.

We recognize the limitations of our study. The cross-sectional design limits our understanding of the temporal relationship between WMHs and slowing gait. Our study sample consisted exclusively of independent community-dwelling older adults who were without significant physical and cognitive impairments. Thus, the results of our study may not generalize beyond this population and we may have underestimated both the direct and indirect effects of WMHs on gait speed. Furthermore, we did not use diffusion tensor imaging which is more sensitive to white matter abnormalities than T2-FLAIR MRI. However, we did apply a DTI-based white matter atlas to register on our MRI data and segment the WMHs in different tracts. Finally, we used a very limited neuropsychological testing battery and thus, did not have a comprehensive assessment of cognitive function. Therefore, future studies should include a broader battery to advance our understanding of which cognitive processes are most impacted by WMHs and are most relevant to mobility impairments in older adults.

3.5 Conclusion

Our current study suggests that executive functions and processing speed significantly mediate the impact of WMHs on gait speed. Current evidence suggests that both aerobic and resistance training has specific benefits for executive functions in older adults. Thus, our findings lend further support that exercise is an essential component in the maintenance of mobility across the lifespan – by improving physical function, such as balance and strength -- but also cognitive function. Exercise may also have the potential to minimize the progression of WMHs and there are ongoing research exploring this possibility. Our results also suggest that mobility
screening in older adults should have far greater attention to the assessment of cognitive processes of executive functions and processing speed.
**Table 3.1 Descriptive Statistics.**

This table presents the descriptive statistics for covariates of age, BMI, quadriceps strength, education, height, independent WMH variables, dependent gait speed variable, and cognitive mediators.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Number</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>Std. Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>253</td>
<td>78</td>
<td>90</td>
<td>82.74</td>
<td>2.68</td>
</tr>
<tr>
<td>% Women</td>
<td>58%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>253</td>
<td>16.88</td>
<td>39.10</td>
<td>27.25</td>
<td>4.43</td>
</tr>
<tr>
<td>Quadriceps Strength (newton meters)</td>
<td>253</td>
<td>18</td>
<td>140</td>
<td>64.53</td>
<td>23.98</td>
</tr>
<tr>
<td>Education (years)</td>
<td>313</td>
<td>1</td>
<td>3</td>
<td>2.37</td>
<td>0.71</td>
</tr>
<tr>
<td>Standing Height (mm)</td>
<td>309</td>
<td>1390.50</td>
<td>1853.50</td>
<td>1621.62</td>
<td>95.34</td>
</tr>
<tr>
<td>% with Chronic Pain</td>
<td>53%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% with Hypertension</td>
<td>67%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total WMH Volume*</td>
<td>253</td>
<td>1.1*10^3</td>
<td>2.69*10^-2</td>
<td>3.34*10^-3</td>
<td>4.11*10^-3</td>
</tr>
<tr>
<td>ATRR WMH Volume*</td>
<td>253</td>
<td>Exp -8</td>
<td>4.31*10^-4</td>
<td>8.18*10^-4</td>
<td>7.54*10^-4</td>
</tr>
<tr>
<td>CCF WMH Volume*</td>
<td>253</td>
<td>Exp -8</td>
<td>6.12*10^-1</td>
<td>5.20*10^-4</td>
<td>7.42*10^-4</td>
</tr>
<tr>
<td>DSST</td>
<td>253</td>
<td>0</td>
<td>68</td>
<td>37.10</td>
<td>13.06</td>
</tr>
<tr>
<td>3MS</td>
<td>253</td>
<td>61</td>
<td>100</td>
<td>92.98</td>
<td>6.83</td>
</tr>
<tr>
<td>Gait Speed (m/s)</td>
<td>253</td>
<td>0.37</td>
<td>1.50</td>
<td>0.91</td>
<td>0.18</td>
</tr>
</tbody>
</table>

*WMH volumes are adjusted for total brain volume.

Abbreviations: BMI: Body Mass Index, WMH: White Matter Hyperintensity, ATRR: Anterior Thalamic Radiation Right, CCF: Corpus Callosum Right, 3MS: Modified Mini-Mental State
<table>
<thead>
<tr>
<th>Variables</th>
<th>Number</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>Std. Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Examination, DSST: Digit Symbol Substitution Test.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 3.2 The Results of Multivariable Regression Analysis.

This table presents the results of multivariable regression analysis for the effect of three selected WMH measures on gait speed.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total WMHs</td>
<td>-0.146*</td>
<td>-0.135*</td>
<td>-0.1244*</td>
<td>-0.109</td>
</tr>
<tr>
<td></td>
<td>[-0.257,-0.035]</td>
<td>[-0.249,-0.023]</td>
<td>[-0.233,-0.015]</td>
<td>[-0.218,0.000]</td>
</tr>
<tr>
<td>ATRR WMHs</td>
<td>-0.152**</td>
<td>-0.159***</td>
<td>-0.130*</td>
<td>-0.123*</td>
</tr>
<tr>
<td></td>
<td>[-0.262,-0.042]</td>
<td>[-0.273,-0.048]</td>
<td>[-0.238,-0.021]</td>
<td>[-0.230,-0.016]</td>
</tr>
<tr>
<td>CCF WMHs</td>
<td>-0.114*</td>
<td>-0.115*</td>
<td>-0.090</td>
<td>-0.073</td>
</tr>
<tr>
<td></td>
<td>[-0.225,-0.002]</td>
<td>[-0.227,-0.003]</td>
<td>[-0.200,0.020]</td>
<td>[-0.183,0.037]</td>
</tr>
</tbody>
</table>

***<0.005 ** p<0.01, * p<0.05

Model 1: Linear regression model for the effect of WMHs on gait speed, controlling for age, sex, BMI, quadriceps strength, education, and height.

Model 2: Linear regression model for the effect of WMHs on gait speed, controlling for age, sex, BMI, quadriceps strength, education, height, chronic pain, and prevalent hypertension.

Model 3: 3MS added to Linear regression Model 1 with the addition of 3MS as an independent variable.
|---------------------------|----------------------------|-----------------------------|----------------------------|----------------------------|

Model 4: DSST added to Linear regression Model 1 with the addition of DSST as an independent variable.

Abbreviations: 3MS: Modified Mini-Mental State Examination, DSST: Digit-Symbol Substitution Test, WMHs: White Matter Hyperintensities, ATRR: Anterior Thalamic Radiation Right, CCF: Corpus Callosum Frontal.
Table 3.3 The Total, Direct, and Indirect Effects for WMHs on Gait Speed.

This table presents the total, direct, and indirect effects of WMH volumes of total brain, ATRR and CCF, on gait speed. All three models are adjusted for age, sex, body mass index, quadriceps strength, education, height, and prevalent hypertension.

<table>
<thead>
<tr>
<th>Variables of Interest: WMH Volumes:</th>
<th>Total Effect</th>
<th>Direct Effect</th>
<th>Indirect Effect through 3MS</th>
<th>Indirect Effect through DSST</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unstandardized B (95% CI)</td>
<td>Standardized Beta (95% CI)</td>
<td>Unstandardized B (95% CI)</td>
<td>Standardized Beta (95% CI)</td>
</tr>
<tr>
<td>Model 1: Total Brain</td>
<td>-6.90** [-11.93, -1.88]</td>
<td>-0.15** [-0.25, -0.04]</td>
<td>-4.96* [-9.87, -0.06]</td>
<td>-0.10* (72%) [-2.02,0.04]</td>
</tr>
<tr>
<td></td>
<td>-0.60</td>
<td>-1.33§ [-3.18,-0.35]</td>
<td>-0.02§</td>
<td></td>
</tr>
<tr>
<td>Model 2: ATRR</td>
<td>-41.31** [-68.49, -14.13]</td>
<td>-0.16** [-0.27, -0.05]</td>
<td>-32.13* [-58.57, -5.68]</td>
<td>-0.12* (78%) [-11.71, 0.23]</td>
</tr>
<tr>
<td></td>
<td>-3.34</td>
<td>-5.84§ [-14.93, -0.42]</td>
<td>-0.02§</td>
<td></td>
</tr>
<tr>
<td>Model 3: CCF</td>
<td>Total Effect</td>
<td>Direct Effect</td>
<td>Indirect Effect through 3MS</td>
<td>Indirect Effect through DSST</td>
</tr>
<tr>
<td>-------------</td>
<td>--------------</td>
<td>---------------</td>
<td>----------------------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td></td>
<td>-29.42*</td>
<td>-0.11*</td>
<td>-17.59</td>
<td>-3.60</td>
</tr>
<tr>
<td></td>
<td>[-57.49, -1.34]</td>
<td>[-0.22, -0.005]</td>
<td>[-45.04, 9.84] (60%)</td>
<td>[-12.22, 0.00]</td>
</tr>
<tr>
<td></td>
<td>-17.59</td>
<td>-0.06</td>
<td>-3.60</td>
<td>-8.21§</td>
</tr>
<tr>
<td></td>
<td>[-45.04, 9.84]</td>
<td>[-0.22, -0.005]</td>
<td>[-12.22, 0.00]</td>
<td>[-19.79, -1.95] (27%)</td>
</tr>
</tbody>
</table>

** p<0.01, * p<0.05

§ Statistically Significant based on 95% Confidence Interval

The direct effect represents the association of WMH volume on gait speed adjusted for age, sex, BMI, quadriceps strength, and prevalent hypertension, when the effect of both cognitive tests on gait speed are taken into consideration. The indirect effect represents the effect of WMH volume on gait speed through cognitive function. The total effect is the sum of the direct effect and the indirect effect.

Abbreviations: WMH: White Matter Hyperintensity, ATRR: Anterior Thalamic Radiation Right, CCF: Corpus Callosum Frontal, 3MS: Modified Mini-Mental State Examination, DSST: Digit-Symbol Substitution Test.
Chapter 4: Cognitive and Physical Decline in Older Adults

4.1 Introduction

The world’s population is aging at a rapid rate, projecting a significant increase in the number of older adults with cognitive impairment and dementia in the coming decades. Current research suggests that the neuropathology of dementia – including brain changes leading to memory impairment and cognitive decline – is evident years before the onset of this disease. Both cross-sectional and longitudinal evidence have indicated the effect of aging on various domains of cognition after the age of 55. Older adults with cognitive decline have reduced functional independence and quality of life, and are at greater risk for developing dementia. Therefore, identifying biomarkers that can be easily assessed within the clinical setting and predict cognitive decline is of prime importance. Early recognition of cognitive decline would promote timely implementation of preventive strategies.

Current research efforts have primarily focused on predicting cognitive decline using neuroimaging – including functional and structural magnetic resonance imaging, positron emission tomography, and electroencephalographic activity – and cerebrospinal fluid biomarkers. However, these biomarkers are costly and resource intensive, and are thus not widely feasible within clinical settings. Therefore, there is an increasing demand to identify biomarkers that can be widely adopted and used by clinicians.

We propose that potential biomarkers are measures of physical function, in particular mobility. Recent studies have demonstrated significant associations between cognitive function and mobility. Specifically, it is now widely recognized that gait depends on both higher level...
cognitive processes and sensorimotor processes. Higher level cognitive processes are known as executive functions and these processes include the ability to concentrate, to attend selectively, and to plan and to strategize. Reduced executive functions are associated with impaired gait and falls. Of particular relevance to our study, recent evidence suggests that impaired mobility precedes cognitive decline in older adults. Buracchio and colleagues found that decline in gait speed was evident 12 years in older adults before the onset of mild cognitive impairment. They concluded that gait speed may be useful in detecting preclinical dementia.

In this regard, using appropriate statistical methods, we aimed to identify a set of clinical measures of physical and health status that are predictive of cognitive function after one year. We purposefully included measures that: 1) require minimal resources and training to implement; and 2) have established reliability and validity. This inclusion was not based on variables’ correlations with cognitive function.

4.2 Methods

4.2.1 Study Design and Participants

We included 89 community-dwelling adults aged 70 years and older who completed a 12-month prospective study aimed at investigating the interaction between cognitive function and mobility. Participants were recruited from metropolitan Vancouver via newspaper advertisements. Individuals were eligible if they: 1) were aged 70 to 80 years; 2) scored ≥ 24/30 on the Mini-Mental State Examination (MMSE); 3) were right hand dominant as measured by the Edinburgh Handedness Inventory; 4) were living independently in their own homes; 5) had
visual acuity of at least 20/40, with or without corrective lenses; and 6) provided informed consent. We excluded those who: 1) had a neurodegenerative disease, stroke, dementia (of any type), or psychiatric condition; 2) had clinically significant peripheral neuropathy or severe musculoskeletal or joint disease; 3) were taking psychotropic medication; 4) had a history indicative of carotid sinus sensitivity; or 5) were living in a nursing home, extended care facility, or assisted-care facility.

Ethics approval was obtained from the Vancouver Coastal Research Health Institute and University of British Columbia’s Clinical Research Ethics Board. All participants provided written consent.

4.2.2 Measurements

We assessed cognitive function at baseline and 12 months. In addition to the cognitive function at baseline, we also collected 31 baseline measures in our model (i.e., a total of 32 baseline measures: four basic descriptors, 18 measures of physical function, nine measures of health status, and one measure of cognitive function). All assessors were trained and standardized protocols were used. For basic descriptors, we measured age in years, standing and sitting height in centimeters, and mass in kilograms.

4.2.2.1 Primary Dependent Variable: Global Cognitive Function

We used the Montreal Cognitive Assessment (MoCA) \(^{216}\) test to assess global cognitive function. This test assesses multiple domains of cognitive function, including executive functions, attention, language, memory, and orientation, in a short 30-point test. The MoCA has good
internal consistency and test-retest reliability and correctly identified 90% of a large sample of individuals with mild cognitive impairment from two different clinics with a cut-off score of < 26/30.

4.2.2.2 Independent Variables (Predictors): Physical Status (Mobility, Balance, Falls Risk, and Fitness)

A total of 18 independent variables were extracted from the following measures of physical status.

The Short Physical Performance Battery (SPPB): For the Short Physical Performance Battery, participants were assessed on performances of standing balance, walking, and sit-to-stand. Each component is rated out of four points, for a maximum of 12 points; a score < 9/12 predicts subsequent disability. In our analysis, we included six measures derived from the SPPB: 1) walking time over a distance of 4 meters, at usual speed; 2) walking score, based on a participant’s ability (4 points maximum) to walk a distance of 4 meters; 3) sit-to-stand time for a set of five repetitions of rising from a chair and sitting down; 4) sit-to-stand score, based on participant’s ability (4 points maximum) to perform five repetitive chair stands; 5) standing score, based on participant’s standing balance (4 points maximum); and 6) the total SPPS score (12 points maximum), based on all the subcomponents.

The Physiological Profile Assessment (PPA): Physiological falls risk was assessed using the short form of the PPA. The PPA is a valid and reliable measure of falls risk. Based on a participant’s performance in five physiological domains – postural sway, reaction time, strength, proprioception, and vision – the PPA computes a falls risk score (standardized score) that has a
75% predictive accuracy for falls among older people\textsuperscript{219,220}. A PPA Z-score of $\geq 0.60$ indicates high physiological falls risk\textsuperscript{221}.

For our analysis, we used 8 measures derived from the PPA: 1) visual contrast sensitivity, using The Melbourne Edge Tests (MET). Participants were presented with 20 circular patches containing edges with reducing contrast and variable orientation. The circle with lowest contrast -- in which participants can correctly identify the orientation of the edge – is considered their MET score. This test has high test-retest reliability\textsuperscript{207} and good external validity as a predictor of falls\textsuperscript{219}; 2) average proprioception score. We asked seated participants (closed eyes) to align their feet on either side of a thick clear sheet. The difference in matching the great toes (in degrees) is considered as proprioception score. We calculated the average from five trials; 3) average hand reaction time. We used a light as the stimulus and asked participants to click on a mouse for 10 times. The average of the 10 trials was considered as the reaction time; 4) best dominant quadriceps strength. We measured the strength of quadriceps while the participants were seated. The best score was selected among three trials; 5) average quadriceps strength from three trials; 6) postural sway on foam. We used a swaymeter that measures displacements of the body at waist level. The device consisted of a 40cm long rod (attached to participants) with a vertically mounted pen at its end. The participants were asked to stand still on an high-density foam with open eyes, and the pen recorded their sway; 7) postural sway on the floor. We repeated the swaymeter measurements on the floor; and 8) overall falls risk score, by combining all the subcomponents of PPA assessment.

The Activities-Specific Balance Confidence (ABC)\textsuperscript{222}: Based on the self-efficacy theory by Tinetti and colleagues\textsuperscript{223}, The ABC questionnaire was used to measure an aspect of the
psychological impact of balance impairment and/or falls. The participants were asked to rate their confidence in performing each of the activities on a scale from 0 (no confidence) to 100% (complete confidence) without losing balance or becoming unsteady. We used the mean ABC score, calculated by averaging all the percentages for each of the 16 items.

Timed Up and Go (TUG)\textsuperscript{224}: This test was used to assess functional mobility. Each participant was timed while he rose from a chair, walked 3 meters, turned, walked back, and sat down again. We repeated this test for two times and used the average.

The Physical Activity Scale for the Elderly (PASE)\textsuperscript{225}: This test is comprised of self-reported movement counts for occupational, household and leisure items over a one-week period. We used the total PASE score.

Six-Minute Walk Test: We assessed physical fitness by the Six-Minute Walk Test (6-MWT)\textsuperscript{226} - a walking test of general cardiovascular capacity in older adults\textsuperscript{227}. The total distance walked in meters in six minutes was recorded.

4.2.2.3 Independent Variables (Predictors): Health Status

A total of nine independent variables were extracted from the following measures of health.

Cardiovascular Risk: We measured hip girth and waist girth in centimeters and then calculated the waist-to-hip ratio using the formula (waist girth / hip girth). The waist-to-hip ratio is a measure of obesity and cardiovascular risk\textsuperscript{228}. Resting heart rate, heart rate immediately post 6MWT, and resting blood pressure were recorded in duplicate, using a oscillometric sphygmomanometer, the Omron HEM-775 Values were presented as an average of two
recordings that were taken one minute apart.

**Mood:** We used the Geriatric Depression Scale (GDS), a 30-point self-rating test, to assess depression in our population. The GDS is a reliable and validated basic screening measure for depression in older adults\(^{229}\).

**Comorbidities:** Comorbidities were assessed with the Functional Comorbidity Index (FCI)\(^{230}\), a 21-item questionnaire that calculates the total number of comorbidities\(^{230}\).

### 4.2.3 Statistical Method

#### 4.2.3.1 Variable Selection

We used a regularized regression model (elastic net) from the Matlab Statistics Toolbox (2012b, The Mathworks, Inc., Natick, Massachusetts, United States) to explore the relation between the 32 baseline measures and cognitive function after one year. Elastic net is an automated shrinkage and penalized statistical method that reduces variability in the estimates of regression coefficients. In elastic net, regularization parameters of L1 (i.e., positive weighting parameter that promotes shrinkage in the regularized regression coefficients) and L2 (i.e., weighting parameter that promotes stability on regularization and protects the fitting from collinearity) are introduced into the standard multiple linear regression model to shrink some coefficients to exactly zero. For a given lambda (i.e., the L1 weighting parameter) and an alpha between 0 and 1 (i.e., the L2 weighting parameter), elastic net minimizes the error, as shown below.

\[
\text{Min} \frac{1}{2N} \left[ ||Y - \beta_0 - X \beta||^2 + \lambda ||\beta_1|| + \frac{(1-\alpha)}{2} \lambda ||\beta_2||^2 \right],
\]
where $||\beta_1|| = \sum_{j=1}^{p} \beta_j$ and $||\beta_2||^2 = \sum_{j=1}^{p} \beta_j^2$

Here, $Y$ represents cognitive function after one year for our 89 participants, $X$ is a 89*32 (participants * independent variables) matrix of physical function and health status measures, $N$ is the number of participants, and $p$ is the predictors. To be able to compare the coefficients and meet elastic net’s assumptions, the independent variables are standardized (i.e., converted to Z-Scores), and the dependent variable is mean-centred. To evaluate the quality of the model, we used standard jack-knife (leave one out cross-validation procedures). Elastic net regression is a preferred alternative to conventional variable selection methods, such as stepwise regression, that have been criticized for their bias, over-fitting, and exaggerated p-values\(^{183}\).

The process of variable selection using the elastic net method is illustrated in Figure 4.1. With Jack-knife resampling technique (Steps 1 to 3; Figure 4.1), the complete process was repeated for each participant in the X matrix separately (i.e., 89 times), to reduce the bias in selecting the minimized error. On each run, one participant was assigned to the testing set, and the rest was assigned to the training set (Step 1; Figure 4.1). Then a Leave-One-Out Cross-Validation (LOOCV) was performed within the training set to select the tuning parameters, which minimize the Mean Squared Error on the training set (Step 2; Figure 4.1).
Figure 4.1 The Process of Variable Selection Using the Elastic Net Method.

Step 1 shows the generation of train and test sets for each cross-validation loop. We used jackknifing technique to assign one participant to the test set and the rest to the training set. In Step 2, the optimized model is estimated for the training set, using elastic net method. This model has minimized squared error on each cross-validation loop. This model is then tested on the test set in Step 3. After the whole process is repeated over all the participants to avoid the bias, we selected the variables which were consistently selected on all the cross-validation loops. There were 6 variables which were selected in this way.

At the end of the variable selection process, we had 89 sets of selected variables with their corresponding coefficients. Six variables were consistently selected in all the 89 sets. We built our final model on top of these six variables, since they had all contributed to minimizing mean squared error in each cross-validation loop.

4.2.3.2 Model Construction and Testing

At the end of each cross-validation loop, we built three linear regression models: 1) based on only one variable of baseline MoCA, 2) based on the six variables selected in every cross-
validation loop, and 3) a full model based on all the 32 variables. This step was added to enable us to compare the models by their R-squares.

4.3 Results

The mean (SD) age of our population was 76 (3.12) years. The demographics and characteristics of the 89 participants are presented in Table 4.1. 58% of our sample population were women. Based on the mean baseline MoCA score (24.16), our participants had mild cognitive impairment. On average, performance on the MoCA reduced by 0.40 over the 12-month study period. Based on the mean baseline PPA score (0.37), our participants were not at high risk for falls.

4.3.1 Statistical Analysis

First, we wanted to ask which variables would be most useful for our predictions. Using elastic net, the six baseline variables consistently selected on every cross-validation loop were reported as best predictors of cognitive decline, as measured by MoCA, over the 12-month study period. The following list is sorted in the order of their contribution to the variance of MoCA: 1) baseline MoCA, 2) hip girth, 3) PASE, 4) age, 5) mean quadriceps strength, and 6) postural sway on the floor.

4.3.2 Model Evaluation

To evaluate our model, we constructed three linear regression models in each cross-validated loop; one using only one variable of baseline MoCA (Model 1), the second one using the six variables consistently selected across all the cross-validation loops (i.e., Model 2), and the third
one using all the 32 variables (i.e., Model 3). Model 2 had the smallest mean squared errors (Table 4.2; mean= 7.47) than Model 1 or 3 (Table 4.2; mean=7.98 and 115.33). Moreover to the improved mean squared errors, model 2 explained 47% of the variance on MoCA after one year, which was significantly higher than that of model 1 (i.e., 37%) by 10% (p<0.001).

4.4 Discussion

Worldwide, one new case of dementia is detected every four seconds. Thus, there is a concentrated effort to identify patient characteristics, or biomarkers, that are predictive of conversion. Early recognition of cognitive decline would promote timely implementation of preventive strategies. Ideally, such biomarkers could be assessed in a wide variety of clinical settings with minimal resources.

Using a statistical approach, we identified a set of six clinical measures that predicted cognitive function after one year among community-dwelling older adults. The six clinical measures were broadly of: 1) falls risk, 2) muscular strength, 3) cardiovascular function, and 4) physical activity. Overall, our results concur with previous studies that examined factors associated with healthy aging and more specifically, cognitive health in older adults.

The prevalence of impaired mobility is 35% for community-dwelling older adults of age 70 years and older. Falls are a significant consequence of impaired mobility. One of the key factors contributing to falls is impaired cognitive function. Even mild cognitive decline in otherwise healthy community-dwelling older adults is a significant risk factor for falls. It is critical to recognize that the relationship between mobility and cognitive function is not unidirectional (i.e., impaired cognitive function leads to falls), but rather it is bidirectional. Thus, there is
growing recognition that clinical gait abnormalities and falls are early biomarkers of cognitive impairment and dementia. For example, gait speed was reported to slow a decade before the diagnosis of MCI \(^{212}\). Thus, our finding of falls risk (i.e., postural sway) as a predictor of cognitive function concur with current evidence.

The measure of dominant quadriceps strength (i.e., average strength) was among the six clinical measures that predicted cognitive function. This concurs and extends the prospective cohort study of Boyle and colleagues \(^{236}\), who demonstrated that in an average follow-up time of 3.6 years, greater muscle strength was significantly associated with a slower rate of global cognitive decline in a cohort of 900 community-based older adults.

Both hip girth and physical activity were consistently selected in all the elastic net models over the jack-knife process. Heitmann and colleagues \(^{237}\) recently demonstrated that a large hip circumference has an independent and beneficial positive effect on both cardiovascular health and mortality in middle-aged adults. Cardiovascular function is highly associated with cognitive function and dementia risk \(^{238}\). Reduced cardiovascular morbidity should be associated with better cognitive performance \(^{239}\).

Epidemiological studies demonstrate a consistent relationship between higher physical activity levels and a reduced risk of developing dementia \(^{108, 240-242}\). A meta-analysis of 16 prospective, epidemiological studies on the incidence of neurodegenerative disease, found more physical activity at baseline reduced the risk of developing all-cause dementia by 28% and of developing AD by 45%, even after controlling for confounding variables \(^{243}\). Thus, it is not surprising physical activity was a significant predictor of cognitive function in our study.
We recognize the limitations of this study. Our model with the six variables is marginally performing better than the model with baseline cognitive function. We speculate that for predictions of longer than one year, additional features might be selected, resulting in lower prediction errors. Moreover, in spite of marginal improvement in error and small change of MoCA from baseline to one year, the R-squared was improved by 10%, which might be representative of the greater variance (total of 47%) explained by our model with six selected variables. Lastly, larger datasets and experiments of longer than one year would be needed to investigate the selection of variables separately for men and women, and with higher validity and predictability.

In summary, we built a parsimonious model based on a selected set of six physical function and health status measures strongly predictive of cognitive function after one year. Complex models with a large number of variables have increased risk of over-fitting in predictive analysis. Over-fitted models generally have poor predictive performance, as they can inflate minor fluctuations in the data. Constructing a model with a smaller set of variables will decrease the complexity of the model, will show a better performance when new data is introduced to the model for prediction, and will be more robust to outliers\textsuperscript{244}. In addition to reducing the complexity of the model without changing the model significantly, our model with the selected variables improved the mean prediction error (7.47 vs. 115.33 with all the 32 variables) and the R-squared (47% vs. 37% with only baseline MoCA). This result further proves the robustness of our model using fewer variables. These six physical function and health status measures can be easily implemented in a clinical setting.
Table 4.1 Descriptive Statistics for the Outcome Measure and 32 Predictors.

The six variables consistently selected in all models are highlighted in gray. Mean coefficients are calculated based on coefficients obtained from elastic net.

<table>
<thead>
<tr>
<th>Variables</th>
<th>N</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>Std. Deviation</th>
<th>Mean Coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>89</td>
<td>70</td>
<td>82</td>
<td>76.07</td>
<td>3.12</td>
<td>-0.29</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>89</td>
<td>45.20</td>
<td>130.15</td>
<td>74.07</td>
<td>16.10</td>
<td>0</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>89</td>
<td>147.60</td>
<td>186.45</td>
<td>165.19</td>
<td>8.63</td>
<td>0</td>
</tr>
<tr>
<td>Sitting Height (cm)</td>
<td>89</td>
<td>121.13</td>
<td>688.60</td>
<td>136.59</td>
<td>59.33</td>
<td>0.08</td>
</tr>
<tr>
<td>Hip Girth (cm)</td>
<td>89</td>
<td>66.93</td>
<td>148.63</td>
<td>94.15</td>
<td>14.15</td>
<td>0.36</td>
</tr>
<tr>
<td>Waist Girth (cm)</td>
<td>89</td>
<td>85.70</td>
<td>142.43</td>
<td>105.94</td>
<td>10.69</td>
<td>0.10</td>
</tr>
<tr>
<td>Waist to Hip Ratio</td>
<td>89</td>
<td>.70</td>
<td>1.22</td>
<td>.88</td>
<td>.08</td>
<td>0</td>
</tr>
<tr>
<td>Total PPA Score</td>
<td>89</td>
<td>-1.29</td>
<td>2.81</td>
<td>.37</td>
<td>.90</td>
<td>-0.18</td>
</tr>
<tr>
<td>Visual Contrast Score (dB)</td>
<td>89</td>
<td>12</td>
<td>24</td>
<td>20.08</td>
<td>2.09</td>
<td>0</td>
</tr>
<tr>
<td>Mean Proprioception</td>
<td>89</td>
<td>.0</td>
<td>6.40</td>
<td>1.60</td>
<td>1.24</td>
<td>0</td>
</tr>
<tr>
<td>Mean Reaction Time (ms)</td>
<td>89</td>
<td>163.9</td>
<td>369.10</td>
<td>232.44</td>
<td>38.05</td>
<td>0</td>
</tr>
<tr>
<td>Mean Quadriceps Strength (kg)</td>
<td>89</td>
<td>4.33</td>
<td>46</td>
<td>27.43</td>
<td>9.17</td>
<td>-0.29</td>
</tr>
<tr>
<td>Best Quadriceps Strength (kg)</td>
<td>89</td>
<td>5</td>
<td>46</td>
<td>29.05</td>
<td>9.37</td>
<td>-0.10</td>
</tr>
<tr>
<td>Floor Sway (mm)</td>
<td>89</td>
<td>33.67</td>
<td>180.98</td>
<td>65.35</td>
<td>30.26</td>
<td>-0.13</td>
</tr>
<tr>
<td>Variables</td>
<td>N</td>
<td>Minimum</td>
<td>Maximum</td>
<td>Mean</td>
<td>Std. Deviation</td>
<td>Mean Coefficients</td>
</tr>
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<td>-------------------</td>
</tr>
<tr>
<td>Foam Sway (mm)</td>
<td>89</td>
<td>55.14</td>
<td>557.41</td>
<td>145.61</td>
<td>92.54</td>
<td>-0.05</td>
</tr>
<tr>
<td>Mean ABC Score</td>
<td>89</td>
<td>38.12</td>
<td>100.00</td>
<td>85.54</td>
<td>13.20</td>
<td>0.08</td>
</tr>
<tr>
<td>GDS</td>
<td>89</td>
<td>0</td>
<td>6</td>
<td>.53</td>
<td>1.24</td>
<td>-0.13</td>
</tr>
<tr>
<td>FCI</td>
<td>89</td>
<td>0</td>
<td>8</td>
<td>3.01</td>
<td>1.89</td>
<td>0</td>
</tr>
<tr>
<td>Baseline MoCA</td>
<td>89</td>
<td>15</td>
<td>30</td>
<td>24.16</td>
<td>3.21</td>
<td>1.61</td>
</tr>
<tr>
<td>Mean TUG (s)</td>
<td>89</td>
<td>4.85</td>
<td>23.88</td>
<td>8.09</td>
<td>2.48</td>
<td>-0.06</td>
</tr>
<tr>
<td>SPPB Standing Score</td>
<td>89</td>
<td>2</td>
<td>4</td>
<td>3.67</td>
<td>.61</td>
<td>0</td>
</tr>
<tr>
<td>SPPB Walking Score</td>
<td>89</td>
<td>2</td>
<td>4</td>
<td>3.94</td>
<td>.27</td>
<td>0</td>
</tr>
<tr>
<td>SPPB Walking Time (s)</td>
<td>89</td>
<td>2.08</td>
<td>6.50</td>
<td>3.37</td>
<td>.69</td>
<td>0</td>
</tr>
<tr>
<td>SPPB Sit to Stand Score</td>
<td>89</td>
<td>1</td>
<td>4</td>
<td>2.99</td>
<td>1.12</td>
<td>0</td>
</tr>
<tr>
<td>SPPS Sit to Stand Time (s)</td>
<td>89</td>
<td>6.21</td>
<td>42.95</td>
<td>12.66</td>
<td>5.08</td>
<td>0</td>
</tr>
<tr>
<td>SPPB Total Score</td>
<td>89</td>
<td>5</td>
<td>12</td>
<td>10.61</td>
<td>1.57</td>
<td>0</td>
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<tr>
<td>Rest Heart Rate</td>
<td>89</td>
<td>45</td>
<td>103</td>
<td>72.21</td>
<td>13.03</td>
<td>0.02</td>
</tr>
<tr>
<td>Post Exercise Heart Rate</td>
<td>89</td>
<td>52</td>
<td>120</td>
<td>85.09</td>
<td>16.26</td>
<td>-0.17</td>
</tr>
<tr>
<td>Resting Blood Pressure – Systolic</td>
<td>89</td>
<td>13</td>
<td>205</td>
<td>145.33</td>
<td>25.19</td>
<td>0</td>
</tr>
<tr>
<td>Variables</td>
<td>N</td>
<td>Minimum</td>
<td>Maximum</td>
<td>Mean</td>
<td>Std. Deviation</td>
<td>Mean Coefficients</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>----</td>
<td>---------</td>
<td>---------</td>
<td>-------</td>
<td>----------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>(mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting Blood Pressure - Diastolic (mm Hg)</td>
<td>89</td>
<td>61</td>
<td>106</td>
<td>80.04</td>
<td>10.10</td>
<td>0</td>
</tr>
<tr>
<td>Six Minute Walk Test (m)</td>
<td>89</td>
<td>180</td>
<td>690</td>
<td>488.46</td>
<td>95.61</td>
<td>0</td>
</tr>
<tr>
<td>PASE</td>
<td>89</td>
<td>.00</td>
<td>489.89</td>
<td>123.88</td>
<td>64.33</td>
<td>0.30</td>
</tr>
<tr>
<td>Outcome: Final MoCA</td>
<td>89</td>
<td>12</td>
<td>30</td>
<td>23.75</td>
<td>3.49</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Table 4.2 The Mean Squared Errors Associated with Model 1, Model 2, and Model 3.

This table presents the a comparison between the model with top six variables selected at each cross-validation loop with the model with only one variable of baseline MoCA and also with model with all the 32 variables.

<table>
<thead>
<tr>
<th>Models</th>
<th>Mean Squared Error</th>
<th>SD</th>
<th>Min</th>
<th>Max</th>
<th>R-Squared</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>7.98</td>
<td>11.98</td>
<td>0.0002</td>
<td>76.50</td>
<td>37%</td>
</tr>
<tr>
<td>Model 2</td>
<td>7.47</td>
<td>12.84</td>
<td>0.001</td>
<td>83.43</td>
<td>47%</td>
</tr>
<tr>
<td>Model 3</td>
<td>115.33</td>
<td>960.19</td>
<td>0.001</td>
<td>9070.21</td>
<td>59%</td>
</tr>
</tbody>
</table>

Model 1: Standard Regression Model with One Variable of Baseline MoCA.

Model 2: Standard Regression Model with Six Variables Consistently Selected at Every Cross-Validation Loop.

Model 3: Standard Regression Model Using All 32 Variables.

Abbreviations: MoCA: Montreal Cognitive Assessment
Chapter 5: Effect of Exercise on WMHs Progression and Mobility in Older Adults

5.1 Introduction

Cognitive impairment and falls are geriatric “giants” that significantly increase morbidity and mortality in older adults. Both geriatric syndromes are associated with white matter hyperintensities (WMHs). White matter hyperintensities appear as hyperintensities on T2-weighted magnetic resonance images (MRI) and are markers of (but not specific to) cerebral small vessel disease. These covert lesions are highly prevalent in older adults; epidemiological studies have reported a prevalence of 85% or greater. Thus, interventions that prevent or slow down the progression of WMHs may be of great societal value by preserving both cognitive function and mobility in older adults.

Recognized mobility and vascular risk factors for WMHs include type 2 diabetes, hypertension, and dyslipidemia. Thus, interventions that reduce vascular risk factors may prevent or slow the progression of WMHs. In this regard, physical activity is a promising strategy. It reduces vascular risk factors as well as overall reduction in morbidity and mortality. Notably, a five-year prospective cohort study showed that higher levels of physical activity were associated with reduced WMH progression in older adults without dementia. Moreover, a recent cross-sectional study of 88 older adults found that moderate to vigorous physical activity, as measured by accelerometry, was significantly associated with lower volume of WMHs.
Of relevance to brain health, there are two distinct forms of physical activity: 1) aerobic training (e.g., running), and 2) resistance training (RT; e.g., lifting weights). There is a third type (i.e., anaerobic training) that its effect on brain function and structure has not been studied much in the literature. Aerobic training is well-known for its potent ability to reduce vascular risk factors \(^{102, 104}\), and thus a focus in research in cerebral small vessel disease \(^{251}\). However, it is now recognized that RT also has significant cardiometabolic benefits \(^{252, 253}\). Specifically, in a meta-analysis of RCTs, Strasser \(^{252}\) and colleagues concluded that RT should be recommended in the management of type 2 diabetes and metabolic disorders. In another meta-analysis of RCTs, Cornelissen and colleagues \(^{253}\) suggested that moderate intensity RT could be considered as an effective intervention strategy to combat and prevent high blood pressure. In a six-month randomized trial of RT, Spence and colleagues \(^{254}\) showed that RT impacted arterial size, function, and wall thickness, which could translate to decreased cardiovascular risk. Additionally, RT may promote cerebrovascular function; a recent small cross-sectional study demonstrated that regular RT was associated with greater cerebral perfusion among otherwise healthy older women \(^{255}\). As such, there is a potential for RT to reduce vascular risk factors and modulate the progression of WMHs. Moreover, recent studies have shown the beneficial effect of RT on cognitive function and mobility \(^{83}\). Improvements in WMHs might be one mechanism through which RT confers benefit on cognitive function and mobility \(^{47}\).

To our knowledge, no RCT has examined the effect of exercise, either resistance training or aerobic training, on WMH progression in older adults. Thus, using neuroimaging data from a 12-month single-blinded RCT (clinicaltrials.gov Identifier: NCT00426881) of exercise \(^{87}\), we conducted a planned exploratory analysis to assess: 1) the effect of RT on the progression of
WMHs in community-dwelling older women; and 2) the association between WMH progression and changes in cognitive function, measured by Stroop test, and mobility, measured by gait speed.

5.2 Methods

5.2.1 Study Design

We conducted a randomized, controlled 52-week prospective study of resistance training (i.e., Brain Power Study; clinicaltrials.gov Identifier: NCT00426881). Assessors were trained by the research team and were blinded to group allocation of the participants. MRI data were acquired at baseline and trial completion in a subset of eligible participants.

5.2.2 Participants

Our sample consisted only of women since cognitive response to exercise differs between sexes. We recruited participants using print advertisements and television features. Individuals were screened by a standardized telephone interview. Briefly, women who lived in Metro Vancouver, Canada, were eligible for study entry if they: 1) were aged 65 to 75 years; 2) were living independently in their own home; 3) scored ≥ 24 on the Mini-Mental State Examination (MMSE); and 4) had a visual acuity of at least 20/40, with or without corrective lenses. We excluded those who: 1) had a current medical condition for which exercise is contraindicated; 2) had participated in RT (i.e., using free weights, machines, or theraband) one or more times per week on a regular basis in the last six months prior to study entry; 3) had a neurodegenerative disease and/or stroke; 4) had depression; 5) did not speak and understand English fluently; 6)
were taking cholinesterase inhibitors; 7) were on estrogen replacement therapy; or 8) were on testosterone therapy.

Figure 5.1, the CONSORT (Consolidated Standards of Reporting Trial) flowchart shows the number and distribution of participants included in this secondary analysis. For this secondary analysis, we included only those who demonstrated WMHs in their baseline MRI. Ethical approval was obtained from the Vancouver Coastal Health Research Institute and the University of British Columbia’s Clinical Research Ethics Board. All participants provided written informed consent.
5.2.3 Descriptive Variables

At baseline, participants underwent a physician assessment to confirm current health status and eligibility for the study. We collected age, years of education, height, weight, MMSE, Montreal Cognitive Assessment (MoCA) scores, blood pressure, and waist-to-hip ratio. Comorbidities, such as type 2 diabetes, hypertension, and dyslipidemia, were assessed with the Functional Comorbidity Index (FCI)\textsuperscript{230}. We used the Geriatric Depression Scale (GDS)\textsuperscript{256} to screen for depression. Current level of physical activity was determined by the Physical Activities Scale for the Elderly (PASE) self-report questionnaire\textsuperscript{257}. In addition, isotonic quadriceps strength (IRM)
and peak muscle power was assessed using the Keiser air-pressured digital resistance leg press machine (Keiser Sports Health Equipment, Fresno, CA, USA).

5.2.4 Dependent Variable: WMHs

5.2.4.1 Structural MRI Data Acquisition

Structural MRI data was acquired on a research-dedicated Philips 3T Achieva MRI scanner (Philips Medical Systems, Best, The Netherlands) at the UBC MRI Research Centre. For each subject, a T2-weighted scan and a Proton-Density-weighted (PD-weighted) scan were acquired. The repetition time (TR) and echo time (TE) for the T2-weighted images were TR = 5431 and TE = 90 ms and for the PD-weighted images were TR = 2000 ms and TE = 8 ms. Both T2- and PD-weighted scans were acquired to have dimensions of 256 x 256 x 60 voxels and a voxel size of 0.937 x 0.937 x 3.000 mm.

5.2.4.2 Structural Data Processing and Analysis

Each MR image underwent the following preprocessing steps before lesion identification and segmentation were performed. Preprocessing was done with publicly available tools that are widely used for neuroimaging studies: 1) MR intensity inhomogeneity was corrected using a multiscale version of the nonparametric non-uniform intensity normalization method (N3)\(^{258}\); 2) a structure-preserving noise-removal filter (SUSAN) was applied\(^{259}\); and 3) all non-brain tissues were removed using the brain extraction tool (BET)\(^{260}\).

The WMHs were identified and digitally marked by a radiologist with extensive experience in WMH identification. The radiologist followed a set of guidelines\(^{60}\) that is minimalistic and
allows the seeding procedure to be efficient and intuitive. Specifically, the radiologist would:

1. Mark all distinct WMHs regardless of their size.

2. Place more than one point on a lesion if the additional points would help define the extent of the lesion.

3. Place at least one point near the center of each lesion.

The WMHs were then segmented by a method that automatically computed the extent of each marked lesion\textsuperscript{136}. Full details on the point placement procedure and subsequent automatic segmentation are described in previous work\textsuperscript{136}, but briefly, the seed points were processed by a customized Parzen windows classifier\textsuperscript{261} to estimate the intensity distribution of the lesions. The algorithm included heuristics to optimize the accuracy of the estimated distributions by dynamically adjusting the position and the number of seed points used for the Parzen window computation, as well as a spatial method that approximated visual shape partitioning to identify areas that were likely to be false positives. The segmentation method was previously validated extensively on large data sets with a large range of lesion loads, and was found to be highly accurate compared to expert segmentations and also robust to variations in the placement of the seed points\textsuperscript{136}. The lesion masks were then used to quantify WMH volumes in mm\textsuperscript{3} at baseline and trial completion. Figure 5.2 represents baseline and trial completion lesion masks overlaid on T2 images from one participant. The seeds marked by the radiologist are shown in red dots.
The seeds marked by the radiologist are shown in red dots.

5.2.5 Executive Functions

White matter hyperintensities are associated with impaired cognitive function, in particular, executive functions\textsuperscript{160}. The primary outcome for the Brain Power Study was the Stroop Colour Word Test, a measure of specific cognitive process of selective attention and conflict resolution\textsuperscript{87, 262}. For the Stroop test, there were three conditions. Participants were required to: 1) read out words printed in black ink (e.g., “blue”); 2) read out the colour of coloured “X’s”; and 3) name the ink colour in which colour words were printed (e.g., the word “blue” printed in red ink), while ignoring the word itself. There were 80 trials for each condition, and we recorded the time. The ability to selectively attend and control response output was calculated as the time difference between the third condition and the second condition; smaller time differences indicate better selective attention and conflict resolution.
5.2.6 Physiological Falls Risk and Gait Speed

Numerous studies have highlighted the association between WMHs and impaired mobility; falls are significant consequences of impaired mobility. We assessed physiological falls risk using the short form of the valid and reliable Physiological Profile Assessment (PPA) and gait speed by asking participants to walk at their usual pace along a four-meter path. Gait speed in meters per second (m/s) was calculated from the mean of two trials.

5.2.7 Randomization

The randomization sequence was generated by www.randomization.com and was concealed until interventions were assigned. This sequence was held independently and remotely by the Research Coordinator. Participants were enrolled and randomised by the Research Coordinator to one of three groups: once-weekly resistance training (1x RT), twice-weekly resistance training (2x RT), or twice-weekly balance and tone (BAT).

5.2.8 Sample Size

This exploratory analysis was planned apriori as indicated by the inclusion of the structural MRI sequences necessary for WMH quantification. The required sample size for this study’s primary research question was calculated based on our previous predictions of 12-month changes in the StroopColour-Word Test. Specifically, we predicted 6% improvement for the 1x RT and a 12% improvement for the 2x RT. We also estimated 10% deterioration in the BAT group (i.e., control group). These estimates were based on our previous work that demonstrated a home-based program of strength and balance training exercises significantly improved Stroop test.
performance. Assuming a 20% attrition rate, using an alpha level of < 0.05, and a common standard deviation of 25 seconds, 52 participants per group ensured a power of 0.80.

5.2.9 Exercise Intervention and Compliance

The exercise classes began one month after the baseline assessments were completed. A detailed description of these classes has been previously reported. The classes were 60 minutes in duration, with 10 minute warm-up, 40 minutes of core content, and 10 minutes of cool-down. All classes were led by certified fitness instructors who received additional training and education from the study investigators. Compliance was calculated based on the percentage of total classes attended.

5.2.9.1 Resistance Training

Both resistance training programs (i.e., 1x RT and 2x RT) were progressive in loading. A combination of Keiser Pressurized Air System (Keiser, Fresno, CA, USA) and free weights were used to provide the training stimulus. The Keiser-based exercises consisted of biceps curls, triceps extension, seated row, latissmus dorsi pull downs, leg press, hamstring curls, and calf raises. The intensity of the training stimulus was at a work range of six to eight repetitions (two sets), and the training stimulus was increased using 7RM method. In addition, mini-squats, mini-lunges, and lunge walks were included in the resistance training programs. The number of sets completed and the load lifted for each exercise was recorded for each participant at every class.
5.2.9.2 Balance and Tone Training

The BAT program consisted of stretching, range of motion, basic core-strength including kegals (i.e., exercises to strengthen the pelvic floor muscles), balance (including Tai Chi-based forms, tandem stand, tandem walking, and single-leg stance), and relaxation exercises. Other than body weight, no additional loading (e.g., hand weights, resistance bands, etc.) was applied to any of the exercises. Participants assigned to the BAT group served as controls to avoid the confounding effect of social interaction and changes in lifestyle secondary to study population.

5.2.9.3 Adverse Effects

Participants were questioned about the presence of any adverse effects, such as musculoskeletal pain or discomfort, at each exercise session. All instructors also monitored participants for symptoms of angina and shortness of breath during the exercise classes.

5.2.10 Statistical Analysis

All analyses were “full analysis set”\(^\text{264}\) (defined as the analysis set which is as complete and as close as possible to the intention-to-treat ideal of including all randomized participants). Statistical analyses were performed using SPSS software (IBM SPSS Statistics for Mac, Version 20.0, Armonk, NY: IBM Corp.). Because WMHs were distributed non-normally, we log-transformed them, checked for their normality after the log transformation, and used them as continuous log-transformed variables in our analyses. The overall alpha was set at \(p \leq 0.05\).
5.2.10.1 Effect of Resistance Training on WMH Volume

Between-group differences in log-transformed WMH volumes at trial completion were compared by multiple linear regression analysis. In the models, baseline WMH volume, experimental group, baseline waist-to-hip ratio, and baseline FCI were included as covariates, based on biological relevance and their association to metabolic and cardiovascular risk. Two planned simple contrasts were performed. These contrasts were employed to assess differences between: 1) the 1x RT group and the BAT group; and 2) the 2x RT group and the BAT group.

5.2.10.2 Correlations between Change in WMH Volume and Change in Stroop Color Word Test Performance, PPA, and Gait Speed

Within the two RT groups, Pearson correlations were calculated to determine whether WMH progression over the 12-month RCT was associated with Stroop Color Word Test performance, PPA, and gait speed. Change in WMHs was calculated as the difference between the log-transformed baseline and trial completion values. Changes in Stroop Color Word Test performance, PPA, and gait speed were also calculated as the difference between baseline and trial completion values. Thus, a positive change score in WMH volume, Stroop Color Word Test performance and PPA would indicate improvement. Conversely, a negative change score in gait speed would indicate improvement. All correlations were adjusted for waist-to-hip ratio and MoCA scores.
5.3 Results

5.3.1 Participants

Eighty-eight out of the 155 participants who consented and were randomized in the Brain Power Study underwent MRI scanning at baseline. Of the 88 participants who completed MRI at baseline, 54 demonstrated evidence of WMHs. Of these 54 participants, 42 completed the trial and the MRI at trial completion (Figure 5.1). Out of these 42 participants, 18 participants were assigned to 1x RT, 13 participants to 2x RT, and 11 participants to BAT programs.

Baseline characteristics of the 54 participants with evidence of WMHs at baseline are reported in Table 5.1. The mean (SD) age of this subset of participants was 69.4 (2.8) years; this is similar to the mean (SD) age of the entire cohort, which was 69.6 (2.9) years. Baseline characteristics of these 54 participants did not significantly differ from that of the original 155 participants. In addition, the three groups were not significantly different at baseline.

5.3.2 Compliance and Adverse Effects

The exercise compliance over one year for the primary study was 67.9%. The 1x RT group had 71.0%, 2x RT group had 70.3%, and the BAT group had 62.0%. Compliance was not significantly different across the three groups. In regards to adverse events, 29.8% of the 1x RT group, 10.9% of the 2x RT group, and 9.5% of the BAT group had musculoskeletal complaints (e.g., knee joint discomfort, bursa irritation in the lateral hip), all of which were resolved or diminished within 4 weeks of onset. One participant in the BAT group experienced one fall during the exercise class, which did not result in injury.
5.3.3 Effect of Exercise on WMH Volume

Table 5.2 provides the baseline and trial completion WMH volume data for the 42 participants who completed the trial and both MRI sessions. It includes both raw data as well as log-transformed values. At trial completion, the 2x RT group had significantly lower WMH volume compared with the BAT group (p=0.03; Figure 5.3). There was no significant difference between the BAT group and the 1x RT group at trial completion (p=0.77). In addition, mean peak muscle power was significantly improved in the 2x RT group at trial completion, compared to the BAT group (p=0.008).

![Bar chart showing the change in WMH volume from baseline to trial completion.](image)

**Figure 5.3 The Change in WMH Volume from Baseline to Trial Completion.**

At trial completion, the 2x RT group had significantly lower rate of WMH progression compared with the BAT group.
5.3.4 Correlations between Change in WMH Volume and Change in Stroop Color Word Test Performance, PPA, and Gait Speed

As demonstrated in Figure 5.4, reduced WMH progression over the 12-month RCT was significantly associated with maintained gait speed ($r=-0.31$, $p=0.049$). Change in WMH volume was not significantly associated with change in Stroop Test performance ($r=0.30$, $p=0.06$) or with PPA ($r=0.13$, $p=0.25$).

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Figure 5.4 The Association between Change in WMH Volume and Change in Gait Speed.

These values are from baseline to trial completion, in 1x RT and 2x RT groups (N=31). Change in WMH volume was calculated as: baseline log-transformed WMH value - trial completion log-transformed WMH value (i.e., not in its original metric of mm$^3$). Thus, a positive change score in WMH volume indicate reduced WMH progression over the six-month intervention period while a negative change score would indicate increased WMH volume progression. Change in gait speed was also calculated as: baseline gait speed - trial
completion gait speed. Hence, a negative change score would indicate improvement while a positive change score would indicate decline in gait speed.

5.4 Discussion

Our novel proof-of-concept findings suggest that in 65 to 75 year old community-dwelling women, 12 months of twice-weekly progressive RT reduces WMH progression. Furthermore, we found that reduced WMH progression during the 12-month trial was associated with improved gait speed.

White matter hyperintensities are known risk factors for both mobility and cognitive decline. Moreover, they are highly prevalent in otherwise healthy older adults and their progression over time has significant clinical consequences which increases the risk of disability and reduces quality of life in older population. Therefore, strategies to prevent or reduce the progression of WMHs are of great importance. To our knowledge, this is the first study to demonstrate that engaging in progressive RT can significantly reduce WMH progression in community-dwelling older women.

Resistance training provides a broad range of systemic benefits, including moderating the development of sarcopenia, or age-related loss in skeletal muscle mass. The multifactorial deleterious sequelae of sarcopenia include increased falls and fracture risk as well as physical disability. Of particular relevance to WMH progression, sarcopenia is an emerging risk factor for metabolic disorders. This may not be surprising given that skeletal muscle is the primary tissue for glucose and triglyceride metabolism. Specifically, the Korea National Health and Nutrition Examination Survey showed that sarcopenia was associated with insulin resistance,
diabetes, and metabolic syndrome in non-obese adults aged 20 years of age or older. Moreover, The US National Health and Nutrition Examination III found that sarcopenia, independent of obesity, was associated with adverse glucose metabolism. Thus, resistance training may reduce WMH progression by reducing cardiometabolic risk factors. This hypothesis is supported by previous RCT that showed resistance training improves insulin resistance and glycemic control. Furthermore, a 2011 review concluded that the cardiovascular benefits of resistance training include improved body composition, reduction of abdominal fat mass, reduced resting blood pressure, improved lipoprotein-lipid profiles, and enhanced glycemic control.

Additionally, RT has benefits for both cardiovascular and cerebrovascular function. Spence and colleagues conducted a six-month randomized longitudinal trial of exercise demonstrating that RT increased the diameter and function in the brachial artery, and decreased carotid arterial wall thickness. More specifically, increased intima-media thickness (IMT) of the carotid artery is known to be closely related to the severity of atherosclerotic changes associated with cardiovascular disease. Previous research has reported mixed results regarding the ability of AT to attenuate age-related increases in IMT. This conflict might be due to the significant shear stress created on the endothelial cell layer of arteries, on general population, which is possibly caused by increased blood flow during AT. In contrast, RT increases blood flow for short periods of time, creating an alternative type of stress on the endothelial cells. In this regard, RT might be one possible modality to enhance arterial endothelial function and decrease cardiovascular risk. In addition, Sabayan and colleagues showed that higher levels of endothelial dysfunction are associated with lower cerebrovascular perfusion. Moreover, of
particular relevance to our population of interest, Xu and colleagues\textsuperscript{255} demonstrated that older women who engaged in RT at least once a week had significantly greater cerebrovascular perfusion than women who did not.

Our results may also suggest that those participants who underwent higher frequency RT (i.e., 2x RT) received greater benefit in regards to WML progression than those who underwent lower frequency RT (i.e., 1x RT) – such that there is a dose-response effect. This notion is supported by our previous observation that 2x RT resulted in significant functional plasticity in two regions of cortex associated with response inhibition and conflict resolution, while 1x RT did not\textsuperscript{275}. However, due to our smaller sample, additional future investigations are needed to adequately examine whether there is a dose-response effect of RT on WML progression.

In addition, we demonstrated that reduced WMH progression was associated with improved gait speed. This finding concurs with and extends previous cross-sectional studies demonstrating a significant association between WMH and gait speed\textsuperscript{47,158}. Our results suggest that strategies that reduce the progression of WMHs may directly contribute to improved gait speed in older adults. Specifically, in a 12-week RCT of gait rehabilitation, Nadkarni and colleagues\textsuperscript{276} demonstrated that improved gait speed was associated with WMH severity. Our current finding suggests that in addition to its severity, WMH progression rate may be an important factor on changes in gait speed. Given that recent evidence suggests that the association between WMHs and mobility is independent of executive functions\textsuperscript{277}, strategies that reduce the progression of WMHs may directly contribute to improved gait speed in older adults.
We recognize the limitations of our study. First, our study sample of older women limits the generalizability of our results to older men. Second, the small number of participants included in this exploratory analysis increased the possibility of Type II error and imbalance in baseline characteristics. Thus, future studies with larger sample sizes are needed to confirm our current findings and to extend our understanding of the role of resistance training on WMH progression. Specifically, based on our log-transformed WMH volume data, the overall effect size (ES) observed was 0.60 (expressed as a standardized difference, Cohen’s d). Based on this ES, assuming an alpha of 0.05 (two-tailed) and a beta of 0.20, future studies should include a minimum of 45 participants per group to provide a power of 0.80 (G*Power 3.1). Moreover, since the beneficial effects of RT on WMH progression might be due to regulations of blood pressure and cerebral perfusion, further studies with proper sample sizes would be needed to investigate this hypothesis. Finally, our study investigated the volume of WMHs in the whole brain. Further research on WMHs in specific localized regions of the brain would advance our understanding of the underlying lesion networks and the effect of exercise on lesion progression in different brain regions and ultimately, on cognitive function and mobility.

5.5 Conclusion

We provided novel proof-of-concept evidence from a RCT that pragmatic resistance training may reduce WMH progression in community-dwelling older women. Furthermore, reduced WMH progression was associated with improved gait speed. The potential clinical implications of our current results are significant as WMHs are prevalent among older adults and have negative consequences for both mobility and cognitive function.
Table 5.1 Baseline Characteristics of the 54 Participants with WMHs.

<table>
<thead>
<tr>
<th>Variable</th>
<th>1x RT (n=22)</th>
<th>2x RT (n=17)</th>
<th>BAT (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Age, year</td>
<td>69.64 (2.64)</td>
<td>69.29 (3.19)</td>
<td>69.33 (2.82)</td>
</tr>
<tr>
<td>Education*, year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than Grade 9</td>
<td>0 (0%)</td>
<td>1 (5.9%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Grade 9 to 12</td>
<td>2 (9.1%)</td>
<td>0 (0%)</td>
<td>2 (13.3%)</td>
</tr>
<tr>
<td>High School Certificate</td>
<td>2 (9.1%)</td>
<td>5 (29.4%)</td>
<td>3 (20%)</td>
</tr>
<tr>
<td>Trades or Professional Certificate</td>
<td>4 (18.2%)</td>
<td>2 (11.8%)</td>
<td>2 (13.3%)</td>
</tr>
<tr>
<td>University Certificate</td>
<td>5 (22.7%)</td>
<td>1 (5.9%)</td>
<td>1 (6.7%)</td>
</tr>
<tr>
<td>University Degree</td>
<td>9 (40.9%)</td>
<td>8 (47.1%)</td>
<td>7 (46.7%)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>160.66 (6.45)</td>
<td>161.27 (7.39)</td>
<td>162.93 (5.79)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>68.18 (14.63)</td>
<td>68.12 (12.54)</td>
<td>69.48 (9.44)</td>
</tr>
<tr>
<td>Diastolic Blood Pressure, mmHG</td>
<td>84.55 (13.84)</td>
<td>80.12 (10.89)</td>
<td>89.07 (24.05)</td>
</tr>
<tr>
<td>Systolic Blood Pressure, mmHG</td>
<td>150.91 (18.13)</td>
<td>135.56 (25.70)</td>
<td>142.40 (20.64)</td>
</tr>
<tr>
<td>Waist-to-Hip Ratio</td>
<td>0.83 (0.07)</td>
<td>0.83 (0.06)</td>
<td>0.84 (0.05)</td>
</tr>
<tr>
<td>Variable</td>
<td>1x RT (n=22)</td>
<td>2x RT (n=17)</td>
<td>BAT (n=15)</td>
</tr>
<tr>
<td>-------------------</td>
<td>--------------</td>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>GDS</td>
<td>0.04 (0.21)</td>
<td>0.64 (1.36)</td>
<td>0.60 (2.06)</td>
</tr>
<tr>
<td>FCI</td>
<td>1.82 (1.86)</td>
<td>2.41 (1.97)</td>
<td>1.93 (1.43)</td>
</tr>
<tr>
<td>MMSE</td>
<td>28.86 (0.99)</td>
<td>28.82 (1.13)</td>
<td>28.73 (1.33)</td>
</tr>
<tr>
<td>MoCA</td>
<td>25.77 (2.87)</td>
<td>25.65 (2.93)</td>
<td>24.40 (3.54)</td>
</tr>
<tr>
<td>Stroop, sec</td>
<td>46.73 (18.25)</td>
<td>48.28 (16.38)</td>
<td>46.93 (17.89)</td>
</tr>
<tr>
<td>PPA</td>
<td>0.12 (1.02)</td>
<td>0.29 (1.11)</td>
<td>0.29 (1.08)</td>
</tr>
<tr>
<td>Gait Speed, m/s</td>
<td>1.14 (0.21)</td>
<td>1.17 (0.19)</td>
<td>1.20 (0.17)</td>
</tr>
<tr>
<td>PASE</td>
<td>124.98 (80.11)</td>
<td>135.11 (61.90)</td>
<td>118.25 (43.83)</td>
</tr>
<tr>
<td>1RM, N</td>
<td>321.07 (81.54)</td>
<td>306.09 (47.58)</td>
<td>345.16 (72.51)</td>
</tr>
<tr>
<td>Peak Muscle Power, W</td>
<td>704.38 (205.55)</td>
<td>565.54 (204.94)</td>
<td>635.00 (192.12)</td>
</tr>
<tr>
<td>WMHs, mm³</td>
<td>1507.19 (1902.97)</td>
<td>1470.95 (2225.20)</td>
<td>2306.24 (4508.45)</td>
</tr>
</tbody>
</table>

Abbreviations: GDS: Geriatric Depression Score; FCI: Functional Comorbidity Index; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; PPA: Physiological Profile Assessment; PASE: Physical Activities Scale for the Elderly; WMHs: White Matter hyperintensities; 1RM: Isotonic Quadriceps Strength

*Count: Number of “Yes” Cases within each Group. %: Percent of “Yes” within each Group.
Table 5.2 Descriptive Values of Raw and Log-Transformed WMH Measures (mm³).
These values are for baseline and trial completion, on paired samples. Forty two participants are included in our analysis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Trial Completion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=18</td>
<td>n=18</td>
</tr>
<tr>
<td>1x RT Group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Raw WMHs (SD)</td>
<td>1774.52 (2007.44)</td>
<td>1920.26 (2127.23)</td>
</tr>
<tr>
<td>Mean Log-Transformed WMHs (SD)</td>
<td>2.81 (0.75)</td>
<td>2.85 (0.74)</td>
</tr>
<tr>
<td>Mean RM1 (SD)</td>
<td>321.07 (81.54)</td>
<td>409.72 (101.63)</td>
</tr>
<tr>
<td>Mean Peak Muscle Power (SD)</td>
<td>704.38 (205.55)</td>
<td>642.18 (261.15)</td>
</tr>
<tr>
<td>2x RT Group</td>
<td>n=13</td>
<td>n=13</td>
</tr>
<tr>
<td>Mean Raw WMHs (SD)</td>
<td>1805.03 (2456.57)</td>
<td>1903.50 (2684.03)</td>
</tr>
<tr>
<td>Mean Log-Transformed WMHs (SD)</td>
<td>2.82 (0.73)</td>
<td>2.80 (0.79)</td>
</tr>
<tr>
<td>Mean RM1 (SD)</td>
<td>306.09 (47.58)</td>
<td>388.45 (91.15)</td>
</tr>
<tr>
<td>Mean Peak Muscle Power (SD)</td>
<td>565.54 (204.94)</td>
<td>696.27 (187.77)</td>
</tr>
<tr>
<td>BAT Group</td>
<td>n=11</td>
<td>n=11</td>
</tr>
<tr>
<td>Mean Raw WMHs (SD)</td>
<td>810.52 (1082.03)</td>
<td>952.51 (1310.84)</td>
</tr>
<tr>
<td>Mean Log-Transformed WMHs (SD)</td>
<td>2.52 (0.75)</td>
<td>2.58 (0.73)</td>
</tr>
<tr>
<td>Mean RM1 (SD)</td>
<td>345.16 (72.51)</td>
<td>339.00 (64.69)</td>
</tr>
<tr>
<td>Mean Peak Muscle Power (SD)</td>
<td>635.00 (192.12)</td>
<td>522.62 (150.77)</td>
</tr>
</tbody>
</table>
Chapter 6: General Discussion

This chapter provides a general discussion to summarize and integrate the information from previous chapters. Results from Chapters 2 and 3 suggest that reduced WMH progression may translate to maintained, or improved, physical and cognitive function. Chapter 4 concurs with the current literature that suggests physical function is important for cognitive health. Collectively, these chapters led to the exploratory analyses of RCT data that provide proof-of-concept evidence that exercise, specifically RT, has beneficial effects on WMH progression, which may translate to improved physical and cognitive function. The next sections will begin with a summary of our studies (Section 6.1), and will follow with a discussion of hypotheses mentioned in Introduction, limitations of this research, and potential future directions.

6.1 Summary of Studies

Chapter 2 was devoted to investigating the association between WMHs and cognitive function in older adults. In this study, we systematically evaluated peer-reviewed evidence on the role of anatomical location in the association between WMHs and cognitive function. Overall, the results suggested that periventricular WMHs may have a greater impact on executive function/processing speed than subcortical WMHs. However, to further clarify the effect of WMHs in different brain regions, we suggested that future studies consider spatial distribution of WMHs on the whole brain.

Chapter 3 was devoted to investigating the associations between WMHs and physical function, and the mediating role of cognitive function in this association. We identified regional WMHs most significantly related to slower gait. Our mediation analyses found that executive functions
significantly mediated the associations between WMHs and gait speed. This result further supported the hypothesis that multi-faceted interventions targeting executive control functions as well as motor functions are candidates to the maintenance of mobility across the lifespan.

Chapter 4 was devoted to investigating the association between physical function and cognitive function. We built a parsimonious model based on a selected set of six physical function and health status measures strongly predictive of cognitive function after one year. These six physical function and health status measures demonstrated the importance of falls risk, muscular strength, cardiovascular function, and physical activity in predicting cognitive functions. This study concurred with the current literature that physical health is important for cognitive health.

Investigations in Chapters 2, 3, and 4 led to our study in Chapter 5, which was an exploratory analysis of the effect of RT on the progression of WMHs. Our results demonstrated that the 2x RT group had significantly lower WMH volume compared with the BAT group at the end of the 12-month trial. There was no significant difference between the BAT group and the 1x RT group at trial completion. Moreover, among participants in the two RT groups, reduced WMH progression over 12-month was significantly associated with improved gait speed.

6.2 Main Research Hypotheses Revisited

We provided four hypotheses in the Introduction, which formed the basis for our four studies. Here, we are revisiting them and will make a conclusion based on the evidence we have gathered from each study.
1. Are WMHs associated with cognitive decline in older adults? Specifically, is the anatomical location of WMHs a moderator to this association?

As discussed in Chapter 2, we believe that WMH load is associated with cognitive decline in adults aged 60 years and older. Of the 14 studies included, only one did not show a significant association between WMH load and cognitive dysfunction. Specifically, this study did not consider age or education as possible confounders, which may have affected the lack of correlation in their analysis. Moreover, our systematic review demonstrated that in addition to load, the anatomical locations of WMHs are significantly associated with cognitive decline. More specifically, periventricular WMHs have been shown to greatly impact processing speed and executive functions. We believe that this association is based on the hypothesis that periventricular WMHs affect longer connections and may affect multiple regions. This result also supports the hypothesis that executive functions depend on multiple brain regions and distant connections. Moreover, most of the studies investigating the regional WMHs demonstrated an association between frontal WMHs and cognitive functions. This result further supports the theory that frontal region of the brain is an integral part for cognitive performance.

Overall, the results show that WMHs have a significant negative impact on cognitive function. As a conclusion, we suggested that in order to understand the differential effect of WMHs in various locations on cognitive function, future research need to focus more on the classification of WMHs in various cerebral locations. To follow these instructions and to provide further support for the association between WMHs and cognitive dysfunction, our second study described in Chapter 3 investigated the association between localized WMHs with cognitive functions. We demonstrated a significant association between WMHs in frontal corpus callosum
and left anterior thalamic radiation with executive functions. This result along with our extensive systematic review from Chapter 2 showing the importance of frontal region demonstrates the strong association between WMHs and cognitive functions, and specifically executive functions.

2. Are WMHs associated with physical decline in older adults? Is this a direct association, or is it modified by cognitive function?

As discussed in Chapter 3, we demonstrated that total WMH volume and WMHs located in right anterior thalamic radiation (ATRR) and frontal corpus callosum (CCF) were most significantly associated with slower gait. One part of this association is considered to be direct, which may show the importance of white matter integrity on physical function in older adults. Specific to this study, disruptions in superior fronto-occipital fasciculus fibers connecting pre-motor areas with the parietal lobe may impair the somatosensory feedback required for gait and thus, directly impair gait. In addition to the direct effect, WMHs indirectly affect physical functions through impairing executive functions. This result might mean that not only intact cerebral connections in motor areas would be needed to maintain efficient gait functionality, but also high performance in executive functions would be needed as well. Therefore, disconnections in either cognitive or motor networks would lead to lower performance on gait. In this regard, multi-faceted interventions targeting motor functions, such as balance and strength training, as well as executive control functions are candidates to the maintenance of mobility across the lifespan.

In summary, our results highlight the negative impact of WMHs on both executive functions and gait. Therefore, interventions to slow down the progression of WMHs may have positive benefits on both executive functions and gait, and ultimately improve mobility in older adults. As
discussed in Introduction, one mechanism by which targeted exercise training might affect WMHs is through reducing metabolic and cardiovascular risk factors. We investigated this hypothesis in a RCT in Chapter 5.

3. Is physical function associated with cognitive function? Specifically, which components of physical function are predictive of cognitive decline?

As discussed in Chapter 4, we believe that physical function is strongly associated with cognitive function, and specifically executive functions. In fact, physical decline is evident years before the onset of executive cognitive decline, and we might be able to use physical measures to predict cognitive decline. Our results showed that six measures in the categories of falls risk, muscle strength, cardiovascular risk, and physical activity were strongly predictive of cognitive decline after one year. Since the six measures are easy to use and implement in a clinical setting, we suggested in this study that these measures need to be practiced to predict cognitive decline in older adults.

Moreover, as discussed earlier in Introduction, we defined three important components of age-associated physical decline as impairments in gait and balance and reduced muscle mass. These three impairments can lead to gait impairments, falls, and sarcopenia in older adults. Confirming the importance of these categories, our analysis in Chapter 4 also selected falls risk and muscle strength as important physical function components predictive of cognitive decline in older adults. Therefore, we might conclude that falls risk and muscle strength are not only important factors for physical impairments in gait, falls, and sarcopenia, but also are essential for intact cognitive functioning in older adults. The other two physical function categories selected in our
Chapter 4 study are cardiovascular risk and physical activity. As discussed in Introduction, cardiovascular disorders are important risk factors for both physical and cognitive decline. Therefore, it is not surprising to see this component as a strong predictor of cognitive decline in older adults. We also discussed earlier that physical activity can reduce the risk for cardiovascular disorders and benefit physical and cognitive functions in older adults. The fact that both components of cardiovascular risk and physical activity are automatically selected in our study further proves the great importance of exercise training in older adults. Moreover, exercise training is beneficial for balance and muscle strength as well, which provide further evidence for its potential benefits on cognitive functions.

In addition, we believe that the relationship between physical function and cognitive function is not unidirectional. Cognitive impairment is also considered an important risk factor for physical decline. One possible mechanism by which impairments in cognitive function might lead to impairments in physical functions might be through disconnections in the cognitive circuits necessary for physical functioning (e.g., disconnections in regions essential for executive functioning which are essential components for navigation, gait, and mobility). In addition, WMHs affect cognitive function, which may lead to reductions in attentional capacity, impaired central processing, decreased judgment and self-regulation, and loss of motivation and initiation. To further investigate the direction of this association, our study discussed in Chapter 3 looked at the mediating effect of executive functions in the association between WMHs and physical function. Our results showed that there is a significant pathway for the effect of executive cognitive functions on physical decline. Our collective conclusion from Chapters 3 and 4 indicates that, based on the bidirectional nature of the association between physical and cognitive
function, we can hypothesize that targeted exercise training is a multi-facet intervention that can not only improve gait, falls, and muscle mass, but has beneficial effects to reduce cardiovascular risk and ultimately improve both physical and executive cognitive functions in older adults.

4. Can exercise reduce WMH progression? What is the association between reduced WMH progression and change in a) executive functions, and b) physical function?

We believe that exercise has beneficial effects on WMH progression. Our prospective study discussed in Chapter 5 demonstrates that exercise, and specifically RT, can reduce the rate of WMH progression in older adults. Moreover, this effect is dose sensitive, as the significant effect was seen only in the 2x RT experimental group, and not 1x RT, compared to the control group. This finding might show that the 1x RT group did not build the minimum power required for older adults in order to benefit from this type of exercise. Waters and colleagues 82 believe that muscular power declines at a faster rate than strength, and power has a greater impact on physical function than strength. Therefore, in order for skeletal muscles to achieve and maintain both strength and power, RT programs need to have progressively increasing load. Our findings extend these results, showing that higher frequency might be needed in order get beneficial effects from RT. Possible mechanisms by which RT affected WMH progression include reductions in metabolic and cardiovascular risk factors.

In addition, we demonstrated that reduced WMH progression was associated with improved gait speed. This finding concurs with and extends previous cross-sectional studies demonstrating a significant association between WML and gait speed 47, 158. Our results suggest that strategies
that reduce the progression of WMLs may directly contribute to improved gait speed in older adults.

6.3 Limitations and Future Directions

Our study discussed in Chapter 5 was focused on investigating the effect of RT on WMHs. Although we did not investigate the effect of AT on progression of WMHs, we hypothesize that similar benefits will be gained. AT has been shown to have great cardiovascular benefits. Moreover, since greatest benefits of AT has been seen when paired with RT, we propose that future studies investigate the effect of AT and RT on WMH progression.

Moreover, all the four studies included in this thesis included healthy older adults. Due to the significant association between WMH volume and cardiovascular risk factors, we propose that future studies include populations with cardiovascular disorders. Since both AT and RT have shown beneficial effects to reduce cardiovascular risk factors, one might be able to find significant exercise-induced reductions in the rate of WMH progression in this population. In addition, since the beneficial effect of exercise might be mediated by medications, especially for treatment of cardiovascular and cardiometabolic disorders, future studies should include this variable in their analyses.

6.4 Final Conclusions

We have provided converging evidence from four separate studies leading to the conclusion that exercise has beneficial effects on WMH progression. Since WMHs are demonstrated to have significant associations with physical and cognitive dysfunctions, we believe that exercise-
induced reductions of WMHs progression might translate to improvements in physical and cognitive functions in older adults.
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Appendix A  The 21 Anatomical WMH Variables for this Study.

1) Total Volume of WMHs

2) Anterior Thalamic Radiation, Left

3) Anterior Thalamic Radiation, Right

4) Corpus Callosum, Frontal

5) Corpus Callosum, Occipital

6) Corticospinal Tract, Left

7) Corticospinal Tract, Right

8) Cingulate, Lower Part Left

9) Cingulate, Lower Part Right

10) Cingulate, Upper Part Left

11) Cingulate, Upper Part Right

12) Inferior Fronto-Occipital Fasciculus, Left

13) Inferior Fronto-Occipital Fasciculus, Right

14) Inferior Longitudinal Fasciculus, Left
15) Inferior Longitudinal Fasciculus, Right

16) Entire Superior Longitudinal Fasciculus, Left

17) Entire Superior Longitudinal Fasciculus, Right

18) Superior Longitudinal Fasciculus, the Branch to the Temporal Lobe, Left

19) Superior Longitudinal Fasciculus, the Branch to the Temporal Lobe, Right

20) Uncinate Fasciculus, Left

21) Uncinate Fasciculus, Right
Appendix B  Data Reduction Procedure.

With Jackknifing resampling technique (Steps 2 to 4; Figure 3.2 (A)), the complete process was repeated for each participant in the X matrix separately (i.e., 253 times). On each run, one participant was assigned to the testing set, and the rest was assigned to the training set (Step 2; Figure 3.2 (A)). Then a Leave-One-Out Cross-Validation (LOOCV) Elastic Net was performed within the training set to minimize the Mean Squared Error (Step 3; Figure 3.2 (A)). The resulting optimal coefficients on training sets were tested on their independent test sets (Step 4; Figure 3.2 (A)).