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Understanding Cognitive and Physical Outcomes in Cerebral Small Vessel Disease

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Abstract

Cerebral small vessel disease (cSVD) is a key contributor to vascular cognitive impairment and Alzheimer’s disease (AD), the two most common causes of cognitive impairment and dementia. Given the pervasiveness of cSVD in older adults, it is critical that we better understand the cognitive and physical outcomes of cerebrovascular damage and identify strategies to mitigate its progression. Moreover, it is important to assess the effect AD pathology in cSVD, as the two often co-exist and share common pathogenic mechanisms. Specifically, I investigated the role of Aβ plaques, a pathological hallmark of AD, on cognitive and physical outcomes in older adults with cSVD. Another feature of cSVD is myelin loss and currently its role is poorly understood; as such, I examined the contribution of myelin to cognition in older adults with cSVD. There is mounting evidence to suggest that aerobic training (AT) is a promising strategy to combat cSVD as key vascular risk factors (i.e., hypertension, hypercholesteremia, and type 2 diabetes) are modifiable by exercise; critically, the efficacy of exercise may vary by biological sex. Thus, I conducted an exploratory analysis of a randomized controlled trial to examine: 1) the impact of AT in mitigating white matter hyperintensity (WMH) progression, a predominant cSVD lesion; and 2) whether AT efficacy varied by sex. My research showed that Aβ plaque deposition was negatively associated with both cognitive and physical outcomes. In addition, less myelin was associated with impaired processing speed and working memory. My exploratory analysis did not find that AT significantly reduced WMH progression. However, there was a sex difference in response to AT; AT trained males demonstrated reduced progression compared with AT trained females. Overall, the results of this thesis suggest that therapeutic trials in people with cSVD should consider the effects of both cerebral Aβ plaque deposition and myelin loss on cognitive or physical function and future studies should account for sex differences to better understand the efficacy of exercise training. There has been limited pharmacological progress in treating cSVD; thus, it is critical that we continue to investigate lifestyle strategies to prevent or slow the progression of cSVD.
Lay summary

The number of Canadians living with dementia is rapidly increasing posing a significant strain to health, financial, and social systems. Cerebral small vessel disease (cSVD) is a key contributor to cognitive impairment and is associated with an increased risk of all-cause dementia. Given the pervasiveness of cSVD, it is critical that we better understanding this disease and identify strategies to slow its progression. The results of this thesis suggest that cerebral Aβ plaque deposition and myelin loss, two types of brain damage associated with cSVD, may contribute to cognitive and physical deteriorations. In addition, aerobic training may slow the progression of cSVD, but the benefit seems to vary between women and men. From a public health standpoint, it is critical that we make cSVD research a priority because strategies to preserve cerebrovascular health may reduce the detrimental effects of dementia, delay early institutional care, and reduce health care costs.
Preface

The content from this dissertation was written and compiled by Elizabeth Dao. Drs. Liu-Ambrose, Tam, and Hsiung reviewed and provided comments that were taken into consideration in generating the final version of this dissertation.

The research studies included in Chapters 2 to 5 were conducted in the Aging, Mobility, and Cognitive Neuroscience Laboratory at the Research Pavilion of the Vancouver General Hospital. A portion of Chapter 2 was conducted with Dr. Hsiung’s research team. Ethics approval for all studies was obtained by the University of British Columbia’s Clinical Research Ethics Board and the Vancouver Coastal Health Research Institute. All research studies included in this dissertation have been published or is in preparation for submission. Detailed study contributions are provided below.

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List of abbreviations

Aβ - amyloid-beta
AD - Alzheimer’s Disease
ADAS-Cog - Alzheimer’s Disease Assessment Scale - cognitive subscale
AT – aerobic training
BBB - blood brain barrier
BDNF – brain-derived neurotrophic factor
BMI - body mass index
BP<sub>ND</sub> - non-displaceable binding potential
CBF - cerebral blood flow
CI+ - cognitive impairment stemming from AD, SIVCI, and mixed AD-SIVCI
CSF - cerebrospinal fluid
cSVD – cerebral small vessel disease
CT - computed tomography
DSST- Digit Symbol Substitution Test
DTI – diffusion tensor imaging
eNOS – endothelial nitric oxide synthase
FA – fractional anisotropy
FLAIR – fluid-attenuated inversion recovery
fMRI – functional magnetic resonance imaging
GM - gray matter
LADIS - Leukoaraiosis And Disability Study
MCI - mild cognitive impairment
MD – mean diffusivity
MMSE – Mini-Mental State Examination
MoCA – Montreal Cognitive Assessment
MRI - magnetic resonance imaging
MS – multiple sclerosis
MTI – magnetization transfer imaging
MTR – magnetization transfer ratio
MWF – myelin water fraction
MWI – myelin water imaging
NAWM - normal appearing white matter
NINDS - CSN - National Institute of Neurological Disorders and Stroke - Association Internationale pour la Recherche et l’Enseignement en Neurosciences - Canadian Stroke Network
NO - nitric oxide
PDF – probability density function
PDw - proton density weighted
PET - positron emission tomography
PIB - 11C Pittsburgh compound B
PPA - Physiological Profile Assessment
PROMoTE – Promotion of the Mind through Exercise Study
RCT - randomized controlled trial
ROI - region of interest
RT – resistance training
SIVCI - subcortical ischemic vascular cognitive impairment
SPPB - Short Physical Performance Battery
T2w - T2 weighted
VASCOG - International Society for Vascular Behavioral and Cognitive Disorders
VCI - vascular cognitive impairment
VEGF - vascular endothelial growth factor
VICCCS - Vascular Impairment of Cognition Classification Consensus Study
WM - white matter
WMH - white matter hyperintensity
6MWT - 6-Minute Walk Test
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Dedication

I dedicate this thesis to my mother and father who have always encouraged me to pursue my education and whose efforts have afforded me the privilege of attending school.

Lisanne, thank you for your endless encouragement.

To Ryan, Linda, and David thanks for picking up the slack when I was busy. Billy, Toby, and Eric thank you for staying up with me during all those late-night writing sessions.
Chapter 1: General introduction

In 2016 there were 564,000 people in Canada living with dementia and this number is expected to almost double by 2031, to 937,000 Canadians, an increase of 66%. When mild cognitive impairment (MCI) is included with dementia rates, the prevalence estimate would be approximately 50% higher. Correspondingly, the total health care systems costs and out of pocket costs of caring for people with dementia is expected to rise from $10.4 million in 2016 to over $16 million by 2031. The high prevalence and cost of dementia pose a significant strain to health, financial, and social systems; thus, it is critical that we continue to make dementia research a priority.

The two most common causes of age-related cognitive impairment and dementia are Alzheimer’s disease (AD) and vascular dementia, accounting for approximately 60% and 20% of all cases, respectively. However, epidemiological studies typically do not require neuroimaging evidence and the prevalence of cerebrovascular disease in cognitive impairment and dementia is often underestimated. Autopsy studies report that all major dementias, including 80% of AD cases, have a vascular component. AD pathology can amplify vascular damage and vascular damage can result in further accumulation of AD pathology suggesting that the two diseases share an interacting pathogenic mechanism. Given the pervasiveness of cerebrovascular disease in cognitive impairment and dementia, it is critical that we better quantify and understand the impact of covert vascular burden and identify strategies that will reduce its progression to
mitigate cognitive decline. Notably, strategies that preserve cerebrovascular health alone may significantly reduce dementia rates 5.

The term vascular cognitive impairment (VCI) encompasses the full spectrum of cognitive deficits, from minor impairments to dementia, stemming from vascular disease 6. This thesis will focus on the most common subtype of VCI, subcortical ischemic vascular cognitive impairment (SIVCI) 7. SIVCI is caused by cerebral small vessel disease (cSVD) and the general goals of this thesis are to further understand the pathological changes associated with cSVD. Moreover, it is important that the study of cSVD consider the inclusion of AD pathology, given their co-existence. This thesis will also investigate aerobic exercise as a strategy to mitigate cSVD progression. Investigating the effect of cSVD damage and strategies to mitigate this damage will aid in therapeutic developments to slow the progression of SIVCI and preserve basic activities of daily living.

Before I address these aims, I will provide an overview of SIVCI with emphasis on subjects relevant to this thesis. I will review the following: 1) broad clinical presentation of SIVCI; 2) cSVD neuropathology, including its interaction with AD pathology; 3) measurement of cSVD pathology in-vivo; 4) cognitive and physical impairments associated with cSVD and; 5) rationale for the potential role of aerobic exercise in mitigating cSVD progression. This section will conclude by summarizing the current gaps in the literature and introduce the four research studies addressing these knowledge gaps.
1.1 Defining subcortical ischemic vascular cognitive impairment

VCI is an umbrella term that encompasses the full spectrum of cognitive and functional impairments associated with vascular brain pathologies, from subjective cognitive decline to dementia. SIVCI is a subtype of VCI, in which cSVD is the main vascular cause. As such, the concept of SIVCI is often incorporated into the diagnosis of VCI. Several diagnostic criteria for VCI have been published, including those from the National Institute of Neurological Disorders and Stroke (NINDS) – Association Internationale pour la Recherche et l’Enseignement en Neurosciences, NINDS-Canadian Stroke Network (CSN), American Stroke Association/American Heart Association, Diagnostic and Statistical Manual of Mental Disorder, fifth edition, International Society for Vascular Behavioral and Cognitive Disorders (VASCOG), and Vascular Impairment of Cognition Classification Consensus Study (VICCCS). With these publications, the criteria for VCI has evolved over time, but generally there are two main aspects in diagnosing VCI. The first aim is to establish the presence of a cognitive disorder with a subjective report and with objective evidence of impairment. The subjective report must indicate decline in cognitive functioning, which may stem from perceived impairment or disability, or fear of future decline. Objective evidence must come from a validated measure assessing cognitive function. Cognitive deficits in VCI may include all cognitive domains; however, there is a preponderance of slowed processing speed and impaired executive functions. The term “executive functions” refer to the ability to orchestrate different cognitive tasks to attain a specific goal. It includes goal formulation, initiation, planning, organizing, sequencing, executing appropriate behavioral responses (including inhibiting inappropriate responses), and abstracting. Generally executive functions are necessary for goal-directed behaviour and the loss of executive functions can result in an inability to
participate in everyday activities such as cooking, dressing, shopping, and housework. The three key executive processes are: 1) set shifting; 2) working memory and; 3) inhibition.

In assessing SIVCI, neuropsychological protocols must therefore include multiple cognitive domains and additionally include measures that are particularly attuned to assessments of executive functions. Experts from the NINDS-CSN working group have recommended a 60-minute, 30-minute, or a 5-minute neuropsychological test battery for clinically evaluating VCI. The 60- and 30-minute protocols include measures of: 1) processing speed; 2) executive functions; 3) learning and memory; 4) language; and 5) visuospatial construction. The brief 5-minute protocol includes the Montreal Cognitive Assessment (MoCA) and potentially the Mini-Mental State Examination (MMSE). Though both tests are commonly used, the MoCA is more relevant in assessing VCI compared with the MMSE because it includes more executive components.

The second aim is to determine whether vascular disease is the dominant, if not exclusive, etiology for the cognitive syndrome. This will rely on patient history, physical examination, and neuroimaging evidence. A history of vascular risk factors, which include physiological and lifestyle risk factors, has been associated with VCI. Physiological risk factors include age, hypertension, type 2 diabetes, hypercholesterolemia, and atrial fibrillation. Lifestyle risk factors include low education, low level of physical activity or physical function, increased alcohol intake, smoking, and obesity. To support the presence of cerebrovascular disease, the VASCOG working group suggests that one of the following features should also be present during the physical examination: 1) early presence of gait disturbance (e.g. small step gait or
parkinsonian gait) 21,22; 2) early urinary frequency, urgency, and other urinary symptoms not explained by urologic diseases 22 and; 3) personality and mood changes (e.g. abulia, depression, or emotional incontinence 23. Critically, the demonstration of abnormalities on neuroimaging is necessary for increased certainty in the diagnosis. Evidence for significant vascular pathology relies on either computed tomography (CT) or magnetic resonance imaging (MRI) scans. SIVCI would require the presence of white matter hyperintensities (WMHs) or lacunes of presumed vascular origin 13. In the next section I will review cSVD neuropathology in greater detail.

1.2 Cerebral small vessel disease neuropathology

The main vascular cause of SIVCI is cSVD. Small vessel damage can result from arteriolosclerosis, lipohyalinosis, or fibrinoid necrosis causing abnormality in the wall or lumen of the small vessels in the brain 11. Damage to cerebral small vessels typically cause more chronic, diffuse, and less severe ischemia. On neuroimaging, cSVD predominantly manifests as WMHs or lacunes. Other neuroimaging biomarkers include dilation of perivascular spaces, microbleeds, and microinfarcts. Additionally, histopathology studies suggest that myelin loss is a common and salient feature in cSVD. Moreover, there is a close link between cSVD and AD pathophysiology, resulting in co-existing amyloid-beta (Aβ) plaque accumulation in people with SIVCI. Though there are a variety of cerebral lesions associated with cSVD, this thesis will focus on the effects of WMHs, myelin loss, and Aβ plaques.

1.2.1 White matter hyperintensities

WMHs are one of the predominant pathological manifestations of SIVCI 24. They can occur in the deep white matter (WM) or in periventricular regions. Perfusion to the deep WM relies on
lenticulostriate and long medullary arterioles, which are vulnerable to chronic hypoperfusion. Even more vulnerable, is the WM adjacent to the walls of the lateral ventricles. Periventricular WM is positioned at the distal end zone territory of blood supply from the choroidal arteries, which is a very low-perfusion region and is very susceptible to ischemic injury, as evident by the large volume of WMHs in this region.

WMHs can be imaged using conventional magnetic resonance imaging (MRI) sequences. The term WMH collectively refers to lesions that appear hyperintense on T2-weighted (T2w), proton density weighted (PDw), and fluid-attenuated inversion-recovery (FLAIR) magnetic resonance sequences. WMHs can either be described qualitatively, measured using a semi-quantitative method (i.e., using a rating scale), or measured quantitatively (e.g., volume). Typically, WMHs are described as “caps” on the frontal and/or occipital horns, “pencil-thin lining” surrounding the lateral wall of the ventricles, “halo” surrounding the ventricles, punctate lesions in the deep WM (i.e., deep WMHs), and early confluent or confluent lesions that surround the ventricles and extend into the deep WM (Figure 1.1). WMHs are more extensive in periventricular regions and often appear bilaterally and symmetrically. As the disease progresses, periventricular WMHs extend into the deep WM, but spare areas protected from hypoperfusion (e.g., subcortical U-fibers and the external capsule, claustrum, and extreme capsule). WMHs can also occur in subcortical grey matter (GM) structures, such as the basal ganglia and brainstem. There are differing opinions about whether deep GM or brainstem hyperintensities should be routinely classified as WMHs as they may have differing pathogenesis, risk factors, and clinical consequences. The general consensus, as determined by the Standards for Reporting Vascular
Changes on Neuroimaging, is that lesions in the subcortical GM or brainstem should not be included in the category of WMHs, unless explicitly stated.

![Figure 1.1](image)

**Figure 1.1** White matter changes on FLAIR scans: a) caps; b) pencil-thin lining; c) halo; d) punctate; e) early confluent and; f) confluent lesions.

Evidence from population-based cohort studies indicate that WMHs are progressive in nature (Figure 1.2). In the Rotterdam Scan Study, 39% of the 668 participants showed visible WMH progression after 3 years. The Leukoaraiosis And Disability (LADIS) Study observed WMH progression in 73.6% of the 394 participants after 3 years. In the Austrian Stroke Prevention Study, participants with early confluent and confluent lesions displayed a 2.7 cm³ to 9.3 cm³ median increase, with a maximum increase of 21.0 cm³ after 6 years, whereas participants with no lesions or punctate lesions at baseline had a low tendency for lesion progression. The
annual increase of WMHs in those with early confluent lesions is 0.23 cm\(^3\) and those with established confluent lesions is 1.60 cm\(^3\). Moreover, baseline WMH burden is the strongest predictor of WMH progression, with females showing greater WMH burden at baseline and greater progression compared with males. Critically, the presence and progression of WMHs are associated with both cognitive and physical impairments (this topic is covered in sections 1.4 and 1.5).

**Figure 1.2** White matter changes on T\(_2\)w scans at baseline and 6-month follow-up. Red arrows indicate regions of WMH progression.

Neuroimaging has greatly advanced our understanding of cSVD pathology; however, conventional MRI sequences only allow the examination of macro-structural WM changes, such as WMHs, and cannot specify the WM substrate that is damaged. Pathology studies suggest that
several microstructural changes are involved in these radiologic lesions. Periventricular WMHs exhibit discontinuous ependyma, gliosis, loosening of WM fibers, and general demyelination. Deep WMHs exhibit gliosis, vacuolation, axonal loss around perivascular spaces, and general demyelination. Overall, the majority of studies investigating the pathologic substrate of WMHs have found demyelination to be a salient feature. Below, I provide greater detail regarding myelin loss in cSVD.

1.2.2 Myelin

Cerebral myelin is produced by oligodendrocytes, a glial cell. Oligodendrocytes generate large amounts of myelin by wrapping their cell membrane around an axonal segment in a concentric lamellar fashion. A single oligodendrocyte can myelinate up to 50 axonal segments. Regions of tightly compacted and insulating myelin sheaths are referred to as internodes and regions between the internodes are short unmyelinated segments called nodes of Ranvier. The myelin bilayer is made up of approximately 80% lipid and 20% protein and is composed of repeating and alternating units of major dense lines and intraperiod lines. The major dense line is composed of the cytoplasmic aspects of the oligodendrocyte process. The intraperiod line is a region of extracellular space that has a relatively high water content. Together, the water in the major dense line and the intraperiod line make up the “myelin water”, which can be used as a surrogate marker for myelin content on MRI (this is discussed in greater detail in section 1.3.2). Myelination in the brain begins before birth within the caudal brain stem and progresses rostrally to the forebrain. That is, the brain stem and cerebellar regions myelinate first, then occipito-parieto-frontal sites myelinate, and anterior frontal and temporal sites myelinate last. The most rapid and dramatic period of human central myelination occurs within the first two years of postnatal life. During this time virtually all the WM tracts are laid, but myelination in
the last sites (i.e. frontal and temporal regions) will steadily continue throughout life until the sixth decade 43.

The fundamental function of myelin is to promote saltatory impulse conduction. Voltage-gated sodium channels located at the nodes of Ranvier mediate an action potential, which jumps from one node of Ranvier to another. It is able to do this because the internodal myelin acts as an insulator of high electrical resistance and low conductance 41. The resulting saltatory conduction of action potentials allows high-speed and high-fidelity signal transmission. These properties are necessary in allowing complex motor, sensory, and cognitive functions to occur 44. Thus, intact myelin is critical for communication within and between dispersed brain networks and is necessary for normal human functioning 41,44.

The importance of myelin is underscored by the presence of various diseases characterized by demyelination 45. Demyelination refers to the loss or destruction of previously healthy myelin and can cause nerve dysfunction due to slowed or blocked nerve conduction 41. The most acknowledged demyelinating disease is multiple sclerosis (MS), an autoimmune disease that attacks the myelin of the central nervous system that can result in severe physical impairments (e.g., lack of coordination, loss of balance, weakness in arm or leg, and loss of motor control) 46 and cognitive changes (e.g., memory, executive functions, attention and concentration, information processing, and visuospatial functions) 47. Demyelination has mostly been studied in the context of MS; however, myelin loss is also a feature of cSVD 39,40,48.
In-vitro and in-vivo rodent models have demonstrated several pathways in which WM ischemia can lead to oligodendrocyte death and subsequent demyelination. Ischemia, either acute or chronic, can cause an excessive accumulation of extracellular glutamate, creating an excitotoxic environment. Oligodendrocytes are vulnerable to excitotoxicity. Rodent models show that glutamate activates several receptors (i.e. NMDA and AMPA/kainate receptors) on the oligodendrocyte membrane to allow an influx of Na$^+$ and Ca$^{2+}$ leading to glutamate-induced excitotoxic oligodendrocyte damage and death. Ischemia can also trigger inflammatory cytokines, such as TNF-alpha and IL-1beta, that impair glutamate uptake triggering further excitotoxicity.

In addition, mouse models of bilateral common carotid artery occlusion or stenosis demonstrated that hypoxia reduced the number of oligodendrocytes and was associated with demyelination with axonal damage. The expression of myelin basic protein, a major component of myelin, was also decreased. Moreover, these animals exhibited an increase in matrix metalloproteinase, which is associated with blood brain barrier (BBB) breakdown. Damage to the BBB can cause extravasation of plasma proteins triggering vascular inflammation and demyelination. In turn, demyelination disrupts energy-saving saltatory conduction, which increases metabolic demands and enhances local energy deficits causing further hypoxic damage.

In humans, an autopsy study of 135 brains examining the natural history of cerebrovascular lesions found myelin loss to be a common occurrence, with 63% and 49% of cases exhibiting demyelination in the frontal and temporal cortex, respectively, in older adults (81 years of age ± 7 years). Demyelination can occur within WMHs and also in the ‘normal appearing’ WM
Damage to the NAWM is ‘invisible’ on conventional MRI, such that the tissue appears normal on MRI but exhibit pathological changes. Whether demyelination is associated with cognitive impairment in SIVCI has not been confirmed; however, it has been suggested that demyelination may contribute to cognitive impairment by impairing signal transmission between dispersed neural networks that underlie cognitive processing.

1.2.3 Interaction between cerebral small vessel disease and Alzheimer’s disease pathophysiology

Over the past two decades, accumulating evidence suggests a close link between cerebrovascular disease and AD. The pathological hallmarks of AD include (but are not limited to) extracellular Aβ plaques and neurofibrillary tangles of hyperphosphorylated tau protein. Though AD is the most clinically prevalent cause of dementia, pathology studies often report mixed AD and cerebrovascular pathology. This trend increases with age and mixed AD-VCI is the leading cause of dementia in the very old. The coexistence of neurodegenerative and ischemic pathology can have a profound effect on clinical outcomes. Vascular lesions, including widespread and diffuse myelin breakdown and WMHs, are present in the early stages of AD and may lower the threshold of AD pathology required for the development of dementia.

Moreover, concomitant cerebral infarcts, including WMHs, are associated with greater cognitive dysfunction in people with AD. It is hypothesized that vascular lesions magnify the effect of mild AD pathology resulting in more severe cognitive impairment. Thus, coexisting ischemic lesions may shorten the preclinical stage of AD and accelerate disease progression.

The high prevalence of co-existing AD and vascular pathology may be attributed to the close interaction between cerebrovascular and AD pathophysiology. Abnormalities in the cerebral
vasculature may contribute to the pathogenic changes in AD, including decreased cerebral perfusion, reduction of glucose transport and utilization, loss of vascular innervation (i.e., cholinergic transmitters), impairment of neurogenic cerebrovascular regulation, ultrastructural changes in capillaries and basement membranes, disruption of the neurovascular unit, and breakdown of the BBB. An important function of the BBB is to regulate the movement of Aβ peptides between the brain, plasma, and cerebrospinal fluid (CSF). Typically, the concentration of Aβ peptides in these three compartments is in equilibrium and the influx of soluble Aβ across the BBB is modulated by its interaction with the receptor for advanced glycation end products and the efflux of Aβ peptides is controlled by the low-density lipoprotein receptor on brain endothelial cells. Evidence from human and animal models of AD suggest that AD brains may suffer from an increase in influx receptors and/or a decrease in efflux receptors causing greater Aβ peptide accumulation within the brain. This suggests that cerebral ischemia may be a powerful modulator in amyloidosis.

In turn, Aβ peptide accumulation may disrupt cerebrovascular function. It has been suggested that the accumulation of Aβ peptides threaten cerebrovascular function by inducing oxidative stress, up-regulating inflammatory mediators, compromising cerebral perfusion, and reducing vascular reserves (the ability of the cerebral blood vessels to respond to stimuli) – these factors increase the propensity for ischemic damage. In turn, hypoxia and/or ischemia up-regulates the expression of amyloid precursor protein and promotes the cleavage of Aβ peptides from the amyloid precursor protein by up-regulating β- and γ-secretase activity. Together, these studies suggest that there is a positive feedback mechanism between cerebrovascular dysfunction and Aβ formation.

The neurovascular unit refers to the interactions among glial, neuronal, and vascular elements.
peptide accumulation that results in greater Aβ peptide accumulation. Figure 1.3 summarizes the interaction between SIVCI and AD.

Figure 1.3 Interaction between SIVCI and AD pathophysiology.

1.3 Neuroimaging cerebral small vessel disease pathology

Advances in MRI technology have significantly contributed to our understanding of SIVCI pathology. Below, I will review the neuroimaging techniques relevant to this thesis. First, I will review conventional MRI techniques (e.g. T₁w, T₂w, PDw, and FLAIR images) that allow us to visualize and quantify macro-structural changes in the brain such as WMHs. In addition, I will review myelin water imaging (MWI) as this technique can provide insight into the underlying micro-structural damage associated with demyelination. Due to the close interaction between AD and cSVD pathology, I have also included the use of positron emission tomography (PET) for
imaging Aβ plaques as the co-existence of Aβ plaques can affect SIVCI outcomes. Below is a brief review of each imaging technique.

**1.3.1 Imaging white matter hyperintensities**

Due to a higher water content, WMHs have different relaxation times compared with healthy WM and emit a higher signal that appears hyperintense on T2w, PDw, and FLAIR images. These three images can be used in conjunction to refine WMH identification. For example, FLAIR images are particularly advantageous because the inversion pulse can null the signal of CSF allowing greater contrast in periventricular regions. The GM signal is also reduced resulting in a homogenous low background signal that allows greater contrast between lesions and the surrounding brain. T2w images display WM damage as hyperintense against the low signal background of WM. However, periventricular lesions are often indistinguishable from the adjacent CSF, which also produces a high signal on T2w images. Identification of WMHs on T2w images can be improved by using them in conjunction with PDw images. On PDw images the CSF signal is lower than periventricular WMHs. Typically, T2w and PDw images can be acquired simultaneously to provide complimentary information (Figure 1.4) 66.
WMHs can be measured using a semi-quantitative visual rating scale or by computational quantitative image analysis measurements of lesion volume. Both techniques have advantages and disadvantages. Numerous visual rating scales have been described that are heterogeneous in range and morphological description (e.g., diameter of lesions or anatomic distribution of hyperintensities [i.e., periventricular or deep WMHs]) in the [73,75]. As an advantage, visual rating scales can be more easily applied to large longitudinal multicenter studies as minor differences in image acquisition are unlikely to affect the visual rating while volumetric analysis requires much more strict guidelines in image acquisition [74,75]. Critically, visual rating scales show high correlation with WMH volume. As a limitation, visual rating scales are unreliable in
people with high WMH volume. That is, the variability in WMH volume is large in people with high visual scores and this may lead to decreased correlation with clinical data \textsuperscript{76}. In addition, visual rating scales can also be insensitive to longitudinal changes \textsuperscript{77,78}. Numerous computational quantitative semi-automated methods have also been developed \textsuperscript{70-72}. However, some methods are better able at distinguishing artifacts (i.e., any non-WMHs) from true WMHs than others and to avoid segmentation errors the user should still inspect the images. As an advantage, automated volumetric methods provide the most objective information. The decision on the best-suited method depends on the type of research, number of scans to analyze, type of scans, resources available, etc. \textsuperscript{27}. Within this thesis, we used both a semi-quantitative visual rating scale and volumetric measurements to study WMHs.

Three commonly used visual rating scales are the Fazekas (range 0 to 3 for global WMH burden) \textsuperscript{67}, Scheltens (13 subcortical regions are given a score between 0-6 and 3 periventricular regions are given a score between 0-2 for a sum score that ranges between 0 and 84) \textsuperscript{68}, and the Age-Related White Matter Changes (5 regions in the left and right hemisphere are given a score between 0-3 for a sum score that ranges between 0 and 30) scale \textsuperscript{69}. These scales are highly correlated with each other, have good intra-rater and inter-rater agreement, and are correlated with WMH volume \textsuperscript{77,79}. Within this thesis, I decided to use the Fazekas scale \textsuperscript{67} as it is commonly used and is correlated with quantitative volumetric measurements (Kendall W = 0.57; p < 0.001) \textsuperscript{77}. Based on the Fazekas scale, the grading of periventricular WMH was defined as: grade 0 = absence; grade 1 = ‘caps’ or pencil-thin lining; grade 2 = smooth ‘halo’ and; grade 3 = irregular periventricular hyperintensities extending into the deep WM; the grading of deep WMH was defined as: grade 0 = absence; grade 1 = punctate foci; grade 2 = beginning confluence of
foci and; grade 3 = large confluent 67 (Figure 1.5). The LADIS study found that WMH volume for each Fazekas grade was significantly different 76. Furthermore, WMH volume and the Fazekas scale show comparable associations with widely used clinical measures for both physical (i.e., Short Physical Performance Battery [SPPB]) and cognitive (i.e., MMSE) outcomes.

![Figure 1.5](image.png)

**Figure 1.5** Examples of Fazekas grade on T2w images: a) Fazekas 1; b) Fazekas 2; c) Fazekas 3.

To obtain lesion volume, I used a method published by McAusland and colleagues 71. Briefly, this is a semi-automated method that uses T2w and PDw scans as inputs. Prior to lesion identification and segmentation, several preprocessing steps are performed including: 1) MR intensity inhomogeneity correction using a multiscale version 80 of the nonparametric non-uniform intensity normalization method (N3) 81; 2) application of a structure-preserving noise-removal filter (Smallest Univalue Segment Assimilating Nucleus) was applied 82 and; 3) removal of all non-brain tissues were removed using the brain extraction tool 83.
After preprocessing, scans undergo two separate segmentation streams. In one stream, automatic
WM, GM, CSF points are generated on a T\textsubscript{2}w/PDw ratio image using their intensity
distributions. In another stream, seed points are manually placed on either T\textsubscript{2}w or PDw images
for WMH lesion identification. The radiologist/neurologist is asked to use the following
guidelines in the seeding procedure, which was designed to be efficient and intuitive: 1) mark all
distinct WMH regardless of size; 2) place more than one point on a lesion if the additional points
would help define the extent of the lesion and; 3) place at least one point near the center of each
lesion. These points are used in a semi-automatic region-growing method to segment each lesion.

The results from each stream are then combined for further processing. Points for WM, GM,
CSF, and WMHs are then fed into a Parzen window classifier to compute the probability density
function (PDF) of each tissue type – the PDF expresses the probability that a voxel/tissue with a
given intensity value belongs to a certain tissue class. Generally, the classifier is attempting to
find the optimal boundaries between the lesion clusters and the other tissue types in a 2D (T\textsubscript{2}w
and PDw) histogram space. To do this, each slice is processed with two adjacent slices (i.e., the
slice before and the slice after). Three slices are chosen to estimate lesion distribution because
most lesions are less than 10mm in diameter, and three slices at 3mm thickness would span most
lesions centered on the middle slice. A 10mm slab would also help to avoid inaccuracies in PDF
estimation due to MR field inhomogeneity and natural variations in tissue intensities. For each
slice, all voxels with the highest probability of being a lesion (based on their intensity) are
grouped together and regions without a radiologist-placed seed point are removed as false
positives (i.e., areas with partial volume).
McAusland and colleagues \textsuperscript{71} developed three additional heuristics to optimize the use of manually placed seed points. The first heuristic was developed to correct positional errors in seed point placements. This algorithm corrected each manually placed seed point position by searching for the brightest voxel in its surrounding vicinity. These seed points are then moved to the brightest voxel as this point represents the purest lesion content. This algorithm prevents an incorrect skew/shift of the estimated lesion intensity distribution for more accurate PDF calculations. The second heuristic dynamically adjusts the number of sample points used for lesion segmentation. As previously stated, the Parzen window is set to use a contiguous slab of three slices; however, this may not contain a sufficient number of seed points for an accurate PDF calculation. This is a potential issue as the Parzen window method aims to estimate a continuous distribution function from discrete sample points; thus, the number of points used can strongly influence the computed PDF. To ensure that there are sufficient lesion points, this algorithm will allow additional slices to be added to the slab (on both sides of the center point) until a minimum number of points are available for accurate PDF calculation (a minimum of 5 points has been found to give the best results). The third heuristic acts to use the corrected seed point position to refine the shape of the lesions to reduce false positives. This algorithm divides each segmented region at angled narrowings so that voxels that do not connect to any radiologist points via a straight line without crossing a boundary are removed from the calculated lesion volume. There are two reasons for this. First, it is hypothesized that the radiologist would place a seed point in each visually distinct sub-region (which is based on basic concepts of shape perception), so sub-regions without seed points should be excluded from the analysis. Second, many false-positive regions lie in relatively thin structures, such as cortical GM or partial volume at the WM/CSF interface that snake away from the true lesion as they follow the curves of the
cortex or ventricles. The exclusion of these sub-regions would result in a more accurate lesion volume calculation.

To summarize, two of these heuristics were designed to improve seed point positions and to ensure that the number of seed points used by the Parzen window computation is sufficient – these heuristics will improve the estimated PDFs. The third heuristic was developed to constrain the spatial distribution of the lesion to avoid including regions that are likely false-positives. This segmentation method was tested and validated in a large clinical trial in relapsing-remitting MS composed of 234 PDw/T2w MRI pairs from 29 different scanning sites. Importantly, this data set included a wide range of lesion loads. The researchers found that the addition of these three heuristics greatly enhanced the performance of the segmentation method, particularly in scans with the lowest lesion load. This is particularly advantageous because most other segmentation programs show reduced segmentation accuracy when applied to scans with low lesion loads. For this reason, we have chosen to use the method by McAusland and colleagues as our cohort consists of people in the milder stage of SIVCI. Figure 1.6 provides an example of WMH segmentation.
1.3.2 Myelin imaging

Changes in myelin content can be estimated, to varying levels of specificity, with a number of MR techniques, including diffusion tensor imaging (DTI), magnetization transfer imaging (MTI) and MWI. DTI metrics such as mean diffusivity ($MD$), fractional anisotropy ($FA$), axial diffusivity, and radial diffusivity measure the movement of water within cerebral tissue and are unable to specify the WM substrate producing the observed signal. DTI metrics nonspecifically reflect microstructural complexity, membrane permeability, fibre density, axonal diameter, and

2 MD describes the mean diffusion coefficient of water molecules independent of any tissue directionality.
3 FA is a scalar value between zero and one that describes the degree of anisotropy of a diffusion process. A value of zero represents isotropic diffusion (i.e., unrestricted/equally restricted in all directions). A value of one represents diffusion along one axis that is fully restricted along all other directions.
4 Axial diffusivity describes the mean diffusion coefficient of water molecules diffusing parallel to the tract.
5 Radial diffusivity is the magnitude of water diffusion perpendicular to the tract.
myelination. MTI provides contrast based on the magnetization exchange between proton pools: 1) a motionally restricted pool that arises from non-aqueous tissue (i.e., which consists of less mobile semi-solid protons attached to macromolecules) and 2) a mobile pool from all MR visible water (i.e., of which myelin water makes up about 10%). Signal from the motionally restricted pool is not visible on an MR image due to the very short T2 relaxation time. However, the motionally restricted pool can be imaged indirectly. This is done by applying a radio frequency saturation pulse that only saturates the motionally restricted pool and does not affect the signal from the mobile water protons. This will cause a magnetization exchange between any mobile water protons in contact with the semi-solid pool, in such a way that the mobile proton pool undergoes a loss in signal. Under the assumption that that most of the macromolecular content in the brain is myelin, MTI can be used as an indirect assessment of myelin content. The effect of magnetization is quantified as magnetization transfer ratio (MTR). Decreased MTR can represent a decreased content in the semi-solid proton pool caused by damage to myelin or other cellular components, but it can also represent an increase in the mobile pool as a result of inflammation and edema. Overall, MTR is strongly influenced by inflammation and edema and is not specific to myelin content. Though DTI and MTI techniques have been used to study myelin, these approaches are inherently limited in their specificity for myelin content.

In contrast to DTI and MTI, MWI is an MR technique that provides myelin-specific signals. This technique allows us to probe specific water environments by using multi-echo T2 relaxation times to separate the signal of mobile protons into different water pools based on their T2 relaxation time. Previous in-vivo work showed that mobile protons in the human brain can
be separated into three compartments: 1) a very long T2 component of approximately > 2 s arising from CSF; 2) an intermediate component of approximately 60 ms arising from intra- and extra-cellular water and; 3) a short T2 component of approximately < 40 ms arising from myelin water trapped tightly between the myelin bilayers. Because myelin water is representative of the total myelin composition, MWI signals are specific to myelin within the brain. Using MWI, myelin is quantified as the ratio of myelin water to total water termed myelin water fraction (MWF – Figure 1.7) – lower MWF values represents reduced myelin content 92,93. MWI has been used to study myelin content in a number of diseases including MS 89,94,95, schizophrenia 96, phenylketonuria 97, and AD 98.

Figure 1.7 Quantification of myelin as MWF (© 2010 Cornelia Laule, with permission)

Critically, MWF correlates with myelin content better than other MR measures of myelination, such as DTI or MTR 93,99-101. Strong quantitative histopathologic correlations have been reported between MWF and myelin content in healthy and injured rat sciatic nerve 101 and postmortem
brain samples of people with MS. In MS, myelin histology stains show strong correlations with MWF acquired in 1.5T (R² = 0.67) and 7T scanners (R² = 0.78), validating MWF as a measure of myelin density. However, we note that MS and cSVD have different pathophysiological processes. Currently, no studies have histologically validated the use of MWI in ischemic WM disease and it is unclear whether MWF is sensitive to demyelination in cSVD. As another limitation, MWI is prone to relatively higher variability that may stem from the low signal-to-noise ratio, partial-volume contamination, or the difficult nature of multiexponential analysis. Notwithstanding these limitations, MWI currently provides the most specific measure of myelin within the nervous system.

1.3.3 Amyloid-beta plaque imaging

PET is a nuclear imaging technique that can be used to image Aβ plaques in-vivo. PET utilizes biologically active molecules labeled with short-lived positron-emitting isotopes called tracers. The successful use of a PET tracer requires that a sufficient amount cross the BBB over a reasonable time period. In addition, the imaging agent should have sufficient affinity for the target so that a large fraction of the tracer remains bound to the target while the majority of the free and non-specifically bound tracer clears from the brain over a period of time that is practical. As the radioactive tracer decays, it releases a positron that will collide with an atomic electron in its immediate vicinity and cause an annihilation reaction. PET scanners are designed to detect and localize these annihilation events making it possible to image and measure biochemical processes.

Currently, the most well studied radioactive tracer for imaging Aβ plaques is 11C-labelled Pittsburgh compound B (11C-PIB). 11C-PIB attaches itself to the amyloid ‘receptor’, this
‘receptor’ is a polymer composed of Aβ peptide subunits that forms the amyloid fibril. The polypeptide backbone of each Aβ peptide in the fibril is folded into a β-pleated sheet or a cross β-structure. The unique stereochemistry of this β-pleated sheet allows 11C-PIB to specifically bind to the fibrils (amyloid plaques) and not diffuse amyloid (oligomeric species) or to neurofibrillary tangles. Currently, other tracers are available to image Aβ plaques, such as 18F-florbetapir, 18F-florbetaben, and 18F-flutemetamol; however, 11C-PIB is the most validated and used radioactive tracer to image Aβ plaques.

1.4 Cognitive function in cerebral small vessel disease

Cognitive impairment in SIVCI has primarily been studied in association with WMHs. However, it is important to note that not all persons with WMHs have clinical complaints and that WMHs are common in the general population occurring in 80% of healthy 60 year-olds and more than 90% of healthy 80 year-olds. Nonetheless, WMHs have been associated with increased risk of stroke, cognitive impairment, and dementia.

Several large population studies have reported a significant association between WMHs and cognitive impairment. For example, cross-sectional data from the Cardiovascular Health Study, Framingham Heart Study, Rotterdam Scan Study, and LADIS Study report an association between increased global WMH burden and decreased cognitive performance. Specifically, the Cardiovascular Health Study found that greater WMH severity was associated with decreased performance on global cognition and processing speed. The Framingham Heart Study found that people with greater WMH volume performed worse on cognitive tests.
compared with people with little to no WMH volume – cognitive measures included: set shifting, new learning, visuospatial memory, and organization. In assessing the effects of region specific WMHs, the Rotterdam Scan Study found that periventricular and deep WMHs were separately correlated with worse cognitive function across several domains including: global cognition, memory, and psychomotor speed. When periventricular WMHs were analyzed controlling for the effect of deep WMHs and vice versa, the relationship between periventricular WMHs remained significantly associated with all cognitive measures whereas deep WMHs showed no significant associations with cognitive measures. Several published results from the LADIS Study report an association between greater WMH severity with increased cognitive decline measured by the MMSE, Alzheimer’s Disease Assessment Scale-Cognitive Subscale (ADAS-Cog, which is a comprehensive measure that assesses orientation, language, ideational and constructional praxis, immediate memory, and delayed recall), Vascular Dementia Assessment Scale-Cognitive Subscale (VADAS-Cog, which includes ADAS-Cog measures with the addition of delayed recall, symbol digit substitution, digit span, mazes, digit cancellation, and verbal fluency), and executive functions. In support of these results, a meta-analysis found that the presence of WMHs affected performance across several cognitive domains, including: general intelligence, perception/construction, language, memory, attention, processing speed, and executive functions. Furthermore, the presence of WMHs is associated with greater declines in global cognition, attention, processing speed, and executive functions over time. Most studies indicate that periventricular WMHs are more closely associated with cognitive decline than deep WMHs.
Studies assessing WMH progression on changes in cognitive function have found similar results. The Cardiovascular Health Study (a 5-year follow-up study) and the Rotterdam Study (a 3-year follow-up study) found that WMH progression was associated with decreased global cognition and information processing speed, but not memory over time – these associations were significant with changes in periventricular WMHs, but not deep WMHs. In contrast, the Austrian Stroke Prevention Study, which included a 3-year and 6-year follow-up, found an association between WMH progression and changes in memory, but not in processing speed or attention. Additionally, the Austrian Stroke Prevention Study found that WMH progression was associated with changes in conceptual reasoning and visuopractical skills (all associations were no longer significant after accounting for brain atrophy). Furthermore, two meta-analyses assessing prospective studies with longitudinal data suggested that WMH progression was most consistently associated with declines in global cognition, processing speed, and executive functions.

Cognitive decline in SIVCI may also be attributed to other pathologic changes, but at this time less is known about the impact of other cSVD neuroimaging biomarkers on cognitive function. The available literature suggests that lacunes, cerebral microbleeds, and enlarged perivascular spaces can independently contribute to cognitive impairment, particularly affecting processing speed and executive functions. In a study that included several cSVD neuroimaging biomarkers, WMHs impacted more cognitive domains – including processing speed, executive

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6 A systematic review identified more than 100 terms used to describe lacunes of presumed vascular origin and the definition for a lacune can range from > 3mm, 3mm to 15mm, or 20mm, and some studies simply state “silent brain infarcts” without further clarification. Because the definition and terminology describing lacunes vary across different publications, it is difficult to summarize this literature.
functions, language, and visuospatial skills – compared with lacunes, enlarged perivascular spaces, and cerebral microbleeds. However, lacunes, cerebral microbleeds, and enlarged perivascular spaces were also associated with measures of processing speed and executive functions. In statistical models that included cSVD markers as competing predictors of cognitive function, the effects of WMHs were generally attenuated and enlarged perivascular spaces accounted for the greatest variance in cognitive performance compared with all other cSVD neuroimaging biomarkers 124. Though WMHs are a significant contribution to cognitive impairment in cSVD, these results highlight the importance of assessing other cSVD biomarkers to fully elucidate the effect of cSVD pathology on cognitive impairment.

An important, but often overlooked feature of cSVD pathophysiology, is its interactions with Aβ pathophysiology. Previous studies assessing the impact of Aβ plaque deposition on cognitive function have focused on healthy older adults and people with MCI and AD 125,126, while studies in people with SIVCI are more limited 127-129. Data from the Amyloid PET Imaging for Subcortical Vascular Dementia Study found that higher Aβ plaque deposition in people with cSVD was associated with impairments in multiple domains of cognitive function including visuospatial function, memory, and executive functions 128,129. A study conducted by our own group found that increased Aβ plaque deposition was significantly associated with worse global cognitive performance as measured by the ADAS-Cog and MoCA 127. Together, these cross-sectional results point to the deleterious impact of Aβ plaque deposition, even among those with a primary SIVCI diagnosis. As such, it is important that we continue these lines of inquiry and assess the long-term effects of Aβ plaque deposition on cognitive function.
In summary, the presence and progression of WMHs are consistently associated with cognitive decline, with the most pronounced effect on processing speed and executive functions. However, recent studies suggest that WMHs are not the only form of ischemic injury that can contribute to cognitive impairment. Thus, it is important that we consider the effect of other pathological changes in cSVD. As indicated in section 1.2.1, histopathology studies report that myelin loss is a major component of the microstructural changes in cSVD. Though myelin is critical for cognitive processing, the effect of myelin loss in SIVCI is currently unknown. In addition, it is important to consider co-existing AD pathologies, particularly Aβ plaque pathology, as it may exacerbate clinical symptoms in SIVCI. Assessing the contribution of these pathologic changes will broaden our understanding of cognitive impairment in SIVCI.

1.5 Physical function in cerebral small vessel disease

SIVCI is predominantly characterized by cognitive symptoms; however, impaired physical function is also observed in the clinical presentation of SIVCI 11. Specifically, patients present with an early gait disturbance, which may manifest as unsteadiness and frequent falls 11. This clinical picture is supported by research, which has provided evidence for an association between WMHs and impaired gait, balance, and mobility and increased falls risk. For example, the LADIS Study, a large population study aimed at understanding the role of WM changes in functional status and disability in older adults, found that moderate to severe levels of WMHs at baseline were cross-sectionally associated with worse performance on measures of gait and balance (measured using the SPPB), single leg stance time, and gait speed 130. The LADIS Study also reported that greater WMH severity at baseline was associated with greater deterioration in
SPPB performance over a 3-year period. These results are supported by the Cardiovascular Health Study, which found that more severe levels of WMHs lead to a greater decline in gait speed over a 4-year period. Moreover, a systematic review found consistent evidence of an association between greater WMH volume and impaired gait (e.g. shorter step length, increased double support time, and slowed gait initiation, and slow gait speed), reduced balance control (i.e. single leg stance, balance on force plates, and postural stress test [stability following a waist pull]), and impaired mobility (e.g. Tinetti Performance Oriented Assessment of Mobility, SPPB, and timed 5 chair stands), despite considerable methodological differences.

WMHs are also associated with a higher frequency of incident falls and falls risk. Cross-sectional studies generally report that fallers have greater WMH volume compared with non-fallers. Data from the LADIS study found that greater WMH severity was significantly associated with a greater number of falls in the 1-year period prior to study inclusion. A prospective population study showed an association between greater baseline WMH volume and a higher number of incident falls and the risk of incident falls was doubled in people with lesion volumes in the highest quintile compared with those in the lowest quintile over a 12-month period. These results were mirrored in another prospective study that found that people with higher levels of WMHs had a 55% greater risk of suffering multiple or injurious falls compared with people with mild levels of WMHs during a 12-month follow-up period. In assessing the region-specific effects, data from the LADIS Study found that periventricular WMHs and deep frontal WMHs were associated with increased falls risk.
In assessing the effects of other cerebrovascular lesions on physical function, one study found that WMH volume and total cSVD burden (i.e., WMHs, lacunes, microbleeds, enlarged perivascular spaces, and brain atrophy) were significantly associated with gait speed; however, lacunes, microbleeds, and enlarged perivascular spaces did not independently predict gait speed \(^{136}\). Another study found that WMHs, but not lacunes, cerebral microbleeds, or enlarged perivascular spaces, were significantly associated with motor performance in upper (i.e., 10-repeat pronation-supination time and 10-repeat finger-tapping time) and lower extremity (i.e., 3-m walking speed and 5 chair-stands) function in community-dwelling older adults \(^{137}\). Together, these findings suggest that WMHs are one of the main contributors to impaired physical function in SIVCI.

However, research indicates that Aβ plaque deposition may also affect physical function. One autopsy study reported that Aβ plaque deposition was associated with declining gait speed over an average follow-up time of 6.4 years prior to death \(^{138}\). A cross-sectional analysis of the Mayo Clinic Study of Aging found that higher global Aβ plaque deposition was associated with slower gait speed, lower cadence, longer double support time, and greater stance time variability in cognitively normal individuals \(^{139}\) – this study controlled for AD associated neurodegeneration, such as cerebral glucose uptake, hippocampal volume, and cortical thickness, but not WMH burden. Furthermore, a 12-month prospective study found that people with preclinical AD who have higher Aβ plaque deposition are more likely to have a fall – this study also did not control for WMH burden \(^{140}\). Given the close association between cSVD and AD pathophysiology and the established link between WMHs and gait, it is important that we also consider the effect of
co-existing Aβ plaque deposition on physical function, independent of WMHs, in people with cSVD.

1.6 Role of aerobic training in mitigating cerebral small vessel disease

There is mounting evidence to suggest that regular physical activity or exercise is a promising strategy to combat cSVD. Physical activity refers to any bodily movement produced by skeletal muscles that require energy expenditure. Exercise is a subcategory of physical activity that is planned, structured, repetitive, and purposive to improving or maintaining physical fitness. Generally, there are two main types of exercise: 1) aerobic training (AT), which targets cardiovascular fitness and; 2) resistance training (RT), which targets muscle mass and strength. This thesis will focus on the effects of AT as there is evidence to suggest that AT may be a promising strategy to mitigate the progression of SIVCI and in the sections below I will review this literature. First, section 1.6.1 will review the role of AT in reducing the risk for cognitive decline and section 1.6.2 will review the role of biological sex as a key moderator of AT efficacy. Section 1.6.3 will review the role of AT in promoting brain health. Lastly, section 1.6.4 will review the potential for AT to mitigate vascular injury associated with cSVD.

1.6.1 Aerobic training is beneficial for cognitive function

Results from several large prospective cohort studies suggest that staying physically active may prevent cognitive decline and dementia onset. For example, the Nurses' Health Study in women (follow-up of up to 15 years) and the Honolulu-Asia Aging Study in men (follow-up of over 30 years) found that higher levels of physical activity, specifically walking, was associated with better cognitive performance and lower risk of cognitive decline. The Canadian
Health and Aging Study found that engaging in regular physical activity may delay or prevent
the onset of cognitive impairment and dementia, particularly in older women. These results are
supported by a meta-analysis of 15 prospective studies. This meta-analysis found that low to
moderate levels of physical activity at baseline reduced the risk of cognitive decline by 35% and
high levels of physical activity at baseline reduced this risk by 38% in older adults without
dementia. In addition, a meta-analysis of 16 prospective studies on the incidence of
neurodegenerative diseases found that higher levels of physical activity was associated with a
reduced risk of all-cause dementia by 28% and AD by 45%. More recently, an analysis of the
Health, Aging, and Body Composition Study found that maintenance of physical activity,
defined as time spent walking, over 10 years was associated with less declines in global
cognition in men and women, and less declines in processing speed and executive functions in
women. Overall, longitudinal studies indicate that increased physical activity, particularly
aerobic activity, may delay cognitive decline.

Moreover, results from observational studies are supported by randomized controlled trials
(RCTs). Evidence from RCTs suggest that AT may be beneficial for cognitive function in both
healthy older adults and people with cognitive impairment. In cognitively healthy but low fitness
older adults, Kramer and colleagues found that 6 months of AT improved executive functions
compared with a stretching-and-toning control group. Among older adults with subjective
cognitive complaints, Lautenschlager and colleagues found that 6 months of moderate
intensity physical activity (predominantly involving AT) improved global cognition compared
with an education and usual care control group. In people with MCI, a study by Baker and
colleagues found that a 6-month AT program improved executive functions compared with a
stretching control group. This study also reported that AT had more pronounced benefits for women than men despite comparable gains in cardiovascular fitness. Additionally, in women with probable MCI, Nagamatsu and colleagues found that 6 months of AT or RT improved spatial memory performance and executive functions compared with a balance-and-tone control group.

Only one published RCT has specifically assessed the impact of exercise in people with a clinical SIVCI diagnosis. The Promotion of the Mind Through Exercise (PROMoTE) Study conducted by Liu-Ambrose and colleagues demonstrated that a 6-month moderate intensity AT program improved general cognitive function, as measured by the ADAS-Cog, in people with mild SIVCI. Improved cognitive performance was associated with reduced diastolic blood pressure suggesting that reduced blood pressure may be a pathway by which AT promotes cognitive health in SIVCI.

Though several RCTs have reported improved cognitive performance with exercise training, particularly AT, some reports have indicated that exercise may not improve cognitive function. The Lifestyle Interventions and Independence for Elders randomized trial, the largest and longest RCT to assess the effect of exercise (i.e., walking, RT, and flexibility exercises) on cognitive function in sedentary older adults with no cognitive impairment, found that a 24-month moderate-intensity exercise intervention did not result in better global or domain specific cognition compared with a health education program. However, the exercise intervention in the Lifestyle Interventions and Independence for Elders Study did not meet exercise prescription guidelines outlined by the American College of Sports Medicine for older adults and the exercise
prescription may have been insufficient to produce changes in cognitive function 161. Similarly, a meta-analysis of exercise training RCTs in people with MCI found that the majority of outcomes were non-significant providing no strong or consistent evidence that exercise improves cognitive function in MCI. However, the authors note that there were methodological problems in defining MCI, exercise prescription, blinding, inadequate sample sizes, and not reporting dropout rates or compliance 157. A systematic review of seven good or moderate quality RCTs found that exercise training was associated with positive outcomes in global cognition, attention, and executive functions in people with MCI 158. In addition, other systemic reviews of RCTs have indicated that exercise, particularly AT, is beneficial for global cognition and executive functions in healthy older adults 162-164. Overall, there is accumulating evidence to support the efficacy of AT in mitigating cognitive decline; however, the negative results within this literature suggests that the effects of AT may be moderated by other factors.

1.6.2 Biological sex may moderate the effect of aerobic training

Evidence suggests biological sex (i.e., female or male) is a key moderator of exercise efficacy 165. As previously mentioned, the Canadian Health and Aging Study 148 and the Health, Aging, and Body Composition Study 151 and an RCT by Baker and colleagues 154 found that AT was more cognitively beneficial for women. In addition, a secondary analysis of the PROMoTE Study found that sex moderated the effect of AT on executive functions in older adults with SIVCI. Compared with the control group, AT significantly improved set-shifting performance in women, but not men, at trial completion. Moreover, improved executive performance was retained in AT females at the 6-month follow-up period (i.e., 6 months after the intervention was completed) 166. Together, these studies suggest that AT may be more cognitively beneficial for females.
The presence of sex differences is further supported by meta-analytic studies. A meta-analysis of 18 RCTs conducted by Colcombe and Kramer 163 found that studies with more women (> 50%) showed larger effect size (Hedges’ g = 0.60) for AT on cognitive function than studies with fewer women (< 50%). These results were confirmed in a more recent meta-analysis conducted by Barha and colleagues 162 that reported greater beneficial effects of AT, RT, and multimodal training (i.e., combined AT and RT) for executive functions in women. That is, studies with a higher percentage of women participants (> 71%) showed a larger effect size (Hedges’ g = 2.06) of exercise training on executive functions. Together, these meta-analyses suggest that women may benefit more than men from exercise training, particularly AT. Notably, results from the PROMoTE Study suggests that biological sex differences in AT efficacy are present in people with SIVCI and studies assessing the impact of AT in SIVCI should consider a sex-stratified analysis.

Sex does not only moderate the effects of AT on cognition, but sex may also influence the regulation of neurotrophic factors by exposure to sex hormones 167. For example, the regulation of brain-derived neurotrophic factor (BDNF), which is important for neuronal health, survival, and plasticity 168,169, fluctuates across the estrus (in rodents) and menstrual (in humans) cycles 170. Specifically, an increase in estradiol concentration is associated with greater BDNF expression 170. Moreover, within the hippocampus, a region important for learning and memory, BDNF expression is sex dependent with estradiol up-regulating and testosterone suppressing BDNF levels 171. Also, results from a meta-analysis of 9 studies suggested that AT was more effective at increasing BNDF levels in female rodents than male rodents 172. Human studies have
also indicated sex differences in BDNF regulation in response to exercise, but the nature of this relationship remains equivocal [173,174] – this topic is further discussed in section 1.6.4.2.

There are also sex differences in physiological adaptations to exercise. This may stem from inherent anatomical sex differences in lung size and volume, airway diameter, diffusion surface, and maximal flow rates that affect exercise capacity across the lifespan [175,176]. For example, the lungs experience mechanical constraints to ventilation during exercise with aging [177], which may be more pronounced in females. Older women experience lower maximal ventilatory reserve and report higher levels of dyspnea (a subjective experience of breathing discomfort) at standardized work rates than age-matched men [178,179]. Also, men have a higher aerobic capacity (i.e., VO2 max) than women through most of the adult lifespan [180,181]. In addition, several studies report sex-specific vascular responses to exercise (endothelial function is further discussed in section 1.6.4.3), with more beneficial effects for men than women [182-184]. Regular aerobic activity was shown to prevent or mitigate age-related endothelial dysfunction in older men [182,183], but this has not been consistently shown in older women [184]. One study found that AT increased flow-mediated dilation in the brachial artery of older men, but not in older post-menopausal women [183]. This is supported by a study that reported that neither AT or RT had an effect on brachial flow-mediated dilation in sedentary, normotensive, post-menopausal women [184]. Together, these studies suggest that benefits in cardiovascular and endothelial function in response to AT may be more potent in males than females.

1.6.3 Aerobic training and brain health

In this section I will provide evidence that suggests that AT has the potential to evoke changes in brain morphology and mitigate cSVD disease progression, particularly WMHs. I will start by
reviewing the role of AT in modifying brain volume, brain function, and WM integrity. I will conclude this section by providing preliminary evidence suggesting that AT may be a promising strategy to mitigate WMH progression.

### 1.6.3.1 Brain volume

Seminal work by Colcombe and colleagues demonstrated that higher cardiovascular fitness was associated with less atrophy in GM (i.e., prefrontal, superior parietal, and temporal cortices) and WM (i.e., anterior tracts and transverse tracts connecting frontal and posterior parietal lobes) regions. In a subsequent RCT, Colcombe and colleagues showed that a 6-month AT program significantly increased GM and WM volume in prefrontal and temporal brain regions in older adults. These regions are particularly susceptible to age-related brain atrophy. Another RCT demonstrated that a 12-month AT program significantly increased hippocampal volume (by 2%) in community dwelling older adults. Increased hippocampal volume correlated with improvements in spatial memory performance. ten Brinke and colleagues extended these findings by demonstrating that a 6-month AT program significantly increased left, right, and total hippocampal volume, as well as verbal learning and memory compared with a control balance-and-tone program in older women with probable MCI. In an SIVCI cohort, ten Brinke and colleagues found that improved functional cardiovascular fitness, derived from a 6-month AT program, was associated with maintenance of cortical thickness over time. Moreover, change in cortical thickness of the right superior frontal gyri was positively correlated with changes in psychomotor speed. Together, these studies demonstrate that AT can modify brain volume to improve cognitive function.
1.6.3.2 Brain function

Evidence suggests that AT may modify brain function, as measured by functional MRI (fMRI) and is used to determine which parts of the brain are involved during cognitive processing. fMRI is a neuroimaging technique that measures changes in cerebral blood flow (CBF) and is used to determine which parts of the brain are involved during cognitive processing.

In a cross-sectional study assessing the effect of cardiovascular fitness (i.e., VO2 max) on brain function, Colcombe and colleagues found that high-fit older adults demonstrated greater activation in attentional control areas (i.e., middle frontal gyrus, superior frontal gyrus, and superior parietal lobe) and less activation in the anterior cingulate cortex compared with low-fit older adults. In a follow-up RCT conducted by the same authors, participants in the 6-month AT group, compared with the stretching-and-toning control group, demonstrated greater task-related activation in the same attentional control areas, providing conceptual replication and extension of the effects of fitness in the cross-sectional results.

Furthermore, Rosano and colleagues found that long-term adherence to moderate-intensity exercise maintained the functional changes demonstrated by Colcombe and colleagues. Specifically, older adults who maintained moderate levels of physical activity (consisting mainly of aerobic activity) over a 2-year period exhibited increased activation in the dorsolateral prefrontal cortex compared with people who remained sedentary. Increased activation in this region was associated with better performance on a test measuring psychomotor speed. Together, these studies suggest that cardiovascular fitness may impact functional plasticity resulting in neurocognitive benefits.

In an SIVCI specific cohort, an analysis of fMRI data from the PROMoTE Study found that improved performance of the flanker task (a measure of selective attention and conflict resolution) was associated with reduced brain activation in the AT group compared with the

7 Successful invocation of the attentional network in the presence of conflicting response cues should result in a relative decrease activation in the anterior cingulate cortex.
control group. Specifically, reduced task-related neural activation was detected in the left lateral occipital cortex and right superior temporal gyrus. Previous studies have reported increased task-related neural activation, as a compensatory process, in people with cSVD and older adults with higher cardiovascular risk. This was supported by another study that reported an association between decreased WM integrity and increased fMRI signal (i.e., less-wiring-more-firing). Thus, it was postulated that AT might maintain or increase neural efficiency among older adults with mild SIVCI by reducing the need for compensatory neural processing.

Overall, this study demonstrates that AT also has the potential to alter brain function in older adults with SIVCI.

1.6.3.3 White matter integrity

In addition to brain volume and function, improved cardiovascular fitness may also modify WM integrity. Microstructural integrity of WM is required for proper transmission of information between cortical regions. Higher cardiovascular fitness (i.e., VO2 peak and total time on a treadmill) has been associated with greater WM integrity (i.e., FA) in the corpus callosum, which enables sensory, motor, and cognitive integration across the hemispheres, in healthy older adults. Moreover, in low-fit older adults light physical activity (measured with accelerometry) was positively correlated with higher temporal lobe WM integrity (i.e., FA). In contrast, an RCT assessing the effect of a 1-year AT intervention did not find significant group differences in WM integrity; however, greater cardiovascular fitness (i.e., VO2 max) derived from the walking program was associated with increased WM integrity in the frontal and temporal regions in sedentary community dwelling older adults. These results parallel findings from the Health, Aging, and Body Composition Study, a large cohort of well-functioning community dwelling older adults. This study found that maintenance of time spent walking over a decade predicted
smaller decreases in WM integrity (i.e., MD in GM and axial diffusivity in WM) and maintenance of global cognition 202.

In a study assessing WM integrity in MCI, greater cardiovascular fitness (i.e., VO2 max) was positively associated with FA and negatively associated with MD and radial diffusivity in the genu of corpus callosum, uncinate fasciculus, superior longitudinal fasciculus, and cingulum. Deterioration of these tracts is common in early AD. Moreover, WM integrity was positively correlated with executive performance, including set shifting, working memory, and semantic verbal fluency 203. In a sample of people in the earliest stages of AD, cardiovascular fitness (i.e. VO2 peak) was associated with preserved WM integrity in the right inferior fronto-occipital fasciculus as measured by FA, while no associations were found for measures of MD, radial diffusivity, or axial diffusivity. The inferior fronto-occipital fasciculus is susceptible to AD-related deterioration later in the disease process, indicating that greater cardiovascular fitness is associated with preserved integrity in WM tracts that have not yet been compromised by AD 204. These results, however, are in contrast with the results from a controlled clinical trial assessing the impact of a 10-week cognitive training and physical training (i.e., aerobic, strength, coordination, balance, and flexibility exercises) intervention compared with a passive control group. Neither the cognitive or physical training program resulted in changes in WM integrity (i.e. FA) or global cognition; however, a cross-sectional analysis revealed that an active lifestyle, as measured by the Senior Fitness Test, was positively correlated with WM integrity (i.e., FA) in the fornix and marginally significantly associated with a composite measure of FA (i.e., FA in the genu of corpus callosum, fornix, and hippocampal cingulum). The authors concluded that
short-term cognitive and physical training did not impact WM integrity, but long-term training may have the potential to impact WM integrity in older adults at risk for dementia 205.

1.6.3.4 Aerobic training may be a promising strategy to mitigate white matter hyperintensity progression

Few studies have assessed the impact of exercise training on WMH progression, but the available literature indicates that exercise may be a promising strategy to mitigate cSVD damage. In a cross-sectional study assessing the link between physical activity (measured with accelerometry) and cardiovascular fitness (i.e., VO2 max) on WMH volume, moderate-to-vigorous physical activity, but not cardiovascular fitness, was correlated with lower WMH volume 200. In contrast, a cross-sectional analysis from the Austrian Stroke Prevention Study found that VO2 max was significantly correlated with WMH load (i.e., graded on a semi-quantitative scale) in males, but not females 206. These results suggest that sex differences may impact the effect of AT on WMH progression. Preliminary data from an RCT in community dwelling older women reported that RT reduced WMH progression over 12 months 121. These results were later supported by the Study of Mental Activity and Resistance Training, an RCT conducted in people with MCI. This study reported that high-intensity progressive RT resulted in a modest regression of WMHs in periventricular and parietal regions while the non-progressive RT groups displayed WMH progression; however, these results did not survive whole-brain correction 207. Currently, no studies have investigated whether AT can mitigate WMH progression in SIVCI. As AT has demonstrated protective effects for brain structure and function by delaying brain atrophy, increasing GM and WM volume, stimulating functional plasticity, and increasing WM integrity, AT may also be a promising strategy to reduce WMH progression.
1.6.4 Mechanisms by which aerobic training may mitigate cerebrovascular injury

In this section, I will provide a rationale for why AT may be particularly effective for combat cSVD. First, I will review the role of AT in reducing vascular risk factors linked to cSVD. Next, I will review the role of AT in promoting neurotrophic factors important for cerebrovascular health. Lastly, I will review the role of AT in promoting endothelial function, a key player in maintaining vessel health.

1.6.4.1 Aerobic training may reduce key vascular risk factors

Vascular risk factors for cSVD include obesity, type 2 diabetes, hypercholesterolemia, and hypertension. However, hypercholesterolemia and hypertension are specifically associated with the progression of WMHs. The Lothian Birth Cohort 1936 Study found that lower high-density lipoprotein cholesterol was a significant predictor of WMH progression from 73 to 76 years of age. A longitudinal population study of non-demented older adults found that people with untreated hypertension had significantly greater WMH progression than people with treated hypertension over a 5-year period. Moreover, the Evaluation of Vascular Care in AD Study, an RCT assessing the impact of intensive vascular care compared with standard care in patients with AD and concomitant cerebrovascular lesions, found that people receiving vascular care showed less WMH progression. Vascular care consisted of lifestyle interventions (i.e., weight loss and dietary advice in cases of overweight participants, physical exercise, and smoking cessation), medication (i.e., acetylsalicylic acid, pyridoxine, and folic acid), treatment of hypertension in a stepped protocol (i.e., reducing salt intake and increasing exercise, diuretic, and if necessary a β-blocker or calcium antagonist), and treatment of hypercholesterolemia (i.e., Pravastatin). However, it should be noted that the two groups did not display differences in clinical function. These results indicate that controlling vascular risk factors, such as
hypercholesteremia and hypertension, may reduce the risk of WMH progression. Critically, AT is an effective method for controlling vascular risk factors associated with WMH progression 211-213. For example, a meta-analysis of AT trials in older adults found that AT significantly increased in high-density lipoprotein (the “good” cholesterol) and reduced total cholesterol/high-density lipoprotein cholesterol ratio, independent of changes in body composition 214. A meta-analysis of 54 RCTs found that AT decreased both systolic and diastolic blood pressure in normotensive and hypertensive adults 215. Thus, AT may be a promising strategy for reducing WMH progression by controlling key vascular risk factors 216.

1.6.4.2 Aerobic training may promote neurotrophic factors

Neurotrophic factors are molecules that enhance the growth and survival of neurons by promoting neuronal proliferation, differentiation, and survival. They are suggested to mediate the beneficial effects of exercise on brain plasticity 168,169,217. Neurotrophic factors specifically associated with AT include BDNF and vascular endothelial-derived growth factor (VEGF) 218-220. BDNF is an important mediator of neuroplasticity and is specifically involved in synaptogenesis and neurogenesis 168,169. BDNF may also have protective effects against ischemic injury 221. For example, in mice lacking one BDNF allele (i.e. expressing reduced BDNF levels), transient occlusion of the middle cerebral artery resulted in larger infarct volume compared with control mice 222. Moreover, rats that received intraventricular infusion of BDNF before the induction of transient ischemia, displayed reduced cell death in the hippocampus 223 and reduced infarct volumes compared to control rats 224. On the other hand, VEGF plays a pivotal role in inducing new vessel formation (i.e., angiogenesis); thus, its function is critical in tissues suffering from ischemia 225-227. One study indicated that blocking VEGF can prevent angiogenesis despite an up-regulation of other angiogenic growth factors 227. Moreover, rats
treated with VEGF after 90 minutes of transient cerebral ischemia exhibited reduced infarct volume, brain edema, and BBB injury. VEGF may also salvage viable neural tissue in the penumbra (a region of ischemic tissue surrounding the necrotic infarct, which is dysfunctional, but potentially salvageable) by improving perfusion. VEGF can improve perfusion by stimulating angiogenesis and vasodilation, and preventing endothelial cell dysfunction.

Exercise induced increases in VEGF levels also stimulates mitosis and migration of endothelial cells and indirectly promotes vasodilation by up-regulating the release of nitric oxide ([NO], the importance of NO and endothelial cells is discussed in the next section). Together, the bioavailability of BDNF and VEGF are vital in reducing ischemic damage.

Animal and human studies generally suggest that AT has the potential to increase the bioavailability of BDNF and VEGF. Neeper and colleagues were the first to show a positive correlation between physical activity and BDNF levels using a voluntary wheel running paradigm in rats. Subsequently, several other rodent studies have reported an increase in BDNF after AT in various regions of the brain including the hippocampus, prefrontal cortex, motor cortex, lateral septum, cerebellum, striatum, and amygdala. Few studies have been conducted in older adults and it is unclear if AT increases BDNF levels. A 1-year AT program in healthy older adults did not result in a significant increase in serum BDNF levels, but within the AT group increased BDNF levels was correlated with increased hippocampal volume and increased functional connectivity between the parahippocampal and middle temporal gyrus.

A study by Baker and colleagues found that high-intensity exercises (75–85% of heart rate

8 Increased connectivity between the parahippocampus and middle temporal gyrus represents greater cohesion of the default mode network. Dysfunctional connectivity within the default mode network is associated with MCI and AD.
reserve) increased peripheral concentrations of BDNF in older males and maintained concentrations of BDNF in older females with MCI. In contrast, a study by Barha and colleagues found that a 6-month AT program increased serum BDNF levels in females and decreased BDNF levels in males with SIVCI. Sex differences have also been noted in meta-analyses with contradicting results. One meta-analysis reported that AT increased resting levels of BDNF with a larger, though not statistically different, effect in females while another meta-analysis found lower levels of BDNF after AT in females compared with males. Overall, more research is needed to ascertain the effect of AT on BDNF levels in older adults; however, the bulk of research in animals and healthy adults indicate that AT is associated with increased BDNF levels and that this effect may be moderated by biological sex.

Few studies have assessed the effect of AT on VEGF concentrations and the results in human studies are not straightforward. In a systematic review of 10 studies, 4 studies found that AT increased serum VEGF levels. Notably, all 4 studies were composed of people with vascular disease (i.e. ischemic coronary artery disease or peripheral arterial occlusive disease) indicating that AT may be effective at up-regulating VEGF concentrations in older adults with existing vascular pathology. Studies in rodent models provide more promising results. In older rats, treadmill running was associated with increased VEGF messenger ribonucleic acid expression and an increase in the density of micro-vessels within the cerebral vasculature. In another rodent model, it was demonstrated that the release of skeletal myofiber VEGF after AT was necessary for enhanced hippocampal blood flow and neurogenesis (i.e., mice with skeletal myofiber gene deletion did not exhibit these benefits). Together, these rodent models demonstrate that exercise-induced VEGF release in the periphery may play a critical role in
cerebral angiogenesis and neurogenesis. Though human studies do not provide consistent evidence for the enhancement of VEGF, there is some evidence to suggest that AT may up-regulate the bioavailability VEGF and supporting evidence from rodent models suggest that AT-induced increases in serum VEGF levels may play a critical role in promoting neurogenesis and cerebral angiogenesis.

1.6.4.3 Aerobic training may promote endothelial function
cSVD is also associated with impaired endothelial-dependent vasodilation, which is detectable before any morphological changes could be observed in the vessel wall. The endothelium is a thin, flat cellular monolayer that lines the entire vascular tree. These cells have many important functions that include diffusion of oxygen and carbon-dioxide across capillary walls and autoregulation of local CBF. Autoregulation of CBF is important because it protects cerebral blood vessels from changes in arterial pressure associated with daily activities and provides a stable CBF baseline. The endothelium has the ability to increase or decrease vessel diameter and distal blood flow by modulating vascular smooth-muscle tone. It does this by releasing several effectors, most notably NO. NO is one of the most important vasodilator mechanisms. It causes contractile smooth muscle cells to relax allowing the vessels to dilate and has various secondary roles in the vasculature such as eliminating free radicals and preventing the buildup of plaques. NO is produced by NO synthase (NOS) proteins, of which the dominant form in endothelial cells is endothelial NOS (eNOS). Dysfunctional endothelial cells may synthesize less eNOS resulting in reduced vascular dilation that can potentially lead to ischemic injury. Furthermore, eNOS also has the ability to promote angiogenesis and vasculogenesis (i.e., blood vessel formation de novo from progenitor cells), as eNOS is an essential mediator of VEGF activity. eNOS may also play a role in preserving ischemic cerebrovascular tissue. Transgenic
mice expressing a form of eNOS showed greater vascular reactivity, developed less severe strokes, and exhibited improved CBF after middle cerebral artery occlusion 237. Critically, AT has the potential to improve vessel health through NO-mediated vasodilation 182,238.

Animal studies investigating both peripheral and coronary vasculature suggest that AT enhances eNOS and NO production and bioactivity 239. For example, AT in rats increased eNOS in skeletal muscles and muscle arterioles and increased vasodilator responses 240. In large conduit vessels, improved endothelium-dependent vasodilation was observed after 7 days of AT in pigs 241. In cerebral arterioles, AT was associated with increased NOS-dependent vasodilation in female rats 242. In human studies, exercise training does not seem to induce NO-vasodilation in healthy adults with normal endothelial function 239,243. However, the majority of studies performed in people with impaired endothelial function report improved NO-mediated endothelial function after exercise 239. AT and RT in people with chronic heart failure 244 or type 2 diabetes 245 improved NO-mediated endothelial function, suggesting that depressed endothelial function is capable of augmentation after exercise training. Moreover, Mairoana and colleagues 244 found evidence for improved vascular function in a vascular bed not directly involved in the exercise stimulus, suggesting that the effects of exercise on the vasculature are generalized 244. Together, data from animal and human studies suggest that AT increases eNOS expression and NO-dependent vascular function. Furthermore, the beneficial effects of AT on the vasculature is pronounced in people with impaired endothelial function 239,244,245.

These results are of particular pertinence to people with cSVD, as increases in vascular NO bioavailability is considered a key factor in the maintenance of cerebrovascular function and
optimal regulation of CBF. In mice with mild brain ischemia, Gertz and colleagues reported that voluntary wheel running increased resting CBF in the ischemic lesion as well as better functional and cognitive outcomes via eNOS-dependent mechanisms related to improved angiogenesis and CBF. Similarly, Endres and colleagues demonstrated that 3 weeks of voluntary wheel-running led to an increase in resting CBF and a reduction of cerebral infarct size in wild-type, but not eNOS knock-out mice, indicating an eNOS-dependent mechanism. Furthermore, in a study assessing the effect of AT on ischemic brain damage in diabetic rats found that the total infarct volume in cortical and subcortical regions were reduced in rats enrolled in a treadmill pre-training protocol of 6 to 8 weeks. The authors concluded that AT has beneficial effects on cerebral circulation and may possess significant therapeutic potential for mitigating ischemic brain injury.

The mechanisms by which AT increases the bioavailability of NO is unclear. NO is produced by endothelial cells upon exposure to mechanical forces; thus, AT may promote NO release by increasing shear stress caused by high cardiac output during sustained exercise. AT also increases sympathetic activity to coordinate blood delivery and energy supply, thus stimulating endothelial function and increasing NO bioavailability. As previously indicated, AT may also up-regulate NO by increasing the bioavailability of VEGF. In general, AT may also protect the cerebral vasculature by delaying age-related stiffening of peripheral large arteries that may cause downstream problems for endothelial function in cerebral arteries.

Though there is evidence to support the protective role of AT on endothelial function, it is important to note the limitations of such studies. Most of these studies are in large vessels and it
is unclear whether these same mechanisms exist in cerebral small vessels. Each vascular bed has its own tissue morphology, physiology, biochemistry, pathology, and pharmacology. There are major differences between endothelial cells lining large conduit arteries, small resistant arteries, and micro-vessels, which further increase the complexity of molecular mechanisms activated in the presence of vascular risk factors. Also, research on endothelial function in the cerebral vasculature is currently not possible in humans; as such, studies are reliant on animal models of hypertension or stroke which is limited in representing human pathophysiology 252. Notwithstanding these limitations, there is evidence to suggest that AT may be neuroprotective for people with cSVD by improving endothelial function, in addition to controlling key vascular risk factors and up-regulating neurotrophic factors. As such, this thesis will investigate AT as a strategy to mitigate WMH progression in people with SIVCI.

1.7 Summary of literature review and thesis overview

In the previous sections, I provided an overview of SIVCI with emphasis on topics related to the aims of this thesis. Below, is a summary of the key points and knowledge gaps from the literature review:

SIVCI is a common cause of cognitive impairment and a major contributor to neurodegenerative pathologies such as AD. Given the pervasiveness of cerebrovascular lesions, it is critical that we better quantify and understand the impact of covert vascular burden and identify strategies that will reduce its progression to mitigate cognitive decline.
• There is a close interaction between cSVD and AD pathophysiology, as such the study of cSVD should garner the consideration of co-existing AD pathology. Currently, there is a dearth of knowledge on the effects of co-existing Aβ plaque pathology on cognitive and physical outcomes in people with SIVCI.

• Conventional imaging techniques are limited in their description of lesion morphology and little is known about the microstructural changes associated with cSVD. Of particular relevance to cognitive function, is the effect of myelin loss; yet, no studies have assessed the role of myelin on cognitive function in people with cSVD.

• cSVD is associated with vascular risk factors and endothelial dysfunction. AT is a promising strategy to control vascular risk factors and improve endothelial function. As such, AT may be a promising strategy to mitigate WMH progression. Currently, no studies have investigated the impact of AT on WMH progression.

• Evidence suggests that biological sex is a key moderator in exercise efficacy. Specifically, biological sex moderates the effect of AT on cognition, regulation of neurotrophins, and endothelial function. Thus, studies assessing the effect of AT should consider potential sex differences.

To address these knowledge gaps, this thesis aims to: 1) investigate the role co-existing Aβ plaque pathology in cognitive and physical outcomes; 2) investigate the role of myelin in
cognitive function and; 3) investigate the role of AT in mitigating WMH progression and determine whether these changes are sex dependent. Figure 1.8 provides a schematic of the specific questions addressed in the following research chapters.

Figure 1.8 Outline of research questions.
Chapter 2: Does coexisting amyloid-beta affect physical function?


2.1 Introduction

Impaired physical function (i.e., slow gait, muscle weakness, and poor mobility) is common in older adults with cognitive impairment and dementia. Notably, physical impairments appear to precede and may predict the onset of both MCI and AD. Though reduced physical function is a known clinical manifestation of AD, little research has been conducted to understand the role of AD pathology, specifically Aβ plaques, on physical outcomes.

To date, research has mainly focused on the effects of cSVD, particularly WMHs, on physical function. Several published studies provide consistent evidence that WMHs negatively impact physical function. For example, the LADIS Study found that moderate to severe levels of age related WM changes were associated with slowed gait speed and poor balance. Similarly, the Cardiovascular Health Study found that greater baseline WMH load was associated with greater decline in gait speed and chair stand time both cross-sectionally and longitudinally. In addition, a systematic review reported that increased WMH load was associated with reduced balance control and gait speed, and increased falls risk. This research has also been important for understanding physical impairments in AD, as WMHs and AD pathology often co-occur –
autopsy studies report incidental WMHs in over 60% of people with AD. It is currently unclear whether vascular lesions are independent or causal in the pathogenic process of AD. Neuroimaging studies predominantly indicate that WMHs and Aβ plaque pathology are not correlated, which suggest that they may arise from independent pathogenic processes. However, epidemiological studies indicate that AD and cerebrovascular pathology share common cardiovascular risk factors. In addition, the co-occurrence of Aβ plaques and WMHs result in worse outcomes. The presence of WMHs among those who have high levels of Aβ deposition show lower cognitive scores, experience more rapid cognitive decline, and are more likely to progress to MCI or AD. These findings suggest that there is a link between AD and cerebrovascular pathology, such that the co-occurrence of WMHs and Aβ plaque deposition may exacerbate clinical symptoms.

Currently, it is unclear whether Aβ plaque deposition may impact physical outcomes, independent of WMH pathology. One autopsy study reported that AD pathology, including both Aβ plaque deposition and neurofibrillary tangles, were associated with declining gait speed over an average follow-up time of 6.4 years prior to death. Researchers have only recently begun to assess the effects of cerebral Aβ plaques in-vivo on physical function. A cross-sectional analysis of the Mayo Clinic Study of Aging found that higher global Aβ deposition was associated with slower gait speed, lower cadence, longer double support time, and greater stance time variability in cognitively normal individuals. This analysis controlled for AD associated neurodegeneration, as measured by cerebral glucose uptake, hippocampal volume, and cortical thickness. A longitudinal analysis of the same study found that higher Aβ plaque deposition was associated with declining gait speed, decreasing cadence, and increasing double support time.
over a median 15.6 months. However, neither study controlled for WMH burden. One study that accounted for the effects of WMH volume, found that regional Aβ deposition was independently associated with slower gait speed in a combine cohort of cognitively normal and MCI participants. These study results indicate that slow gait speed may be an early marker of AD pathology.

The goal of our study was to further investigate the relationship between Aβ plaque deposition and physical function, which is defined as the ability to perform the basic actions that are essential for maintaining independence and carrying out complex activities. The majority of studies to date assessing the effect of Aβ plaque deposition on physical function have included gait speed as an outcome measure, but few studies have assessed other subdomains of physical function, such as muscle strength, balance, and mobility. Thus, we currently do not know how broadly Aβ plaque deposition may impact physical function in older adults with cognitive impairment. We address these knowledge gaps by including measures of gait speed, muscle strength, balance, and functional mobility using the SPPB and the Timed Up and Go Test. We hypothesize that Aβ deposition has a broad and negative impact on measures of physical function in people with cognitive impairment.

2.2 Methods

2.2.1 Study design and participants

Ethical approval was obtained from the Vancouver Coastal Health Research Institute (V07-01160 and V13-01573) and the University of British Columbia’s Clinical Research Ethics Board.
(H07-01160 and H13-01573). All subjects gave written informed consent in accordance with the Declaration of Helsinki.

This study included participants from two studies. Nineteen participants were included from the PROMoTE Study 156,267, which was a proof of concept RCT assessing the effect of aerobic exercise on cognitive function in older adults with SIVCI 156. For these 19 participants, their baseline data were used in this study. Another 11 participants were included from a cross-sectional study aimed at characterizing AD, SIVCI, and mixed AD-SIVCI. All participants were recruited from either the University of British Columbia Hospital Clinic for AD and Related Disorders, the Vancouver General Hospital Stroke Prevention Clinic, or specialized geriatric clinics in Metro Vancouver, British Columbia. The diagnosis of cognitive impairment stemming from AD, SIVCI, or mixed AD-SIVCI pathology was confirmed in each participant by a neurologist. Cognitive impairment primarily due to AD was based on the core clinical criteria of possible or probable AD based on recommendations from the National Institute on Aging and the Alzheimer’s Association guidelines 268. Cognitive impairment primarily due to SIVCI was based on the presence of cSVD and cognitive impairment 269,270. cSVD was based on the presence of periventricular or deep WMHs and at least one lacunar infarct and the absence of non-lacunar territorial (cortical and/or cortico-subcortical) strokes or other specific causes of WMHs (e.g., MS, leukodystrophies, sarcoidosis, brain irradiation, etc.) on clinical MRI or CT scans. Cognitive impairment was defined as a MoCA score < 26/30 at baseline 17. Mixed AD-SIVCI required a diagnosis of possible AD 268 and SIVCI 270. Participants within our study will be referred to as cognitive impairment plus (CI+), to reflect the inclusion of AD, SIVCI, and mixed AD-SIVCI.
Individuals were eligible for study entry if they met the following criteria: 1) fulfilling the criteria for cognitive impairment due to AD, SIVCI, or mixed AD-SIVCI; 2) ≥ 55 years-old; 3) MMSE ≥ 20/30 and; 4) provide written informed consent. Study exclusion criteria included: 1) diagnosed with moderate or severe dementia (MMSE < 20) – only participants with milder impairment were included; 2) diagnosed with another type of dementia other than AD, SIVCI, or mixed AD-SIVCI (e.g., Lewy body, frontal temporal dementia, etc.); 3) diagnosed with other neurological conditions (e.g., MS, Parkinson’s disease, etc.) and; 4) participation in a clinical drug trial concurrent to this study.

2.2.2 Descriptive variables

Information regarding age, biological sex, and body mass index (BMI = weight in kg/height in squared meters) were collected at baseline. Depression was measured using the Geriatric Depression Scale 271. In addition, information regarding WMH load was rated by a neurologist (GYRH or WAK) on either clinical (5 participants) or research (25 participants) MRI scans using the Fazekas rating scale 67. The grading of periventricular WMH was defined as: grade 0 = absence; grade 1 = ‘caps’ or pencil-thin lining; grade 2 = smooth ‘halo’ and; grade 3 = irregular periventricular hyperintensities extending into the deep WM. The grading of deep WMH was defined as: grade 0 = absence; grade 1 = punctate foci; grade 2 = beginning confluence of foci and; grade 3 = large confluent 67.

2.2.3 Dependent variables: Gait speed and lower extremity function

Usual Gait Speed: This measure was extracted from the SPPB 4-meter walk test, in which participants were asked to walk at their usual pace along a 4-meter path. Gait speed (m/s) was calculated from the better of two trials. The test-retest reliability (interclass correlation coefficient) of gait speed in our laboratory is 0.95 272.
SPPB: Participants were assessed on performances of standing balance (i.e. side-by-side stand, semi-tandem stand, and tandem stand), 4-meter walk test, and repeated chair stands. Each component was rated from 0 (inability to perform the task) to 4 (optimum performance), for a maximum of 12 points; a score of < 9/12 predicts subsequent disability. Specifically, this test assesses balance, usual gait speed, and strength, and has high test-retest reliability.

Timed Up and Go Test: Participants were instructed to rise from a standard chair without using armrests, walk a distance of 3 meters at usual pace, turn, walk back to the chair, and sit down again. A stopwatch was used to measure the time to complete the Timed Up and Go Test and the mean of two trials was calculated. Specifically, this test assesses functional mobility.

2.2.4 Independent variable: Amyloid-beta plaque deposition

PET scans were performed using \(^{11}\)C-PIB produced at UBC TRIUMF. Scans were performed in 3-D mode using the GE Advance tomograph (General Electric, Canada/USA). A 90-minute dynamic acquisition started at tracer injection and data were framed into an \(18 \times 300\) sec imaging sequence.

After image reconstruction, data were first frame-to-frame realigned using AIR to minimize the impact of head motion. Using SPM 8 (Wellcome Department of Cognitive Neurology, Institute of Neurology, University College London), a mean PIB-PET image was created by averaging radiotracer concentration over the entire scan duration – this image was used for coregistration and ROI definition purposes. In the next step, each subject’s mean PIB-PET image was normalized to a mean PIB-PET image template in MNI space. Normalization was performed using non-linear regularization, 16 nonlinear iterations, 8mm smoothing, and affine
regularization into an average sized template. The corresponding transformation parameters were then applied to all the PIB-PET frames for that subject to bring all scans into MNI space. The PIB-PET template was created by averaging PIB-PET scans from a cohort of healthy controls that had all been warped with their own T1w image to the SPM MNI305 template. To quantify Aβ plaque deposition we used standardized uptake value ratio from 40 to 90 minutes after injection. Standardized uptake value ratio was calculated by normalizing standardized uptake value (tracer concentration/(injected dose/body weight)) images to the cerebellar cortex standardized uptake value.

ROI analysis: A custom set of ROIs were defined on the coronal view of the MNI305 template. These ROIs were transposed to each subject’s warped MRI and mean-PET images (in MNI space) and adjusted as necessary. The modified set of ROIs was then applied to the PIB-PET and the average Aβ plaque deposition within each ROI was extracted. Global Aβ plaque deposition was determined by averaging values in bilateral frontal (orbitofrontal and medial prefrontal cortex), parietal (angular gyrus, superior parietal, precuneus, and supramarginal gyrus), temporal (lateral temporal gyrus, medial temporal gyrus, and temporal pole), sensory-motor, occipital, posterior and anterior cingulate gyrus, caudate, and putamen.

2.2.5 Statistical analysis

All statistical analyses were performed using Statistical Package for the Social Sciences 22.0. A multiple linear regression analysis was conducted to obtain estimates for the unique contribution of global Aβ plaque deposition. All statistical models controlled for the effects of age, BMI (previous studies indicate that BMI is associated with both physical function 278,279 and Aβ deposition 280), and Fazekas grade. These variables were entered in the first step as covariates,
then global Aβ plaque deposition was entered in the second step to determine the unique contribution of global Aβ plaque deposition on each physical measure. To determine region specific effects, we conducted the same analyses with Aβ plaque deposition of each ROI in the second step. We report standardized betas and not p-values for the ROI analysis, as multiple significance testing (i.e. 9 ROIs × 3 dependent variables for a total of 27 statistical tests) would be inappropriate for our sample size. Given the large number of tests, our sample size would not have sufficient power for Type I error adjustments. For each regression model, we computed collinearity statistics (tolerance and variance inflation factor), histograms of the residuals, and scatterplots of the predicted versus residual values to ensure that the assumptions of linear regression were met. In all models, multicollinearity was not an issue among predictor variables, and the residuals were normally distributed and homoscedastic.

2.3 Results

2.3.1 Participants

Thirty participants (8 females, 22 males) were included in this study. Clinical diagnosis included: 4 participants with AD; 22 with SIVCI; and 4 with mixed AD-SIVCI. The mean age was 72 years with an average MMSE score of 25.93 and MoCA score of 22.30. Of the 30 participants, 12 were Aβ -positive (Aβ plaque deposition > 1.5281) including 3 AD, 6 SIVCI, and 3 mixed AD-SIVCI participants. Global Aβ plaque deposition was 1.44. Detailed demographic characteristics are presented in Table 2.1.
Table 2.1 Descriptive characteristics (N=30)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean or No.</th>
<th>SD or %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
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<td>8.09</td>
</tr>
<tr>
<td>Female Sex, No. (%)</td>
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<td>27</td>
</tr>
<tr>
<td>Clinical diagnosis, No. (%)</td>
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<td></td>
</tr>
<tr>
<td>AD</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>SIVCI</td>
<td>22</td>
<td>73</td>
</tr>
<tr>
<td>Mixed AD-SIVCI</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>MMSE (max. score 30)</td>
<td>25.93</td>
<td>2.79</td>
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<tr>
<td>MoCA (max. score 30)</td>
<td>22.30</td>
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</tr>
<tr>
<td>BMI</td>
<td>26.83</td>
<td>4.89</td>
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<tr>
<td>GDS</td>
<td>2.37</td>
<td>2.22</td>
</tr>
<tr>
<td>WMH Load, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fazekas 0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Fazekas 1</td>
<td>13</td>
<td>43</td>
</tr>
<tr>
<td>Fazekas 2</td>
<td>8</td>
<td>27</td>
</tr>
<tr>
<td>Fazekas 3</td>
<td>8</td>
<td>27</td>
</tr>
<tr>
<td>PIB-positive, No. (%)</td>
<td>12</td>
<td>40</td>
</tr>
<tr>
<td>Global Aβ plaque deposition</td>
<td>1.44</td>
<td>0.45</td>
</tr>
</tbody>
</table>

Mobility Assessments

<table>
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<tr>
<th>Assessment</th>
<th>Mean or No.</th>
<th>SD or %</th>
</tr>
</thead>
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<tr>
<td>Usual Gait Speed</td>
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<td>0.27</td>
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<tr>
<td>Short Physical Performance Battery</td>
<td>10.43</td>
<td>1.43</td>
</tr>
<tr>
<td>Timed Up and Go Test</td>
<td>8.66</td>
<td>2.39</td>
</tr>
</tbody>
</table>

MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessments; BMI = Body Mass Index; GDS = Geriatric Depression Scale; WMH = White Matter Hyperintensity;

2.3.2 Association between amyloid-beta plaque deposition and physical function

Higher global Aβ plaque deposition was statistically significantly associated with reduced gait speed ($\beta = -0.52$, $p = 0.01$); the total adjusted variance accounted by the final model was 39.4% – Table 2.2. Higher global Aβ plaque deposition was also statistically significantly associated with
reduced SPPB performance ($\beta = -0.47$, $p = 0.02$); the total adjusted variance accounted by the final model was 34.9% – Table 2.3. Global Aβ plaque deposition was not statistically significantly associated with the Timed Up and Go Test ($\beta = 0.32$, $p = 0.08$) – Table 2.4. Please refer to Table 2.5 for standardized betas for each ROI.

### Table 2.2 Multiple linear regression assessing the contribution of Aβ plaque deposition on usual gait speed

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>$R_2$</th>
<th>Adjusted $R_2$</th>
<th>$R_2$ Change</th>
<th>Unstandardized B (Standard Error)</th>
<th>Standardized $\beta$</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong></td>
<td>0.20</td>
<td>0.11</td>
<td>0.20</td>
<td></td>
<td></td>
<td>0.95</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td>-0.01 (0.01)</td>
<td>-0.42</td>
<td>0.05</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
<td>-0.01 (0.01)</td>
<td>-0.21</td>
<td>0.25</td>
</tr>
<tr>
<td>Fazekas Score</td>
<td></td>
<td></td>
<td></td>
<td>-0.00 (0.06)</td>
<td>-0.01</td>
<td>0.95</td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
<td>0.39</td>
<td>0.30</td>
<td>0.19*</td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td>-0.01 (0.01)</td>
<td>-0.38</td>
<td>0.05</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
<td>-0.03 (0.01)</td>
<td>-0.47</td>
<td>0.02</td>
</tr>
<tr>
<td>Fazekas score</td>
<td></td>
<td></td>
<td></td>
<td>0.02 (0.06)</td>
<td>0.06</td>
<td>0.75</td>
</tr>
<tr>
<td>Aβ deposition</td>
<td></td>
<td></td>
<td></td>
<td>-0.31 (0.11)</td>
<td>-0.52</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*significant at $p \leq 0.05$

### Table 2.3 Multiple linear regression assessing the contribution of Aβ plaque deposition on the short physical performance battery

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>$R_2$</th>
<th>Adjusted $R_2$</th>
<th>$R_2$ Change</th>
<th>Unstandardized B (Standard Error)</th>
<th>Standardized $\beta$</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong></td>
<td>0.19</td>
<td>0.10</td>
<td>0.19</td>
<td></td>
<td></td>
<td>0.76</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td>-0.06 (0.04)</td>
<td>-0.36</td>
<td>0.10</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
<td>-0.07 (0.05)</td>
<td>-0.23</td>
<td>0.20</td>
</tr>
<tr>
<td>Fazekas Score</td>
<td></td>
<td></td>
<td></td>
<td>-0.10 (0.33)</td>
<td>-0.07</td>
<td>0.76</td>
</tr>
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</table>
Table 2.4 Multiple linear regression assessing the contribution of Aβ plaque deposition on Timed Up and Go Test

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>R²</th>
<th>Adjusted R²</th>
<th>R² Change</th>
<th>Unstandardized B (Standard Error)</th>
<th>Standardized β</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.38</td>
<td>0.31</td>
<td>0.38</td>
<td>0.02 (0.05)</td>
<td>0.05</td>
<td>0.77</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
<td>0.28 (0.08)</td>
<td>0.57</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fazekas Score</td>
<td></td>
<td></td>
<td></td>
<td>0.64 (0.48)</td>
<td>0.24</td>
<td>0.19</td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.46</td>
<td>0.37</td>
<td>0.07</td>
<td>0.01 (0.05)</td>
<td>0.03</td>
<td>0.85</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
<td>0.36 (0.08)</td>
<td>0.73</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fazekas Score</td>
<td></td>
<td></td>
<td></td>
<td>0.53 (0.46)</td>
<td>0.20</td>
<td>0.27</td>
</tr>
<tr>
<td>Aβ deposition</td>
<td></td>
<td></td>
<td></td>
<td>1.70 (0.93)</td>
<td>0.32</td>
<td>0.08</td>
</tr>
</tbody>
</table>

*significant at p ≤ 0.05

Table 2.5 Standardized betas for ROIs

<table>
<thead>
<tr>
<th>ROIs</th>
<th>Gait Speed</th>
<th>SPPB</th>
<th>Timed Up and Go Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal cortex</td>
<td>-0.41</td>
<td>-0.40</td>
<td>0.25</td>
</tr>
<tr>
<td>Parietal cortex</td>
<td>-0.45</td>
<td>-0.42</td>
<td>0.25</td>
</tr>
<tr>
<td>Temporal cortex</td>
<td>-0.50</td>
<td>-0.48</td>
<td>0.40</td>
</tr>
<tr>
<td>Sensory-motor cortex</td>
<td>-0.53</td>
<td>-0.46</td>
<td>0.31</td>
</tr>
<tr>
<td>Occipital cortex</td>
<td>-0.05</td>
<td>0.11</td>
<td>0.13</td>
</tr>
<tr>
<td>Posterior cingulate gyrus</td>
<td>-0.25</td>
<td>-0.17</td>
<td>0.02</td>
</tr>
</tbody>
</table>
ROIs = Regions of interest

<table>
<thead>
<tr>
<th>ROIs</th>
<th>Gait Speed</th>
<th>SPPB</th>
<th>Timed Up and Go Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior cingulate gyrus</td>
<td>-0.52</td>
<td>-0.49</td>
<td>0.34</td>
</tr>
<tr>
<td>Caudate</td>
<td>-0.60</td>
<td>-0.51</td>
<td>0.35</td>
</tr>
<tr>
<td>Putamen</td>
<td>-0.63</td>
<td>-0.55</td>
<td>0.39</td>
</tr>
</tbody>
</table>

2.4 Discussion

Previous studies assessing the effect of cerebral Aβ plaque deposition on physical function have largely focused on healthy older adults and few investigations have been conducted in people with cognitive impairment. Among those with CI+, we found that cerebral Aβ plaque deposition was statistically significantly associated with reduced gait speed and SPPB performance, which additionally measures balance and muscle strength. However, cerebral Aβ deposition was not statistically significantly associated with functional mobility as measured by the Timed Up and Go Test. The results of our study corroborate existing literature implicating Aβ plaque pathology in impaired physical function.

Several studies have linked higher levels of Aβ plaque deposition with reduced gait speed and increased gait variability in healthy older adults. Similar results have been reported in a combined cohort of healthy older adults and older adults with MCI. Del Campo and colleagues found that greater levels of Aβ plaques in motor related regions (i.e., posterior and anterior putamen, occipital cortex, precuneus, and anterior cingulate) was associated with decreased gait speed; however, this study was not able to control for the potential effects of
WMH load. In another study with a combined cohort of cognitively normal and MCI participants, regional Aβ plaque deposition was associated with slower gait speed independent of demographics, cardiac risk, hippocampal volume, and WMH volume 263. In extension of these findings, the results of our study further affirm the relationship between Aβ plaque pathology and reduced gait speed in people with CI+.

Furthermore, we found an association between higher Aβ plaque deposition and impaired SPPB performance. To our knowledge, few studies have assessed the relationship between Aβ plaques and physical function of the lower extremities in people with cognitive impairment. In a study with healthy older adults, the Baltimore Longitudinal Study of Aging - NeuroImaging sub-study found that higher baseline Aβ plaque deposition was associated with a decline in lower extremity performance, as measured by the Health, Aging, and Body Composition Physical Performance Battery (i.e., timed performance on five repeated chair stands, timed standing balance, timed 6-m walk at a usual pace, and timed narrow 6-m walk test) 266. In assessing functional mobility, we did not find a significant association between Aβ plaque deposition and the Timed Up and Go Test. Perhaps a more comprehensive measure of lower extremity function, such as the SPPB or the Health, Aging, and Body Composition Physical Performance Battery, is more sensitive to Aβ pathology. The SPPB includes measures of gait speed, balance, and muscle strength, whereas the Timed Up and Go Test is a basic functional mobility test. Notably, the SPPB is a highly relevant measure in geriatric medicine as it is predictive of declines in activities of daily living, disability, hospitalization, and mortality 274,283,284. Overall, our findings expand previous research by highlighting the deleterious effects of Aβ plaque deposition on lower extremity function in people with CI+.
The exact mechanisms by which AD pathology can lead to impaired physical function remains unknown. One hypothesis postulates that Aβ pathology may cause physical impairments by disrupting striatal circuits. The striatum is anatomically composed of the caudate nucleus and putamen and is responsible for proper motor function. Disruptions to these circuits are implicated in neurodegenerative diseases characterized by motor symptoms. Though the striatum is not conventionally associated with AD pathology, striatal Aβ plaque deposition has been observed in AD and in people without dementia. Moreover, a study assessing the effect of Aβ plaques in motor related regions found that plaques in the putamen, occipital cortex, precuneus, and anterior cingulate were significantly associated with slowed gait speed, with the putamen and precuneus showing the strongest effects (i.e., highest beta coefficients). Within this study, we also found that Aβ plaque deposition in the putamen and caudate had the strongest effect on gait speed. The putamen also had the strongest effect on lower extremity function (i.e., SPPB and Timed Up and Go Test). These results are consistent with our understanding of motor pathways – the striatal region is uniquely interlinked with primary motor, premotor, supplementary motor, and primary somatosensory cortex, and thus plays a pivotal role in modulating motor circuits.

The results of our study should be evaluated within its limitations. First, our analyses included people with SIVCI, AD, and mixed AD-SIVCI and it is not clear how Aβ plaque deposition may affect physical function within each specific diagnosis. Second, this work focuses on the effect of cerebral Aβ plaque deposition without considering other brain pathologies such as tauopathies, cerebral atrophy or cortical thinning, but evidence from other studies suggest that

Appendix A includes additional analyses to assess the effect of Aβ plaque deposition on physical function in people with a primary SIVCI diagnosis.
measures of neurodegeneration such as hippocampal volume, cortical thickness, and glucose metabolism do not attenuate the relationship between Aβ deposition and impaired physical function. Third, we did not find an association between WMH load and physical function. This may be due to the limited range or accuracy of the Fazekas scale – though we note that previous studies such as the LADIS Study and the Cardiovascular Health Study were able to detect an association between impaired physical function and WMH load using a graded rating scale. Though these studies included a much larger sample compared with our study indicating that we may not have had sufficient power to detect an association between WMH load and physical function. Had we used a more sensitive measure of WMH quantification, such as WMH volume, we would predict an attenuated, but persisting, association between Aβ and physical function. As supporting evidence for this, a study by Nadkarni and colleagues found that the association between Aβ and gait speed persisted after adjusting for multiple covariates including WMH volume in cognitively normal and MCI participants. Lastly, this was a cross-sectional analysis with a modest sample size; thus, future studies with a larger sample size and longitudinal design are needed to determine the prognostic value of Aβ plaque deposition on future physical performance. To date, dementia research has primarily focused on cognitive outcomes; however, it is critical that we continue to highlight the effect of AD pathology on physical function as physical function is a reliable marker of current and future health and is associated with an increased risk for developing dementia.
2.5 Conclusion

The results from this chapter demonstrate that cerebral Aβ plaque deposition is cross-sectionally associated with reduced physical function as measured by gait speed and the SPPB. In addition to physical function, previous studies have reported an association between Aβ plaque deposition and cognitive function (refs). Specifically, a published secondary analysis of the PROMoTE Study found that higher global Aβ plaque deposition was cross-sectionally associated with worse performance on global cognition and executive functions (i.e., ADAS-Cog and MoCA) 127. To extend these cross-sectional findings, in the next chapter I will examine the effect of baseline Aβ plaque deposition on change in cognitive and physical function over time.
Chapter 3: Does coexisting amyloid-beta affect change in cognitive function and falls risk over time?


3.1 Introduction

AD and SIVCI are the two most common causes of cognitive impairment and dementia. Pathological hallmarks of AD include the presence of Aβ plaques and neurofibrillary tangles and AD is predominantly characterized by memory loss. On the other hand, SIVCI is often associated with the presence of WMHs and clinical symptoms include executive dysfunctions (rather than memory) and gait disturbance. However, over the past decade there has been a growing recognition for the high prevalence of mixed presentations, such that most people present with both Aβ and cerebrovascular pathology. Many studies have begun to investigate the impact of cerebrovascular pathology in AD, but few studies have considered mixed pathology from the perspective of a primary SIVCI diagnosis.

It is important to consider co-existing AD pathology within an SIVCI diagnosis because AD and SIVCI share interacting pathogenic mechanisms. For example, Aβ may cause vascular dysregulation by compromising cerebral perfusion and reducing vascular reserves, which increases the propensity for ischemic damage. In return, hypoxia and/or ischemia may promote
production of the Aβ peptide resulting in greater Aβ plaque accumulation. As such, people with SIVCI are likely to exhibit Aβ pathology; yet, few studies have been conducted to investigate the effect Aβ plaque deposition on cognitive and physical function in people with SIVCI.

It is important to consider the effects of Aβ pathology in SIVCI because studies in healthy older adults and people with MCI and AD indicate that Aβ plaque deposition is detrimental for both cognitive and physical outcomes. Specifically, increased Aβ plaque deposition, identified by PET, is associated with decreased episodic memory performance and global cognition in healthy older adults and older adults with MCI and AD. Though executive dysfunction is a characteristic of early AD, few studies have assessed the potential impact of Aβ plaques on executive functions. A study by Lim and colleagues found that Aβ plaque deposition was not significantly associated with executive functions in people with MCI; however, the assessment of executive functions was limited to a composite of response inhibition and verbal fluency. In another study with MCI participants, global Aβ plaque deposition in frontal, parietal, and medial temporal cortices was associated with decrements in executive functions, language, attention, information processing speed, and visuospatial function two years later. These results suggest that Aβ plaque deposition may affect several cognitive domains and processes. Furthermore, several recent studies have reported an association between Aβ plaque deposition and decreased physical function. Specifically, high levels of Aβ plaque deposition was associated with decreased gait speed in cognitively normal and mildly impaired older adults. One study assessing specific gait parameters reported slower gait speed, lower cadence, longer double support time, and greater stance time variability in older adults with higher Aβ plaque deposition.
Of particular relevance to our study, a 12-month prospective study found that higher Aβ plaque deposition was associated with a faster time to first fall in community-dwelling healthy older adults.

Although Aβ plaque deposition is known to be detrimental for cognitive and physical function in healthy older adults and older adults with MCI and AD, such studies in people with SIVCI are more limited. Also, much of current knowledge is based on cross-sectional studies and few studies have assessed the association of cerebral Aβ plaque deposition on change in cognitive and physical outcomes. Particularly, few studies have assessed the effect of Aβ plaques on executive functions, information processing speed, and falls risk in people with SIVCI. To address these knowledge gaps, we conducted a secondary analysis of an RCT to assess the association between Aβ plaque deposition and change in cognitive function (i.e., global cognition, executive functions, and information processing speed) and falls risk over a 12-month period. We hypothesized that elevated Aβ plaque deposition would be associated with larger decrements in these measures over a 12-month period.

3.2 Methods

3.2.1 Study design and participants

Ethical approval was obtained from the Vancouver Coastal Health Research Institute (V07-01160) and the University of British Columbia’s Clinical Research Ethics Board (H07-01160). All subjects gave written informed consent in accordance with the Declaration of Helsinki.
This was a planned secondary analysis of data acquired from the PROMoTE Study, which was a proof of concept RCT assessing the effect of aerobic exercise on cognitive function in older adults with SIVCI (NCT01027858) 267. Briefly, participants were randomized to either a 6-month thrice-weekly AT group or a usual care control group. Participants were followed for an additional 6-months after completing the 6-month intervention period. Cognitive function and falls risk were assessed at baseline, 6-month, and 12-month time points. To maximize our ability to detect changes in cognitive function and falls risk over time, we used baseline and 12-month data for our analyses.

Participants were recruited from the University of British Columbia Hospital Clinic for AD and Related Disorders, the Vancouver General Hospital Stroke Prevention Clinic, and specialized geriatric clinics in Metro Vancouver, British Columbia. The diagnosis of SIVCI was confirmed in each participant by a neurologist based on the presence of cSVD and cognitive impairment 9. A clinical MRI or CT scan was used to determine the presence of cSVD, which was based on the presence of periventricular or deep WMHs and at least one lacunar infarct and the absence of non-lacunar territorial (cortical and/or cortico-subcortical) strokes or other specific causes of WMHs (e.g., MS, leukodystrophies, sarcoidosis, brain irradiation, etc.). MCI was defined as a MoCA score < 26/30 at baseline [26]. SIVCI diagnosis also required evidence of progressive cognitive decline (compared with previous level of cognitive function) as confirmed through medical records or caregiver/family member interviews. Overall, participants were generally functioning independently and living in the community with minimal assistance by family or caregiver.
Study inclusion and exclusion criteria have been published previously. Briefly, individuals were eligible for study inclusion if they met the following criteria: 1) ≥ 55 years-old; 2) MoCA < 26/30 at screening; 3) MMSE ≥ 20/30 at screening; 4) if on a cognitive medication (e.g., donepezil, galantamine, rivastigmine, memantine, etc.), remaining on a fixed dose during the study period, and; 5) provide written informed consent. Study exclusion criteria included: 1) diagnosed with dementia of any type (e.g., AD, Lewy body dementia, frontal-temporal dementia, etc.) or other neurological conditions (e.g., MS, Parkinson’s disease, etc.); 2) taking medications that may negatively affect cognitive function such as anticholinergics, including agents with pronounced anticholinergic properties (e.g., amitriptyline), major tranquilizers (typical and atypical antipsychotics), and anticonvulsants (e.g., gabapentin, valproic acid, etc.) and; 3) participation in a clinical drug trial concurrent to this study.

This analysis included a sub-set of 22 participants (exercise group n=11; control group n=11) who met the overall study eligibility criteria and volunteered to complete a PET scan to measure Aβ plaque deposition.

3.2.2 Descriptive variables

At baseline, we collected information regarding age, sex, body mass index, waist-hip ratio (waist circumference/hip circumference), and comorbid conditions were measured using the Functional Comorbidity Index. In addition, we report WMH volume for a subset of participants.
3.2.3 Dependent variables: Cognitive function and falls risk

3.2.3.1 Cognitive assessments

Global cognitive function

ADAS-Cog: This test assesses orientation, language, ideational and constructional praxis, immediate memory, and delayed recall. There are 11 items and scores range from 0 to 70 with higher scores indicating greater cognitive dysfunction 304.

Executive functions

Trail Making Test (Part B minus A): This test primarily measures set shifting 305. Participants were asked to draw lines connecting encircled numbers sequentially (Part A) and to alternate between numbers and letters (Part B). The difference in time was calculated as Part B minus Part A; smaller difference indicates better set shifting performance.

Verbal Digit Span Test (Forwards minus Backwards): This test primarily measures working memory 306. Participants repeated progressively longer random number sequences in the same order as presented (forwards) and in the reversed order (backwards). The difference in score between the two tests was calculated as forwards minus backwards; smaller difference indicates better working memory performance.

Stroop Test: This test primarily measures inhibition 307. Participants completed three conditions (80 trials each): 1) reading out color words printed in black ink; 2) reading out the display color of colored-X’s; and 3) participants were shown a page with color-words printed in incongruent colored inks and were asked to name the ink color in which the words were printed. The time
difference between the third condition and second condition (i.e. color-words minus colored-Xs) was calculated; smaller difference indicates response inhibition.

Processing speed

Digit Symbol Substitution Test (DSST): This test primarily measures processing speed and psychomotor speed. Participants were first presented with a legend of numbers (1 to 9) and their corresponding symbols. They were then presented with a series of numbers, organized in a pre-defined random order, and were asked to fill in the corresponding symbol. Participants were given 90 seconds to complete the task. A higher number of correct answers in this time period indicates faster processing speed.

3.2.3.2 Falls risk assessment

Physiological Profile Assessment (PPA): This test assesses falls risk. The PPA involves the following subscales: 1) proprioception; 2) edge contrast sensitivity; 3) quadriceps strength; 4) hand reaction time and; 5) postural sway. Each item has a relative weighting and a summary z-score is calculated that indicates: mild risk (0-1); moderate risk (1-2); high risk (2-3) and; marked risk for future fall (3 and above). The PPA is a reliable and valid measure of falls risk in older adults.

3.2.4 Independent variable: Amyloid-beta plaque deposition

Details of the PET imaging protocol have been published previously. PET scans were performed using $^{11}$C-PIB produced at UBC TRIUMF. Scans were performed in 3-D mode using the GE Advance tomograph (General Electric, Canada/USA). A 90-minute dynamic acquisition started at tracer injection and data were framed into an $18 \times 300$ sec imaging sequence.
After image reconstruction, data were first frame-to-frame realigned using AIR 277 to minimize the impact of head motion. To quantify Aβ plaque deposition, parametric images of the non-displaceable binding potential 313 were generated using tissue input Logan graphical analysis 314,315 with the cerebellum as the reference region from 40 to 90 minutes after injection 109,316. Using SPM 8 (Wellcome Department of Cognitive Neurology, Institute of Neurology, University College London), a mean PIB-PET image was created by averaging radiotracer concentration over the entire scan duration – this image was used for co-registration and ROI definition purposes. In the next step, each subject’s T1w MRI image was co-registered to the corresponding mean PIB-PET image. Each subject’s MRI image was then normalized to the SPM MNI305 template and the corresponding transformation parameters were applied to the subject’s PET images (mean and parametric images). For those without MRI scans (5 subjects did not scan due to MR contraindications), the subject’s mean PIB-PET image was normalized to an average PIB-PET image template was created from a cohort of healthy controls.

Regions of interest (ROIs) analysis: A custom set of ROIs was defined on the coronal view of the MNI305 template 317. These ROIs were transposed to each subject’s warped MRI and mean-PET images (in MNI space) and adjusted as necessary. The modified set of ROIs was then applied to the parametric PIB-PET image and the average Aβ plaque deposition within each ROI was extracted. Global Aβ plaque deposition was determined by averaging values in bilateral frontal (combined orbitofrontal and medial prefrontal cortex), parietal (combined angular gyrus, superior parietal, precuneus, and supramarginal gyrus), temporal (combined lateral temporal and middle temporal gyrus), and occipital cortices, striatum (putamen and caudate nucleus), and anterior and posterior cingulate gyrus.
3.2.5 Statistical analysis

All statistical analyses were performed using Statistical Package for the Social Sciences 22.0. We conducted a multiple linear regression to determine the unique contribution of Aβ plaque deposition on change in cognitive function and falls risk. We controlled for experimental group (i.e. aerobic exercise training or usual care control) and baseline score. Age was initially included as a covariate, but it did not significantly alter the results and was removed for a more parsimonious model (please refer to Appendix B for these results). The dependent variable for all models was change in the outcome variable of interest. Change in ADAS-Cog, Trail Making Test (Part B minus A), Verbal Digit Span Test (Forwards minus Backwards), Stroop Test, and PPA was calculated as baseline minus 12-month scores. Change in DSST was calculated as 12-month minus baseline scores. In all instances, higher change scores represent improved performance. We report adjusted $R^2$ values, which penalizes the explained variance for each additional covariate, resulting in a more realistic estimate of the explained variance. For each regression model, we computed collinearity statistics (tolerance and variance inflation factor), histograms of the residuals, and scatterplots of the predicted versus residual values to ensure that the assumptions of linear regression were met. In all models, multicollinearity was not an issue among predictor variables, and the residuals were normally distributed and homoscedastic. To correct for multiple comparisons across all regression models, we applied the Benjamini-Hochberg procedure to obtain a false discovery rate corrected threshold using alpha 0.05.
3.3 Results

3.3.1 Participants

The mean age was 72 years (minimum age = 56 years; maximum age = 84 years), the average MoCA score was 23.32, and MMSE score was 27.50. Five out of 22 participants did not complete an MRI scan due to MR contraindications and 1 MRI scan was discarded from WMH volume quantification due to motion artifacts. Among the 16 participants with MRI data, WMH volume ranged from $76.38 - 10058.89 \text{ mm}^3$ with an average of $2004.40 \text{ mm}^3$. Compared with the participants in the RCT that did not complete PET scans, this subset was similar in age (mean difference $= 3.80$, $p > 0.05$), but had a higher mean MoCA score (mean difference $= 3.14$, $p \leq 0.05$). Detailed demographic characteristics and neuropsychological test results are presented in Table 3.1.

Table 3.1 Descriptive characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Exercise Group n = 11</th>
<th>Control Group n = 11</th>
<th>Total N = 22</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean or No.</td>
<td>SD or %</td>
<td>Mean or No.</td>
</tr>
<tr>
<td>Age</td>
<td>70.00</td>
<td>7.29</td>
<td>73.45</td>
</tr>
<tr>
<td>Female sex, No. (%)</td>
<td>3</td>
<td>27.3</td>
<td>4</td>
</tr>
<tr>
<td>MoCA</td>
<td>22.73</td>
<td>2.20</td>
<td>23.91</td>
</tr>
<tr>
<td>MMSE</td>
<td>27.45</td>
<td>2.30</td>
<td>27.55</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.90</td>
<td>0.08</td>
<td>0.93</td>
</tr>
<tr>
<td>Body mass index</td>
<td>27.14</td>
<td>6.24</td>
<td>26.75</td>
</tr>
<tr>
<td>FCI</td>
<td>3.09</td>
<td>1.81</td>
<td>3.55</td>
</tr>
<tr>
<td>Beta-blockers, No. (%)</td>
<td>3</td>
<td>27</td>
<td>2</td>
</tr>
<tr>
<td>Global Aβ deposition</td>
<td>0.14</td>
<td>0.24</td>
<td>0.07</td>
</tr>
<tr>
<td>WMH volume (mm$^3$)</td>
<td>1277.82*</td>
<td>1446.90†</td>
<td>2569.52†</td>
</tr>
<tr>
<td>Variable</td>
<td>Exercise Group n = 11</td>
<td>Control Group n = 11</td>
<td>Total N = 22</td>
</tr>
<tr>
<td>----------</td>
<td>-----------------------</td>
<td>----------------------</td>
<td>--------------</td>
</tr>
<tr>
<td></td>
<td>Mean or No.</td>
<td>SD or %</td>
<td>Mean or No.</td>
</tr>
<tr>
<td><strong>Baseline Assessments</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADAS-Cog</td>
<td>10.65</td>
<td>4.76</td>
<td>8.61</td>
</tr>
<tr>
<td>TMT (Part B minus A), sec.</td>
<td>45.07</td>
<td>20.93</td>
<td>55.95</td>
</tr>
<tr>
<td>VDST (F minus B), sec.</td>
<td>2.45</td>
<td>2.88</td>
<td>4.00</td>
</tr>
<tr>
<td>Stroop Test, sec.</td>
<td>68.33</td>
<td>30.26</td>
<td>54.54</td>
</tr>
<tr>
<td>DSST</td>
<td>26.27</td>
<td>8.01</td>
<td>25.27</td>
</tr>
<tr>
<td>PPA</td>
<td>0.54</td>
<td>1.50</td>
<td>0.47</td>
</tr>
<tr>
<td><strong>Final (12-month) Assessments</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADAS-Cog</td>
<td>9.57</td>
<td>4.70</td>
<td>6.86</td>
</tr>
<tr>
<td>TMT (Part B minus A), sec.</td>
<td>76.43</td>
<td>69.32</td>
<td>66.45</td>
</tr>
<tr>
<td>VDST (F minus B), sec.</td>
<td>2.18</td>
<td>1.83</td>
<td>3.27</td>
</tr>
<tr>
<td>Stroop Test, sec.</td>
<td>66.41</td>
<td>25.91</td>
<td>55.60</td>
</tr>
<tr>
<td>DSST</td>
<td>26.09</td>
<td>8.93</td>
<td>23.55</td>
</tr>
<tr>
<td>PPA</td>
<td>0.12</td>
<td>1.23</td>
<td>0.54</td>
</tr>
</tbody>
</table>

SD = Standard Deviation; MoCA = Montreal Cognitive Assessment (max. score 30); FCI = Functional comorbidity index (total number of comorbidities); ADAS-Cog = Alzheimer’s Disease Assessment Scale – Cognitive subscale (max. score of 70); TMT (B minus A) = Trail Making Test (Part B minus Part A); VDST (F minus B) = Verbal Digit Span Test (Forwards minus Backwards); DSST = Digit Symbol Substitution Test; PPA = Physiological Profile Assessment; * = n=7; † = n=9; ‡ = n=16

### 3.3.2 Association between amyloid-beta plaque deposition and cognitive function

*Global cognitive function*

Global Aβ plaque deposition was not statistically significantly associated with change in ADAS-Cog performance (p = 0.38) – Table 3.2.
Table 3.2 Multiple linear regression assessing the contribution of Aβ plaque deposition on change in ADAS-Cog performance

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>R²</th>
<th>Adjusted R²</th>
<th>R² Change</th>
<th>Unstandardized B (Standard Error)</th>
<th>Standardized β</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>0.17</td>
<td>0.08</td>
<td>0.17</td>
<td></td>
<td></td>
<td>0.18</td>
</tr>
<tr>
<td>ADAS baseline</td>
<td>1.31 (1.28)</td>
<td>0.22</td>
<td>0.32</td>
<td>0.18 (0.17)</td>
<td>0.41</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>0.20</td>
<td>0.07</td>
<td>0.04</td>
<td></td>
<td></td>
<td>0.42</td>
</tr>
<tr>
<td>ADAS-Cog baseline</td>
<td>1.34 (1.30)</td>
<td>0.23</td>
<td>0.44</td>
<td>0.42 (0.21)</td>
<td>0.54</td>
<td>0.06</td>
</tr>
<tr>
<td>Aβ deposition</td>
<td>-2.87 (3.47)</td>
<td>-0.22</td>
<td></td>
<td></td>
<td></td>
<td>0.42</td>
</tr>
</tbody>
</table>

ADAS-Cog = Alzheimer’s Disease Assessment Scale - Cognitive subscale baseline score

Executive functions

Trail Making Test (Part B minus A): Higher global Aβ plaque deposition was statistically significantly associated with decreased set shifting (β = -0.68, p < 0.01), the total adjusted variance accounted by the final model was 38.5% – Table 3.3.

Table 3.3 Multiple linear regression assessing the contribution of Aβ plaque deposition on change in Trail Making Test (Part B minus A)

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>R²</th>
<th>Adjusted R²</th>
<th>R² Change</th>
<th>Unstandardized B (Standard Error)</th>
<th>Standardized β</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>0.04</td>
<td>-0.07</td>
<td>0.04</td>
<td></td>
<td></td>
<td>0.70</td>
</tr>
<tr>
<td>TMT baseline</td>
<td>20.16 (25.44)</td>
<td>0.18</td>
<td>0.44</td>
<td></td>
<td>0.44</td>
<td></td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>0.47</td>
<td>0.39</td>
<td>0.44*</td>
<td></td>
<td></td>
<td>&lt;0.01</td>
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<tr>
<td>TMT baseline</td>
<td>5.42 (19.70)</td>
<td>0.05</td>
<td>0.79</td>
<td></td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>Aβ deposition</td>
<td>-166.43 (43.09)</td>
<td>-0.68</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

TMT = Trail Making Test (Part B minus A) baseline score
* Significant after false discovery rate adjustment
Verbal Digit Span Test (Forwards minus Backwards): Global Aβ plaque deposition was not statistically significantly associated with change in working memory ($p = 0.13$) – Table 3.4.

Table 3.4 Multiple linear regression assessing the contribution of Aβ plaque deposition on change in Verbal Digit Span Test (Forwards minus Backwards)

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>$R^2$</th>
<th>Adjusted $R^2$</th>
<th>$R^2$ Change</th>
<th>Unstandardized B (Standard Error)</th>
<th>Standardized $\beta$</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong></td>
<td>0.67</td>
<td>0.63</td>
<td>0.67</td>
<td></td>
<td></td>
<td>$&lt;0.01$</td>
</tr>
<tr>
<td>Group</td>
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<td></td>
<td>-1.00 (0.84)</td>
<td>-0.17</td>
<td>0.25</td>
</tr>
<tr>
<td>VDST baseline</td>
<td></td>
<td>0.94 (0.15)</td>
<td>0.85</td>
<td></td>
<td></td>
<td>$&lt;0.01$</td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
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<td>0.66</td>
<td>0.04</td>
<td></td>
<td></td>
<td>0.14</td>
</tr>
<tr>
<td>Group</td>
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<td></td>
<td></td>
<td>-1.19 (0.82)</td>
<td>-0.20</td>
<td>0.16</td>
</tr>
<tr>
<td>VDST baseline</td>
<td></td>
<td>0.95 (0.15)</td>
<td>0.86</td>
<td></td>
<td></td>
<td>$&lt;0.01$</td>
</tr>
<tr>
<td>Aβ deposition</td>
<td></td>
<td>-2.70 (1.73)</td>
<td>0.20</td>
<td></td>
<td>0.14</td>
<td>0.14</td>
</tr>
</tbody>
</table>

VDST = Verbal Digit Span Test (Forwards minus Backwards) baseline score

Stroop Test: Higher global Aβ plaque deposition was statistically significantly associated with decreased inhibition ($\beta = -0.54$, $p = 0.01$), the total adjusted variance accounted by the final model was 31.4% – Table 3.5.

Table 3.5 Multiple linear regression assessing the contribution of Aβ plaque deposition on change in Stroop Test

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>$R^2$</th>
<th>Adjusted $R^2$</th>
<th>$R^2$ Change</th>
<th>Unstandardized B (Standard Error)</th>
<th>Standardized $\beta$</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong></td>
<td>0.13</td>
<td>0.04</td>
<td>0.13</td>
<td></td>
<td></td>
<td>0.26</td>
</tr>
<tr>
<td>Group</td>
<td></td>
<td></td>
<td></td>
<td>-2.12 (11.12)</td>
<td>0.04</td>
<td>0.85</td>
</tr>
<tr>
<td>Stroop Test baseline</td>
<td></td>
<td>0.37 (0.22)</td>
<td>0.38</td>
<td></td>
<td>0.11</td>
<td>0.11</td>
</tr>
<tr>
<td>Independent Variables</td>
<td>R²</td>
<td>Adjusted R²</td>
<td>R² Change</td>
<td>Unstandardized B (Standard Error)</td>
<td>Standardized β</td>
<td>P-Value</td>
</tr>
<tr>
<td>-----------------------</td>
<td>------</td>
<td>-------------</td>
<td>-----------</td>
<td>-----------------------------------</td>
<td>----------------</td>
<td>---------</td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
<td>0.41</td>
<td>0.31</td>
<td>0.28*</td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>Group</td>
<td></td>
<td></td>
<td></td>
<td>-0.74 (9.46)</td>
<td>-0.02</td>
<td>0.94</td>
</tr>
<tr>
<td>Stroop Test baseline</td>
<td></td>
<td></td>
<td></td>
<td>0.45 (0.19)</td>
<td>0.46</td>
<td>0.03</td>
</tr>
<tr>
<td>Aβ deposition</td>
<td></td>
<td></td>
<td></td>
<td>-59.67 (20.46)</td>
<td>-0.54</td>
<td>0.01</td>
</tr>
</tbody>
</table>

* Significant after false discovery rate adjustment

**Information processing speed**

Higher global Aβ plaque deposition was statistically significantly associated with decreased information processing speed, as measured by the DSST ($\beta = -0.56$, $p = 0.01$), the total adjusted variance accounted by the final model was 20.6% – Table 3.6.

**Table 3.6** Multiple linear regression assessing the contribution of Aβ plaque deposition on change in DSST

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>R²</th>
<th>Adjusted R²</th>
<th>R² Change</th>
<th>Unstandardized B (Standard Error)</th>
<th>Standardized β</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong></td>
<td>0.02</td>
<td>-0.08</td>
<td>0.02</td>
<td></td>
<td></td>
<td>0.79</td>
</tr>
<tr>
<td>Group</td>
<td></td>
<td></td>
<td></td>
<td>-1.55 (2.26)</td>
<td>-0.16</td>
<td>0.50</td>
</tr>
<tr>
<td>DSST baseline</td>
<td></td>
<td></td>
<td></td>
<td>-0.01 (0.17)</td>
<td>-0.01</td>
<td>0.96</td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
<td>0.32</td>
<td>0.21</td>
<td>0.30*</td>
<td></td>
<td></td>
<td>0.01</td>
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<tr>
<td>Group</td>
<td></td>
<td></td>
<td></td>
<td>-2.45 (1.97)</td>
<td>-0.25</td>
<td>0.23</td>
</tr>
<tr>
<td>DSST baseline</td>
<td></td>
<td></td>
<td></td>
<td>-0.09 (0.15)</td>
<td>-0.12</td>
<td>0.56</td>
</tr>
<tr>
<td>Aβ deposition</td>
<td></td>
<td></td>
<td></td>
<td>-12.31 (4.41)</td>
<td>-0.56</td>
<td>0.01</td>
</tr>
</tbody>
</table>

DSST = Digit Symbol Substitution Test baseline score

* Significant after false discovery rate adjustment
3.3.3 Association between amyloid-beta plaque deposition and falls risk

Higher global Aβ plaque deposition was statistically significantly associated with increased falls risk, as measured by the PPA (β = -0.39, p = 0.03), the total adjusted variance accounted by the final model was 51.3% – Table 3.7.

**Table 3.7** Multiple linear regression assessing the contribution of Aβ plaque deposition on change in PPA

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>R²</th>
<th>Adjusted R²</th>
<th>R² Change</th>
<th>Unstandardized B (Standard Error)</th>
<th>Standardized β</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>0.45</td>
<td>0.39</td>
<td>0.45</td>
<td>-0.45 (0.32)</td>
<td>-0.24</td>
<td>0.17</td>
</tr>
<tr>
<td>PPA baseline</td>
<td></td>
<td></td>
<td></td>
<td>0.49 (0.13)</td>
<td>0.62</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>0.58</td>
<td>0.51</td>
<td>0.13*</td>
<td>-0.56 (0.29)</td>
<td>-0.30</td>
<td>0.07</td>
</tr>
<tr>
<td>PPA baseline</td>
<td></td>
<td></td>
<td></td>
<td>0.39 (0.13)</td>
<td>0.50</td>
<td>0.01</td>
</tr>
<tr>
<td>Aβ deposition</td>
<td></td>
<td></td>
<td></td>
<td>-1.60 (0.67)</td>
<td>-0.39</td>
<td>0.03</td>
</tr>
</tbody>
</table>

PPA = Physiological Profile Assessment baseline score

* Significant after false discovery rate adjustment

3.4 Discussion

Currently, much of our knowledge on the effects of co-existing Aβ pathology in SIVCI is based on cross-sectional studies 127-129 and little is known about their impact on change in cognitive and physical function over time. We found that higher global Aβ plaque deposition was statistically significantly associated with greater decrements in set shifting, inhibition, and information processing speed, and increased falls risk over a 12-month period. These results indicate that co-
existing Aβ plaque deposition may play a role in subsequent cognitive and physical declines in older adults with SIVCI.

Few studies have been conducted to assess the impact of Aβ plaques on change in cognitive function in people with a clinical diagnosis of SIVCI. The Amyloid PET Imaging for Subcortical Vascular Dementia study found that higher Aβ plaque deposition was associated with faster declines in attention, visuospatial skills, visual memory, and episodic memory, but no significant declines in executive functions were detected over a 3-year period [303]. However, we note that only a single executive measure was included, phonemic and semantic verbal fluency. Although verbal fluency tests do involve aspects of executive control, they do not isolate the three main components of executive functions (i.e., set shifting, working memory, and inhibition of dominant responses [16]), which we targeted in the present study. In addition to declines in set shifting and working memory, we also report that higher Aβ plaque deposition was associated with reduced information processing speed over time. In summary, these preliminary results indicate that co-existing Aβ plaque pathology may contribute to the evolution of impairment in executive functions (i.e., set shifting and response inhibition) and processing speed in people with SIVCI.

We did not find a significant association between global Aβ plaque deposition and change in global cognition as measured by the ADAS-Cog. This finding is contrary to a published cross-sectional analysis of the same data set, which reported a significant association between global Aβ plaque deposition and ADAS-Cog performance [127]. In the current analysis, we may not have found a significant association between global Aβ plaque deposition and change in ADAS-Cog
scores because the ADAS-Cog lacks sensitivity for measuring cognitive change in patients with relatively high MMSE scores (i.e., MMSE > 20) \textsuperscript{319}. We note that the average MMSE score in our cohort was 27.50 out of 30.

We also found that increased Aβ plaque deposition was also associated with increased falls risk. This concurs with previous literature. A study in healthy community-dwelling older adults found that higher Aβ plaque deposition was associated with faster time to first fall over 12 months \textsuperscript{140}. In addition, epidemiological studies found that 42\% of a community sample with mild to moderately severe AD fell within a 12-month period \textsuperscript{320,321}. This is supported by studies that have identified impaired static and dynamic balance, mobility, and gait dysfunction \textsuperscript{321}, which may contribute to an increased risk of falling in early AD. Furthermore, there is a strong association between executive functions, gait, and balance. Executive dysfunctions may increase falls risk via impaired planning, control, and execution of movements \textsuperscript{322}. Correspondingly, older adults with poor executive control walk slower, have increased stride variability, exhibit worse performance on complex mobility tasks, and fall more frequently \textsuperscript{323}.

Our findings are not without limitations. First, this study was a secondary analysis of an exercise intervention trial and it is unclear how exercise may have influenced cognitive function and falls risk. To minimize exercise effects, we statistically controlled for group membership and used data collected 6 months after the exercise intervention was completed (please refer to Appendix C for group specific regression analyses). Second, our small sample size requires that these findings be confirmed in larger follow-up studies. Third, we did not control for the presence of other AD and SIVCI pathologies such as neurofibrillary tangles, lacunes, or WMHs. This is
important to note, as neurofibrillary tangles have been associated with cognitive outcomes in AD. Also, lacunes and WMHs have been associated with both executive dysfunctions and falls risk. However, controlling for WMH volume and age, in a subset with available MRI data, did not significantly alter the results (please refer to Appendix D for these results). As such, it is plausible that Aβ plaque deposition may independently contribute to changes in executive functions, information processing speed, and falls risk in people with SIVCI. In summary, our findings suggest that Aβ plaque pathology may contribute to clinical symptoms characteristic of SIVCI (i.e., executive dysfunctions and gait disturbance); thus, future therapies for SIVCI may need to account for the potential presence and effect of Aβ plaque pathology for the optimal care of those with SIVCI.

3.5 Conclusion

Data from Chapter 3 indicates that higher global Aβ plaque deposition is associated with reduced executive functions and processing speed and increased falls risk over a 12-month period. Together, the results of Chapters 2 and 3 suggest that global Aβ plaque deposition may be predictive of both current (i.e., cross-sectionally) and subsequent (i.e., prospectively) cognitive and physical function. In the next chapter, I aim to further our understanding of SIVCI pathology by assessing the role of myelin content in cognitive function.
Chapter 4: What is the role of demyelination in cognitive function?

A version of this chapter has been submitted for publication.

4.1 Introduction

Cerebral small vessel ischemic WM damage, particularly the presence and progression of WMHs, is associated with both VCI\textsuperscript{11} and AD\textsuperscript{324}. While the association between WMHs and cognitive decline is consistent and robust, the observed effect is small ($r = -0.10$ [95\% confidence interval = -0.13 to -0.08])\textsuperscript{120}. This small observed effect size may be due to the heterogeneity of pathologic microstructural changes between and within WMHs. Post-mortem pathology studies suggest that small vessel ischemic WM damage can involve an array of changes including discontinuous ependymal, gliosis, loosening of WM fibers, or myelin loss\textsuperscript{38,48}. Notably, intact myelin is essential for proper brain function\textsuperscript{41}.

Myelin loss can severely compromise cerebral communication. Myelin is responsible for saltatory conduction of nerve impulses that allow high-speed and high-fidelity signal transmission. These properties are necessary to integrate information across dispersed neural networks that underlie cognitive abilities\textsuperscript{44}. Yet, the specific role of myelin content on cognitive outcomes is poorly understood. This, in part, has been due to the technical limitations in quantifying myelin in-vivo. Conventional T\textsubscript{1}w and T\textsubscript{2}w imaging can only capture macro-structural WM changes such as WMHs or WM volume, and are not specific for studies of myelin\textsuperscript{42}. Other imaging techniques, such as DTI and MTI (quantified as MTR) do not specifically measure myelin content\textsuperscript{45,89}. DTI metrics such as MD or FA measure the movement of water
within cerebral tissue and are unable to specify the WM substrate producing the observed signal. DTI metrics nonspecifically reflect microstructural complexity, membrane permeability, axonal density, and myelination 84. MTR is strongly influenced by inflammation and edema and is not specific to myelin content 88.

Notwithstanding the limitations of DTI and MTI in assessing myelin content, these techniques have demonstrated the importance of WM microstructure for cognitive function. Current evidence suggests that MD, FA, and MTR correlate with cognition, with FA as the most sensitive measure of age-related cognitive decline 325. Critically, both DTI and MTI have revealed changes in the NAWM, thought to represent early microstructural damage before lesions are seen as WMHs on conventional imaging 326. For example, a study using DTI and MTI reported reduced NAWM integrity with increasing WMH severity 327. Also, reduced NAWM integrity (i.e. MD and FA) was associated with cognitive impairment in several domains, including processing speed and executive functions 328-330.

Despite the growing recognition that subtle damage in NAWM microstructure impacts cognitive outcomes, the contribution of myelin content remains unclear. To better understand the role of myelin, studies need to use advanced neuroimaging techniques that allow myelin specific quantification in-vivo. Myelin can be measured with MWI using a multi-component T2-relaxation technique. The T2 signal is partitioned into water components representing cerebrospinal fluid, intra- and extra-cellular water, and myelin water trapped tightly between the myelin bilayers 89,331,332. Thus, myelin can be quantified as a ratio of myelin water to total water (the sum of all three T2 components), termed MWF. Histopathological studies report strong
correlations between MWF and myelin staining. To date, MWF correlates with myelin content better than other MR measures associated with myelin, such as MD, FA, or MTR.

Collectively, evidence suggests that pathological changes occur beyond the lesion to include cerebral NAWM and that damage to WM is primarily associated with changes in processing speed and executive functions. Myelin is a critical component of WM microstructure; yet, it is currently unclear whether myelin specific changes contribute to cognitive decline. Using an advanced imaging technique that allows myelin specific measurements (i.e., MWI), the objective of this study was investigate the association between myelin content (i.e., MWF) in the NAWM and cognitive function, specifically processing speed and executive functions, in older adults with MCI. We hypothesized that low myelin content in the NAWM will be associated with reduced processing speed and executive function performance.

4.2 Methods

4.2.1 Study design and participants

Ethical approval was obtained from the University of British Columbia’s Clinical Research Ethics Board (H15-00972 and H07-01160) and the Vancouver Coastal Health Research Institute (V15-00972 and V07-0172). All subjects gave written informed consent in accordance with the Declaration of Helsinki.

This study included participants from two studies. Thirty-three participants were included from an RCT assessing the effect of RT on cognitive function in older adults with MCI stemming
from cSVD (NCT02669394). For these 33 participants, their baseline data were used in this study. Another 22 participants were included from a cross-sectional study assessing differences in cognitive function between fallers with MCI and non-fallers with MCI (theses 22 participants exhibited WMHs on MRI). Participants were recruited from either the University of British Columbia Hospital Clinic for AD and Related Disorders or from advertisements placed in the community (i.e., newspaper advertisements, flyers, and brochures).

Individuals were eligible if they met the following criteria: 1) ≥ 50 years-old; 2) displayed cSVD based on the presence of WMHs on CT or MRI scans; 3) MoCA < 26/30; 4) MMSE ≥ 20/30; 4) community-dwelling and; 5) provide informed consent. Individuals were excluded if: 1) diagnosed with another type of neurodegenerative or neurological condition (e.g., AD, MS, Parkinson’s disease, etc.); 2) taking medications that may negatively affect cognitive function, such as anticholinergics, including agents with pronounced anticholinergic properties (e.g., amitriptyline), major tranquilizers (typical and atypical antipsychotics), and anticonvulsants (e.g., gabapentin, valproic acid, etc.); 3) participation in a clinical drug trial concurrent to this study and; 4) have contraindications to MRI scanning.

4.2.2 Descriptive variables

Information regarding age, sex, BMI (weight in kg/height in squared meters), and global cognition (MoCA and MMSE) were collected. We also acquired information on co-morbidities using the Functional Comorbidity Index, which estimates the degree of comorbidity associated with physical functioning.
4.2.3 Measures of cognitive function

We focused on processing speed and executive functions because these cognitive processes are strongly associated with WM ischemic damage 112,120.

Trail Making Test (Part A): This test measures processing speed, specifically psychomotor speed and visual scanning speed 335,336. In Part A, participants were asked to draw lines connecting encircled numbers sequentially.

Trail Making Test (Part B minus A): This test measures set shifting 335,336. Participants were asked to draw lines connecting encircled numbers sequentially (Part A) and to alternate between numbers and letters (Part B). The difference in time was calculated as Part B minus Part A; smaller difference indicates better set-shifting performance.

Verbal Digit Span Backwards Test: This test measures working memory 306,337. Participants are verbally presented with number sequences and are asked to repeat the number sequences in the reversed order. A higher score indicates better working memory performance.

Stroop Test: Participants completed three conditions (80 trials each): 1) reading out color words printed in black ink; 2) reading out the display color of colored-X’s; and 3) participants were shown a page with color-words printed in incongruent colored inks and were asked to name the ink color in which the words were printed. To measure the executive process of inhibition 307, the time difference between the third condition and second condition (i.e., color-words minus colored-Xs) was calculated; smaller difference indicates better response inhibition.
4.2.4 Magnetic resonance imaging acquisition

Magnetic resonance data was acquired at the University of British Columbia MRI Research Centre on a 3T Philips Achieva MRI scanner (Philips Medical Systems, Best, The Netherlands) using an eight-channel sensitivity encoding head coil and parallel imaging. The following scans were collected: 1) 3D T\textsubscript{1}w with an inversion recovery magnetization-prepared rapid gradient echo (MPRAGE) (TR = 1800 ms, TE = 3.5 ms, TI = 809.9 ms, flip angle θ = 8°, FOV = 256 × 200 mm, transverse orientation, 170 slices, acquired and reconstructed voxel = 1.00 × 1.00 × 1.00 mm); 2) 3D T\textsubscript{2}w (TR = 2500 ms, TE = 363 ms, flip angle θ = 90°, FOV = 256 × 256 mm, sagittal orientation, 200 slices, acquired voxel = 1.00 × 1.00 × 1.60 mm, reconstructed voxel = 0.80 × 0.80 × 0.80 mm); 3) PD\textsubscript{w} (TR = 3000 ms, TE = 30 ms, flip angle θ = 90°, FOV = 250 × 250 mm, sagittal orientation, 170 slices, acquired voxel = 0.99 × 1.00 × 1.00 mm, reconstructed voxel = 0.98 × 0.98 × 1.00 mm) and; 4) whole-cerebrum 48-echo 3D gradient and spin echo (GRASE) for T\textsubscript{2} measurement (TR = 1073, TE = 8, 16, 24…384, flip angle θ = 90°, FOV = 230 × 190 mm, slice oversampling factor = 1.3, SENSE = 2, transverse orientation, acquired in-plane voxel = .99 × 2.04, reconstructed in-plane voxel = 0.96 × 0.95, 20 slices acquired at 5 mm slice thickness, 40 slices reconstructed at 2.5 mm slice thickness) \textsuperscript{338}.

4.2.5 Myelin water fraction map of the normal appearing white matter

T\textsubscript{2} relaxation analysis used a modified non-negative least squares approach \textsuperscript{339} to reconstruct MWF maps from the acquired T\textsubscript{2} distributions. This approach reduced noise while improving border delineation of structures by using weighted averaging to avoid combining T\textsubscript{2} distributions that are very different. The T\textsubscript{2} signal was partitioned into long (>2 s – arising from cerebrospinal fluid), intermediate (40-200 ms – arising from intra- and extra-cellular water), and short (15-40 ms – arising from myelin water trapped tightly between the myelin bilayers) \textsuperscript{89,331,332} components.
using in-house software code developed at the University of British Columbia. MWF was quantified as a ratio by dividing the amplitude of the short T2 component (myelin water) by the amplitude across the entire distribution (total water, the sum of all three T2 components).

A NAWM MWF map was created for each participant. First, WM masks were generated from high-resolution 3DT1 images using an automated brain segmentation algorithm in FSL-FAST, followed by in-plane thresholding of voxels < 1. These WM masks were then co-registered to the GRASE image using FLIRT (transformation = 6 DOF rigid body; interpolation = nearest neighbor) to generate WM MWF masks. To remove WMHs (details of WMH segmentation are described below) from the WM mask, the T2w image was co-registered to the GRASE image using FLIRT (transformation = 6 DOF rigid body; interpolation = spline) to obtain a transformation matrix. Using the applywarp command in FSL, the WMH mask was resampled to the GRASE image using the transformation matrix and nearest neighbor interpolation. The resampled WMH mask was then used to remove WMH voxels from the WM mask to generate a NAWM mask for each participant. These NAWM masks were used to generate NAWM MWF maps. All WM masks and NAWM WM masks were visually inspected ensure accurate co-registration with GRASE images. When necessary, the masks were edited in FSLeyes. The NAWM MWF maps were also visually inspected to ensure the maps were accurately generated.

To calculate an average NAWM MWF value for each participant, histograms were calculated by summing the number of voxels with MWF values between 0 and 30% into 100 uniform bins. To account for differences in brain size and tissue volume, each participant’s histogram was scaled
by the total number of data points. The histogram mean reflects the average value of myelin content within the NAWM.

### 4.2.6 White matter hyperintensity volume

Full details on WMH segmentation procedures are described in previous work \(^71\). This segmentation method has been validated in large data sets with a wide range of lesion loads, has high agreement with a gold standard manual method (dice coefficient = 80% and Spearman’s rank correlation = 0.99), and is robust to variations in seed point placements \(^71\). Briefly, WMHs were identified and digitally marked by a radiologist with experience in WMH identification. Next, WMHs were segmented by a method that automatically computed the extent of each marked lesion. Specifically, the seed points were processed by a customized Parzen windows classifier \(^342\) 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 \(^71\). The lesion masks were then used to quantify WMH volumes in cubic millimeters (mm\(^3\)). All WMH lesion masks were reviewed by a trained research assistant (E.D.) to ensure accuracy.

### 4.2.7 Statistical analysis

All statistical analyses were performed using Statistical Package for the Social Sciences 22.0. Statistical significance was based on an alpha of \(\leq .05\). A bivariate correlation analysis assessed the relationship between NAWM MWF and log-transformed total WMH volume (WMHs were non-normally distributed so they were log-transformed). Multiple linear regression analyses were conducted to obtain estimates for the independent contribution of NAWM MWF on cognitive
function. Four separate models were constructed to assess the effect of NAWM MWF on Trail Making Test (Part A), Trail Making Test (Part B minus A), Verbal Digit Span Backwards Test, and Stroop Test. In each statistical model, we first controlled for age, MoCA score, and total WMH volume. NAWM MWF was then entered to determine its unique and additional contribution to cognitive function.

For each regression model, we computed collinearity statistics (tolerance and variance inflation factor), histograms of the residuals, and scatterplots of the predicted versus residual values to ensure that the assumptions of linear regression were met. In all models, multicollinearity was not an issue among predictor variables, and the residuals were normally distributed and homoscedastic.

4.3 Results

4.3.1 Participants

Fifty-five participants (34 females) were included in this cross-sectional study. The mean age was 76 years old. The mean MoCA score was 21 and the mean MMSE score was 27. Table 4.1 reports descriptive characteristics.
### Table 4.1 Descriptive characteristics (N=55)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean or No.</th>
<th>SD or %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>75.71</td>
<td>5.83</td>
</tr>
<tr>
<td>Female Sex, No. (%)</td>
<td>34</td>
<td>61.82</td>
</tr>
<tr>
<td>MoCA (max. score 30)</td>
<td>21.44</td>
<td>3.46</td>
</tr>
<tr>
<td>MMSE (max. score 30)</td>
<td>27.40</td>
<td>1.83</td>
</tr>
<tr>
<td>BMI</td>
<td>26.60</td>
<td>4.67</td>
</tr>
<tr>
<td>FCI</td>
<td>3.20</td>
<td>1.83</td>
</tr>
<tr>
<td>Neuroimaging Biomarkers</td>
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<td></td>
</tr>
<tr>
<td>NAWM MWF</td>
<td>0.10</td>
<td>0.01</td>
</tr>
<tr>
<td>Total WMH volume</td>
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<td>9861.17</td>
</tr>
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<td>Cognitive Function Tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMT (Part A), sec.</td>
<td>41.02</td>
<td>17.04</td>
</tr>
<tr>
<td>TMT (Part B minus A), sec.</td>
<td>88.54</td>
<td>106.20</td>
</tr>
<tr>
<td>Verbal Digit Span Backwards Test</td>
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<td>1.93</td>
</tr>
<tr>
<td>Stroop Test, sec.</td>
<td>52.23</td>
<td>40.63</td>
</tr>
</tbody>
</table>

MoCA = Montreal Cognitive Assessment; MMSE = Mini-Mental State Examination; BMI = Body Mass Index; FCI = Functional Comorbidity Index; NAWM MWF = Normal Appearing White Matter Myelin Water Fraction; WMH = White Matter Hyperintensity; TMT Part A = Trail Making Test Part A; TMT (Part B minus A) = Trail Making Test (Part B minus A)

#### 4.3.2 Bivariate correlation

NAWM MWF was statistically significantly correlated with total log-transformed WMH volume

\( r = -0.28, p = 0.04 \) – Figure 4.1.
**Figure 4.1** Bivariate correlation between NAWM MWF and log-transformed WMH volume

### 4.3.3 Associations between normal appearing white matter myelin water fraction and cognitive function

For processing speed, after accounting for age, MoCA, and total log-transformed WMH volume, higher NAWM MWF was statistically significantly associated with faster processing speed (i.e., Trail Making Test [Part A]; $\beta = -0.32; p = 0.01$); the total variance accounted by the model was 35% (Table 4.2 and Figure 4.2).

<table>
<thead>
<tr>
<th>Table 4.2 Multiple linear regression assessing the contribution of NAWM MWF on Trail Making Test (Part A)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Independent Variables</strong></td>
</tr>
<tr>
<td>----------------------------</td>
</tr>
<tr>
<td><strong>Step 1</strong></td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>MOCA</td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>MOCA</td>
</tr>
<tr>
<td>WMH volume logged</td>
</tr>
<tr>
<td><strong>Step 3</strong></td>
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</tr>
<tr>
<td>MOCA</td>
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<tr>
<td>WMH volume logged</td>
</tr>
<tr>
<td>NAWM MWF</td>
</tr>
</tbody>
</table>

*Significant at $p \leq 0.05$
For executive functions, NAWM MWF was not statistically significantly associated with set shifting (i.e., Trail Making Test [Part B minus A]; \( p = 0.11 \); Table 4.3 and Figure 4.3). After accounting for age, MoCA, and total log-transformed WMH volume, higher NAWM MWF was statistically significantly associated with better working memory performance (i.e., Verbal Digit Span Backwards Test, \( \beta = 0.29 \); \( p = 0.04 \)); the total variance accounted by the model was 17% (Table 4.4 and Figure 4.4). NAWM MWF was not statistically significantly associated with inhibitory control (i.e., Stroop Test; \( p = 0.84 \); Table 5.5).
Table 4.3 Multiple linear regression assessing the contribution of NAWM MWF on Trail Making Test (Part B minus A)

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>$R^2$</th>
<th>Adjusted $R^2$</th>
<th>$R^2$ Change</th>
<th>Unstandardized B (Standard Error)</th>
<th>Standardized $\beta$</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age</td>
<td>0.21</td>
<td>0.17</td>
<td>0.21</td>
<td>2.12 (2.28)</td>
<td>0.12</td>
<td>0.36</td>
</tr>
<tr>
<td>MOCA</td>
<td></td>
<td></td>
<td></td>
<td>-13.91 (3.83)</td>
<td>-0.45</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Age</td>
<td>0.21</td>
<td>0.16</td>
<td>0.00</td>
<td>1.82 (2.51)</td>
<td>0.10</td>
<td>0.47</td>
</tr>
<tr>
<td>MOCA</td>
<td></td>
<td></td>
<td></td>
<td>-13.69 (3.94)</td>
<td>-0.45</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>WMH volume logged</td>
<td></td>
<td></td>
<td></td>
<td>6.07 (20.68)</td>
<td>-0.04</td>
<td>0.77</td>
</tr>
<tr>
<td><strong>Step 3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.25</td>
<td>0.19</td>
<td>0.04</td>
<td>0.63 (2.57)</td>
<td>0.03</td>
<td>0.81</td>
</tr>
<tr>
<td>MOCA</td>
<td></td>
<td></td>
<td></td>
<td>-14.06 (3.88)</td>
<td>-0.46</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>WMH volume logged</td>
<td></td>
<td></td>
<td></td>
<td>0.25 (20.65)</td>
<td>&lt;0.01</td>
<td>0.99</td>
</tr>
<tr>
<td>NAWM MWF</td>
<td></td>
<td></td>
<td></td>
<td>-1847.47 (1119.24)</td>
<td>-0.22</td>
<td>0.11</td>
</tr>
</tbody>
</table>

$R^2 = 0.25$

Figure 4.3 Multiple linear regression line for Table 4.3
Table 4.4 Multiple linear regression assessing the contribution of NAWM MWF on Verbal Digit Span Backwards Test

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>R²</th>
<th>Adjusted R²</th>
<th>R² Change</th>
<th>Unstandardized B (Standard Error)</th>
<th>Standardized β</th>
<th>P-Value</th>
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</thead>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.09</td>
<td>0.05</td>
<td>0.09</td>
<td>0.02 (0.04)</td>
<td>0.06</td>
<td>0.68</td>
</tr>
<tr>
<td>MOCA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.16 (0.07)</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.10</td>
<td>0.04</td>
<td>0.01</td>
<td>0.03 (0.05)</td>
<td>0.10</td>
<td>0.50</td>
</tr>
<tr>
<td>MOCA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.15 (0.08)</td>
<td>0.06</td>
</tr>
<tr>
<td>WMH volume logged</td>
<td></td>
<td></td>
<td></td>
<td>-0.30 (0.40)</td>
<td>-0.11</td>
<td>0.47</td>
</tr>
<tr>
<td><strong>Step 3</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.17</td>
<td>0.10</td>
<td>0.07*</td>
<td>0.06 (0.05)</td>
<td>0.19</td>
<td>0.22</td>
</tr>
<tr>
<td>MOCA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.16 (0.07)</td>
<td>0.04</td>
</tr>
<tr>
<td>WMH volume logged</td>
<td></td>
<td></td>
<td></td>
<td>-0.16 (0.39)</td>
<td>-0.06</td>
<td>0.70</td>
</tr>
<tr>
<td>NAWM MWF</td>
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<td></td>
<td></td>
<td>44.41 (21.32)</td>
<td>0.29</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*Significant at p ≤ 0.05

Figure 4.4 Multiple linear regression line for Table 4.4  
*Significant at p ≤ 0.05
Table 4.5 Multiple linear regression assessing the contribution of NAWM MWF on Stroop Test

<table>
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<tr>
<th>Step 1</th>
<th>R²</th>
<th>Adjusted R²</th>
<th>R² Change</th>
<th>Unstandardized B (Standard Error)</th>
<th>Standardized β</th>
<th>P-Value</th>
</tr>
</thead>
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<td>0.07</td>
<td>1.03 (.94)</td>
<td>0.15</td>
<td>0.28</td>
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<tr>
<td>MOCA</td>
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<td>0.03</td>
<td>0.01</td>
<td>-2.68 (1.59)</td>
<td>-0.23</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Step 2

<table>
<thead>
<tr>
<th>Step 2</th>
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<th>Adjusted R²</th>
<th>R² Change</th>
<th>Unstandardized B (Standard Error)</th>
<th>Standardized β</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.08</td>
<td>0.03</td>
<td>0.01</td>
<td>0.66 (1.03)</td>
<td>0.09</td>
<td>0.53</td>
</tr>
<tr>
<td>MOCA</td>
<td>0.08</td>
<td>0.03</td>
<td>0.01</td>
<td>-2.40 (1.62)</td>
<td>-0.20</td>
<td>0.15</td>
</tr>
<tr>
<td>WMH volume logged</td>
<td>0.08</td>
<td>0.03</td>
<td>0.01</td>
<td>7.70 (8.52)</td>
<td>0.13</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Step 3

<table>
<thead>
<tr>
<th>Step 3</th>
<th>R²</th>
<th>Adjusted R²</th>
<th>R² Change</th>
<th>Unstandardized B (Standard Error)</th>
<th>Standardized β</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.08</td>
<td>0.01</td>
<td>&lt;0.01</td>
<td>0.72 (1.09)</td>
<td>0.10</td>
<td>0.51</td>
</tr>
<tr>
<td>MOCA</td>
<td>0.08</td>
<td>0.01</td>
<td>&lt;0.01</td>
<td>-2.38 (1.64)</td>
<td>-0.20</td>
<td>0.15</td>
</tr>
<tr>
<td>WMH volume logged</td>
<td>0.08</td>
<td>0.01</td>
<td>&lt;0.01</td>
<td>7.99 (8.73)</td>
<td>0.14</td>
<td>0.36</td>
</tr>
<tr>
<td>NAWM MWF</td>
<td>0.08</td>
<td>0.01</td>
<td>&lt;0.01</td>
<td>93.64 (473.31)</td>
<td>0.03</td>
<td>0.84</td>
</tr>
</tbody>
</table>

R² = 0.08

Table 4.5 Multiple linear regression line for Table 4.5
4.4 Discussion

The primary objective of this study was to assess the independent contribution of myelin content on cognitive function in older adults with MCI. After accounting for age, global cognition, and total WMH volume lower myelin content was statistically significantly associated with worse performance on processing speed and working memory. To our knowledge, this is the first study to use a myelin specific imaging technique to report an association between myelin loss and impairments in processing speed and working memory in people with MCI.

Both processing speed and working memory are sensitive to the effects of aging, which steadily declines starting from the third decade of life. In tandem to these age-related changes in cognitive function, myelin content peaks in the mid-30’s then begins to deteriorate with advancing age, depicting a quadratic (inverted U) trajectory. Thus, declines in processing speed and working memory and myelin breakdown may be associated as they follow a similar time trajectory.

Moreover, our results concur and extend prior studies implicating WM microstructural changes in processing speed, using qualitative imaging. Lu and colleagues reported that myelin integrity in the prefrontal lobe WM and the genu of the corpus callosum was associated with slower processing speed, as measured by a composite of the Trail Making Test (Part A) and Digit Symbol Test from the Wechsler Adult Intelligence Scale-R, in healthy older adults. In a study assessing myelination in specific WM tracts, myelin breakdown in the anterior limb of the internal capsule and the left splenium of the corpus callosum was associated with slower processing speed, as measured by the Trail Making Test (Part A). However, in assessing the
association between whole brain WM myelin and processing speed, a significant association was not found. This finding is in contrast to our results, but we note that Lu et al. and Chopra et al. used qualitative imaging techniques (i.e., transverse relaxation time from T2w images and T1w/T2w ratio, respectively) that do not specifically measure myelin content. Using a myelin specific imaging technique, we affirm the relationship between myelin and processing speed previously suggested by qualitative imaging sequences and DTI imaging.

To our knowledge, this is the first study to report an association between myelin content and working memory. Working memory involves widespread cerebral networks, including bilateral frontal-parietal, frontal-temporal, and parietal-temporal tracts. Consequently, working memory performance may be influenced by the strength of the anatomical connectivity between these cerebral networks. Notably, myelin is crucial in the sharing and integration of information across these distant brain regions. Our results suggest that a widespread reduction in myelin content may negatively impact working memory.

We did not find an association between myelin content and set shifting or inhibition. This may be due to subtle differences in brain regions sub-serving set shifting and inhibition compared with processing speed and working memory. Neuroimaging studies suggest that set shifting and inhibition may elicit greater activation of posterior (i.e., parietal) regions compared with anterior (i.e., frontal) brain regions. For example, a DTI study found that age-related degradation in the posterior regions were associated with both task switching costs and reduced inhibitory control, whereas reduced WM integrity in anterior brain regions was associated with slower processing speed and poorer working memory. This is supported by another study that found
that lower WM integrity in the posterior (i.e., inferior longitudinal fasciculus) but not anterior (i.e., superior longitudinal fasciculus) tracts mediated age related declines in inhibitory control measured by the Stroop Test 359. Critically, myelin deterioration also has an anterior-posterior trajectory.

Myelination of the human brain generally progresses from posterior to anterior regions (e.g., occipital poles myelinate before frontotemporal poles), but myelin breakdown in aging shows the reverse trajectory from development. Myelin breakdown begins in anterior regions before progressing to posterior brain regions 44,346,360. This is further supported by DTI data showing that age associated differences in WM integrity exhibit an anterior-to-posterior gradient, with anterior regions showing greater age associated WM deterioration 361-364. As indicated earlier, processing speed and working are associated with both anterior and posterior regions, and early damage to anterior WM may largely account for the association between reduced myelin content and these executive measures. In contrast, task switching and inhibition are more associated with posterior regions of the brain, which may exhibit delayed myelin breakdown. An unequal distribution of myelin breakdown may explain, at least in part, why myelin content was associated with processing speed and working memory, but not with set shifting and inhibition.

There are limitations to this study. First, this is a cross-sectional study and no conclusions can be made about causality. Second, different regions of the brain may exhibit different rates of myelin loss; as such, our global measure of MWF may overlook the regional effects of cerebral demyelination on cognitive function. Furthermore, there are limitations inherent to MWI such as
low signal-to-noise ratio and partial-volume contamination, but as a strength, MWI is currently the most specific measure of cerebral myelin 92,93.

Using an advanced imaging technique, the results of our study suggest that demyelination may play a distinct role in cognitive impairment, specifically processing speed and working memory. Future studies, with a longitudinal design, are needed to fully elucidate the role of myelin loss in cognitive outcomes and to affirm MWF as a potential biomarker for cognitive impairment. It is important that we continue this line of inquiry as MWF may prove to be a sensitive marker in monitoring disease progression and may be applicable in assessing clinical intervention studies in people with cognitive impairment.

4.5 Conclusion

The results of Chapter 4 indicate that lower myelin content is associated with worse performance on processing speed and working memory after accounting for the effects of WMHs. Overall, data from Chapters 2, 3, and 4 suggest that brain pathologies such as cerebral Aβ plaque deposition and myelin content, which are often overlooked in the assessment of SIVCI, are associated with cognitive and physical dysfunction. In the following final research chapter, I will assess strategies that may reduce the progression of cSVD, specifically I will assess the efficacy of AT in mitigating the progression of WMHs.
Chapter 5: Can aerobic training mitigate white matter hyperintensity progression and are these changes sex dependent?


5.1 Introduction

SIVCI is the second most common cause of cognitive impairment and dementia. It is associated with low-grade chronic ischemia resulting in WMHs. Epidemiological data consistently characterize WMHs as progressive in nature. Both the Rotterdam Scan Study and the LADIS Study report visible WMH progression after 3 years in community dwelling non-demented older adults. Evidence also suggests there is a sex difference in WMH burden and progression with females having greater burden and progression over time than males. Critically, WMH progression is associated with subsequent declines in global cognition and executive functions; therefore, it is crucial to develop strategies to mitigate WMH progression.

Aerobic exercise may be a promising strategy to mitigate WMH progression by controlling vascular risk factors such as obesity, type 2 diabetes, hypercholesterolemia, and hypertension. For example, in a 4.1-year average follow-up Finnish study, people who spent at least 2.5 hours a
week walking for exercise were 63-69% less likely to develop type 2 diabetes compared with those who walked less than 1 hour a week. Regular physical activity may also aid in reducing lipid levels. A meta-analysis of AT programs in older adults found that AT increased high density lipoprotein (the “good” cholesterol) and decreased the ratio of total cholesterol to high density lipoprotein cholesterol (higher ratios indicate higher risk of cardiovascular disease), independent of changes in body composition. In addition, a meta-analysis of 54 RCTs found that regular aerobic exercise decreased systolic and diastolic blood pressure in hypertensive adults. Increased aerobic activity may reduce vascular risk factors by reducing aortic stiffness and enhancing flow-mediated arterial dilation.

In addition, aerobic exercise has been shown to induce positive structural brain plasticity. Specifically, an RCT conducted by Colcombe and colleagues showed that a 6-month AT program significantly increased GM and WM volume in brain regions susceptible to age-related brain atrophy (i.e., prefrontal and temporal regions) in older adults. Another study demonstrated that a 6-month AT program significantly increased total hippocampal volume in older women with probable MCI. In an SIVCI cohort, ten Brinke and colleagues found that improved functional cardiovascular fitness, derived from a 6-month AT program, was associated with maintenance of cortical thickness over time. In addition, improved cardiovascular fitness may modify WM integrity and WMH volume. Higher cardiovascular fitness (i.e., VO2 peak and total time on a treadmill) was associated with greater WM integrity (i.e., FA) in the corpus callosum, which enables sensory, motor, and cognitive integration across the hemispheres, in healthy older adults. Moreover, a cross-sectional study assessing the link between physical activity found that moderate-to-vigorous physical activity was correlated with lower WMH volume.
Together, these studies demonstrate that aerobic exercise or increased aerobic fitness may have protective effects on brain structure including reduced WMH volume.

Aerobic exercise is also effective for promoting cognitive function, including executive functions and spatial memory. Several RCTs have established the beneficial effects of AT on cognitive function in healthy older adults, people with MCI, and recently in people with SIVCI. However, the magnitude of exercise effects on cognition may be moderated by biological sex. Specifically, a meta-analysis conducted by Colcombe and Kramer found that studies with more women (>50%) showed a significantly larger effect size (Hedges’ g = 0.60) for AT on cognition than studies with fewer women. These results were confirmed by a more recent meta-analysis that reported greater beneficial effects of AT compared to controls on executive functions (i.e., significantly larger effect size, Hedges’ g = 2.06) in studies with a higher percentage of women participants (>71%). Furthermore, cross-sectional studies have indicated that a greater amount, duration, and frequency of daily walking activity and greater cardiorespiratory fitness was associated with structural brain changes, specifically a larger hippocampal volume (a region important for learning and memory) in non-demented women but not men. The exact mechanisms for these sex differences are not well understood, but could potentially stem from sex differences in exercise-induced neuronal changes.

Overall, current evidence indicates that regular aerobic activity may be a promising strategy to reduce vascular risk factors and promote positive structural plasticity in the brain. Hence, the goal of this secondary analysis of data acquired from an RCT was to investigate the effect of a 6-month, thrice weekly AT program on WMH progression. In addition,
we conducted an exploratory analysis to determine whether these changes are sex dependent. We hypothesized that AT would reduce WMH progression compared with usual care (i.e., control group), with greater effects observed among females than males. The examination of sex differences in health research is a timely endeavor, as this is currently lacking within the context of Canadian RCTs.

5.2 Methods

5.2.1 Study design and participants

Ethical approval was obtained from the Vancouver Coastal Health Research Institute (V07-01160) and the University of British Columbia’s Clinical Research Ethics Board (H07-01160). All subjects gave written informed consent in accordance with the Declaration of Helsinki.

This is a secondary (i.e., the effect of AT on WMH progression) and exploratory (i.e., sex-differences) analysis of data acquired from the PROMoTE Study, a proof-of-concept RCT designed to assess the effect of a 6-month, thrice-weekly, progressive AT program on cognitive function in older adults with mild SIVCI. Eligible participants were randomized into either a 6-month AT or a usual care (control; CON) group. This study used measurements taken at baseline and at trial completion (6 months post-randomization). A subset of participants volunteered and was eligible for MRI, which was completed at baseline and trial completion.

Appendix E includes an additional analysis assessing the association between change in WMH volume and change in cognitive function.
These scans were used for WMH volume quantification. The design and primary results of the parent study have been published 156,267.

Participants were recruited from the University of British Columbia Hospital Clinic for AD and Related Disorders, the Vancouver General Hospital Stroke Prevention Clinic, and specialized geriatric clinics in Metro Vancouver, British Columbia. Clinical diagnosis of SIVCI was confirmed in each participant by a neurologist based on the presence of cSVD and cognitive impairment 269. Clinical MRI or CT scans were used to ascertain the presence of cSVD, defined as the presence of periventricular or deep WMHs and the absence of cortical-subcortical nonlacunar territorial infarcts and watershed infarcts, hemorrhages indicating large vessel disease, signs of normal-pressure hydrocephalus, or other specific signs of WMHs (i.e., MS, leukodystrophies, sarcoidosis, brain irradiation). Cognitive impairment was defined as a MoCA score < 26/30. Diagnosis of SIVCI also required evidence of progressive cognitive decline (compared with previous level of cognitive function) as confirmed through medical records or caregiver/family member interviews. Overall, participants were community dwelling and living independently with minimal assistance from family or caregiver.

Both inclusion and exclusion criteria have been published previously 267. Briefly, individuals were eligible for study entry if they met the following criteria: 1) ≥ 55 years-old; 2) MoCA score < 26/30 17; 3) MMSE score ≥ 20/30 18; 4) if on cognitive medication (e.g., donepezil, galantamine, rivastigmine, memantine, etc.), remaining on a fixed dosage during the study period and; 5) provide written informed consent.
Study exclusion criteria included: 1) being diagnosed with dementia of any type (e.g. AD, vascular dementia, Lewy body dementia, frontal-temporal dementia, etc.) or other neurological conditions (e.g. MS, Parkinson’s disease, etc.); 2) taking medications that may negatively affect cognitive function, such as anticholinergics, including agents with pronounced anticholinergic properties (e.g., amitriptyline), major tranquilizers (typical and atypical antipsychotics), and anticonvulsants (e.g., gabapentin, valproic acid, etc.) and; 3) participation in a clinical drug trial concurrent to this study.

5.2.2 Descriptive variables

At baseline, information regarding age, sex, BMI (weight in kg/height in squared meters), waist-to-hip ratio (waist circumference/hip circumference), and global cognition (MMSE and MoCA) were collected. We also acquired information on co-morbidities using the Functional Comorbidity Index, which estimates the degree of comorbidity associated with physical functioning. Depression was assessed using the 15 item Geriatric Depression Scale.

5.2.3 ApoE ε4 genotype

ApoE genotype was determined using TaqMan® assay systems for the single nucleotide polymorphisms – 219G/T. DNA was extracted from whole blood using an automated DNA extraction machine (AutogenflexStar, Autogen Inc, Hollisten, MA). Because the ApoE ε4 genotype is relatively rare, the ApoE ε4 genotype odds ratios were collapsed into two main categories: those with at least one ε4 allele or those with no ε4 allele.
5.2.4 Change in general functional cardiovascular capacity and change in white matter hyperintensity volume

5.2.4.1 Change in general functional cardiovascular capacity
General functional cardiovascular capacity was assessed using the 6-Minute Walk Test (6MWT). Participants were instructed to walk as quickly as possible for 6 minutes, and the distance walked in meters was recorded. Performance on this test has been used as an indicator of cardiovascular capacity. It is correlated with peak oxygen uptake and is used in RCTs as a fitness outcome measure. A meaningful change for moderate effects in 6MWT performance is 47 to 49 meters and the standard error of measurement is 22 meters.

5.2.4.2 Change in white matter hyperintensity volume
Structural MRI data was acquired at baseline and trial completion on a Philips 3T Achieva MRI scanner (Philips Medical Systems, Best, The Netherlands) at the UBC MRI Research Centre. A T₂w (TR = 5428 ms, TE = 90 ms, flip angle θ = 90°, FOV = 240 × 191 mm, axial orientation, 60 slices, voxel size = 0.94 × 0.94 × 3.00 mm) and PDw (TR = 2000 ms, TE = 8 ms, flip angle θ = 90°, FOV = 240 × 1910 mm, transverse orientation, 60 slices, reconstructed voxel = 0.94 × 0.94 × 3.00 mm).

All WMH volume was computed using MRI scans. Magnetic resonance images were preprocessed using standard and publicly available neuroimaging tools that included: 1) MR intensity inhomogeneity correction using a multiscale version of the nonparametric non-uniform intensity normalization method (N3); 2) application of a structure-preserving noise-removal
filter (Smallest Univalve Segment Assimilating Nucleus) was applied and; 3) removal of all non-brain tissues were removed using the brain extraction tool.

WMHs were then identified and digitally marked by a radiologist with experience in WMH identification. The radiologist was blinded to all participant information, including treatment assignment. Baseline and 6-month scans were co-registered and reviewed together to ensure consistency of identification of small lesions across time. The radiologist used the following guidelines in the seeding procedure, which was designed to be efficient and intuitive: 1) mark all distinct WMHs regardless of size; 2) place more than one point on a lesion if the additional points helped define the extent of the lesion and; 3) place at least one point near the center of each lesion.

WMHs were segmented by a method that automatically computed the extent of each marked lesion. This segmentation method has been validated in large data sets with a wide range of lesion loads, has high inter-rater agreement (dice coefficient = 80% and Spearman’s rank correlation = 0.99), and is robust to variations in seed point placements. Full details on the point placement procedure and subsequent automatic segmentation are described in previous work. Briefly, the seed points were processed by a customized Parzen windows classifier 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 lesion masks were then used to quantify WMH volumes in mm$^3$. All lesion masks were reviewed by a trained research assistant (E.D.) to ensure accuracy.

### 5.2.6 Randomization and allocation concealment

Participants were randomly assigned (1:1) to either a 6-month AT or CON group. The randomization sequence was generated by a web-based randomization service at, http://www.randomization.net.

### 5.2.7 Experimental group: Aerobic training group

Certified exercise instructors led all AT classes. Classes occurred three times a week, and each class was 60 minutes long and consisted of 40 minutes of walking with a 10-minute warm-up and cool down session. Participants walked along a predetermined outdoor route. Over the 6-month intervention period, we progressed the intensity of the AT program and monitored participants’ progression with the following techniques: 1) Participants wore a heart rate monitor and were initially asked to work at approximately 40% of their age-specific target heart rate (i.e., heart rate reserve). Over the first 12 weeks, participants were asked to gradually increase the intensity to 60%-70% of heart rate reserve, with the target being 65%. Once the target was achieved, it was sustained by the participant for the remainder of the intervention period. 2) We subjectively monitored the intensity of each workout using the Borg's Rating of Perceived Exertion with a target of 14-15 (i.e., “somewhat hard” to “hard”). 3) We used a "talk" test in which participants were asked to initially walk at a pace at which they could converse comfortably without effort and gradually progress to a pace at which conversation required some effort.
5.2.8 Control group: Usual care plus education group

Participants in the CON group met monthly in a group setting to receive educational material about SIVCI and a healthy diet. This information was also offered to participants in the AT group. In addition, research staff phoned the CON participants on a monthly basis to maintain contact and to acquire research data.

5.2.9 Compliance and adverse events

Compliance was calculated based on the percentage of total classes attended. To monitor adverse effects, participants were questioned about the presence of any discomforts (i.e. musculoskeletal pain) at each session. During AT, instructors also monitored participants for symptoms of angina pectoris and shortness of breath.

5.2.10 Statistical analysis

All statistical analyses were performed using Statistical Package for the Social Sciences 24.0. Data were checked to ensure that the assumptions of analysis of covariance were met. Plots of standardized residuals indicated that the data were normally distributed and homoscedastic.

To assess change in functional cardiovascular capacity, a $2 \times 2$ analysis of covariance was conducted to determine the effect of group (AT vs. CON), sex, and group $\times$ sex interaction. The dependent variable was change in 6MWT (trial completion minus baseline values; higher values indicate improved performance). We controlled for baseline 6MWT performance, age, and BMI. If a significant interaction was identified, planned pairwise comparisons (with Bonferroni corrected $p$ values) were done to examine sex differences within and between groups.
To determine the effect of AT and sex on change in WMH volume, we conducted a $2 \times 2$ analysis of covariance to determine the effect of group (AT vs. CON), sex, and group $\times$ sex interaction. The dependent variable was change in WMH volume (trial completion minus baseline WMH volume; higher values indicate increased WMH volume at trial completion). We controlled for baseline WMH volume, age, and ApoE $\varepsilon 4$ status. If a significant interaction was identified, planned pairwise comparisons (with Bonferroni corrected p-values) were done to examine sex differences within and between groups.

5.3 Results

5.3.1 Participants

Seventy eligible participants consented and were randomized in the parent study. Of the 70 participants, 39 consented to MRI scans, but 3 were ineligible due to MRI contraindications. Of the 36 people who completed baseline MRI scan, 29 completed MRI scan at trial completion. Of these 29 participants that completed both baseline and trial completion MRI scans, 16 participants were randomized to the AT group and 13 participants were randomized to the CON group.

Table 5.1 reports baseline descriptive characteristics of these 29 participants. Compared with the remaining participants in the parent study, this subset had a higher mean MoCA score (mean difference = 1.86, $p = 0.05$). No other differences in descriptive characteristics were observed, including age ($p > 0.05$) and MMSE score ($p > 0.05$). Furthermore, independent samples t-test
reported no significant baseline differences in WMH volume (p > 0.05) or 6MWT (p > 0.05) between AT and CON females or males.

**Table 5.1** Descriptive characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>AT group</th>
<th>CON group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td></td>
<td>Females (n=7)</td>
<td>Males (n=9)</td>
</tr>
<tr>
<td>Age</td>
<td>69.86 (7.60)</td>
<td>73.89 (10.25)</td>
</tr>
<tr>
<td>BMI</td>
<td>24.38 (2.82)</td>
<td>27.02 (6.85)</td>
</tr>
<tr>
<td>WHR</td>
<td>0.86 (0.06)</td>
<td>0.93 (0.06)</td>
</tr>
<tr>
<td>MoCA</td>
<td>20.00 (2.89)</td>
<td>21.56 (4.16)</td>
</tr>
<tr>
<td>MMSE</td>
<td>27.57 (2.44)</td>
<td>25.22 (3.03)</td>
</tr>
<tr>
<td>FCI</td>
<td>3.14 (1.68)</td>
<td>2.67 (1.58)</td>
</tr>
<tr>
<td>GDS</td>
<td>2.00 (2.00)</td>
<td>2.22 (2.95)</td>
</tr>
<tr>
<td>6MWT, m</td>
<td>521.14 (132.94)</td>
<td>530.13 (110.34)†</td>
</tr>
<tr>
<td>Baseline WMH volume</td>
<td>4001.28 (3897.11)</td>
<td>3363.21 (3640.26)</td>
</tr>
<tr>
<td>Baseline WMH volume, median (interquartile range)</td>
<td>3310.82 (7799.00)</td>
<td>3126.45 (4251.13)</td>
</tr>
<tr>
<td>6-month WMH volume</td>
<td>4567.95 (4603.85)</td>
<td>3260.48 (3425.17)</td>
</tr>
<tr>
<td>6-month WMH volume, median (interquartile range)</td>
<td>3755.95 (9297.69)</td>
<td>3297.65 (4359.12)</td>
</tr>
</tbody>
</table>

BMI = Body Mass Index; WHR = Waist-to-Hip Ratio; MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; FCI = Functional Comorbidity Index; GDS = Geriatric Depression Scale; 6MWT = 6-minute walk test; WMH = White Matter Hyperintensity Volume, measured in mm³
† = n=8
5.3.2 Compliance and adverse events

Within this subset, the average exercise compliance in the AT group was 72%. One study-related adverse event was reported in the AT group and none were reported in the CON group. The AT-related adverse event was a non-syncopal fall; the participant who experienced this continued with the study and completed all assessments. Compliance in AT females was 67% and in AT males was 75%.

5.3.3 Change in general functional cardiovascular capacity

Accounting for baseline 6MWT, age, and BMI, we found no main effect of group (p = 0.24) or sex (p = 0.11). However, there was a significant sex × group interaction (F [1, 21] = 6.90, p = 0.02, ηp² = 0.25). AT males statistically significantly displayed improved functional cardiovascular capacity compared with CON males (mean difference = 71.18 m, standard error = 23.20 m, pBonferroni = 0.01). There was no statistically significant difference between females in the AT and CON group (pBonferroni = 0.36). Within the AT group, males displayed statistically significantly greater improvement in functional cardiovascular capacity than females (mean difference = 79.23 m, standard error = 25.34 m, pBonferroni = 0.01). Within the CON group, males and females did not statistically significantly differ (pBonferroni = 0.49). For estimated marginal means please refer to Table 5.2 and Figure 5.1.

5.3.4 Interaction effect between aerobic training and sex on white matter hyperintensity progression

Accounting for baseline WMH volume, age, and ApoE ε4 status, we found no significant main effect of group (p = 0.33) or sex (p = 0.09). However, there was a significant sex × group interaction (F [1, 22] = 5.43, p = 0.03, ηp² = 0.20). Over the 6-month study, AT females, who had a greater average baseline WMH volume than CON females, demonstrated statistically
significantly greater WMH progression than CON females (mean difference = 491.92 mm$^3$, standard error = 235.08 mm$^3$, $p_{\text{Bonferroni}} = 0.05$). Among males, there were no statistically significant between-group differences in WMH volume change ($p_{\text{Bonferroni}} = 0.31$). Within the AT group, males demonstrated statistically significantly less WMH progression than females at 6 months (mean difference = 595.36 mm$^3$, standard error = 194.30 mm$^3$, $p_{\text{Bonferroni}} = 0.01$). Within the CON group, there were no statistically significant sex differences in WMH volume change ($p_{\text{Bonferroni}} = 0.69$). For estimated marginal means please refer to Table 5.2 and Figure 5.2.

**Table 5.2** Estimated adjusted means (standard error) for change in 6MWT performance and WMH volume

<table>
<thead>
<tr>
<th></th>
<th>Females</th>
<th></th>
<th>Males</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AT (n=7)</td>
<td>CON (n=5)</td>
<td>AT (n=9)</td>
<td>CON (n=8)</td>
</tr>
<tr>
<td>6MWT, m$^*$</td>
<td>-6.13 (18.47)</td>
<td>20.77 (20.92)</td>
<td>73.09 (16.43)$^+$</td>
<td>1.92 (16.45)</td>
</tr>
<tr>
<td>WMH, mm$^3$‡</td>
<td>486.47 (148.31)</td>
<td>-5.45 (172.15)</td>
<td>-108.90 (124.19)</td>
<td>80.86 (132.16)</td>
</tr>
</tbody>
</table>

* Change in 6-Minute Walk Test (6MWT) performance was adjusted for baseline 6MWT, age, and body mass index. There was a significant sex × group interaction, $p = 0.02$

† = n=8

‡ Change in white matter hyperintensity (WMH) volume was adjusted for baseline WMH volume, age, and ApoE ε4 status. There was a significant sex × group interaction, $p = 0.03$.

Change values were calculated as 6-months minus baseline, higher values indicate improved performance on 6MWT and increased WMH volume at trial completion.
Figure 5.1 Estimated adjusted means (standard error) for change in 6MWT performance. Change values were calculated as 6 months minus baseline. Higher values indicate improved 6MWT performance. * Significantly different at p ≤ 0.05

Figure 5.2 Estimated adjusted means (standard error) for change in WMH volume. Change values were calculated as 6 months minus baseline. Higher values indicate increased WMH volume. * Significantly different at p ≤ 0.05
5.4 Discussion

We found that a 6-month moderate-intense AT program did not have a statistically significant effect on WMH progression among older adults with mild SIVCI. However, our preliminary results suggest that the effect of moderate-intense AT on WMH progression may vary by sex. Among males there were no statistically significant group difference in WMH progression. Females in the AT group, who exhibited the greatest burden of WMH volume at baseline, demonstrated statistically significantly greater WMH progression compared with CON females. Within the AT group, males displayed statistically significantly less WMH progression than females.

Despite the small sample in these exploratory analyses, these results align with findings from large cohort studies regarding WMH burden and progression. Both the Personality and Total Health Through Life Project and the Rotterdam Scan Study reported greater WMH burden in older women compared with older men, in both periventricular and deep WM regions. Furthermore, longitudinal data from the Prospective Study of Pravastatin in the Elderly at Risk found that women accumulated approximately twice as much deep WMHs than men over a 3-year period. Critically, several studies have indicated that the strongest predictor of WMH progression is baseline WMH volume, whereby greater WMH burden at baseline predicts greater WMH progression. Based on these evidence, one can reasonably expect the females in the AT group to demonstrate the greatest progression in WMH volume, given they had the greatest WMH volume at baseline.
Moreover, females in the AT group did not show improved functional cardiovascular capacity; as such, the potential physiological health benefits of AT may not have been attained in females. Higher levels of physical fitness have greater therapeutic benefits, particularly for the management of vascular risk factors 213. Moreover, AT may need to be performed at a level that can modify the endothelium to impact WMH progression. Proper endothelial function is necessary in vascular homeostasis and endothelial dysfunction contributes to disease states, including cSVD 251,376. Specifically, the endothelium is important for regulating vascular tone by balancing the production of vasodilators, such as NO 377. Endothelium NO signaling plays a key role in local CBF regulation, and studies have found that participants with more WMHs display reduced CBF 378. Critically, AT intensity is an important factor in endothelium-dependent NO release, with higher cardiovascular fitness resulting in better endothelial function 379. It is also important to note that females may be at a greater disadvantage than males in cardiovascular adaptations to exercise 380. Specifically, older women experience lower maximal ventilatory reserve and report higher levels of dyspnea (a subjective experience of breathing discomfort) at standardized work rates than age-matched men 178,179. Because the AT females of this sub-study did not exhibit improved functional cardiovascular capacity, any potential benefits of AT on WM health may have been attenuated.

Within the AT group, males displayed significantly less WMH progression than females at trial completion. This finding is paired with significantly larger improvements in functional cardiovascular capacity in AT males compared with AT females at trial completion; thus, the physiological benefits of AT may have been greater in males than females. These results align with studies that report sex-specific vascular responses to AT, with more beneficial effects for
men than women. For example, AT has been shown to prevent or mitigate age-related endothelial dysfunction in older men, but this has not been consistently shown in older women. One study found that AT increased flow-mediated dilation in the brachial artery of older men, but not in older post-menopausal women. This is supported by another study that reported that neither AT or RT had an effect on brachial flow-mediated dilation in sedentary, normotensive, post-menopausal women. Sex differences in AT effectiveness may also be related to hormonal differences. Specifically, estrogen status appears to modulate endothelial function in AT. A study conducted by Moreau and colleagues found that a 12-week AT program increased endothelial function in sedentary postmenopausal women treated with either oral or transdermal estradiol compared with a placebo group. It was suspected that reduced NO played a role in endothelial dysfunction in estrogen-deficient postmenopausal women. Thus, reduced estrogen levels in post-menopausal women may further reduce the beneficial effects of AT on vascular function. Together, these studies suggest that AT may have mitigated WMH progression in males and not females because the physiological benefits of AT may be more potent in males than females.

The results from our study should be evaluated within the context of its limitations. First, this was a secondary analysis with a limited sample size and more studies are needed to determine the efficacy of AT in mitigating WMH progression. Currently, there are no exercise recommendations for people with cSVD; however, we know that hypertension is most strongly associated with WMH progression. For individuals with hypertension, the American College of Sports Medicine recommends aerobic exercise for a minimum of 3 days per week for 30-60 minutes at 40-70% of heart rate reserve, but for optimal results, exercise should be performed
daily. In addition, the American College of Sports Medicine recommends RT activities twice a week, focusing on lower weights but higher number of repetitions (8-12 per set) 382. The benefit of RT was further demonstrated in the Study of Mental Activity and Resistance Training, conducted in people with MCI. This study found that high-intensity progressive RT resulted in a modest regression of WMHs in periventricular and parietal regions, whereas non-progressive RT groups displayed WMH progression 207. This is supported by another RCT that found that RT reduced WMH progression over 12 months in community dwelling older women 121. Similar to AT, RT also modulates endothelial function, but by exerting periodic increases in blood flow creating an alternative type of shear stress on endothelial cells 383. RT may also be neuroprotective by up-regulating insulin-like growth factor-1 (IGF-1) levels; IGF-1 plays a key role in reducing myelin loss, which is a key feature in WM damage. Specifically, IGF-1 can increase myelination by increasing the number of myelinated axons and the thickness of myelin sheaths 384; the presence of IGF-1 can also protect oligodendrocyte progenitors from hypoxic-ischemic WM damage 385. Thus, future studies should consider combining both AT and RT to optimally reduce WMH progression. Additionally, future studies should consider including DTI or MWI as these techniques are sensitive to detecting subtle microstructural WM changes that are not captured in T2w, PDw, and FLAIR sequences. Our study was also limited in determining the efficacy of AT in mitigating WMH progression in females, as AT females did not show improved functional cardiovascular capacity, measured by the 6MWT. As there are sex differences in physiological adaptations to exercise, with greater benefits conferred to men 380, the same exercise prescription applied to both men and women may actually fall short of providing the optimal therapeutic benefit for older women. Thus, the AT intervention may need to be performed at a higher intensity or longer duration to effectively demonstrate improvements
in cardiovascular function and reduce WMH progression in females. Larger trials assessing the effect of physical activity on delaying WMH progression, such as the Australian Imaging Biomarkers and Lifestyle Flagship Study of Aging Active Trial \cite{386} and the ExCersion-Vascular Cognitive Impairment study \cite{387}, may wish to consider potential sex differences to more fully elucidate the efficacy of exercise in mitigating WM damage. The results of our secondary and exploratory study provide the basis for the development of future exercise prescriptions and draw attention to the potential role of biological sex as a modifier in WMH progression.

5.5 Conclusion

The results of Chapter 5 suggest that the effect of AT on WMH progression may vary by sex, with greater benefits conferred to males than females. I note that this was an exploratory analysis with a small sample size; thus, more studies are needed to elucidate the efficacy of AT in mitigating WMH progression. In the following chapter, I will further discuss the limitations of small sample sizes and secondary/exploratory analyses and provide directions for future research, but first I will amalgamate the results of the research chapters.
Chapter 6: General discussion

6.1 Summarizing the research chapters

Over the past several decades, cSVD has been increasingly recognized as a key contributor to late-life cognitive impairment and dementia. On routine MRI sequences, WMHs are regarded as the radiological signature of SIVCI. Due to its conspicuous presence, WMHs have been the primary focus of SIVCI research. However, SIVCI has diverse pathological manifestations including co-existing Aβ plaque pathology and myelin loss. This thesis focused on advancing our understanding of the impact of Aβ plaque pathology (Chapters 2 & 3) and myelin loss (Chapter 4) on physical and cognitive function among older adults with cSVD. Furthermore, this thesis assessed AT as a lifestyle strategy to mitigate WMH progression (Chapter 5). Table 6.1 summarizes the objective, hypothesis, key findings, and overall contribution of each research chapter.
Table 6.1 Summary of research chapters

<table>
<thead>
<tr>
<th>Chapter 2</th>
<th>Objective and Hypothesis</th>
<th>Key Findings</th>
<th>Overall Contribution</th>
</tr>
</thead>
</table>
|           | Objective: To cross-sectionally examine the effect Aβ plaque deposition on physical function independent of WMH load in older adults with CI+. | Higher Aβ plaque deposition was significantly associated with:  
- Slower gait speed  
- Impaired SPPB performance (i.e., balance, gait speed, and muscle strength) | Dementia research has primarily investigated the association between Aβ plaque deposition and cognitive function, but it is critical that we understand how Aβ plaque pathology may affect physical function as dementia is characterized by a gradual and progressive decline in both cognitive and physical abilities. |
| Hypothesis: Aβ plaque deposition has a broad and negative impact on measures of physical function. | Aβ plaque deposition was not significantly associated with:  
- TUGT (i.e., functional mobility) | |

| Chapter 3 | Objective: To examine the association between Aβ plaque deposition and changes in global cognition, executive functions, information processing speed, and falls risk over a 12-month period in older adults with SIVCI. | Higher Aβ plaque deposition at baseline was significantly associated with greater decrements in:  
- Trail Making Test (Part B minus A) (i.e., set shifting)  
- Stroop Test (i.e., inhibitory control)  
- Digit Symbol Substitution Test (i.e., information processing speed)  
- Physiological Profile Assessment performance (i.e., increased falls risk) | These results suggest that the presence of co-existing Aβ plaque pathology may contribute to declines in cognition and increased falls risk. Thus, therapies for SIVCI may need to account for the potential presence and effect of Aβ plaques to optimally care of those with SIVCI. |
| Hypothesis: Elevated Aβ plaque deposition would be associated with greater decrements in cognitive and physical function over a 12-month period. | Aβ plaque deposition at baseline was not significantly associated with:  
- ADAS-Cog (i.e., global cognition)  
- Verbal Digit Span Test (Forwards minus Backwards) (i.e., working memory) | |
<table>
<thead>
<tr>
<th>Chapter</th>
<th>Objective and Hypothesis</th>
<th>Key Findings</th>
<th>Overall Contribution</th>
</tr>
</thead>
</table>
| Chapter 4 | Objective: To cross-sectionally examine the association between myelin in the NAWM and cognitive function in older adults with cSVD.  
Hypothesis: Low myelin content in the NAWM will be associated with slower processing speed and executive functions. | Decreased myelin content was significantly associated with:  
- Trail Making Test (Part A) (i.e., slowed processing speed)  
- Verbal Digit Span Backwards (i.e., worse working memory performance)  
Myelin content was not significantly associated with:  
- Trail Making Test (Part B minus A) (i.e., set shifting)  
- Stroop Test (i.e., inhibitory control) | These results suggest that pathological changes in the NAWM, specifically myelin loss, are associated with impaired processing speed and working memory. Future longitudinal studies are needed to fully elucidate the role of demyelination on cognitive decline. It is important that we continue this line of inquiry, as MWI may be a promising new imaging biomarker for monitoring disease progression. |
| Chapter 5 | Objective: To explore the efficacy of a 6-month (1hr classes, 3 times a week) AT program in mitigating WMH progression compared with a usual care control (CON) group. In addition, determine whether the effect of AT on WMH progression is sex dependent.  
Hypothesis: AT would reduce WMH progression, with greater effects observed among females. | Between group differences:  
- AT females demonstrated significantly greater WMH progression compared with CON females.  
- No significant difference between AT and CON males  
Within group differences:  
- Within the AT group, males demonstrated significantly less WMH progression compared with females | These results suggest that the effects of AT on WMH progression may vary by sex. |
Currently, there is a dearth of knowledge on the effects of co-existing Aβ plaque deposition in people with SIVCI. In a published secondary analysis of the PROMoTE Study, I previously found that higher global Aβ plaque deposition was cross-sectionally associated with worse performance on global cognition and executive functions (i.e., ADAS-Cog and MoCA) 127. Here, in this thesis, I examined the effect of baseline Aβ plaque deposition on change in cognitive and physical function over a 1-year period. I found that higher baseline Aβ plaque deposition was associated with greater reductions in processing speed, inhibitory control, and set shifting. Additionally, I cross-sectionally assessed the effect of myelin content on cognitive function and found that less myelin in the NAWM was associated with slower processing speed and poorer working memory. Within this thesis I was not able to assess the effect of myelin content on change in cognitive function; however, future studies should consider the longitudinal effects of myelin content to better understand the pathological consequences of myelin loss in SIVCI.

To integrate the above results, I will discuss the relevance of these findings in the context of SIVCI. Processing speed generally slows with age, but occurs at an accelerated rate in people with dementia, including AD and SIVCI 388. Thus, it is reasonable that both Aβ plaque deposition and myelin content would be associated with slower processing speed. It is also reasonable that inhibitory control, as measured by the Stroop Test, would be associated with Aβ plaque deposition as the Stroop Test appears to be particularly sensitive to detecting impairments in AD 389,390. However, inhibitory control is not often implicated in SIVCI 9,391 suggesting that Aβ plaque deposition may promote reduced inhibitory control in people with SIVCI. In AD, set shifting has not been measured as frequently as inhibitory control, but the available data
indicates that set shifting is not consistently associated with AD. In contrast, older adults with SIVCI show preponderance for reduced set-shifting ability. Given that we detected an association between Aβ plaque deposition and the Trail Making Test (Part B minus A), it is possible that co-existing Aβ plaque deposition might further promote reduced set-shifting performance in older adults with SIVCI. Working memory also seems to be relatively intact in early AD. As such, it is fitting that we did not find an association between working memory and Aβ plaque deposition and instead found that working memory was associated with myelin loss. Impaired working memory is routinely observed in SIVCI and myelin loss is a key feature of cSVD. Overall, these results suggest that co-existing Aβ plaques and myelin loss, which are often overlooked in the assessment of SIVCI, may also contribute to cognitive impairment.

In addition, higher baseline Aβ plaque deposition was associated with impaired gait, balance, and strength cross-sectionally and increased falls risk over time. These findings concur with the clinical observation that people with dementia have impaired physical function. People with AD exhibit greater gait variability and have a higher risk of falling. Moreover, impaired gait, balance, and strength are associated with subsequent development of AD and higher Aβ plaque deposition is associated with an increased risk for falling among older adults with preclinical AD. Thus, it is plausible that Aβ plaque deposition may independently contribute to impaired physical function in older adults with SIVCI. As impaired physical function is characteristic of SIVCI and has also been closely associated with WMHs, future studies should determine whether the effects of Aβ plaque deposition are additive or synergistic.
Within this thesis I was not able to determine the effect of myelin content on physical function. However, future studies may wish to pursue this line of inquiry as evidence from DTI studies suggest that WM integrity, and potentially myelin content, may affect physical function. Specifically, lower FA was associated with impairments in gait and balance and people who have a high falls risk show reduced FA in several WM tracts. No studies have assessed the effect of myelin on physical function in older adults with SIVCI, but myelin studies in people with MS indicate that myelin deterioration may be associated with reduced physical function. For example, lower MWF was significantly correlated with reduced physical function, as measured by the Expanded Disability Status Scale, in people with MS. In a study assessing the effects of myelin loss over 5 years in people with MS, change in MWF was not significantly correlated with change on the Expanded Disability Status Scale, but the authors noted that the Expanded Disability Status Scale is not a sensitive measure for detecting changes in physical function over time. In a study assessing the effect of an eccentric exercise training program (i.e., down-hill walking), change in MWF was associated with change in functional mobility as measured by the Timed Up and Go Test, suggesting that MWF may be a sensitive biomarker for intervention studies targeting functional impairments in MS. Although MS and SIVCI are different neurological diseases and exhibit myelin loss via different mechanisms (i.e., inflammation vs. ischemia), studies in people with MS suggest that myelin loss may also be associated with physical impairments in SIVCI. As such, MWI may provide some insight into the pathological changes responsible for physical impairments in older adults with SIVCI.

In assessing AT as a strategy to slow WMH progression, we did not find a significant difference between the AT and CON group. However, within the AT group males displayed reduced WMH
progression compared with females, suggesting that the effects of AT on WMH progression may be moderated by biological sex. This may stem from sex differences in vascular responsiveness to AT, with greater benefits conferred to men than women 380. Specifically, men may experience greater NO release, as indicated by greater flow-mediated dilation, than women 183,184. NO is a principle mediator in smooth muscle cell relaxation and vasodilation, and has antiatherogenic and antithrombotic properties 403. Critically, NO release has been postulated as the vehicle for exercise-induced improvement in cardiovascular diseases, such as hypertension 404, which is closely associated with WMH progression 405,406. Of note, epidemiological studies have shown that systolic and diastolic pressure is higher in older women than men due to a marked increase in sympathetic activity and a decrease in ventricular-arterial function 407. The influence of sex on AT-induced changes in blood pressure has not been extensively studied, but a study by Collier and colleagues 408, comparing the effect of AT in males and females, found that AT similarly reduced blood pressure in men and women. However, considering that women exhibit higher baseline blood pressure, a standard exercise prescription may fall short of providing the optimal therapeutic benefit for older women. It may be that exercise prescriptions for women need to be of higher intensity and longer duration for women to experience equal improvements in cardiovascular function as their male counterparts. That said, future research should consider sex differences in training adaptations to increase the utility of AT in combating cSVD.

Future studies may also consider targeting co-existing Aβ plaque pathology and myelin loss as these pathologies also contribute to clinical outcomes in SIVCI. In a transgenic mice model of AD, 5 months of voluntary wheel running resulted in reduced Aβ levels in the frontal cortex, temporal cortex, and hippocampus. Reduced Aβ levels may be mediated by a change in amyloid
precursor protein processing after exercise. Another study found that transgenic mice exposed to an “enriched environment” exhibited reduced Aβ levels compared with mice in “standard housing”. Importantly, enriched high-activity mice (i.e., spent more than 40% of their time in a running wheel) displayed the greatest reduction in Aβ levels. AT may also indirectly protect against some mechanisms of Aβ induced neurotoxicity, such as oxidative stress and neuroinflammation. Animal research also indicates that aerobic exercise may restore myelin loss. Results from a systematic review and meta-analysis of rodent models suggest that physical activity (most studies implemented wheel running and treadmill training) may enhance myelin sheath regeneration. Moreover, voluntary wheel running prevented an up-regulation of myelin-associated glycoprotein and Nogo-A, both are expressed by oligodendrocytes to inhibit the growth of neurites after brain injury. Overall, evidence from animal models indicates that AT has multifaceted benefits that may mitigate cSVD progression.

In preserving cerebral WM health, future studies should also consider implementing RT. As previously discussed, AT may be neuroprotective by up-regulating BDNF and VEGF levels; RT may also be neuroprotective by up-regulating IGF-1 levels. Similar to VEGF, IGF-1 is involved in vascular maintenance and remodeling, and age-related reductions in IGF-1 are associated with decreased cerebral vascular density and blood flow. Critically, the presence of IGF-1 can have profound effects on oligodendrocytes and myelination. IGF-1 can increase the number of oligodendrocytes, stimulate oligodendrocyte progenitors, promote regeneration of oligodendrocytes after injury, and initiate myelination. Also, IGF-1 can increase myelination by increasing the number of myelinated axons and the thickness of myelin sheaths via stimulating the expression of myelin protein genes and increasing the number of...
Overall, data in transgenic mice models indicate that RT can be particularly protective for WM. Indeed, preliminary studies have shown that RT can mitigate WMH progression \cite{121,421}, but it remains unclear whether this was driven by increased IGF-1 levels and which WM substrates were altered. To further elucidate the potential role of RT in mitigating cSVD, future studies may wish to examine the underlying mechanisms by which RT may be neuroprotective and include imaging techniques such as DTI and MWI to provide greater insight into the WM substrates affected by RT.

6.2 Overall limitations and future directions

In addition to the limitations noted within each research chapter, this section will attempt to cover some overarching limitations associated with the results of this thesis. The objective of this thesis was to further understand cSVD neuropathology, specifically its effect on cognitive and physical function, and factors that may mitigate its progression. However, the profile and temporal evolution of cognitive and physical deficits in SIVCI are variable as cognitive decline in SIVCI may develop gradually, stepwise, or through a combination of both. This variability may be related to several factors (Figure 6.1). First, the neuropathology of cSVD is heterogeneous and complex. As previously discussed, common lesions associated with cSVD include WMHs, lacunes, microbleeds, microinfarcts, and perivascular spaces. In this thesis, we extend this lesion profile and report that co-existing Aβ plaques and myelin loss in the NAWM may also contribute to impaired cognitive and physical function. Although it should be noted that co-existing Aβ plaques and myelin loss were not assessed in relation to the full spectrum of cSVD lesions and it remains unclear whether these effects are additive, synergistic, or attenuated...
when other cSVD lesions are included. Within this lesion profile, it is also unclear which lesion pathology is the most sensitive predictor of cognitive and physical outcomes. Future studies need to account for the full spectrum of cSVD lesions to better understand the unique contribution of each lesion type and the interactions between lesion types in relation to cognitive and physical change.

In addition to understanding the effects of common cSVD lesions, it is important to recognize that cSVD is a dynamic, whole-brain disease. Focal cSVD lesions may initiate several secondary pathogenic processes. For example, periventricular WMHs have been associated with thinning of the frontal cortex causing executive dysfunctions. This association might be mediated by damage to WM tracts. One study found WM fiber tracts connecting a region of infarct to the cortex showed reduced WM integrity compared with the same tract in the contralesional hemisphere. Furthermore, changes in tract integrity were associated with changes in cortical thickness. Cortical thinning might occur via retrograde degeneration in which degeneration propagates from the axonal lesion to the soma, leading to degeneration of the entire neuron. In addition, DTI studies in structural connectivity found that people with greater cSVD severity (indicated by higher WMH load, number of lacunes and microbleeds, and lower total brain volume) had networks with lower global efficiency (global efficiency reflects the extent to which information communication is globally integrated in the network), which was correlated with lower scores on cognitive performance. It was also suggested that lower global efficiency might mediate the associations between MRI markers of cSVD and cognition. Functional connectivity (defined as the temporal dependency of neuronal activation patterns in anatomically separate regions) may also be affected in cSVD. It is theorized that damage to long association
fibers may cause reductions in functional connectivity between the default-mode network, dorsal attention network, and frontoparietal network, which play important roles in executive processing. Together, these studies indicate that cSVD lesions can lead to widespread effects throughout the brain and highlights the importance of understanding the effects of focal lesions in a global context.

Studies in cSVD should also consider changes to the neurovasculature, specifically changes in CBF, cerebrovascular reactivity (CVR), and the BBB. Delivery of oxygen and glucose to the brain is the most critical function of CBF. A systematic review of 24 cross-sectional studies found that CBF is lower in people with more WMHs. Longitudinal evidence for reduced CBF predating WMH development is conflicting, but lower CBF at baseline in the NAWM neighboring WMHs has been associated with both future development of WMHs and reduced WM integrity. In addition to serving as a conduit for blood flow, the vasculature is constantly working to adjust blood flow to meet tissue demands. CVR is defined as the ability to augment CBF in response to increased neuronal activity, metabolic demand, or a vasodilatory stimulus. Studies in CVR are equivocal, but there is some evidence to suggest an association between reduced CVR in WMHs and NAWM. However, it is important to note that it is unclear whether low CBF or CVR is the cause or consequence of WM damage and more longitudinal studies are needed to determine the directionality of this phenomenon. Lastly, the role of the BBB is to limit entry of potentially neurotoxic plasma components into the brain. Data from a large cohort study found increased BBB leakage within WMHs and also in the surrounding NAWM. This leakage was worse in people with greater WMH burden. In addition, baseline BBB leakage in WMHs predicted cognitive impairment at 1-year in people with lacunar stroke.
Together, these studies suggest that changes in neurovascular function may also be associated with cSVD; thus, future studies may consider targeting the neurovasculature in mitigating cSVD progression.

In addition to neuropathology, studies in cSVD should also consider ‘resilience’ as a factor in disease progression. The concept of cognitive reserve has been proposed as a moderating factor between pathology and clinical outcomes; thus, accounting for individual differences in susceptibility to age-related brain changes. This concept is still under development and currently cognitive reserve is often operationalized as educational attainment, occupation, or environmental richness. Within the context of cSVD, cognitive reserve has primarily been studied in association with WMHs. One study found that low educational attainment was significantly associated with severe WMHs and lower cognitive performance. Conversely, in people with high educational attainment, there was no significant association between severity of WMHs and cognitive function. Based on these findings, the authors suggested that a high level of educational attainment might protect against cognitive deterioration related to cSVD.

Another study found that cognitively stimulating leisure activities (e.g., reading, using the computer, attending a class/lecture or public meeting, doing artwork, carpentry or sewing, crossword puzzles, attending religious services/meetings, playing board or card games, writing letters or poems) attenuated the effect of WMHs on cognitive function. High cognitive reserve, defined as educational and occupational attainment, may also delay the onset of cognitive decline. Cognitive reserve has also been associated with physical outcomes. People with a higher level of educational attainment were less susceptible to the detrimental effects of WMHs on gait speed, although repeated gait speed assessment over 10 years was not associated
with education. This suggests that cognitive reserve may impact the threshold at which the
 damaging effects of WMHs become functionally apparent but does not alter the course of the
disease. Together, these studies highlight the relevance of cognitive reserve in cSVD, particularly because cSVD lesions only account for a small portion of the variability in clinical
symptoms. Thus, future studies should develop a model of disease progression that integrates
the complex interrelations between pathology and environmental influences for a more complete
understanding of the evolution of SIVCI.

Figure 6.1 Factors influencing the presentation of cSVD.
Lastly, it is important to acknowledge that the results of this thesis were generated from secondary or exploratory analyses. Specifically, Chapter 2 was a cross-sectional planned secondary analysis using data from two separate studies – the PRoMOTe Study which was an RCT assessing the effect of AT on cognitive function in people with mild SIVCI (ClinicalTrials.gov Protocol Registration Number: NCT01027858) and a cross-sectional study aimed at characterizing AD, SIVCI, and mixed AD-VCI. Chapter 3 was a planned secondary analysis assessing change between baseline and 1-year follow-up using data from the PRoMOTe Study. Chapter 4 was a cross-sectional planned secondary analysis using baseline data from two separate studies – an RCT assessing the effect of RT on cognitive function in people with mild SIVCI (ClinicalTrials.gov Protocol Registration Number: NCT02669394) and a prospective study assessing differences in cognitive function between fallers with MCI and non-fallers with MCI. Chapter 5 was a secondary (i.e., the effect of AT on WMH progression) and exploratory (i.e., sex-differences) analysis using data from the PRoMOTe Study. Below is a review of the limitations associated with secondary and exploratory analyses.

As secondary analyses, the data used in this thesis were collected for another purpose and there are several limitations associated with this. First, this thesis utilized data from various sources and this introduced a level of heterogeneity in the participant pool – for example, Chapter 2 included participants with a primary AD diagnosis and Chapter 4 included participants who are fallers. Though all participants had cognitive impairment with cSVD (i.e., WMHs), it is unclear how characteristics associated with AD or falling may have influenced the results. Second, selection bias may be an issue as Chapters 2, 3, and 4 utilized data from a subset of participants who volunteered to complete neuroimaging – these participants may share characteristics that
make them different from those who did not complete neuroimaging (e.g., these participants tend to be higher functioning). Third, the sample size of the research chapters was limited as neuroimaging was only completed in a subset of participants due to cost. Small samples are more likely to produce a wide range of estimates, which adds a level of uncertainty to the results. Furthermore, a small sample size yields low statistical power; low statistical power negatively affects the likelihood that a statistically significant finding actually reflects a true effect. Issues associated with a small sample and low power are also present in Chapter 5. In addition, Chapter 5 was an exploratory analysis; thus, the $p$-values should be interpreted with caution. $P$-values are meant for testing predictions in confirmatory studies and in an exploratory study they have an unknown diagnostic value for making a statistical inference. Thus, it is critical that the results of this thesis be replicated in confirmation studies with adequate samples sizes.

6.3 Final conclusions

cSVD is the main cause of SIVCI, often occurs with AD, and is the cause of approximately a quarter of ischemic strokes, and thus contributes to approximately 50% of dementias worldwide. Critically, vascular contributions to cognitive impairment and dementia are preventable as vascular risk factors can be targeted throughout the life course. In fact, research suggests that rates of dementia may be decreasing through the control of vascular risk factors. As such, it is critical that we continue to develop a better understanding of cSVD pathology and pathophysiology. This knowledge may lead to novel targets for treatment and aid in the development of more sensitive biomarkers for diagnosis and monitoring disease progression. In addition, there has been limited pharmacological progress in the management of SIVCI, so it
is necessary that we continue to investigate lifestyle strategies that may prevent or slow the progression of cSVD and promote brain health. The preservation of cognitive and physical function will likely maintain and prolong the ability of people with SIVCI to live independently. These efforts are critical at this point in time as cognitive impairment and dementia pose an enormous socioeconomic burden, negatively affecting families, communities, and health-care systems.
References


112. Debette S, Markus HS. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. *BMJ.* 2010;341:c3666.


Fissler P, Muller HP, Kuster OC, et al. No evidence that short-term cognitive or physical training programs or lifestyles are related to changes in white matter integrity in older adults at risk of dementia. *Frontiers in Human Neuroscience*. 2017;11:110.


Appendices

Appendix A

Chapter 2 Regression analyses assessing the effect of Aβ plaque deposition in people with a primary SIVCI diagnosis (n = 22)

Global Aβ plaque deposition was not statistically significantly associated with reduced gait speed (β = -0.14, p = 0.55, Table A.1), SPPB (β = -0.24, p = 0.32, Table A.2), or Timed Up and Go Test (β = 0.15, p = 0.41, Table A.3). Though we did not find statistical significance between global Aβ plaque deposition and physical function in people with a primary SIVCI diagnosis, potentially due to reduced power, we note that the standardized βs are trending in the same direction as the main analyses.

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>R2</th>
<th>Adjusted R2</th>
<th>R2 Change</th>
<th>Unstandardized B (Standard Error)</th>
<th>Standardized β</th>
<th>P-Value</th>
</tr>
</thead>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
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<td>0.15</td>
<td>0.27</td>
<td>-0.01 (0.01)</td>
<td>-0.19</td>
<td>0.38</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>-0.03 (0.01)</td>
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<td>0.03</td>
</tr>
<tr>
<td>Fazekas Score</td>
<td></td>
<td></td>
<td></td>
<td>-0.02 (0.06)</td>
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<td>Age</td>
<td>0.29</td>
<td>0.12</td>
<td>0.02</td>
<td>-0.01 (0.01)</td>
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<td>0.36</td>
</tr>
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<td>BMI</td>
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<td></td>
<td></td>
<td>-0.03 (0.01)</td>
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<td>0.03</td>
</tr>
<tr>
<td>Fazekas score</td>
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<td></td>
<td></td>
<td>0.01 (0.07)</td>
<td>0.04</td>
<td>0.85</td>
</tr>
<tr>
<td>Aβ deposition</td>
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<td></td>
<td>-0.11 (0.19)</td>
<td>-0.14</td>
<td>0.55</td>
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### Table A.2 Multiple linear regression assessing the contribution of Aβ plaque deposition on SPPB

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<th>Adjusted R²</th>
<th>R² Change</th>
<th>Unstandardized B (Standard Error)</th>
<th>Standardized β</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
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<td><strong>Step 1</strong></td>
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<td>0.09</td>
<td>0.22</td>
<td></td>
<td></td>
<td>0.20</td>
</tr>
<tr>
<td>Age</td>
<td>-0.03 (0.03)</td>
<td>-0.21</td>
<td>0.36</td>
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<td></td>
</tr>
<tr>
<td>BMI</td>
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<td>-0.30</td>
<td>0.17</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fazekas Score</td>
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<td>-0.20</td>
<td>0.38</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
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<td>0.10</td>
<td>0.05</td>
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<td>0.32</td>
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<td>Age</td>
<td>-0.03 (0.03)</td>
<td>-0.23</td>
<td>0.31</td>
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<td></td>
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<tr>
<td>BMI</td>
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<td>-0.40</td>
<td>0.10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fazekas Score</td>
<td>-0.30 (0.30)</td>
<td>-0.22</td>
<td>0.33</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aβ deposition</td>
<td>-0.88 (0.86)</td>
<td>-0.24</td>
<td>0.32</td>
<td></td>
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</table>

SPPB = Short Physical Performance Battery

### Table A.3 Multiple linear regression assessing the contribution of Aβ plaque deposition on Timed Up and Go Test

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<th>Independent Variables</th>
<th>R²</th>
<th>Adjusted R²</th>
<th>R² Change</th>
<th>Unstandardized B (Standard Error)</th>
<th>Standardized β</th>
<th>P-Value</th>
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<td><strong>Step 1</strong></td>
<td>0.58</td>
<td>0.51</td>
<td>0.58</td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
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<td>Age</td>
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<td>-0.11</td>
<td>0.52</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>0.35 (0.09)</td>
<td>0.63</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fazekas Score</td>
<td>1.13 (0.52)</td>
<td>0.36</td>
<td>0.04</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
<td>0.59</td>
<td>0.50</td>
<td>0.01</td>
<td></td>
<td></td>
<td>0.41</td>
</tr>
<tr>
<td>Age</td>
<td>-0.03 (0.06)</td>
<td>-0.09</td>
<td>0.58</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>0.38 (0.09)</td>
<td>0.69</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fazekas Score</td>
<td>1.17 (0.52)</td>
<td>0.37</td>
<td>0.04</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aβ deposition</td>
<td>1.27 (1.52)</td>
<td>0.15</td>
<td>0.41</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix B

Chapter 3: Regression analyses including age as a covariate

Below are the analyses that included age as a covariate. In the final analyses, age was removed for a more parsimonious model because it did not significantly alter the results.

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>R²</th>
<th>Adjusted R²</th>
<th>R² Change</th>
<th>Unstandardized B (Standard Error)</th>
<th>Standardized β</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.18</td>
<td>0.04</td>
<td>0.18</td>
<td>0.04 (0.09)</td>
<td>0.11</td>
<td>0.64</td>
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<tr>
<td>Group</td>
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<td></td>
<td></td>
<td>1.13 (1.37)</td>
<td>0.19</td>
<td>0.42</td>
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<tr>
<td>ADAS-Cog baseline</td>
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<td></td>
<td></td>
<td>0.29 (0.18)</td>
<td>0.38</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.20</td>
<td>0.02</td>
<td>0.03</td>
<td>0.04 (0.09)</td>
<td>0.09</td>
<td>0.70</td>
</tr>
<tr>
<td>Group</td>
<td></td>
<td></td>
<td></td>
<td>1.18 (1.38)</td>
<td>0.20</td>
<td>0.41</td>
</tr>
<tr>
<td>ADAS-Cog baseline</td>
<td></td>
<td></td>
<td></td>
<td>0.40 (0.23)</td>
<td>0.51</td>
<td>0.10</td>
</tr>
<tr>
<td>Aβ deposition</td>
<td></td>
<td></td>
<td></td>
<td>-2.74 (3.57)</td>
<td>-0.21</td>
<td>0.45</td>
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</table>

ADAS-Cog = Alzheimer’s Disease Assessment Scale - Cognitive subscale baseline score
Table B.2 Multiple linear regression assessing the contribution of Aβ plaque deposition on change in Trail Making Test (Part B minus A) with age as a covariate

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>R²</th>
<th>Adjusted R²</th>
<th>R² Change</th>
<th>Unstandardized B (Standard Error)</th>
<th>Standardized β</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.07</td>
<td>-0.08</td>
<td>0.07</td>
<td>1.43 (1.67)</td>
<td>-0.20</td>
<td>0.40</td>
</tr>
<tr>
<td>Group</td>
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<td></td>
<td></td>
<td>25.79 (26.46)</td>
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<td>0.34</td>
</tr>
<tr>
<td>TMT baseline</td>
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<td></td>
<td></td>
<td>0.00 (0.53)</td>
<td>0.00</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
<td>0.49</td>
<td>0.37</td>
<td>0.42*</td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td>-0.94 (1.29)</td>
<td>-0.13</td>
<td>0.48</td>
</tr>
<tr>
<td>Group</td>
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<td></td>
<td></td>
<td>9.40 (20.70)</td>
<td>0.09</td>
<td>0.66</td>
</tr>
<tr>
<td>TMT baseline</td>
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<td></td>
<td></td>
<td>0.36 (0.42)</td>
<td>0.16</td>
<td>0.41</td>
</tr>
<tr>
<td>Aβ deposition</td>
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<td></td>
<td>-163.13 (43.90)</td>
<td>-0.67</td>
<td>&lt;0.01</td>
</tr>
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</table>

TMT = Trail Making Test (Part B minus A) baseline score
* Significant at p ≤ 0.05

Table B.3 Multiple linear regression assessing the contribution of Aβ plaque deposition on change in Verbal Digit Span Test (Forwards minus Backwards) with age as a covariate

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>R²</th>
<th>Adjusted R²</th>
<th>R² Change</th>
<th>Unstandardized B (Standard Error)</th>
<th>Standardized β</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
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<td>0.63</td>
<td>0.68</td>
<td>0.05 (0.05)</td>
<td>0.12</td>
<td>0.40</td>
</tr>
<tr>
<td>Group</td>
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<td></td>
<td>-1.14 (0.86)</td>
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<td>0.20</td>
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<tr>
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<td></td>
<td>0.93 (0.16)</td>
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<td>&lt;0.01</td>
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<td>0.66</td>
<td>0.04</td>
<td></td>
<td></td>
<td>0.12</td>
</tr>
<tr>
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<td>0.05 (0.05)</td>
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<td>0.33</td>
</tr>
<tr>
<td>Group</td>
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<td></td>
<td>-1.35 (0.83)</td>
<td>-0.22</td>
<td>0.12</td>
</tr>
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<td>VDST baseline</td>
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<td>0.93 (0.15)</td>
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<td>Aβ deposition</td>
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<td>-2.82 (1.73)</td>
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</table>

VDST = Verbal Digit Span Test (Forwards minus Backwards) baseline score
Table B.4 Multiple linear regression assessing the contribution of Aβ plaque deposition on change in Stroop Test with age as a covariate

<table>
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<th>Independent Variables</th>
<th>R²</th>
<th>Adjusted R²</th>
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<th>Standardized β</th>
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<tr>
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<tr>
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<td>0.37 (0.22)</td>
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<td>0.11</td>
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<td></td>
<td>0.01</td>
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<td></td>
<td>0.90 (0.58)</td>
<td>0.28</td>
<td>0.14</td>
</tr>
<tr>
<td>Group</td>
<td></td>
<td></td>
<td></td>
<td>-3.93 (9.35)</td>
<td>-0.08</td>
<td>0.68</td>
</tr>
<tr>
<td>Stroop Test baseline</td>
<td></td>
<td></td>
<td></td>
<td>0.45 (0.18)</td>
<td>0.46</td>
<td>0.02</td>
</tr>
<tr>
<td>Aβ deposition</td>
<td></td>
<td></td>
<td></td>
<td>-61.82 (19.77)</td>
<td>-0.56</td>
<td>0.01</td>
</tr>
</tbody>
</table>

* Significant at p ≤ 0.05

Table B.5 Multiple linear regression assessing the contribution of Aβ plaque deposition on change in DSST with age as a covariate

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>R²</th>
<th>Adjusted R²</th>
<th>R² Change</th>
<th>Unstandardized B (Standard Error)</th>
<th>Standardized β</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong></td>
<td>0.03</td>
<td>-0.14</td>
<td>0.03</td>
<td></td>
<td></td>
<td>0.93</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td>0.02 (0.16)</td>
<td>0.03</td>
<td>0.90</td>
</tr>
<tr>
<td>Group</td>
<td></td>
<td></td>
<td></td>
<td>-1.63 (2.40)</td>
<td>-0.16</td>
<td>0.51</td>
</tr>
<tr>
<td>DSST baseline</td>
<td></td>
<td></td>
<td></td>
<td>-0.01 (0.18)</td>
<td>-0.02</td>
<td>0.94</td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
<td>0.33</td>
<td>0.17</td>
<td>0.30*</td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td>0.06 (0.14)</td>
<td>0.10</td>
<td>0.64</td>
</tr>
<tr>
<td>Group</td>
<td></td>
<td></td>
<td></td>
<td>-2.71 (2.08)</td>
<td>-0.27</td>
<td>0.21</td>
</tr>
<tr>
<td>DSST baseline</td>
<td></td>
<td></td>
<td></td>
<td>-0.11 (0.15)</td>
<td>-0.14</td>
<td>0.50</td>
</tr>
<tr>
<td>Aβ deposition</td>
<td></td>
<td></td>
<td></td>
<td>-12.56 (4.54)</td>
<td>-0.57</td>
<td>0.01</td>
</tr>
</tbody>
</table>

DSST = Digit Symbol Substitution Test baseline score
* Significant at p ≤ 0.05
Table B.6 Multiple linear regression assessing the contribution of Aβ plaque deposition on change in PPA with age as a covariate

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>R²</th>
<th>Adjusted R²</th>
<th>ΔR²</th>
<th>Unstandardized B (Standard Error)</th>
<th>Standardized β</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.53</td>
<td>0.46</td>
<td>0.53</td>
<td>-0.04 (0.02)</td>
<td>-0.30</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Group</td>
<td></td>
<td></td>
<td></td>
<td>-0.33 (0.31)</td>
<td>-0.18</td>
<td>0.30</td>
</tr>
<tr>
<td>PPA baseline</td>
<td></td>
<td></td>
<td></td>
<td>0.50 (0.13)</td>
<td>0.64</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.65</td>
<td>0.56</td>
<td>0.11*</td>
<td>-0.03 (0.02)</td>
<td>-0.26</td>
<td>0.10</td>
</tr>
<tr>
<td>Group</td>
<td></td>
<td></td>
<td></td>
<td>-0.45 (0.28)</td>
<td>-0.24</td>
<td>0.13</td>
</tr>
<tr>
<td>PPA baseline</td>
<td></td>
<td></td>
<td></td>
<td>0.41 (0.12)</td>
<td>0.52</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Aβ deposition</td>
<td></td>
<td></td>
<td></td>
<td>-1.49 (0.64)</td>
<td>-0.36</td>
<td>0.03</td>
</tr>
</tbody>
</table>

PPA = Physiological Profile Assessment baseline score

* Significant at p ≤ 0.05
Appendix C

Chapter 3: Regression analyses by group

To determine whether group assignment (i.e., aerobic training [AT] or control [CON] group) moderated the effect of baseline Aβ plaque deposition on change in cognition and falls risk, we conducted regression analyses in the AT group and CON group separately. In global cognitive function, Aβ plaque deposition was not statistically significantly associated with ADAS-Cog in both the AT group (β = -0.25, p = 0.61) and CON group (β = -0.25, p = 0.57). In executive functions: 1) increased Aβ plaque deposition was statistically significantly associated with worse performance on the Trail Making Test (Part B minus A) in the AT group (β = -0.83, p = 0.01), but not in the CON group (β = -0.44, p = 0.37); 2) Aβ plaque deposition was not statistically associated with Verbal Digit Span Test (Forwards minus Backwards) in both the AT group (β = -0.36, p = 0.15) and CON group (β = -0.06, p = 0.73); 3) Aβ plaque deposition was not statistically significantly associated with the Stroop Test in the AT group (β = -0.09, p = 0.83), but increased Aβ plaque deposition was statistically significantly associated with worse Stroop Test performance in the CON group (β = -0.68, p = 0.02). In processing speed, Aβ plaque deposition was not statistically significantly associated with the DSST in the AT group (β = -0.70, p = 0.35), but increased Aβ plaque deposition was statistically significantly associated with worse DSST performance in the CON group (β = -0.90, p = 0.01). In falls risk, Aβ plaque deposition was not statistically significantly associated with the PPA in both the AT group (β = -0.31, p = 0.24) and CON group (β = -0.08, p = 0.74). These results suggest that the effect of baseline Aβ plaque deposition on cognitive function (i.e., Trail Making Test (Part B minus A),
Stroop Test, and DSST) differed according to group assignment; thus, in the analyses of Chapter 3 we controlled for group assignment.
Appendix D

Chapter 3: Additional analyses including age and WMH volume as covariates

We were able to quantify WMH volume in a subset of participants (n=16). In this subset, including age and WMH volume as covariates did not alter the results – please find the results below.

Table D.1 Multiple linear regression assessing the contribution of Aβ plaque deposition on change in ADAS-Cog with age and WMH volume as covariates

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>R²</th>
<th>Adjusted R²</th>
<th>R² Change</th>
<th>Unstandardized B (Standard Error)</th>
<th>Standardized β</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.46</td>
<td>0.32</td>
<td>0.46</td>
<td>0.09 (0.09)</td>
<td>0.22</td>
<td>0.35</td>
</tr>
<tr>
<td>Group</td>
<td>1.32 (1.48)</td>
<td>0.21</td>
<td>0.39</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADAS-Cog baseline</td>
<td>0.49 (0.18)</td>
<td>0.62</td>
<td>0.02</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.49</td>
<td>0.30</td>
<td>0.03</td>
<td>0.14 (0.11)</td>
<td>0.35</td>
<td>0.24</td>
</tr>
<tr>
<td>Group</td>
<td>1.31 (1.50)</td>
<td>0.21</td>
<td>0.40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADAS-Cog baseline</td>
<td>0.43 (0.20)</td>
<td>0.54</td>
<td>0.06</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WMH volume</td>
<td>0.00 (0.00)</td>
<td>-0.23</td>
<td>0.44</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Step 3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.50</td>
<td>0.25</td>
<td>0.01</td>
<td>0.14 (0.11)</td>
<td>0.35</td>
<td>0.25</td>
</tr>
<tr>
<td>Group</td>
<td>1.39 (1.56)</td>
<td>0.22</td>
<td>0.40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADAS-Cog baseline</td>
<td>0.48 (0.23)</td>
<td>0.60</td>
<td>0.07</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WMH volume</td>
<td>0.00 (0.00)</td>
<td>-0.27</td>
<td>0.40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aβ deposition</td>
<td>-1.77 (3.69)</td>
<td>-0.14</td>
<td>0.64</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ADAS-Cog = Alzheimer’s Disease Assessment Scale - Cognitive subscale baseline score; WMH = white matter hyperintensity
Table D.2 Multiple linear regression assessing the contribution of Aβ plaque deposition on change in Trail Making Test (Part B minus A) with age and WMH volume as covariates

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>R²</th>
<th>Adjusted R²</th>
<th>R² Change</th>
<th>Unstandardized B (Standard Error)</th>
<th>Standardized β</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.07</td>
<td>-0.17</td>
<td>0.07</td>
<td>-0.33 (1.48)</td>
<td>-0.07</td>
<td>0.83</td>
</tr>
<tr>
<td>Group</td>
<td></td>
<td></td>
<td></td>
<td>24.67 (26.75)</td>
<td>0.30</td>
<td>0.38</td>
</tr>
<tr>
<td>TMT baseline</td>
<td></td>
<td></td>
<td></td>
<td>-0.26 (0.51)</td>
<td>-0.16</td>
<td>0.62</td>
</tr>
<tr>
<td>Step 2</td>
<td>0.11</td>
<td>-0.22</td>
<td>0.04</td>
<td>-0.96 (1.77)</td>
<td>-0.19</td>
<td>0.60</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td>23.23 (27.43)</td>
<td>0.28</td>
<td>0.42</td>
</tr>
<tr>
<td>Group</td>
<td></td>
<td></td>
<td></td>
<td>-0.29 (0.52)</td>
<td>-0.18</td>
<td>0.59</td>
</tr>
<tr>
<td>TMT baseline</td>
<td></td>
<td></td>
<td></td>
<td>0.00 (0.01)</td>
<td>0.24</td>
<td>0.50</td>
</tr>
<tr>
<td>WMH volume</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step 3</td>
<td>0.44</td>
<td>0.16</td>
<td>0.34*</td>
<td>0.15 (1.53)</td>
<td>0.03</td>
<td>0.93</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td>10.83 (23.31)</td>
<td>0.13</td>
<td>0.65</td>
</tr>
<tr>
<td>Group</td>
<td></td>
<td></td>
<td></td>
<td>0.13 (0.47)</td>
<td>0.08</td>
<td>0.79</td>
</tr>
<tr>
<td>TMT baseline</td>
<td></td>
<td></td>
<td></td>
<td>0.00 (0.01)</td>
<td>-0.15</td>
<td>0.66</td>
</tr>
<tr>
<td>WMH volume</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aβ deposition</td>
<td></td>
<td></td>
<td></td>
<td>-119.04 (48.66)</td>
<td>-0.70</td>
<td>0.03</td>
</tr>
</tbody>
</table>

TMT = Trail Making Test (Part B minus A) baseline score; WMH = white matter hyperintensity
* Significant at p ≤ 0.05
Table D.3 Multiple linear regression assessing the contribution of Aβ plaque deposition on change in Verbal Digit Span Test (Forwards minus Backwards) with age and WMH volume as covariates

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>R²</th>
<th>Adjusted R²</th>
<th>R² Change</th>
<th>Unstandardized B</th>
<th>Standardized β</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong></td>
<td>0.74</td>
<td>0.68</td>
<td>0.74</td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age</td>
<td>0.09 (0.05)</td>
<td>0.26</td>
<td>0.11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>-2.12 (0.86)</td>
<td>-0.39</td>
<td>0.03</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VDST baseline</td>
<td>0.85 (0.16)</td>
<td>0.83</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
<td>0.75</td>
<td>0.66</td>
<td>0.01</td>
<td></td>
<td></td>
<td>0.52</td>
</tr>
<tr>
<td>Age</td>
<td>0.07 (0.06)</td>
<td>0.20</td>
<td>0.30</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>-2.13 (0.88)</td>
<td>-0.39</td>
<td>0.03</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VDST baseline</td>
<td>0.80 (0.18)</td>
<td>0.78</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WMH volume</td>
<td>0.00 (0.00)</td>
<td>0.13</td>
<td>0.52</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Step 3</strong></td>
<td>0.77</td>
<td>0.66</td>
<td>0.02</td>
<td></td>
<td></td>
<td>0.36</td>
</tr>
<tr>
<td>Age</td>
<td>0.09 (0.07)</td>
<td>0.26</td>
<td>0.21</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>-2.29 (0.90)</td>
<td>-0.42</td>
<td>0.03</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VDST baseline</td>
<td>0.90 (0.21)</td>
<td>0.88</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WMH volume</td>
<td>0.00 (0.00)</td>
<td>-0.02</td>
<td>0.95</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aβ deposition</td>
<td>-2.13 (2.21)</td>
<td>-0.19</td>
<td>0.36</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

VDST F-B = Verbal Digit Span Test (Forwards minus Backwards) baseline score; WMH = White Matter Hyperintensity
### Table D.4 Multiple linear regression assessing the contribution of Aβ plaque deposition on change in Stroop Test with age and WMH volume as covariates

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>R²</th>
<th>Adjusted R²</th>
<th>R² Change</th>
<th>Unstandardized B (Standard Error)</th>
<th>Standardized β</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.30</td>
<td>0.12</td>
<td>0.30</td>
<td>1.35 (0.86)</td>
<td>0.40</td>
<td>0.22</td>
</tr>
<tr>
<td>Group</td>
<td></td>
<td></td>
<td></td>
<td>-8.48 (14.98)</td>
<td>-0.15</td>
<td>0.58</td>
</tr>
<tr>
<td>Stroop Test baseline</td>
<td></td>
<td></td>
<td></td>
<td>0.50 (0.32)</td>
<td>0.43</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.30</td>
<td>0.05</td>
<td>0.00</td>
<td>1.29 (1.09)</td>
<td>0.39</td>
<td>0.26</td>
</tr>
<tr>
<td>Group</td>
<td></td>
<td></td>
<td></td>
<td>-8.91 (16.27)</td>
<td>-0.16</td>
<td>0.60</td>
</tr>
<tr>
<td>Stroop Test baseline</td>
<td></td>
<td></td>
<td></td>
<td>0.49 (0.37)</td>
<td>0.41</td>
<td>0.21</td>
</tr>
<tr>
<td>WMH volume</td>
<td></td>
<td></td>
<td></td>
<td>0.00 (0.00)</td>
<td>0.03</td>
<td>0.92</td>
</tr>
<tr>
<td><strong>Step 3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.57</td>
<td>0.35</td>
<td>0.27*</td>
<td>1.94 (0.93)</td>
<td>0.58</td>
<td>0.03</td>
</tr>
<tr>
<td>Group</td>
<td></td>
<td></td>
<td></td>
<td>-6.80 (13.41)</td>
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<td>0.62</td>
</tr>
<tr>
<td>Stroop Test baseline</td>
<td></td>
<td></td>
<td></td>
<td>0.67 (0.31)</td>
<td>0.56</td>
<td>0.06</td>
</tr>
<tr>
<td>WMH volume</td>
<td></td>
<td></td>
<td></td>
<td>0.00 (0.00)</td>
<td>-0.33</td>
<td>0.30</td>
</tr>
<tr>
<td>Aβ deposition</td>
<td></td>
<td></td>
<td></td>
<td>-67.63 (27.05)</td>
<td>-0.60</td>
<td>0.03</td>
</tr>
</tbody>
</table>

WMH = white matter hyperintensity
* Significant at p ≤ 0.05
Table D.5 Multiple linear regression assessing the contribution of Aβ plaque deposition on change in DSST with age and WMH volume as covariates

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>R²</th>
<th>Adjusted R²</th>
<th>R² Change</th>
<th>Unstandardized B (Standard Error)</th>
<th>Standardized β</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
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<td><strong>Step 1</strong></td>
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<td>-0.11</td>
<td>0.11</td>
<td></td>
<td></td>
<td>0.70</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td>0.04 (0.20)</td>
<td>0.05</td>
<td>0.86</td>
</tr>
<tr>
<td>Group</td>
<td></td>
<td></td>
<td></td>
<td>-3.79 (3.17)</td>
<td>-0.34</td>
<td>0.26</td>
</tr>
<tr>
<td>DSST baseline</td>
<td></td>
<td></td>
<td></td>
<td>0.06 (0.27)</td>
<td>0.06</td>
<td>0.83</td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
<td>0.12</td>
<td>-0.20</td>
<td>0.01</td>
<td></td>
<td></td>
<td>0.73</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td>0.08 (0.24)</td>
<td>0.12</td>
<td>0.75</td>
</tr>
<tr>
<td>Group</td>
<td></td>
<td></td>
<td></td>
<td>-3.64 (3.32)</td>
<td>-0.32</td>
<td>0.30</td>
</tr>
<tr>
<td>DSST baseline</td>
<td></td>
<td></td>
<td></td>
<td>0.06 (0.28)</td>
<td>0.06</td>
<td>0.85</td>
</tr>
<tr>
<td>WMH volume</td>
<td></td>
<td></td>
<td></td>
<td>0.00 (0.00)</td>
<td>-0.12</td>
<td>0.73</td>
</tr>
<tr>
<td><strong>Step 3</strong></td>
<td>0.58</td>
<td>0.38</td>
<td>0.46*</td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td>0.178 (0.172)</td>
<td>0.26</td>
<td>0.33</td>
</tr>
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<td>Group</td>
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<td></td>
<td></td>
<td>-3.789 (2.323)</td>
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<td>0.13</td>
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<td></td>
<td>0.012 (0.194)</td>
<td>0.01</td>
<td>0.95</td>
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<tr>
<td>WMH volume</td>
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<td></td>
<td></td>
<td>0.00 (0.00)</td>
<td>-0.49</td>
<td>0.09</td>
</tr>
<tr>
<td>Aβ deposition</td>
<td></td>
<td></td>
<td></td>
<td>-18.348 (5.186)</td>
<td>-0.77</td>
<td>0.01</td>
</tr>
</tbody>
</table>

DSST = Digit Symbol Substitution Test baseline score; WMH = white matter hyperintensity
* Significant at p ≤ 0.05
Table D.6 Multiple linear regression model assessing the contribution of Aβ plaque deposition on change in PPA performance with age and WMH volume as covariates

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>R²</th>
<th>Adjusted R²</th>
<th>R² Change</th>
<th>Unstandardized B (Standard Error)</th>
<th>Standardized β</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
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<td>0.49</td>
<td>0.59</td>
<td>-0.03 (0.02)</td>
<td>-0.22</td>
<td>0.01</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>-0.35 (0.36)</td>
<td>-0.19</td>
<td>0.35</td>
</tr>
<tr>
<td>PPA baseline</td>
<td>0.47 (0.13)</td>
<td>0.68</td>
<td>&lt;0.01</td>
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</tr>
<tr>
<td><strong>Step 2</strong></td>
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<td></td>
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</tr>
<tr>
<td>Age</td>
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<td>0.45</td>
<td>0.00</td>
<td>-0.02 (0.03)</td>
<td>-0.19</td>
<td>0.44</td>
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<tr>
<td>Group</td>
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<td>-0.18</td>
<td>0.40</td>
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<td></td>
</tr>
<tr>
<td>PPA baseline</td>
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<td>0.69</td>
<td>0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WMH volume</td>
<td>0.00 (0.00)</td>
<td>-0.07</td>
<td>0.77</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Step 3</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>-0.01 (0.02)</td>
<td>-0.10</td>
<td>0.64</td>
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</tr>
<tr>
<td>Group</td>
<td>-0.41 (0.32)</td>
<td>-0.22</td>
<td>0.23</td>
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</tr>
<tr>
<td>PPA baseline</td>
<td>0.39 (0.12)</td>
<td>0.56</td>
<td>0.01</td>
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</tr>
<tr>
<td>WMH volume</td>
<td>0.00 (0.00)</td>
<td>-0.27</td>
<td>0.25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aβ deposition</td>
<td>-1.74 (0.74)</td>
<td>-0.45</td>
<td>0.04</td>
<td></td>
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</tr>
</tbody>
</table>

PPA = Physiological Profile Assessment baseline score; WMH = white matter hyperintensity
* Significant at p ≤ 0.05
Chapter 5: Bivariate correlation assessing the association between change in WMH volume and change in global cognitive function

Cognitive function was assessed using the ADAS-Cog, this was the primary outcome of the parent RCT. This scale assesses memory, language, and praxis. There are 11 tests and scores range from 0 to 70 with higher scores indicating greater cognitive dysfunction.

To assess the relationship between change in WMH volume and change in ADAS-Cog, I conducted a partial correlation controlling for age in the combined AT and CON group. Change in ADAS-Cog was calculated as baseline minus trial completion scores, a positive change indicates improved ADAS-Cog performance.

Controlling for age, change in WMH volume was not associated with change in ADAS-Cog ($r = -0.05, p = 0.79$). In addition, change in WMH volume was not associated with change in ADAS-Cog in either males ($r = -0.30, p = 0.28$) or females ($r = -0.35, p = 0.30$).