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The effects of resistance training on cognition and brain health in older adults at risk for diabetes: A pilot feasibility study

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Abstract

Type 2 diabetes is associated with neurocognitive deficits and increased risk for dementia, with high prevalence of diabetes occurring in old age. There are many known risk factors for diabetes, including physical inactivity, obesity, and prediabetes. Studies show that individuals who are at risk for diabetes (i.e., have one or more risk factors) already experience some brain deficits seen in diabetes. One way to combat these deficits is aerobic exercise; however the effects of resistance exercise in this population are relatively unknown. The objectives of this thesis were to report on the current evidence of brain deficits in prediabetes, and to assess the feasibility and preliminary efficacy of resistance training to improve cognition and brain health (structure and function) in older adults at risk for diabetes. A systematic review of cross-sectional and longitudinal studies assessing brain deficits in prediabetes was conducted, as well as a 26-week pilot feasibility randomized controlled trial (RCT) of resistance exercise among older adults at risk for diabetes (i.e., those living with prediabetes and/or obesity). The systematic review found that prediabetic adults may experience deficits in structural connectivity, but whether deficits in brain volume and cerebrovascular health are present is somewhat inconclusive and may be due to inconsistencies across study methodologies. Results from the pilot feasibility RCT found that resistance exercise, compared to a balance and stretching exercise control group, may improve selective cognitive functions, mainly task-switching, selective attention and conflict resolution, and item memory. Resistance exercise also led to less age-related decline in total brain volume, less hippocampal atrophy, and increased functional activation patterns that mimic that of younger adults and healthy older adults. When assessing feasibility, study adherence, retention, and self-reported enjoyment were high, but recruitment was shown to be challenging. As such, important recruitment recommendations for improving future trials are included in this thesis. In conclusion, resistance exercise may lead to some improvements in cognition and brain health in older adults at risk for diabetes, however a full-scale, powered RCT is needed to further explore these possible effects.

Keywords

Aging, brain health, cognition, magnetic resonance imaging, prediabetes, obesity, randomized controlled trial, resistance exercise, pilot feasibility study

Summary for Lay Audience

Type 2 diabetes is a leading cause of disability among older adults and is associated with brain and cognitive deficits. Individuals who have one or more risk factors for diabetes including physical inactivity, obesity, or prediabetes (the state of having elevated blood sugar levels that are below the diabetes threshold) already show signs of similar impairment. Aerobic exercise, which aims to enhance cardiovascular function, is known to improve cognition and brain health (structure and function) in this population; however, the effects of resistance exercise, which aims to build muscle mass, are relatively unknown. The objectives of this thesis were to summarize the results from studies published to date regarding the brain deficits associated with prediabetes, and to determine whether resistance training may benefit cognition and neuroimaging outcomes in older adults at risk for diabetes (i.e., prediabetics and/or overweight or obese individuals) compared to balance and stretching exercises. The literature review found that studies assessing brain deficits in prediabetes have yielded largely mixed results, however deficits in structural connectivity may exist in prediabetes. The resistance exercise study found that this type of exercise may improve certain areas of cognition, such as the ability to switch focus between tasks. Additionally, neuroimaging findings from this study showed that resistance exercise may slow age- and disease-related brain shrinkage and lead to functional activation patterns that are seen in healthy adults. In summary, resistance exercise may improve cognition and brain health in older adults at risk for diabetes, however large-scale studies are needed to confirm these preliminary findings. Important recommendations for future trials are also included in this thesis.

Co-Authorship Statement

Joyla A. Furlano contributed to the conceptualization, data collection, data extraction, and manuscript writing of the published systematic review presented in Chapter 2. Becky R. Horst contributed to the data collection, data extraction, and manuscript editing of the systematic review. Lindsay S. Nagamatsu contributed to the conceptualization, data reviewing, and manuscript editing of the systematic review.

Joyla A. Furlano contributed to the conceptualization and manuscript writing of the published protocol manuscript partially included in Chapters 3 and 4. Lindsay S. Nagamatsu contributed to the conceptualization and manuscript editing of the protocol manuscript.

Joyla A. Furlano contributed to the conceptualization, data collection, and data analysis of the pilot study presented in Chapters 3-5. Lindsay S. Nagamatsu acquired funding for this study and contributed to the conceptualization, data reviewing, and study supervision. The results presented in Chapter 3 are currently in preparation for publication by Joyla A. Furlano in collaboration with Lindsay S. Nagamatsu. Becky R. Horst contributed to the MRI data collection and data analysis of Chapter 4. The results presented in Chapter 4 are currently in preparation for publication by Joyla A. Furlano in collaboration with Lindsay S. Nagamatsu and Becky R. Horst.

Joyla A. Furlano contributed to the conceptualization, data collection, data analysis, and manuscript writing of the published feasibility manuscript presented in Chapter 5. Lindsay S. Nagamatsu contributed to the conceptualization, data reviewing, and manuscript editing of the feasibility manuscript.

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List of Abbreviations

ABCC8	Adenosine triphosphate-binding cassette transporter sub-family C member 8
ACC	Anterior cingulate cortex
AD	Axial diffusivity
ADA	American Diabetes Association
ADAS-Cog 12	Alzheimer's Disease Assessment Scale–Cognitive 12
AGE	Advanced glycation end product
APC	Annual percent change
APOE	Apolipoprotein E
ARWMC	Age-related white matter changes
ATR	Anterior thalamic radiation
β-cell	Beta islet cell
BDNF	Brain-derived neurotrophic factor
BET	Brain Extraction Tool
BMI	Body mass index
BOLD	Blood oxygenation level-dependent
CBF	Cerebral blood flow
CI	Confidence interval
CMB	Cerebral microbleed
CONSORT	Consolidated Standards of Reporting Trials
CSFV	Cerebrospinal fluid volume
dMRI	Diffusion-magnetic resonance imaging
DSM-5	Diagnostic and Statistical Manual of Mental Diseases, 5th Edition
DTI	Diffusion tensor imaging
DXA	Dual-energy X-ray absorptiometry
FA	Fractional anisotropy
FAST	FMRIB's Automated Segmentation Tool
FCI	Functional Comorbidity Index
FEAT	FMRI Expert Analysis Tool
FIRST	FMRIB's Integrated Registration and Segmentation Tool
fMRI	Functional magnetic resonance imaging

FMRIB	Functional Magnetic Resonance Imaging of the Brain
FPG	Fasting plasma glucose
FSL	FMRIB's Software Library
FWHM	Full-width at half-maximum
GDS	Geriatric Depression Scale
GLM	General linear modelling
GLUT4	Glucose transporter type 4
GMV	Grey matter volume
HbA1c	Hemoglobin A1c
HR	Hemodynamic response
HV	Hippocampal volume
IADL	Instrumental Activities of Daily Living
ICV	Intracranial volume
IFG	Impaired fasting glucose
IGF-1	Insulin-like growth factor-1
IGT	Impaired glucose tolerance
ILF	Inferior longitudinal fasciculus
LI	Lacunar infarct
LRP	Lipoprotein receptor-related protein
LTP	Long-term potentiation
MCFLIRT	Motion Correction using FMRIB's Linear Image Registration Tool
MCI	Mild cognitive impairment
MCID	Minimal clinically important difference
MC4R	Melanocortin-4 receptor gene
MD	Mean diffusivity
MeSH	Medical Subject Headings
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MRI	Magnetic resonance imaging
MTG	Middle temporal gyrus
MTL	Medial temporal lobe
NFG	Normal fasting glucose

NGT	Normal glucose tolerance
OGTT	Oral glucose tolerance test
PASE	Physical Activity Scale for the Elderly
PBVC	Percent brain volume change
PFC	Prefrontal cortex
PSC	Percent signal change
QALY	Quality Adjusted Life Year
RA	Research assistant
RAVLT	Rey Auditory Verbal Learning Test
RCT	Randomized controlled trial
RD	Radial diffusivity
RF	Radio wave frequency
ROI	Region of interest
SD	Standard deviation
SE	Standard error
SIENA	Structural Image Evaluation, using Normalization, of Atrophy
SLF	Superior longitudinal fasciculus
sMRI	Structural magnetic resonance imaging
SPPB	Short Physical Performance Battery
TBV	Total brain volume
TCF7L2	Transcription factor 7-like-2
TE	Echo time
TMT	Trail Making Test
TR	Repetition time
TUG	Timed Up and Go Test
T2D	Type 2 diabetes
VEGF	Vascular endothelial growth factor
WHO	World Health Organization
WMH	White matter hyperintensity
WMHV	White matter hyperintensity volume
WML	White matter lesion
WMV	White matter volume

1RM	One repetition maximum
2-h PG	2-hour plasma glucose
7RM	Seven repetition maximum

Chapter 1

1 Introduction

Cognitive impairment and associated brain dysfunction is a major health concern among older adults. Worldwide, up to 41% of individuals over the age of 50 are suffering from cognitive impairment,[1] and this often leads to a decline in mobility, functional independence, and quality of life. Although neurocognitive decline occurs as a natural part of the aging process, it is often exacerbated in clinical populations of older adults such as those with diabetes, prediabetes, or obesity. This thesis will specifically examine such deficits in prediabetic and overweight/obese older adults, and will investigate whether exercise can be used as a lifestyle intervention strategy to improve cognition and brain health (structure and function) in this population.

1.1 Neurocognition

Cognition is broadly defined as the mental functions involved in the gathering and comprehension of knowledge. According to the fifth and most recent edition of the Diagnostic and Statical Manual of Mental Diseases (DSM-5),[2] there are six main domains that make up cognition: complex attention, executive function, learning and memory, language, perceptual-motor function, and social cognition, each containing subdomains. As my research focuses primarily on the first three domains, the latter three will not be described in detail in this thesis.

The first domain, complex attention, is made up of functions related to attention, or the ability to actively process specific information. One subdomain of complex attention is selective attention, the process of focusing on selected environmental stimuli while ignoring irrelevant stimuli. This is a fundamental cognitive function as attention is a limited resource, thus the ability to selectively direct one's focus is extremely valuable. Moreover, selective attention is considered a key underlying function for other cognitive abilities such as working memory (described below) and nonverbal intelligence (the ability to analyze information and problem-solve using visual reasoning).[3] Evidence from functional magnetic resonance imaging (fMRI; described in Chapter 1.2) research has shown that activation of sensory cortical areas, primarily the parietal and frontal lobes, occurs during both auditory and visual

selective attention;[4] specific areas involved include the posterior parietal cortex and prefrontal cortex (PFC).[5] While the DSM-5 recognizes complex attention as being distinct from executive function, attention is commonly considered a type of executive function within the literature.

Executive function refers to a set of mental skills that are required for the cognitive control of behaviour, that is the selecting and monitoring of behaviours to achieve a goal. Two commonly studied subdomains of executive function are conflict resolution, the ability to overcome conflicting perceptual inputs to achieve a desired behaviour, and task-switching (commonly called set-shifting), the ability to shift focus between tasks. A number of fMRI studies have found that the PFC, specifically the dorsolateral areas, underlies both conflict resolution and task-switching.[6,7] The anterior cingulate cortex (ACC) is also known to support conflict resolution,[6] while areas including the pre-supplementary motor area, parietal cortex, and the frontopolar cortex also support task-switching.[7] In addition, working memory, which is the ability to hold a small amount of information in mind and use it in the execution of cognitive tasks, is another important component of executive functioning that depends critically on the medial temporal lobe (MTL) and PFC.[8,9]

The third DSM-5 cognitive domain includes both learning, the process of acquiring skill or knowledge, and memory, the storing and recalling of information. Generally, the main brain areas involved in these processes are the frontal lobe, hippocampus (a subcortical brain region located within the MTL that plays an important role in memory consolidation and storage), and other temporal lobe structures.[10,11] Under the umbrella term of memory, there are several types and ‘phases’, the latter of which includes short-term and long-term memory. Short-term memory is defined as the ability to store information in one’s mind for short periods of time (typically within seconds), whereas long-term memory (sometimes referred to as delayed memory) deals with the storage of information for extended periods. While working memory is a form of short-term memory since it involves the storage of information for short periods of time, it is defined as an executive function as it uses information to immediately plan and carry out behaviour.

For all memory types, there are three processes that are essential to its function; these are encoding, storage, and retrieval. Encoding is the process by which information is learned,

perceived, and related to existing knowledge, while storage is the process of maintaining this information overtime. Retrieval (or recognition), on the other hand, is the process of recalling and accessing information when it is needed. While each of these three processes are distinct, they are also related and strongly rely on one another. For example, the strength by which a memory is encoded is correlated to the likelihood that it will be effectively retrieved.[12]

1.1.1 Associative memory

One type of memory particularly relevant to this thesis is associative memory, defined as the ability to learn and remember the relationship between items that are unrelated (e.g., faces and names). Associative memory is thought to be one of the most essential memory functions due to its usefulness and applicability, and has been argued to be critical for higher and more complex memory performance.[13] Associative memory allows people to make connections and inferences, and is commonly applied to many life scenarios including observations and interactions with others.[14] Further, the ability to process multiple stimuli together allows individuals to process information faster and more efficiently.[15] This type of memory is often used subconsciously in everyday life as we frequently memorize items within our environment in conjunction with one another.

The neuroanatomical structures that underlie associative memory are largely located within the MTL and surrounding areas of the brain.[16] One of the main implicated MTL structures in this type of memory is the hippocampus.[16] Evidence from primate research shows that hippocampal cells exhibit increased patterns of learning-related neural activity during the formation of novel associative memories.[16] However, some studies have also shown that cells in other brain areas including the PFC, frontal motor-related areas, and striatum exhibit similar patterns of neural activity during associative learning.[16] Moreover, structures that are functionally related to the hippocampus, such as the entorhinal, perirhinal, and parahippocampal cortices, have been shown to underlie associative memory ability.[16] These areas are known to support memory encoding as well as related functions including memory formation and memory consolidation;[17,18] the latter occurs when temporarily learned experiences are transformed into long-term memories.

1.1.2 Neurocognition in aging and disease

The majority of cognitive functions, including functions previously discussed (e.g., selective attention, conflict resolution, task-switching, working memory, long-term memory, associative memory), are known to decline naturally with age.[19–21] Such declines in cognitive ability are said to begin in one's 20's and worsen with advanced age, with most decline occurring after the age of 70.[22] However, the rate and degree at which cognition declines with age is highly dependent on a myriad of hereditary and environmental factors, including one's genetic makeup, education level, sex, and health behaviours (e.g., physical activity levels, sleep patterns, diet). For example, higher fitness levels are positively correlated with preserved cognitive ability late in life;[23] this particular relationship will be further explored in Chapter 1.6.

Evidence from neuroimaging studies demonstrate that age-related cognitive decline occurs with neurodegeneration.[24] As we age, humans experience a loss of neurons (fundamental units (cells) of the brain; the brain contains roughly 86 billion neurons)[25] and neuronal connections that results in atrophy of brain tissue. Total brain volume (TBV) atrophy in healthy individuals has been shown to occur by the age of 30, with greater decline in old age.[26] In fact, by the time healthy individuals reach the age of 60, the brain naturally decreases ~0.3% per year.[27] One brain area that is particularly susceptible to age-related atrophy is the hippocampus.[28] A meta-analysis estimated that the average annual rate of hippocampal atrophy in healthy aging is 1.4%; in this review, the mean age range of study participants was 69-83 years old.[29] Moreover, hippocampal atrophy has been shown to be correlated with deficits in memory function,[30] and memory problems is one of the most common cognitive complaints among older adults.[19]

In addition to atrophy, age is associated with changes in the brain's hemodynamic response (HR),[31] which reflects the delivery of blood and oxygen to active neurons to support their function (to be discussed further in Chapter 1.2.1). Specifically, studies show that age is correlated with a decrease in neural activation in task-specific areas. For example, one study found that age was associated with a linear decrease in neural activity in memory-related areas (right middle frontal gyrus, bilateral precunei) during a spatial working memory task.[32] In this study, age was also associated with decreased accuracy in task performance.[32]

Another study assessed age-related differences in brain activation during working memory, visual attention, and episodic retrieval tasks.[33] In all three tasks, older versus younger adults had weaker activity in the occipital lobe (consistent with decline in age-related sensory processing abilities) but stronger prefrontal and parietal activity which may reflect functional compensation.[33] Taken together, it appears that the level in which brain areas are engaged in cognitive tasks may differ with age, and decreases in neural activity in task-related areas may reflect worsened cognitive performance. Research also shows that aging has a negative impact on connectivity strength within functional and structural brain networks, particularly those related to high level cognitive functions.[34]

Although declines in cognition and brain health are a natural part of aging, such declines can occur at a faster rate than expected as a result of neurodegenerative disease. For example, mild cognitive impairment (MCI), the precursor stage of dementia, occurs when individuals experience declines in cognitive function (associated with a loss of brain tissue) that are beyond normative aging (**Figure 1.1**). However, these declines do not significantly interfere with everyday life. Dementia, on the other hand, occurs when there is more severe impairment than MCI (**Figure 1.1**) that does interfere with activities of daily living. The most common form of dementia is Alzheimer's disease, which accounts for 60-70% of all dementia cases and is characterized by severe deficits in memory, thinking, or decision-making abilities.[35] It is believed to occur when there is an abnormal build-up of the proteins beta-amyloid and tau in the brain. Beta-amyloid makes up a larger protein (amyloid) and contributes to the formation of amyloid plaques around neurons which disrupts neuronal communication and function; tau, however, creates neurofibrillary tangles in the brain which disrupts the transport of nutrients and other important substances within neuronal cells.[36] While Alzheimer's disease can occur in young-to-middle adulthood, it primarily affects individuals aged 60+, and is currently the fifth leading cause of death in older adults.[37]

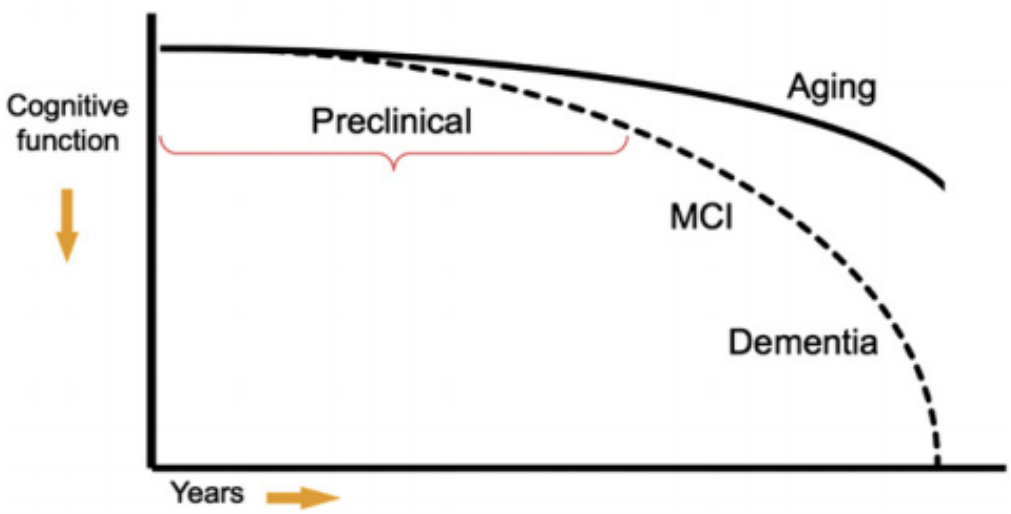

Figure 1.1: Model of clinical trajectory of dementia as compared to normal aging.

Source: Sperling RA et al. (2011)[38] (copyright access granted via Copyright Clearance Center)

1.2 Magnetic resonance imaging

Magnetic resonance imaging (MRI) is a non-invasive imaging technique that uses magnetic fields and radio waves to produce high-resolution images of tissues and organs within the body. It is commonly used to examine neurocognitive abilities and detect abnormalities in the brain, and is the most frequently used imaging technique of the brain and spinal cord.[39] The strength of the magnetic field applied is measured in Tesla units, named after Nikola Tesla who discovered the rotating magnetic field in 1882.[40] The greater the Tesla strength of a scanner, the greater the detail and quality of the images that it produces. The majority of research studies use scanners that operate at a strength of 1.5 or 3 Tesla.

To briefly describe the physical principles behind MRI,[41] we must first consider the properties of water molecules within the body. The human body is made up of 60-70% water, and each water molecule contains two hydrogen atoms and one oxygen atom. Protons (nuclei) of hydrogen atoms are naturally charged particles that spin around an axis and behave like a magnet (have a north and south pole). At any moment in time, the billions of hydrogen protons within the body are in random positions as they spin on their axes. However, when a strong external magnetic field is applied during an MRI scan, hydrogen protons in the body are temporarily aligned with that field. Radio waves are then applied to deflect the magnetic field and force the protons to spin out of equilibrium. When the radio wave frequency (RF) source is turned off, protons 'relax' and realign with the magnetic field, and this causes a signal (also a radio wave) to be emitted. These emitted signals are detected by MRI coils in the form of an electrical current and are transformed using a mathematical calculation called a Fourier transformation[42] to produce cross-sectional images of tissues within the body.

Different tissues in the body relax at different rates when the RF source is turned off, therefore the intensity of the received signals allows us to differentiate between various tissue types. The time taken for the hydrogen protons to fully relax once the RF source is removed is measured in two ways: (1) the time it takes to realign with the magnetic field, which is called T1 relaxation, and (2) the time it takes to return to their previous axial spins, which is called T2 relaxation. MRI, then, is made up of a series of RF pulse sequences which determine the appearance of the outputted images. Repetition time (TR) is the time between

RF pulses, and echo time (TE) is the time between the RF pulse and the produced signal. T1-weighted images (characterized by short TR and TE) provide excellent structural anatomical detail, while T2-weighted images (characterized by long TR and TE) are useful in identifying pathology. In brain MRI, these images provide static information on the shape, size, and integrity of grey matter and white matter in the brain (i.e., components of structural MRI, or sMRI). In addition, the two main characteristics that determine MRI image quality are spatial resolution and signal-to-noise ratio. Spatial resolution is mainly determined by the imaging voxels (volumes that makes up three-dimensional space), while signal-to-noise ratio is a measure of the true MRI signal versus unavoidable background quantum noise. Further details on the complexity of principles underlying MRI is beyond the scope of this thesis.

There are several advantages of MRI in comparison to other imaging techniques. Generally, some of its advantages are that it: (1) has high spatial resolution, (2) can produce images in multiple planes, (3) does not use ionizing radiation, which can damage cells following high exposure, and (4) is non-invasive. There are, however, some disadvantages to this imaging technique, including that it (1) may be uncomfortable for patients (e.g., is loud), (2) requires patients to remain extremely still while inside the scanner, as motion can cause artefacts resulting in distorted images, (3) cannot be done in patients with metal implants or electronic devices due to the strong magnetic field applied in the scanner, and (4) is expensive.

1.2.1 Functional MRI and the brain

Functional MRI, unlike sMRI, provides dynamic physiological information about the brain (e.g., what areas of the brain are used for specific functions). It is an indirect measure of brain activity based on changes in cerebral blood flow. An increase in neural activity, which involves the firing of neurons in a specific area of the brain (e.g., during a cognitive task), stimulates an increase in blood (hemoglobin) to that brain region in order to supply active neurons with the energy they need; this process makes up the HR. During the HR, oxygenated hemoglobin (i.e., hemoglobin that has oxygen molecules attached to it) increases in brain areas that are active. Hemoglobin is a protein within red blood cells that is responsible for transporting oxygen throughout the body. Oxygenated hemoglobin is diamagnetic, meaning that it repels magnetic forces, while deoxygenated hemoglobin (i.e., hemoglobin that does not have oxygen molecules attached to it) is paramagnetic and is

attracted to magnetic fields. Therefore, fMRI picks up stronger signals from areas that have higher levels of oxygenated hemoglobin compared to deoxygenated hemoglobin which creates more magnetic distortion, and this concept forms the basis of blood oxygen level-dependent (BOLD) fMRI. To note, in comparison to neuronal activity, the HR is quite slow (milliseconds versus seconds, respectively). Thus, fMRI has lower temporal resolution compared to other measures of neural activity such as electroencephalography (which records electrical activity directly from the scalp). However, as briefly mentioned, fMRI has high spatial resolution (approximately 3-4 mm).[43]

1.3 Type 2 diabetes

Type 2 diabetes (T2D), a chronic health condition characterized by impaired glucose regulation in the body, is the most common form of diabetes making up 90-95% of all cases.[44] An estimated 462 million people, or 6.28% of the world's population, have T2D,[45] which is considered the fastest growing global epidemic.[46] Type 2 diabetes occurs as a result of the body's ineffective use of insulin (**Figure 1.2**), a hormone produced by beta islet cells (β-cells*)* in the pancreas to regulate blood glucose (sugar) levels. Glucose, the body's primary source of energy that mainly comes from food, enters the bloodstream upon the digestion of food; insulin is then released from the pancreas to allow muscle, fat, and liver cells to absorb the sugar for energy and storage. In T2D, cells become resistant to insulin and are unable to properly absorb sugar from the blood, leading to excess glucose in the bloodstream. By comparison, type 1 diabetes occurs when β-cells in the pancreas can no longer produce insulin (**Figure 1.2**), and is caused by an autoimmune reaction.

There are many factors that contribute to the development of T2D. One such factor is one's genetic makeup, including mutations in genes involved in controlling glucose levels. For example, mutations of the TCF7L2 (transcription factor 7-like-2) gene have been shown to disrupt insulin secretion and glucose production,[47] while ABCC8 (adenosine triphosphate-binding cassette transporter sub-family C member 8) mutations are known to negatively affect insulin regulation.[48] In addition, a major lifestyle risk factor for T2D is a lack of regular exercise, which can contribute to both the development and progression of T2D and its complications. This was demonstrated in a large prospective cohort study that found that the risk for T2D was significantly higher in those with low versus high levels of moderate-to-

vigorous exercise per week.[49] In line with this, a review found that exercise (e.g., walking) can reduce the risk for T2D by up to 50%.[50] Additional factors that can contribute to the development of T2D include excess body weight, poor sleep, smoking, alcohol consumption, and characteristics of metabolic syndrome including high fat around the waist, high triglycerides, and low levels of high-density lipoprotein cholesterol.

Chronic hyperglycemia (excess blood glucose levels) as a result of T2D leads to many physical health complications, including deficits in the body's nervous, circulatory, and immune systems. For example, hyperglycemia disrupts the body's immune response and impairs its ability to fight off invading pathogens; this may occur as a result of cytokine (protein that supports immune cells) production suppression, deficits in phagocytosis (process by which cells engulf bacteria and foreign substances), and immune cell dysfunction associated with T2D.[51] Additionally, chronically high blood sugar levels lead to blood vessel damage, specifically atherosclerosis (thickening or hardening of arteries). As such, patients with T2D often experience hypertension (high blood pressure), coronary artery disease, eye damage (i.e., damage to blood vessels in the eye), and even premature mortality.[52,53] Furthermore, diabetes is among the leading causes of kidney failure, and individuals with T2D have a two- to three-fold increased risk of a heart attack or stroke.[53] According to the American Heart Association, approximately 68% of people aged 65 or older with T2D will die from heart disease and 16% from stroke.[54]

The majority of T2D cases occur in older adults aged 60+ compared to other age groups.[55] Thus, as the world's aging population continues to rapidly increase, so will the prevalence of T2D. Previous projections have suggested that the number of T2D cases in older adults aged 65+ will increase by 4.5-fold between 2005 and 2050.[56] The prevalence of T2D in older adults may be even higher than what is known, as it has been reported that up to one-third of older adults with T2D go undiagnosed.[57] Compared to younger adults, older adults may be especially at high risk for T2D due to a combination of insulin de-sensitivity and impaired pancreatic function,[58] as well as cardiovascular comorbidities, that occur with age. Moreover, age-related insulin resistance appears to be primarily associated with adiposity, sarcopenia, and physical inactivity, all of which also typically increase with age.[59]

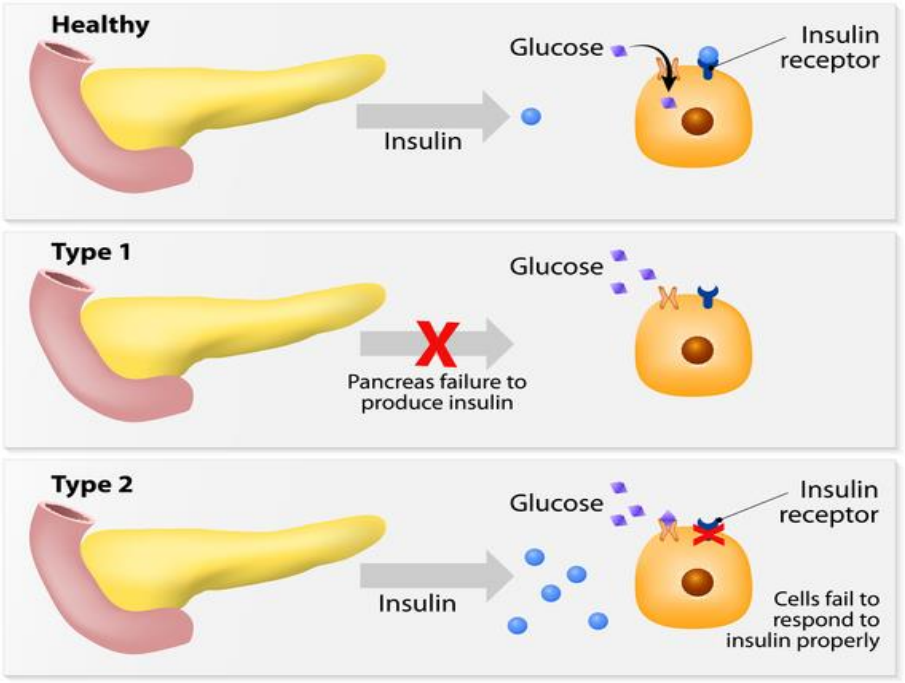

Figure 1.2: Healthy pancreatic function and pancreatic function in type 1 and type 2 diabetes.
Source: MedlinePlus, National Library of Medicine[60] (non-copyrighted)

1.3.1 Neurocognition in type 2 diabetes

Type 2 diabetes is a known risk factor for both MCI and Alzheimer's disease. In fact, research shows that individuals with T2D have more than a 50% higher risk of developing dementia compared to those without diabetes.[61,62] Specifically, a meta-analysis found that those with T2D had a 73% greater risk of developing all type dementia and a 56% risk of developing Alzheimer's disease.[62] Interestingly, T2D has been shown to share some of the same etiological mechanisms as MCI and Alzheimer's disease. For example, the dominant gene associated with the presence of Alzheimer's disease is apolipoprotein E (APOE), specifically the ε4 allelic variant, and this gene is also involved in the regulation of glucose and lipid metabolism.[63] Studies have found that brains that express APOE ε4 display significant deficiencies in glucose uptake and metabolism.[64] It has also been shown that the presence of APOE ε4 in those with T2D significantly increases the risk for Alzheimer's disease.[63]

In relation to dementia risk, T2D is associated with a significant reduction in cognitive ability. A meta-analysis of cross-sectional studies showed that people with T2D perform worse than those without T2D in the cognitive domains of information-processing, visual memory, verbal memory, attention, and executive function.[65] Similarly, a systemic review found deficits in processing speed, attention, memory, and cognitive flexibility (the general ability to adapt thinking and behaviour to one's environment) in T2D, and these effects were greater in those aged 65+.[66] In a longitudinal study, T2D was also shown to be a significant predictor of cognitive decline across six years in measures of global cognitive function, perceptual speed, and declarative memory (a form of long-term memory that involves conscious recall).[67] Further, there is evidence to suggest that the duration of T2D may have an impact on cognitive impairment severity, with longer durations being correlated with greater dysfunction.[68]

Neuroimaging studies have also revealed that individuals with T2D exhibit reduced brain volumes (including total and regional white matter volume (WMV) and grey matter volume (GMV)) and other brain heath deficits when compared to those without diabetes.[69] For example, a large cross-sectional study found that patients with T2D, compared to those without, had lower total GMV, WMV and hippocampal volume (HV) that was associated

with worse cognitive function.[70] In this study, a loss of grey matter was found in the medial temporal, anterior cingulate, and medial frontal lobes, while white matter atrophy was localized to the frontal and temporal regions.[70] Likewise, a review by Ryan et al. (2014) found less GMV, WMV and HV in diabetics compared to healthy controls.[71] Specifically, grey matter atrophy was shown to occur in the temporal, frontal, and limbic brain regions, which is a hallmark of early Alzheimer's disease.[71] This review also demonstrated that grey matter atrophy may contribute to the cognitive deficits that are observed in T2D.[71] Deficits in functional brain connectivity and cerebrovascular health including cerebral infarcts, white matter hyperintensities (WMHs), and microbleeds (which will be explored later on in this thesis) have also been shown to be associated with T2D in many studies, and are linked to cognitive dysfunction.[72–74]

Cognitive and brain dysfunction in T2D can be attributed to several potential underlying mechanisms. Firstly, cerebral infarcts are known to lower the threshold of amyloid in the brain, allowing for the development of amyloid plaques as seen in Alzheimer's disease.[75] Secondly, WMHs associated with T2D have been shown to occur with cerebral amyloid angiopathy (the buildup of amyloid on artery walls in the brain) which leads to cerebrovascular decline.[75] Thirdly, in hyperinsulinemia (high blood insulin levels) which often occurs in T2D, peripheral insulin can cross the blood brain barrier and result in the deposition of beta-amyloid and tau.[75] Additionally, hyperglycemia has been shown to be linked to increased advanced products of glycosylation (AGEs; proteins or lipids that become harmful when they combine with glucose in the blood) that are related to microvascular complications in T2D.[75] Finally, a reduction of lipoprotein receptor-related proteins (LRPs), which help remove beta-amyloid and mediates its transportation from the brain, has been shown to occur in T2D.[75] While these mechanisms are believed to mediate the effects of T2D on cognitive and brain health, the direction of causality remains debated upon (i.e., whether they contribute to deficits in T2D or vice versa).

1.4 Prediabetes

One major risk factor for T2D is prediabetes. Sometimes referred to as intermediate hyperglycemia, prediabetes is the state of having elevated blood glucose levels that are beyond the normal range but below the T2D threshold. Globally, the number of people with

prediabetes (based on impaired glucose tolerance (IGT), described below) is estimated to be around 352 million (7.3% of the adult population), and this number is projected to reach 587 million by 2045.[76] These estimates are based on IGT only, thus actual prevalence rates may be even higher based on other diagnostic criteria[76] that will be explored in this Chapter. Of those with prediabetes, most are unaware that they have it,[77] as common symptoms (e.g., increased thirst and urination, fatigue, excess hunger) often go undetected. Additionally, up to 70% of prediabetes cases will progress to T2D.[78] Annually, prediabetes has a T2D conversion rate of approximately 5-10%, with a similar rate of cases converting back to normoglycemia each year.[78] Potential causes of prediabetes are similar to that of T2D, and have been discussed in Chapter 1.3.

According to the World Health Organization (WHO), prediabetes is defined as having (1) impaired fasting glucose (IFG) based on fasting plasma glucose (FPG) 6.1 to 6.9 mmol/l (110 to 125 mg/dl), and, if measured, 2-hour plasma glucose (2-h PG) <7.8 mmol/l (140 mg/dl), and/or (2) IGT based on FPG <7.0 mmol/l (126 mg/dl) and 2-h PG ≥7.8 and <11.1 mmol/l (140 and 200 mg/dl); glucose refers to venous plasma glucose levels, and the 2-hour test occurs after ingestion of 75 g of an oral glucose load.[79] In comparison, diagnostic criteria for the American Diabetes Association (ADA) includes a lower FPG threshold (5.6 to 6.9 mmol/l, or 100 to 125 mg/dl) for IFG, does not recommend a 2-h PG measurement for IFG, does not include a FPG measurement for IGT (but has the same 2-h PG criteria of ≥7.8 and <11.1mmol/l (140 and 200 mg/dl), and has an additional diagnostic measure of glycated hemoglobin (HbA1c; occurs when sugar molecules attach to hemoglobin) 5.7 to 6.4%.[80] Differences between these criteria, and their potential effects on diagnoses of prediabetes, will be explored in Chapter 2.

1.4.1 Neurocognition in prediabetes

Within the literature, prediabetes has been shown to be associated with an increased risk for cognitive decline and accelerated cognitive dysfunction across many studies. Examples of cognitive domains that are disrupted in prediabetes include global cognitive function, verbal fluency, memory, and executive function.[81,82] One study found that prediabetes was associated with faster cognitive decline over nine years when compared to diabetes-free status.[81] In this study, older adults with prediabetes had a clinically relevant decline in

performance on the Mini-Mental State Examination (MMSE), a measure of global cognition (including orientation, language, complex commands, etc.).[81] Other studies, described in a review by Papunen et al. (2020), show fairly consistent findings of cognitive decline in prediabetes.[83] However, when assessing underlying structural deficits in prediabetes, results are largely inconsistent between studies. Cui and colleagues (2019) found that prediabetic adults, compared to healthy controls, had reduced left HV, which is commonly seen in T2D.[84] In contrast, a study by Schneider et al. (2017) found no significant difference in HV between prediabetics and healthy participants.[85] Other conflicting evidence has been found for volumetric measures of total brain, grey matter, white matter, and additional regional brain areas in prediabetics, as well as measures of cerebrovascular health and structural connectivity, which will be closely examined in Chapter 2.

Alterations in functional connectivity and hemodynamic activity in the brain may underlie cognitive deficits seen in prediabetics. However, very little research has been conducted on these topics in prediabetes. One cross-sectional study in adults assessed brain functional connectivity patterns in the default mode network, an area that has disrupted connectivity in T2D, but found no differences in functional connectivity between prediabetics and healthy controls.[86] Another study by van Bussel and colleagues (2016) found that prediabetics, on the other hand, had disrupted global functional brain networks when compared to healthy controls, but to a lesser extent than diabetics (trending).[87] Aside from these two studies, however, functional brain health in prediabetics is largely unknown.

1.5 Obesity

A second major risk factor for T2D is obesity, a complex and progressive disease defined as having excessive body fat (adiposity) that is associated with health risk.[88] Essentially, it occurs when the body's energy intake is greater than energy expenditure. Obesity is often diagnosed by calculating body mass index (BMI), which takes into account one's height (in meters (m)) and weight (in kilograms (kg)) and is calculated by height / weight. A BMI of under 25 is considered healthy, while a BMI of 25 or greater is considered a health concern (25-29.9 is defined as being overweight, and 30+ as obese). Body mass index is the most commonly used and convenient measure of obesity. While it does not directly measure body fat, it has been shown to be moderately correlated with direct measures taken via skinfold

measurements, bioelectrical impedance, dual-energy X-ray absorptiometry (DXA), and other tests.[89] Further, there is evidence to suggest that BMI is similarly correlated to health status as direct measures of obesity. For example, one study showed that BMI measures were highly correlated with DXA measures, and these were related to cardiovascular risk factors in similar ways.[90]

Along with T2D, obesity is a major global health epidemic. The prevalence of obesity has nearly tripled since the mid-1970's, and its rate continues to steadily increase.[91] In 2016, 1.9 billion people (39% of adults) worldwide were overweight, and, of these, 650 million were obese.[91] Further, more than 2.8 million people die each year as a result of being overweight or obese, and this disproportionally affects older adults who are at greater risk for premature death.[92] Obesity increases the risk of developing many debilitating chronic illnesses in addition to T2D, including coronary heart disease.[93] Moreover, health complications (e.g., cardiovascular impairment, including hypertension) associated with obesity appear to worsen as BMI increases.[94] In old age, obesity is also associated with greater limitations in activities of daily living and functional disabilities.[95] A review found that obesity is related to the development of mobility impairments in older adults, and this included the ability to walk, climb stairs, and rise up from a seated chair position (i.e., daily tasks).[95] Hospitalization is also common among older overweight and obese populations, which amounts to a heavy burden on the healthcare system.[96]

Like T2D, there are many variables that contribute to obesity, including environmental, genetic, biological, and socioeconomic factors. Risk factors include, but are not limited to, an unhealthy diet, lack of physical activity, low socioeconomic status, exposure to obesogens (artificial chemicals that disrupt lipid metabolism), and mutations of specific genes.[97] The most commonly implicated gene in obesity is MC4R (melanocortin-4 receptor gene), which plays a key role in regulating energy homeostasis in the body; mutations of this gene have especially been implicated in early-onset obesity (i.e., in young children).[98] The disruption of hormones that regulate food intake and metabolism, such as leptin, can also lead to obesity.[99] Leptin is produced in adipose tissue and signals the hypothalamus in the brain to regulate appetite.[100] In addition, insulin resistance that often occurs in obesity may be the result of impaired insulin-stimulated glucose transport in adipocytes (cells that store fat), which is caused by the downregulation of the protein GLUT4 (glucose transporter type 4).[101] To note,

there are many additional physiological mechanisms that may underlie obesity, however they are beyond this dissertation's scope.

1.5.1 Neurocognition in obesity

Research has shown that obesity is associated with cognitive impairment and is a known risk factor for dementia.[102] In a cross-sectional study, adults with obesity (based on BMI) versus those with normal weight were almost four times more likely to exhibit poor executive function as measured via the Trail Making Test (TMT).[103] Additionally, a systematic review of 17 cross-sectional studies in adults found that obesity was associated with cognitive dysfunction in all cognitive domains that were measured, including complex attention, verbal and visual memory, and decision-making.[104] However, it should be noted that included studies in this review varied in terms of comorbidities that were controlled for in analyses, and this makes it challenging to compare between studies.[104] Another review assessing the associations between obesity and cognition found that weight gain was associated with impaired executive function, which may be caused by mechanisms such as systemic inflammation or insulin resistance.[105] Studies have also shown that cognitive impairment in those who are overweight or obese may occur in response to impaired cerebral metabolism and neuronal degradation.[104]

Interestingly, some studies in older adults have found that increased weight may have a neuroprotective ability in old age,[106] and the presence of leptin may be responsible for this. Higher leptin levels in the body, which often occur in obesity,[99] have been related to better cognitive abilities,[107] and have been found to modulate the clearance of beta-amyloid in rodent research.[108] Increased leptin levels may especially be important in late life, given that leptin levels decrease naturally with age.[109] One study in older adults aged 70-79 found that those with higher serum leptin levels had less cognitive decline.[110] Despite this, more research on the effects of leptin on the brain in old age is needed, as this relationship is not fully understood. Specifically, research on the potential interactions of increased leptin levels and other obesity-related underlying mechanisms is needed.

Numerous studies have also shown that obesity is correlated with brain dysfunction, including atrophy. Brain areas that appear to be most vulnerable to atrophy in overweight and obese individuals include the hippocampus, cingulate cortex, and frontal lobes, and this

parallels findings of impaired executive function and memory ability in obesity.[111] A study by Raji et al. (2010) found that obese individuals had atrophy in the frontal lobes, anterior cingulate gyrus, hippocampus, and thalamus when compared to those with normal BMI.[112] Similarly, a meta-analysis found associations between BMI and lower GMV in the medial prefrontal cortex, bilateral cerebellum, and left temporal pole.[113] Obese individuals have also been shown to have smaller TBV compared to those with normal weight.[114] In addition, BMI is associated with a reduction in neuronal fiber bundle length, which is thought to contribute to brain atrophy,[111] and is marked by alterations in functional connectivity networks and reductions in brain activation in areas associated with cognitive control.[115,116]

1.6 Exercise

Exercise is defined as a form of physical activity that is planned, structured, and repetitive, and done with the intent of improving physical fitness. To note, the terms 'physical activity' and 'exercise' may be used interchangeably throughout this thesis, as this is a common occurrence in the literature. Exercise is considered to be one of the most beneficial behavioural therapies to promote health and prevent disease. Evidence from the literature suggests that there is a linear relationship between exercise and health status, such that greater amounts of exercise is related to larger health benefits.[117] In general, exercise is known to lower blood pressure and improve cardiovascular health, aid in weight management, help maintain balance and stability, improve joint and muscle function, and prevent depression, among many other benefits. Moreover, exercise is effective in the primary prevention of over 35 chronic illnesses, including T2D, cardiovascular disease, and certain cancers.[118] In late life, exercise also helps prevent falls and falls-related injuries including bone fractures. This is especially important given that falls are the most common cause of injury in old age.[119] In addition, studies show that exercise can reduce the risk of death by 20-35%, however physical inactivity can increase one's risk of all-cause mortality by 52%.[120]

The two most common forms of exercise are aerobic and resistance exercise. The first, aerobic exercise, is made up of endurance-type exercises (e.g., running, cycling, swimming, rowing) that require increased oxygen intake to produce the energy needed for performance output. Moreover, this type of exercise focuses on improving cardiovascular function.

Resistance exercise (i.e., weight training), on the other hand, is exercise that increases muscle mass and strength and requires less oxygen intake. While both exercise types are associated with numerous health benefits, resistance exercise is particularly useful in old age as most older adults, even those with mobility limitations, can perform some form of this exercise; by comparison, older adults are often limited in aerobic capability. Improving muscle strength through resistance exercise also helps reduce the prevalence of falls and age-related sarcopenia,[121] which is characterized by progressive muscle loss.

The WHO recommends that adults aged 18-64 get a minimum of 150 minutes of moderate intensity (or 75 minutes of vigorous-intensity) aerobic exercise per week for sustained health benefits.[122] Additionally, it is suggested that adults participate in muscle-strengthening activities (at a moderate or vigorous intensity) that involve all major muscle groups at least twice per week.[122] Older adults over the age of 65 are recommended to follow the same guidelines as younger adults, but to also practice functional balance and strength training at a moderate intensity or greater three times per week to enhance functional capacity.[122] Older adults with chronic conditions are encouraged to be as physically active as their abilities and conditions allow.[122]

Despite existing recommendations, physical inactivity is recognized as one of the largest public health challenges. Worldwide, less than 25% of adults meet the recommended levels of physical activity,[123] and older adults are often among the least active.[124] In Canada, only 16.0% of adults aged 18 to 79 meet the recommended exercise amounts,[125] and this number continues to decrease after the age of 80.[126] Exercise rates in older adults may be lower than other age groups due to the prevalence of physical impairments and chronic illnesses common in later life that prevent participation (e.g., osteoarthritis, osteoporosis). Moreover, previously self-reported barriers to exercise in old age include a lack of self-discipline, interest, enjoyment, knowledge, company, facilities, energy, and motivation to participate.[127,128]

1.6.1 Exercise and neurocognition

There is increasing evidence that exercise not only improves bodily function, but also preserves and promotes cognition and brain health. These neurocognitive benefits are largely seen in childhood and old age when the brain is undergoing changes in structural and

functional circuitry (i.e., developmental changes in childhood, age-related decline in old age).[129] Nevertheless, studies show that exercise benefits the brain across the entire lifespan.[129] In general, these benefits occur as a result of exercise-induced decreases in neuroinflammation, increases in blood flow (and with this, oxygen and nutrients) to the brain, and increases in brain chemicals that promote the growth of neurons.[129–131] Importantly, exercise is also known to help protect against Alzheimer's disease and other types of dementia. Combined results from several prospective studies have shown that regular exercise can significantly reduce the risk for Alzheimer's disease by 45%.[132] Larson and colleagues (2006) demonstrated that people over the age of 65 who engaged in any form of exercise three or more times per week were less likely to develop dementia later on in life when compared to those who exercised less than three times per week.[133]

1.6.1.1 Aerobic exercise

The majority of research in the exercise neuroscience field has primarily focused on aerobic exercise, perhaps due to its important cardiovascular benefits. Findings from several studies demonstrate that aerobic exercise leads to strong improvements in cognition and brain structure and function, and these results occur well into old age.[129,134] Cognitively, aerobic training in older adults is known to improve executive functions that are supported by the frontal cortex, including processing speed, concept formation, and fluency,[135] as well as memory.[136] Evidence from fMRI research has found that six months of thrice-weekly aerobic exercise increased brain activation in regions involved in attentional control and inhibitory processes, namely the middle frontal gyrus and superior parietal cortex, in community-dwelling older adults.[137] Six months of aerobic exercise has also been shown to increase GMV and WMV in sedentary older adults, with the largest changes in GMV seen in the frontal lobe in areas implicated in attention and memory.[138]

Converging evidence from both animal and human research shows that aerobic exercise is associated with an increase in brain-derived neurotrophic factor (BDNF), which may serve as a main underlying mechanism leading to neurocognitive improvements.[139,140] Brain-derived neurotrophic factor is a neuronal growth factor known to promote neuronal health and neurogenesis (the development of new neurons) especially in the hippocampus.[129] Increased BDNF levels in the brain is associated with increases in long-term potentiation (LTP), which

enhances neuronal synaptic transmission and synaptic plasticity.[129] Studies show that decreased BDNF levels, particularly in older adults, may lead to neurodegeneration as well as patterns of cognitive dysfunction seen in Alzheimer's disease.[141] In addition to the release of BDNF, other neurophysiological processes that occur in response to aerobic exercise include increased cerebral blood flow, brain angiogenesis (the development of new blood vessels) supported by increased vascular endothelial growth factor (VEGF) levels, and the release of neurotransmitters (chemical messengers in the brain) including dopamine, serotonin, and acetylcholine which promote neuronal communication and cognitive functioning.[129,142]

1.6.1.2 Resistance exercise

Resistance exercise has also been shown to preserve and improve neurocognition, although there is less literature on this type of exercise compared to aerobic exercise. A recent systematic review assessed the effects of acute and long-term resistance training on the brain in young and older adults who were either healthy or diagnosed with a chronic illness (e.g., MCI, multiple sclerosis).[143] All included studies showed improvements in at least one or more cognitive or neurophysiological domain (e.g., improved executive function, increased hemodynamic activity, increased cortical thickness) following resistance training.[143] In older adults specifically, a study by Liu-Ambrose and colleagues (2012) found that community-dwelling females who performed 52 weeks of twice-weekly progressive resistance training exhibited better performance in tasks of executive function than those who engaged in balance and toning exercises (control group).[144] In this study, positive functional changes in hemodynamic activity were also found in areas implicated in response inhibition (the ability to suppress certain actions that interfere with goal-driven behaviour), including the left anterior insula, lateral orbital frontal cortex, and anterior portion of the left middle temporal gyrus (MTG).[144] In another study, Suo and colleagues (2016) found that six months of resistance training in older adults with MCI led to improvements in global cognition, and this was related to increased grey matter in the posterior cingulate regions.[145] Other studies have shown that resistance exercise lowers white matter atrophy, reduces the development of white matter lesions (WMLs), and preserves hippocampal atrophy in subfields that are susceptible to Alzheimer's disease.[143,146]

Despite evidence demonstrating the positive impact of resistance exercise on the brain, some studies have found contradictory results. For example, despite a randomized controlled trial (RCT) in older adults showing improved memory performance following 24 weeks of thrice-weekly resistance training,[147] a separate RCT found no improvement in memory, but did in executive function, following 52 weeks of twice-weekly resistance exercise.[145] Differences in findings may be attributed to differences in study designs, specifically the frequency, duration, and intensity of the exercises. Indeed, studies have shown that these elements of resistance training protocols are important to study results. For example, studies using lower-intensity resistance exercises have found no significant improvements in memory following six months of exercise.[148] However, studies using a resistance load of 50-80% of a one repetition maximum (i.e., 1RM, described further in Chapter 3) have found positive neurocognitive changes.[129] Moreover, it appears that RCTs of resistance exercise that are six months or greater yield the largest benefits to cognition and brain health, as do exercise trials that involve more frequent training.[129] One study assessing the effects of once- versus twice-weekly resistance training in older adults found improvements in selective attention and conflict resolution in both groups after 52 weeks, however only the twice-weekly group had improvements in functional plasticity of response inhibition processes.[144]

Improvements in cognition and the brain following resistance exercise are believed to be mediated by various molecular and cellular changes. For example, studies show that resistance exercise stimulates the release of insulin-like growth factor-1 (IGF-1), a neuronal growth factor that promotes the growth, survival, and differentiation of neurons and is known to play an important role in preventing Alzheimer's disease.[149] In animal models, low IGF-1 levels is associated with microvasculature degeneration in the brain as well as reduced neurogenesis in the hippocampus.[149] In a study in humans, higher serum IGF-1 levels were found following moderate (50% of 1RM) and high (80% of 1RM) levels of resistance exercise when compared to a stretching control group in older men.[147] Additionally, older adults with MCI had increased serum IGF-1 levels by ~15% following high-intensity resistance training.[150]

There is also evidence to suggest that resistance training reduces homocysteine, an amino acid produced by the body that is used to make other substances in the body.[151] High levels of homocysteine in the body is a known risk factor for vascular disease and brain atrophy.[152]

Twelve months of high-intensity resistance exercise (75-80% 1RM) has been shown to lead to declines in serum homocysteine levels in older adults.[153] Resistance exercise is also known to have a positive effect on adipokines, which are signaling proteins secreted in adipose tissue. Adiponectin, a type of adipokine, plays an important role in improving insulin sensitivity, and low levels are correlated with insulin resistance and cognitive dysfunction.[154,155] A study by Park and colleagues (2019) found significant increases in adiponectin following resistance exercise in postmenopausal women.[156] Finally, decreases in resistin (an adipose-derived protein correlated with inflammatory markers in Alzheimer's disease), increases in peripheral lactate (substance that allows glucose breakdown) concentrations, and increases in plasma BDNF and VEGF have also been found to occur following resistance training and are correlated with improved neurocognitive health.[129,157–159]

1.7 Exercise in type 2 diabetes

Exercise is often used to combat physical and neurocognitive impairment that occurs in T2D. It is well established that regular exercise plays an important role in blood glucose control, insulin sensitivity, and cardiovascular functioning in T2D.[160] In one of the largest randomized trials evaluating the effects of physical activity in older adults with T2D (expanding 16 study centres), it was found that physical activity (e.g., walking; up to 175 minutes per week) significantly improved HbA1c levels and cardiovascular risk factors.[161] Specifically, moderate and vigorous aerobic training has been shown to improve insulin sensitivity and glucose metabolism, increase GLUT4 protein expression which is key to glucose homeostasis, and decrease adiposity in T2D.[160,162,163] In a rat model, aerobic exercise reduced blood glucose levels and led to higher neuronal density in the hippocampus.[164] Additionally, aerobic exercise is known to improve cognitive outcomes among people with T2D, specifically executive function, memory, and global cognitive function, and these are related to reductions in insulin resistance.[165] A study in older women with T2D found that participants who underwent six months of aerobic training, compared to a control group, had decreased HbA1c levels and improvements in performance on the MMSE.[166]

Evidence demonstrates that resistance exercise may also lead to important improvements in health outcomes for those with T2D. Following 16 weeks of twice-weekly resistance

training, older diabetic men had a 46.3% increase in insulin action and a 7.1% decrease in glucose levels, and also had decreased levels of visceral fat.[167] An increase in muscle mass following resistance exercise may be the key contributor to improving blood glucose uptake in T2D. Since muscles are important targets for insulin, improving muscle function is directly related to improving insulin sensitivity.[168] Moreover, studies have shown that resistance training in T2D populations may lead to similar or greater improvements in cognition compared to aerobic training. For example, in one study, 10 weeks of either aerobic or resistance exercise led to decreases in blood glucose levels, with a larger reduction seen following resistance exercise compared to aerobic exercise.[169] Six months of a combined aerobic and resistance training program also led to improvements in white matter integrity, HV, and TBV, as well as less decline in WMV in older adults with T2D.[170] However, it cannot be discerned how aerobic and resistance exercise may have interacted to produce positive effects in this study.

1.8 Exercise in prediabetes and obesity

As previously touched upon, both aerobic and resistance exercise have been shown to improve health complications that are associated with prediabetes and obesity including insulin resistance and cardiovascular impairment. Exercise is important to reducing blood pressure, for example, which is often elevated in both obesity and prediabetes. In obesity especially, exercise is key to increasing one's total energy expenditure, which helps maintain energy homeostasis and promotes weight loss (or prevents further weight gain). One longitudinal study found that among older men, those with lower levels of general physical activity (i.e., climbing stairs, walking, and participating in sports and recreational activities) were more likely to gain weight overtime than those with higher levels of physical activity.[171] Exercise-induced weight loss in overweight and obese adults has also been shown to improve attention and executive control.[172] In addition, a reduction in adiposity may be associated with improved β-cell function.[173]

Further studies assessing cognition have shown that exercise can significantly improve cognitive function in overweight and obese adults. For example, a cross-sectional study by Coll-Padrós et al. (2019) found that aerobic exercise was associated with better global cognitive function and improvements in functions related to the frontal lobe (attention,

cognitive flexibility, working memory) in overweight and obese older people.[174] Another study assessed the combined effects of aerobic, resistance, flexibility, and balance training program on cognition in older obese adults and found that this combination of exercises led to improved cognition in areas such as word fluency and global cognition.[175] However, it is unclear which of these exercise modalities contributed to the positive findings. Research on the independent effects of resistance exercise, in particular, on cognition in obese older adults are needed. Similarly, studies that have assessed the effects of physical activity interventions on brain health in overweight or obese adults have largely focused on the combined effects of both physical activity and diet instead of physical activity alone. For example, Espeland et al. (2016) found that a diet and physical activity intervention led to reduced WMHs overtime in overweight or obese older adults; to note, this group were also diagnosed with diabetes.[176]

Examining the effects of exercise on prediabetes, Malin and colleagues (2012) found that those who underwent 12 weeks of thrice-weekly aerobic and resistance training improved in insulin sensitivity relative to a control group.[177] In this study, the authors also found that exercise led to similar improvements to insulin sensitivity as metformin, which is a common antihyperglycemic medication.[177] While these are positive findings, they too do not provide information on which exercise modality contributed more to the results. Studies assessing the neurocognitive benefits of exercise in older prediabetic participants, however, are quite scarce. One study by Baker and colleagues (2010) found that six months of aerobic training, compared to stretching exercises, in prediabetic older adults or those newly diagnosed with T2D led to improvements in selective and divided attention, cognitive flexibility, and working memory.[178] However, whether resistance training would have similar effects in this population, and whether they would improve in brain health in addition, is unknown.

1.9 Thesis overview

Neurodegeneration and cognitive dysfunction are major threats to our aging population. As such, lifestyle strategies to improve and preserve cognition and brain health, especially in clinical populations of older adults that are at high risk of impairment, are imperative. Based on the literature, resistance exercise has been identified as one modifiable behaviour that can benefit and preserve cognition and brain health. Importantly, this type of exercise has been shown to have unique benefits to older adults compared to aerobic exercise. With this

knowledge, the overarching goal of this thesis was to determine whether resistance exercise could be used to improve neurocognitive function in a population of older adults that are already experiencing neurocognitive decline (i.e., those who are prediabetic and/or overweight or obese) and are at risk of further impairment associated with T2D.

Within the literature, less is known about the neurocognitive deficits experienced in prediabetes compared to obesity, particularly in regards to structural brain impairments. Thus, a systematic review was first conducted to compare studies that have assessed structural deficits (brain volume, connectivity, cerebrovascular health) in prediabetes (Chapter 2). The goal of this review was to determine where consistencies and inconsistencies in findings may lie. Following this, a pilot RCT study was conducted to assess the preliminary effects of a 26-week resistance exercise program on cognition, brain structure, and brain function in older adults at risk for diabetes (Chapters 3 and 4). Specifically, this pilot study aimed to establish whether older adults at risk for diabetes would improve in complex attention, executive function, and memory following progressive resistance training, and whether improvements in volumetric brain measures and neural activation patterns would also be evident. Finally, the feasibility of conducting an RCT study in our target population was examined (Chapter 5). This was important in identifying whether a large-scale study would be feasible, and, if so, determining how the study protocol could be improved to better meet the needs of our targeted population in future trials.

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Chapter 2

2 Brain deficits in prediabetic adults: A systematic review

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2.1 Introduction

Globally, diabetes is the fourth leading cause of disability,[1] with over 400 million documented cases worldwide.[2] Type 2 diabetes (T2D) is characterized by high blood glucose levels associated with insulin resistance and glucose intolerance. While T2D is often accompanied by physical comorbidities such as cardiovascular disease and obesity, it is also associated with neural dysfunction. Specifically, studies have shown that T2D is correlated with deficits in brain health, including cortical and subcortical atrophy, reduced structural connectivity, and cerebrovascular pathology such as WMHs.[3-6] Possible mechanisms linking T2D to neural dysfunction include hyperinsulinemia and abnormal β-cell function, chronic systematic inflammation, vascular risk factors (e.g., hypertension, hypercholesterolemia), and oxidative stress leading to neuronal death.[7]

One major risk factor for T2D is prediabetes, which is the state of having elevated blood glucose levels that are below the T2D classification threshold (i.e., an intermediate level between normal and diabetic levels). The full diagnostic criteria for prediabetes has been presented in Chapter 1; briefly, some of the main differences between the WHO[8] and ADA[9] definitions of prediabetes are that the ADA uses a lower threshold for FPG and has an additional measure of HbA1c. Prediabetes has been shown to be associated with cognitive deficits in areas such as global cognitive function, visuospatial processing, language, episodic memory, and executive function.[5,10,11] As such, underlying deficits in brain structure and cerebrovascular function in this population are expected. However, previous research assessing the association between prediabetes and brain health have yielded largely mixed results. While some studies have found no differences in brain volume or cerebrovascular function between adults with normal blood glucose levels (normoglycemia) and those with

prediabetes, other studies have found significant differences suggesting that prediabetics experience some neural decline. For example, Schneider and colleagues (2017) found no differences in TBV and HV between these two populations,[12] while Hou and colleagues (2016) found lower GMV for prediabetics in areas such as the right (ACC) and left MTG.[13] Evidently, the relationship between prediabetes and brain health is unclear, and conducting a systematic review of the literature will help summarize what is known thus far and identify what future research may be needed.

One 2019 meta-analysis examining prediabetes and structural brain abnormalities found that prediabetes is associated with increased risk for cerebral infarcts and WMHs, and decreased GMV and WMV.[14] However, this paper included some studies in which clinical comorbidities that have been associated with neurological decline (e.g., stroke) were present.[14] Importantly, our review focused on individuals with prediabetes that were otherwise neurologically healthy, which allows us to better understand potential brain abnormalities that may be the result of prediabetes alone.

To our knowledge, this is the first systematic review to examine prediabetes and brain deficits in otherwise healthy adults. In our review, we focused on brain volume (e.g., TBV, GMV, WMV, cortical thickness), structural connectivity, and cerebrovascular pathology (e.g., cerebral infarcts, microbleeds), as measured by MRI. These measures of brain health were chosen based on what is currently known about neural deficits in T2D. Ultimately, we aimed to identify areas of the brain that may be affected in prediabetes and the degree of possible deficits, in hopes that our findings will help inform future research including interventions targeted at improving brain health in this population.

2.2 Methods

2.2.1 Search strategy

Following the PRISMA reporting standards for systematic reviews, we conducted a systematic search of PsychINFO, Scopus, Web of Science, Ovid MEDLINE, CINAHL and EMbase databases to identify studies that examined the association between prediabetes and brain health. We included the following medical subject headings (MeSH): (a) ‘Prediabetic State’; (b) ‘Grey Matter’; (c) ‘White Matter’; and (d) ‘Magnetic Resonance Imaging’.

Additionally, free text words such as ‘prediabetes’ ‘pre-diabetes’, ‘potential diabetes’, ‘prediabetic’, ‘frontal lobe’, ‘prefrontal cortex’, ‘medial temporal lobe’, ‘temporal cortex’, ‘parahippocampus’, ‘fusiform’, ‘hippocampus’, ‘diagnostic imaging’, ‘structural imaging’, and ‘diffusion tensor imaging’ were included in the search with their related MeSH concept using the Boolean operator ‘OR’, and main concepts were further searched together using ‘AND’. Studies were exported into Mendeley for review.

2.2.2 Selection of studies

Two reviewers (JAF and BRH) conducted an initial screening of exported studies based on titles and abstracts. Only peer-reviewed articles that were published in English between 2009 and April 2020 were included in our study. Additional inclusion criteria included: (a) human research; (b) participants aged 18 or older; (c) inclusion of a prediabetes group; (d) inclusion of a healthy normoglycemic control group; and (e) outcome measures related to brain health as measured using MRI. We excluded studies with the following criteria: (a) animal research; (b) samples that had other clinical diagnoses (e.g., stroke, bipolar disorder); or (c) non-primary research (e.g., abstracts, reviews, book chapters). Following the initial screening, a full-text review was conducted by both authors (JAF and BRH). Reference lists from selected studies were then reviewed and subjected to title and abstract evaluation in order to collect relevant studies that may have been missed in our original search. Individual results of the two reviewers were then compared, and consensus of final inclusion of articles was reached by discussion with the third author (LSN).

2.2.3 Data extraction

Using a standardized form, two authors (JAF and BRH) performed data extraction. Extracted data included: author(s), year of publication, study objective, study type, setting, population, inclusion/exclusion criteria, brain health outcome measures, statistical analysis and health covariates, summary of findings, study limitations, MRI resolution, MRI analysis and exclusion criteria, classification metric for diabetes type, and specific details regarding each group (i.e., T2D, prediabetes, normoglycemic control) if applicable including number of participants, mean age and sex breakdown, average FPG, average 2-h PG, and average HbA1c %.

2.2.4 Quality assessment

To assess the quality of each study, we used eight questions based on the National Institutes of Health Quality Assessment Tool for Observational Cohort and Cross-sectional Studies (**Table 2.1**).[15] The eight questions included were: (1) Was the research question or objective clearly stated?; (2) Was the study population clearly specified and defined?; (3) Were participant inclusion and exclusion criteria specified?; (4) Was a sample size justification or power description provided?; (5) Are the main outcome measures clearly described?; (6) Were key potential confounding variables measured and adjusted for in analyses (for outcomes of interest)?; and (7) Was the prediabetes classification used recognized by an international association? Question 7 was created specifically for this study. Two authors (JAF and BRH) independently evaluated each study, and any discrepancies were discussed with the third author (LSN).

Table 2.1: Quality assessment of included studies.

Reference	1. Was the research question or objective clearly stated?	2. Was the study population clearly specified and defined?	3. Were participant inclusion and exclusion criteria specified?	4. Was a sample size justification or power description provided?	5. Are the main outcome measures clearly described?	6. Were key potential confounding variables measured and adjusted for in analyses (for outcomes of interest)?	7. Was the prediabetes classification used recognized by an international association?
Bamberg et al 2017	+	+	+	-	+	+	+
Cui et al. 2019	+	+	+	-	+	+	+
Dong et al. 2019	+	+	+	-	+	+	+
Hirabayashi et al. 2016	+	+	+	-	+	+	+
Hou et al. 2016[21]	+	+	+	-	+	+	+
Hou et al. 2016[12]	+	+	+	+	+	+	+
Liang et al. 2019	+	+	+	-	+	-	+
Markus et al. 2017	+	+	+	-	+	+	+
Marseglia et al. 2019	+	+	+	-	+	+	+

Reitz et al. 2017	+	+	+	-	+	+	+
Rusinek et al. 2015	+	+	+	-	+	-	-
Saczynski et al. 2009	+	+	+	-	+	+	+
Samaras et al. 2014	+	+	+	-	+	+	+
Schneider et al. 2017	+	+	+	-	+	+	+
Shaw et al. 2017	+	+	+	-	+	+	+
Storz et al. 2018	+	+	+	-	+	-	+
van Agtmaal et al. 2018	+	+	+	-	+	+	+
Vergoossen et al. 2020	+	+	+	-	+	+	+
Walsh et al. 2018	+	+	+	-	+	+	+

“+” indicates the item was addressed in the article and “-” indicates that it was not addressed.

2.3 Results

2.3.1 Selected studies

Our search of the combined databases yielded 1171 results, with 948 studies remaining after duplicates were excluded. After completion of initial title and abstract screening, 52 articles remained for full-text assessment. From these full-text articles, 64 additional studies from the reference lists were identified for further screening based on titles. After further abstract screening, 50 of these articles were excluded, leaving a total of 66 full text articles (original database plus reference-mined) to be evaluated. After full-text review using eligibility criteria, 19 studies were selected for data extraction. **Figure 2.1** shows a flow diagram of the review process for study selection, and **Table 2.2** includes the description and characteristics of included studies. To report study findings in our review, studies were divided into three categories: volumetric measures, structural connectivity, and cerebrovascular health, wherein some studies were included in more than one category.

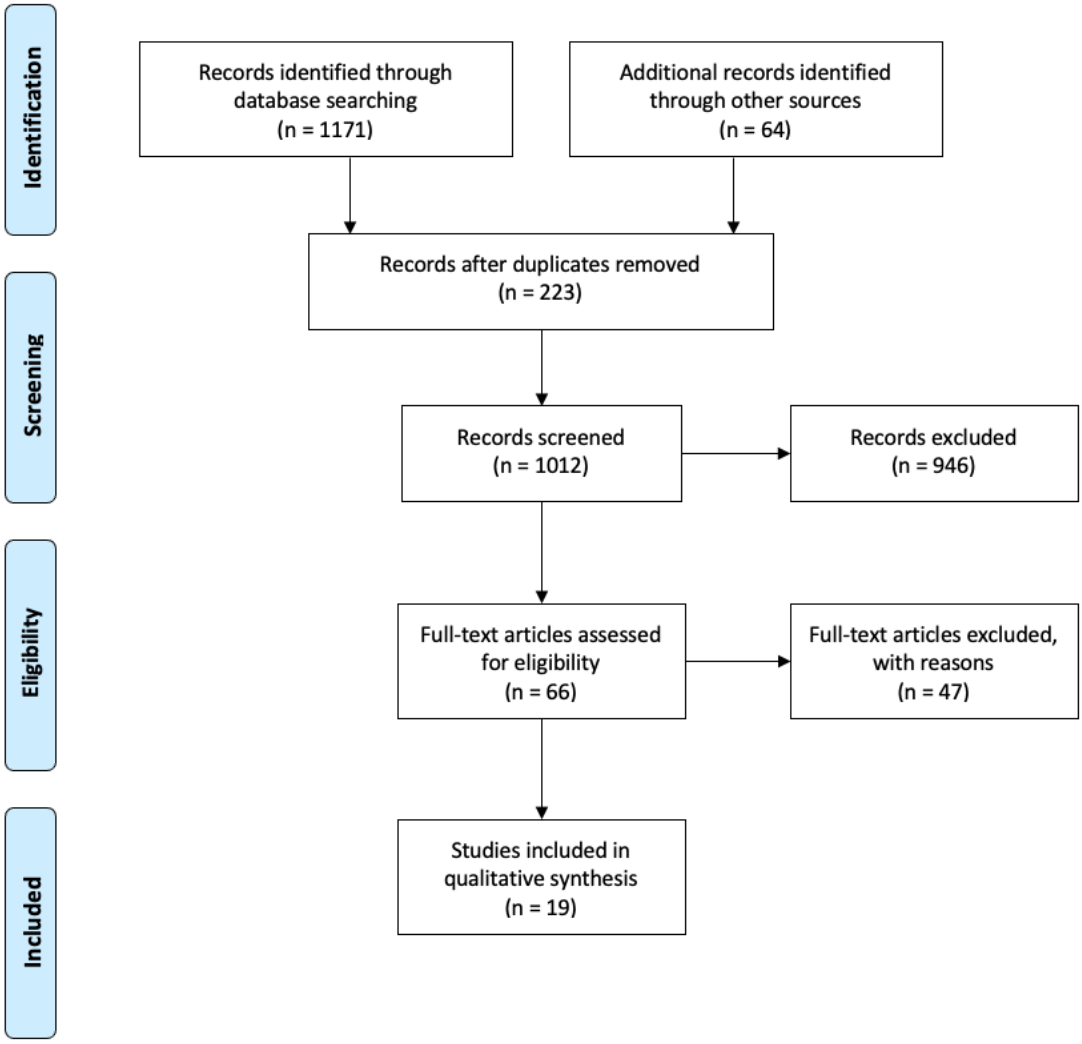

Figure 2.1: Flow diagram of included studies.

Table 2.2: Study description and characteristics.

Reference	Location	Study sample	Study design	Diabetes classification (prediabetes diagnostic measure)	Brain health outcomes	Confounding variables adjusted in analyses (for outcomes of interest)	MRI resolution
Bamberg et al. 2017	Germany	Community-dwelling Total: *N*=400, 56.3 ± 9.0 years† 42.2% female Prediabetes: *N*=103, 58.3 ± 9.0 years† 35.9% female Healthy controls: *N*=243, 54.2 ± 9.0 years† 48.6% female	Cross-sectional (case-control) Data from the Cooperative Health Research in Region of Augsburg (KORA)	WHO	WMLs ARWMC CMBs	Age Sex Systolic blood pressure Smoking status HDL level LDL level Triglyceride level	3T
Cui et al. 2019	China	Hospital patients Total: *N*=63, 55.9 ± 8.0	Cross-sectional	WHO	Subcortical GMV: Thalamus Caudate Putamen	Age Sex Education Head size	1.5T

		years† 65.1% female Prediabetes: *N*=21, 57.7 ± 6.6 years† 61.9% female Healthy controls: *N*=21, 52.4 ± 8.0 years† 66.7% female			Pallidum Hippocampus Amygdala Nucleus accumbens		
Dong et al. 2019	China	Memory clinic patients Total: *N*=60, 58.2 ± 4.6 years† 50% female Prediabetes: *N*=17, 58.1 ± 4.6 years† 52.9% female Healthy controls: *N*=22, 57.2 ± 4.1 years† 45.5% female	Cross-sectional	ADA (HbA1c)	Hippocampal subfield volumes: CA1 CA2 + CA3 CA4 Dentate gyrus Hippocampal tail Fimbria Hippocampal fissure Molecular layer Subiculum Parasubiculum Presubiculum GMV WMV CSFV	Age Gender Education BMI Hypertension Total cholesterol level Presence of ApoE4	3T

Hirabayashi et al. 2016	Japan	Community-dwelling Total: *N*=1238, 74.8 ± 6.8 years† 56.4% female Prediabetes: Not provided ‡Non-T2D: *N*=952, 75 ± 7.0 years† 60.3% female	Cross-sectional Data from the Hisayama Study	WHO	TBV to ICV (global brain atrophy) HV to ICV (hippocampal atrophy) HV to TBV (hippocampal atrophy beyond global brain atrophy)	Fully adjusted models: Age Sex Education Hypertension Total cholesterol level BMI Smoking status Alcohol intake Regular exercise Cerebrovascular lesions on MRI Antidiabetic medication	1.5T
Hou et al. 2016[21]	Taiwan	Hospital outpatients Total: *N*=118, 53.1 ± 8.9 years† 44.1% female Prediabetes: *N*=64, 52.8 ± 9.7 years† 43.8% female Healthy controls:	Cross-sectional	ADA (FPG)	WM tracts (FA, RD, AD)	Global brain V Age Gender	3T

		N=54, 53.5 ± 7.9 years† 44.4% female					
Hou et al. 2016[12]	Taiwan	Hospital outpatients Total: *N*=118, 53.1 ± 8.9 years† 44.1% female Prediabetes: *N*=64, 52.8 ± 9.7 years† 43.8% female Healthy controls: *N*=54, 53.5 ± 7.9 years† 44.4% female	Cross-sectional	ADA (FPG)	GMV ACC V PCC V MTG V STG V Insula V	Fully adjusted models: Global brain V Age Gender BMI Education	3T
Liang et al. 2019	China	Hospital inpatients/outpatients Total: *N*=60, 53.9 ± 7.1 years† 66.7% female Prediabetes:	Cross-sectional	ADA (IFG and/or IGT)	WMLs (FA, MD, RD, AD)	N/A Initial t-test revealed no differences in gender, age, education, BMI, hypertension, total cholesterol level, LDL level between groups (prediabetes versus normoglycemia), but	3T

		N=30, 55.0 ± 6.7 years† 66.7% female Healthy controls: *N*=30, age=52.8 ± 7.5 years† 66.7% female				significant differences were found for triglyceride level and HDL level	
Markus et al. 2017	Germany	Community-dwelling Total: *N*=1330, 49.3 (36, 69)§ years† 55.9% female Healthy controls: *N*=759, 45 (36, 55)§ years† 62.5% female IFG: *N*=310, 54 (45, 62)§ years† 42.9 female IGT: *N*=83, 50 (40, 61)§ years†	Cross-sectional Data from the Study of Health in Pomerania (SHIP)	ADA (IFG and/or IGT)	GMV WMV	Sex Age Weight Total brain V/intracranial V ratio Education Smoking status Total cholesterol level/HDL level ratio Estimated glomerular filtration rate Fasting time	1.5T

		71.1% female IFG+IGT: *N*=114, 59 (51, 66)[§] years[†] 45.6% female					
Marseglia et al. 2019	Sweden	Community-dwelling or institutional living Total: *N*=2746, 72.7 ± 10.2 years[†] 62.7% female Prediabetes: *N*=947, 74.6 ± 10.4 years[†] 65.6% female Healthy controls: *N*=1557, 71.3 ± 10.0 years[†] 63.4% female	Longitudinal (cohort) (6 years) Data from the Swedish National Study on Aging and Care-Kungholmen (SNAC-K)	ADA (HbA1c)	TBV GMV WMV HV WMHV	Sex Education Socioeconomic status BMI Hypertension Heart diseases	1.5T
Reitz et al. 2017	United States	Community-dwelling, Medicare recipients Total:	Cross-sectional and longitudinal (cohort) (4 years)	ADA (HbA1c)	GMV WMV HV Cerebral infarcts WMHV	Fully adjusted models: ICV Age Sex Education	1.5T

		N=618, 80.0 ± 5.4 years† 69.3% female Prediabetes: *N*=224, 80.6 ± 5.6 years† 71.0% female Healthy controls: *N*=115, 79.8 ± 5.4 years† 66.1% female				Ethnic group Presence of ApoE4 Hypertension Smoking status BMI HDL level	
Rusinek et al. 2015	United States	Not specified Total: *N*=87, 52.2 ± 4.6 years† 57.5% female Prediabetes: *N*=27, 50.9 ± 4.5 years† 52% female Healthy controls: *N*=37, 51.8 ± 3.8 years† 59% female	Cross-sectional	Not association recognized; Quantitative insulin sensitivity check index	GM CBF	N/A	3T

Saczynski et al. 2009	Iceland	Community-dwelling Total: *N*=4415; 76.2 ± 5.5 years† 58.5% female Prediabetes: *N*=1599, 75.9 ± 5.4 years† 52.5% female Healthy controls: *N*=2327, 76.4 ± 5.5 years† 65% female	Cross-sectional Data from the Age Gene/Environment Susceptibility-Reykjavik Study (AGES-Reykjavik)	ADA (FPG) and WHO (FPG)	TBV GMV WMV Cerebral infarcts WMLs	Fully adjusted models: Age Sex Education Hypertension Smoking status Physical activity BMI Myocardial infarction	1.5T
Samaras et al. 2014	Australia	Community-dwelling Total: *N*=795, 78.3 ± 4.79 years† 51.4% female Prediabetes: *N*=346, 78.6 ± 4.8 years† 44% female	Longitudinal (cohort) (2 years) Data from the Sydney Memory and Ageing (MAS) Study	ADA (FPG)	TBV HV CSFV Parahippocampal gyrus V Precuneus V Frontal lobe V	Age Sex Education Non-English speaking background Smoking status Hypertension Lipid-lowering or antihypertensive medications ICV	1.5T

		Healthy controls: *N*=343, 78.0 ± 4.8 years† 56% female					
Schneider et al. 2017	United States	Community-dwelling Total: *N*=1713, 75.2 years† 60.6.% female Prediabetes: *N*=514, 75.2 years† 61.7% female Healthy controls: *N*=597, 75 years† 59.7% female	Cross-sectional Data from the Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS)	ADA (HbA1c, FPG)	TBV Lobule V: Frontal Temporal Occipital Parietal Deep grey subcortical structure V: Thalamus + Caudate + Putamen + Global Pallidum Alzheimer's disease signature region V: Parahippocampal + Entorhinal + Inferior parietal lobules + Hippocampus + Precuneus + Cuneus HV Cerebral infarcts LIs	Age Sex Race/field centre location Education Smoking status Hypertension Cardiovascular disease Presence of ApoE4 ICV	3T

					Lobar microhemorrhages Subcortical microhemorrhages WMHV		
Shaw et al. 2017	Australia	Community-dwelling Total: *N*=322, 63.1 ± 1.5 years† 50% female Prediabetes: *N*=62, 62.9 ± 1.4 years† 34% female Healthy controls: *N*=212, 63.1 ± 1.5 years† 55% female	Cross-sectional and longitudinal (12 years) Data from the Personality and Total Health Through Life (PATH) Study	WHO (FPG; two or more measurements)	Cortical thickness	Age Age^2 Sex Education BMI Presence of ApoE4 Hypertension Physical activity Depression status ICV Note, these covariates varied across analyses	1.5T
Storz et al. 2018	Germany	Community-dwelling Total: *N*=243, 55.6 ± 8.9 years† 37.9% female	Cross-sectional (case-control)	WHO	ARWMC	N/A	3T

		Prediabetes: *N*=48, 55.9 ± 8.9 years† 29.2% female Healthy controls: *N*=157, 54.2 ± 8.8 years† 43.3% female					
van Agtmaal et al. 2018	Netherlands	Community-dwelling Total: *N*=2228, 59.3 ± 8.2 years† 48.3% female Prediabetes: *N*=347, 61.1 ± 7.6 years† 44.5% female Healthy controls: *N*=1373, 57.6 ± 8.1 years† 55.6% female	Cross-sectional Data from the Maastricht Study	WHO	GMV WMV CFSV LIs WMHV CMBs	Fully adjusted models: Age Sex ICV Time between baseline and MRI BMI Education Smoking status Total cholesterol level/HDL level ratio Triglyceride level Estimated glomerular filtration rate Office systolic blood pressure or 24-hour systolic blood pressure Blood pressure-lowering and lipid-modifying	3T

						medication Urinary albumin excretion	
Vergoossen et al. 2020	Netherlands	Community-dwelling Total: *N*=2219, 59.3 ± 8.2 years† 48.5% female Prediabetes: *N*=348, 61.2 ± 7.5 years† 44.8% female Healthy controls: *N*=1361, 57.6 ± 8.1 years† 55.8% female	Cross-sectional Data from the Maastricht Study	WHO	WM tractography: Node degree Topology: Clustering coefficient Local efficiency Global efficacy Communicability	Age Sex Education MRI date BMI Total cholesterol level/HDL level ratio Lipid-modifying medication Office systolic blood pressure Antihypertensive medication Cardiovascular disease MRI lag time Average node degree Note, these covariates varied across analyses	3T
Walsh et al. 2018	Australia	Community-dwelling Total: *N*=494, 64.7 ± 9.8 years† 49.2% female	Cross-sectional Data from the Personality and Total Health Through Life (PATH) Study	ADA (FPG; two or more measurements)	TBV GMV WMV Thalamus V Corpus callosum V	Age Sex ICV Cohort (age group) Education Hypertension Smoking status	1.5T

		Prediabetes: *N*=95, 65.8 ± 10.0 years† 32.6% female Healthy controls: *N*=353, 63.7 ± 9.6 years† 55.0% female				Physical activity	

†Mean age.

§Age range.

‡Non-T2D group included both healthy controls (normoglycemic) and prediabetics.

F = female; T = tesla; V = volume; WM = white matter; GM = grey matter; TBV = total brain volume; GMV = grey matter volume; WMV = white matter volume; HV = hippocampal volume; CFSV = cerebrospinal fluid volume; ICV = intracranial volume; WMHV = white matter hyperintensity volume; WMLs = white matter lesions; CMBs = cerebral microbleeds; LIs = lacunar infarcts; CBF = cerebral blood flow; ARWMC = age-related white matter changes; FA = fractional anisotropy; MD = mean diffusivity; RD = radial diffusivity; AD = axial diffusivity; ACC = anterior cingulate cortex; PCC = posterior cingulate cortex; MTG = middle temporal gyrus; STG = superior temporal gyrus; BMI = body mass index; HDL = high-density lipoprotein; LDL = low-density lipoprotein; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; FPG = fasting plasma glucose; HbA1c = hemoglobin A1c; WHO = World Health Organization; ADA = American Diabetes Association.

2.3.2 Volumetric measures – 13 studies

Thirteen studies (nine cross-sectional, four longitudinal) assessed volumetric brain measures, including TBV, GMV, WMV, cerebrospinal fluid volume (CSFV), HV, regional subfield volumes, and cortical thickness. Results of these studies (comparing prediabetic and normoglycemic groups) are summarized in **Table 2.3**.

2.3.2.1 Cross-sectional

One study by Hirabayashi and colleagues (2016) assessed the relationship between diabetes status (normoglycemia, IFG, IGT, T2D) and brain atrophy in older adults.[16] The authors examined ratios of TBV to intracranial volume (ICV) as an indicator of global brain atrophy, HV to ICV as an indicator of hippocampal atrophy, and HV to TBV as an indicator of hippocampal atrophy beyond global brain atrophy.[16] When compared to those with normoglycemia, mean values for the three ratios were found to be similar in the IFG and IGT groups.[16] However, the 2-h PG (but not FPG) trend was significant for all three ratios, indicating differences in diabetes measures.[16]

In another study examining IFG and IGT separately, Markus and colleagues (2017) measured GMV and WMV in adults with normal glucose tolerance (NGT), isolated IFG, isolated IGT, combined IFG and IGT (IFG+IGT), and undiagnosed T2D.[17] Results showed significantly lower GMV in the IFG group, but not in the IGT or IFG+IGT groups, when compared to the NGT group.[17] However, the IGT groups were underpowered.[17] Significant inverse associations were also found for FPG and 2-h PG levels with GMV, but no association was found for HbA1c levels and GMV.[17] Moreover, a 1 mmol/l increase in FPG was associated with a decrease of 7.02 ml in GMV, whereas a 1 mmol/l increase in 2-h PG was associated with a decrease of 1.97 ml in GMV.[17] For WMV, no between group differences were found across all groups.[17]

A third cross-sectional study examined WMV, GMV, and CSFV in adults.[6] Compared to normoglycemia, prediabetes was associated with significantly smaller WMV and larger

CSFV.[6] Interestingly, the regression coefficient of prediabetes with WMV was approximately one-half that of T2D, suggesting a progressive decline.[6] No differences were found between prediabetes and normoglycemia for GMV.[6] In general, higher HbA1c, FPG, and 2-h PG levels were associated with lower WMV and GMV and higher CSFV.[6]

In a similar study, Saczynski and colleagues (2009) assessed differences in TBV, GMV, and WMV in older adults with normoglycemia, IFG, and T2D.[3] In adjusted models, no significant associations were present between those with normoglycemia and IFG for any volumetric measures.[3] HbA1c levels were also not associated with brain volumes in general analyses.[3]

Walsh and colleagues (2019) took a unique approach to examining TBV, GMV, WMV, thalamus volume, and volume of the corpus callosum in adults.[18] Participants were characterized as having normal fasting glucose (NFG), IFG, or T2D based on glucose measurements, and data was divided into quartiles based on brain volume sizes.[18] In those with average and small brains (50th and 25th percentiles, respectively), regression analyses showed that IFG was positively associated with TBV.[18] In individuals with average-sized brains, IFG was positively associated with GMV, and in those with small brains, IFG was positively associated with WMV.[18] In those with large brains (75th percentile), BMI × blood glucose interaction was positively associated with TBV.[18]

In a cross-sectional study measuring grey matter alterations in adults with IFG and those with normoglycemia, those with IFG were found to have lower GMVs than those with normoglycemia in the right ACC, right posterior cingulate cortex, left insula, left superior temporal gyrus, and left MTG.[13] In addition, serum glucose levels were negatively correlated with total GMV and right ACC GMV.[13] Similarly, a study assessing reductions in subcortical grey matter structures (thalamus, caudate, putamen, pallidum, hippocampus, amygdala, nucleus accumbens) showed significantly lower volumes for the left hippocampus, left amygdala, and right putamen in prediabetics when compared to those with normoglycemia.[19] No significant differences were found between prediabetes and T2D in this study.[19]

Additionally, Dong and colleagues (2019) examined HV, hippocampal subfield volumes (CA1, CA2 + CA3 combined, CA4, dentate gyrus, hippocampal tail, fimbria, hippocampal fissure, molecular layer, subiculum, parasubiculum, and presubiculum), GMV, WMV, and CSFV in adults with normoglycemia, prediabetes, and T2D.[4] Compared to those with normoglycemia, prediabetics had smaller left hippocampal tail volumes.[4] No significant differences were found between these two groups for other brain measures.[4] Among all participants, significant correlations were found between HbA1c levels and total HV, left hippocampal tail, right presubiculum, and bilateral dentate gyrus, subiculum, and molecular layer.[4]

A final cross-sectional study examined regional brain volumes in adults with normoglycemia, prediabetes, and T2D.[12] Volumetric measures were reported for total brain, lobules (frontal, temporal, occipital, parietal), deep grey subcortical structure (defined as total volume of the thalamus, caudate, putamen, globus pallidum), Alzheimer's disease signature region (defined as total volume of the parahippocampal, entorhinal, and inferior parietal lobules, hippocampus, precuneus, cuneus), and hippocampus.[12] Prediabetics did not significantly differ in brain volumes when compared to those with normoglycemia.[12] In general however, increased HbA1c levels were associated with decreased TBV.[12]

2.3.2.2 Longitudinal

In a longitudinal cohort study in older adults, Reitz and colleagues (2017) assessed GMV, WMV, and HV in those with NGT, prediabetes, undiagnosed T2D, and known T2D.[10] At baseline, there were no significant differences in measures between prediabetes and NGT.[10] Comparatively, dysglycemia was associated with decreased WMV, GMV, and HV; however, since prediabetes and T2D were grouped together within the dysglycemia classification, it is unclear which group may be driving this association.[10] In adjusted models, continuous HbA1c levels were associated with lower TBV when the sample was restricted to NGT and prediabetic individuals.[10] Longitudinal analyses across four years also found that increased dysglycemia was associated with a significant decline in GMV, but not WMV or HV,

compared to NGT.[10] When dysglycemia was separated into prediabetic and T2D groups, no significant rate of change was observed, but it was noted that WMV and HV were appreciably lower in these groups compared to NGT.[10]

A second longitudinal cohort study measured brain volumes (TBV, HV, CSFV, parahippocampal gyrus volume, precuneus volume, and frontal lobe volume) in older adults with NFG, IFG, and T2D.[20] At the two-year follow-up, individuals who had IFG at baseline showed significant declines in HV and parahippocampal gyrus volume compared to those who had NFG at baseline.[20] However, this relationship was altered when the blood glucose status at the two-year follow-up was considered.[20] Those who maintained stable IFG status (IFG at both assessment times) had similar declines in brain volumes as those who had stable NFG.[20] Comparatively, those who developed an incident glucose disorder (NFG at baseline, and IFG at follow-up) had significant decline in TBV and frontal lobe volumes, but not HV or parahippocampal gyrus volume.[20]

Shaw and colleagues (2017) conducted a 12-year longitudinal study in older adults to examine the association between blood glucose levels and cortical thinning in NFG, IFG, and T2D.[21] At baseline, cortical thickness did not significantly differ between those with IFG and NFG.[21] For IFG, a trending, yet non-significant difference was found between higher FPG levels and age-related cortical thinning in the right insular cortex and an at-trend level result was found in the right posterior cingulate cortex, right parahippocampal gyrus, left medial orbitofrontal cortex, and left fusiform gyrus.[21] Additionally, mean annual percent change (APC) in cortical thickness was significantly associated with baseline FPG levels for IFG.[21] Finally, increased FPG levels were associated with higher APC regardless of diabetes status.[21]

In a final longitudinal cohort study in older adults, prediabetes but not T2D was associated with smaller TBV, particularly in the WMV, when compared to those with normoglycemia; no differences existed between prediabetes or T2D and normoglycemia for HV or GMV.[5] However, hyperglycemia in general was positively associated with smaller TBV.[5]

Longitudinally across six years, no significant differences in rate of decline for brain measures were found between prediabetes or T2D and normoglycemia.[5]

In summary, of the 13 studies assessing volumetric measures, seven provide evidence that prediabetics experience some brain volumetric decline compared to those with normoglycemia.[4,5,6,13,17,19,20] One study argued that brain deficits seen in prediabetes occur in a progressive declining manner,[6] such that prediabetics experience decline greater than those with normal glucose levels but less than diabetics. Another study showed that prediabetes is positively associated with various volumetric measures, depending on one's brain volume size.[18] In addition, multiple studies showed that blood glucose level is positively correlated with neural decline,[4,5,6,10,12,13,16,17,21] even irrespective of diabetes status.[21] Two studies also found differences in results based on the varying diagnostic measures used,[16,17] suggesting that this may account for the variation in findings.

Table 2.3: Results of volumetric measure studies.

Reference	TBV	GMV	WMV	HV	CSFV	Thalamus	Other
Cui et al. 2019	N/A	N/A	N/A	+ (left)	N/A	-	+ left amygdala, right putamen - caudate, pallidum, nucleus accumbens
Dong et al. 2019	N/A	-	-	-	-	N/A	+ left hippocampal tail - CA1, CA2 + CA3, CA4, dentate gyrus, fimbria, hippocampal fissure, molecular layer, subiculum, parasubiculum, presubiculum
Hirabayashi et al. 2016	N/A	N/A	N/A	N/A	N/A	N/A	- global brain atrophy, hippocampal atrophy, hippocampal atrophy beyond global brain atrophy
Hou et al. 2016[12]	N/A	N/A	N/A	N/A	N/A	N/A	+ right ACC, right PCC, left insula, left STG, left MTG
Markus et al. 2017	N/A	+ (IFG group, but not IGT or IFG+IGT groups)	-	N/A	N/A	N/A	N/A
Marseglia et al.	+	-	+	-	N/A	N/A	N/A

2019							
Reitz et al. 2017	N/A	-	-	-	N/A	N/A	N/A
Saczynski et al. 2009	-	-	-	N/A	N/A	N/A	N/A
Samaras et al. 2014	+ (incident glucose disorder)	N/A	N/A	-	-	N/A	+ Frontal lobe (incident glucose disorder) - Parahippocampal gyrus, precuneus
Schneider et al. 2017	-	N/A	N/A	-	N/A	N/A	- lobules: frontal, temporal, occipital, parietal; deep grey subcortical structure: thalamus + caudate + putamen + globus pallidum; Alzheimer's disease signature region: parahippocampal + entorhinal + inferior parietal lobules, + hippocampus + precuneus + cuneus)
Shaw et al. 2017	N/A	N/A	N/A	N/A	N/A	N/A	- cortical thickness
van Agtmaal et al. 2018	N/A	-	+	N/A	+‡	N/A	N/A
Walsh et al. 2018	+‡	+‡	+‡	N/A	N/A	-	- corpus callosum

"+" indicates significant findings in the prediabetes group (smaller volume) compared to the normoglycemic group; all results were statistically significant.

"-" indicates non-significant differences between the prediabetes and normoglycemic groups.

‡larger volume in the prediabetes group compared to the normoglycemic group.

IFG = impaired fasting glucose; IGT = impaired glucose tolerance; ACC = anterior cingulate cortex; PCC = posterior cingulate cortex; MTG = middle temporal gyrus; STG = superior temporal gyrus.

2.3.3 Structural connectivity – 3 studies

Three cross-sectional studies examined structural connectivity in adults (e.g., microintegrity, white matter organization). Results of these studies (comparing prediabetic and normoglycemic groups) are summarized in **Table 2.4**.

In one study, Hou and colleagues (2016) used a type of diffusion-weighted MRI (dMRI) known as diffusion tensor imaging (DTI) to assess microintegrity alterations of white matter tracts in both adults with IFG and those with NFG.[22] Three parameters were used to assess microintegrity: fractional anisotropy (FA; measures the fraction of diffusion of water in tissue that is directionally dependent), radial diffusivity (RD; the magnitude of diffusion perpendicular to axonal fiber tracts), and axial diffusivity (AD; the magnitude of diffusion parallel to axonal fiber tracts).[22,23] FA values were found to be lower in the bilateral anterior thalamic radiation (ATR), left superior longitudinal fasciculus (SLF), and left inferior longitudinal fasciculus (ILF) of those with IFG compared to those with NFG.[22] Additionally, those with IFG had lower RD values in the bilateral ATR and left ILF, and lower AD values in the bilateral ATR and left SLF.[22] Serum preprandial glucose levels were also negatively correlated with FA values in the left ATR and left ILF in those with IFG.[22]

A second DTI study measured FA, mean diffusivity (MD; the overall directionally averaged magnitude of diffusion[23]), RD, and AD to assess microscopic WMLs.[24] Compared to adults with normoglycemia, FA was smaller in the right part of the corpus callosum body, right superior longitudinal fasciculus, and SLF in prediabetics.[24] No significant differences were found in MD, RD, or AD values between these groups.[24]

In a final dMRI study, Vergoossen and colleagues (2020) assessed white matter network organization in adults.[25] Specifically, the authors examined the number of white matter connections (node degree) between several brain regions as well as topology (graph measures, including clustering coefficient - number of connections between nearest neighbours of a region as a proportion of total possible connections, labelled as “clusters”; local efficiency - average efficiency of local clusters; global efficiency - the inverse of the

average shortest path length; and communicability - a measure of all possible paths of communication between regions).[25] Results showed that individuals with prediabetes had significantly lower node degrees (i.e., fewer white matter connections) compared to those with normoglycemia.[25] Prediabetics also had smaller tract volumes of several intrahemispheric connections associated with aging, compared to those with normoglycemia.[25] In addition, the local efficiency and clustering coefficient were lower (i.e., weaker local connectivity) in prediabetics compared to those with normoglycemia, although these effects diminished in fully adjusted models.[25] In general, continuous measures of hyperglycemia were associated with lower node degree, as well as higher communicability (likely the result of increased WML load).[25] However, in fully adjusted analyses, the association between HbA1c and communicability was non-significant, but was significant for FPG and 2-h PG.[25]

In summary, all three studies assessing structural connectivity demonstrated some deficits in prediabetes.[22,24,25] Deficits seen in prediabetes included DTI abnormalities and altered neural network organization and function. One study argued that prediabetes accelerates aging processes in the brain, and found varying results based on diagnostic measures used.[25] Two studies also provided more evidence that continuous levels of hyperglycemia is associated with neural decline.[22,25]

Table 2.4: Results of structural connectivity studies.

Reference	FA	RD	AD	MD	Node degree	Other
Hou et al. 2016[21]	+ ATR, left SLF, left ILF	+ ATR, left ILF	+ ATR, left SLF	N/A	N/A	N/A
Liang et al. 2019	+ corpus callosum body, left and right SLF	-	-	-	N/A	N/A
Vergoossen et al. 2020	N/A	N/A	N/A	N/A	+	+ tract volumes of intrahemisphereic connections - clustering coefficient, local efficiency global efficiency, communicability

"+" indicates significant findings in the prediabetes group (greater deficits in structural connectivity) compared to the normoglycemic group; all results were statistically significant.
"-" indicates non-significant differences between the prediabetes and normoglycemic groups.
ATR = anterior thalamic radiation; SLF = superior longitudinal fasciculus; ILF = inferior longitudinal fasciculus.

2.3.4 Cerebrovascular health – 8 studies

Eight studies (six cross-sectional, two longitudinal) examined cerebrovascular pathology, including cerebral infarcts, cerebral microbleeds (CMBs), WMHs, and WMLs. Results of these studies (comparing prediabetic and normoglycemic groups) are summarized in **Table 2.5**.

2.3.4.1 Cross-sectional

One study assessed differences in vascular pathology (cerebral infarcts, lacunar infarcts (LI), lobar microhemorrhages, subcortical microhemorrhages) and WMH volume (WMHV) in adults with normoglycemia, prediabetes, and T2D.[12] No significant differences in cerebrovascular measures were found between prediabetes and normoglycemia.[12]

A similar cross-sectional study in adults assessed differences in LIs, WMHV, and CMBs.[6] Compared to normoglycemia, prediabetes was associated with more LIs and larger WMHV, specifically deep cortical WMHs and periventricular WMHs.[6] Interestingly, the regression coefficients of prediabetes for WMHV were approximately one-third to one-half that of the T2D coefficient, suggesting a progressive nature of decline.[6] Prediabetes was not associated with the presence of CMBs.[6] Additionally, continuous hyperglycemia was associated with LIs and higher WMHV.[6] Another study measuring cerebral infarcts and WMLs in older adults found no differences between IFG and normoglycemia.[3] In this study, HbA1c levels were also not associated with cerebral infarcts in general analyses.[3]

A fourth cross-sectional study examined grey matter cortical perfusion in adults using arterial spin labeling MRI in normoglycemia, prediabetes (insulin resistant), and T2D.[26] Grey matter cerebral blood flow was found to be significantly lower in prediabetes, compared to normoglycemia, but not in T2D as most diabetics were being treated with medications to lower their blood pressure.[26]

Finally, in a cross-sectional case-cohort study, Bamberg and colleagues (2017) examined the presence of WMLs, CMBs, and age-related white matter changes (ARWMC) in adults.[27] No

significant differences in WMLs were found between normoglycemia and prediabetes.[27] Prediabetics were shown to have higher ARWMC scores compared to those with normoglycemia, but these results attenuated after adjustment.[27] No significant differences were observed in CMBs across all groups (normoglycemia, prediabetes, T2D).[27] On the contrary, one cross-sectional case-control study did find significantly higher ARWMC scores in adults with prediabetics compared to those with normoglycemia.[28]

2.3.4.2 Longitudinal

One longitudinal cohort study assessed WMHV and number of cerebral infarcts in older adults with NGT, prediabetes, and T2D.[10] The authors found no significant differences between measures in NGT versus prediabetes at baseline.[10] In adjusted models, continuous HbA1c levels were positively associated with WMHV.[10] Moreover, continuous HbA1c levels in NGT only were associated with higher WMHV.[10] Dysglycemia was associated with higher WMHV and more cerebral infarcts, however as previously mentioned prediabetes and T2D were grouped together within the dysglycemia classification.[10] In longitudinal analyses across four years, no significant differences in rate of change of brain measures were found, but those with dysglycemia had persistently higher WMHV compared to NGT.[10]

Lastly, a separate longitudinal study in older adults found that prediabetes was not associated with larger WMHV or faster WMHV accumulation over time (across six years) compared to those with normoglycemia.[5] However, hyperglycemia was positively associated with larger WMHV in this study.[5]

In summary, only three of the eight studies assessing cerebrovascular health showed deficits in prediabetes (cerebral infarcts, CMBs, WMHs, WMLs).[6,26,28] One study previously mentioned again provided evidence of the progressive nature of decline,[6] such that prediabetics experience decline greater than those with normoglycemia but less than diabetics. Three studies also demonstrated that increased hyperglycemia in general is associated with decline in cerebrovascular health.[5,6,10] Even within a normoglycemic range, increased HbA1c levels was shown to be associated with brain deficits.[10]

Table 2.5: Results of cerebrovascular health studies.

Reference	Cerebral infarcts	LIs	CMBs	WMHV	WMLs	ARWMC	Other
Bamberg et al. 2017	N/A	N/A	-	N/A	-	-	N/A
Marseglia et al. 2019	N/A	N/A	N/A	-	N/A	N/A	N/A
Reitz et al. 2017	-	N/A	N/A	-	N/A	N/A	N/A
Rusinek et al. 2015	N/A	N/A	N/A	N/A	N/A	N/A	+ CBF
Saczynski et al. 2009	-	N/A	N/A	N/A	-	N/A	N/A
Schneider et al. 2017	-	-	N/A	-	N/A		- lobular microhemorrhages, subcortical microhemorrhages
Storz et al. 2018	N/A	N/A	N/A	N/A	N/A	+	N/A
van Agtmaal et al. 2018	N/A	+	-	+	N/A	N/A	N/A

"+" indicates significant findings in the prediabetes group (greater cerebrovascular pathology) compared to the normoglycemic group; all results were statistically significant.

"-" indicates non-significant differences between the prediabetes and normoglycemic groups.

LIs = lacunar infarcts; CMBs = cerebral microbleeds; WMHV = white matter hyperintensity volume; WMLs = white matter lesions; ARWMC = age-related white matter changes; CBF = cerebral blood flow.

2.3.5 Quality of included studies

As described in **Table 2.1**, all 19 articles included in this systematic review stated their research objective clearly, defined their study population, specified their inclusion and exclusion criteria, and described their outcome measures in detail. Of the 19 articles, only one provided a sample size calculation or power description, and 16 accounted for appropriate confounding variables in their relevant MRI data analyses. One article did not use a prediabetes classification that was recognized by an international association (e.g., WHO or ADA).

2.4 Discussion

We conducted the first systematic review to our knowledge examining brain health in adults who have prediabetes but are otherwise healthy. Based on our review, we found that deficits in structural connectivity appear to be present in prediabetics. Other deficits that may exist in this population include smaller brain volumes and cerebrovascular pathology; however, mixed results in these areas were found.

Specifically, for studies that examined brain volume, no single brain region had consistent positive findings (indicative of reduced brain volume in prediabetes) across studies. For example, HV was lower in prediabetics compared to those with normoglycemia in Cui et al. (2019)[19] but no significant differences between groups were found in Marseglia et al. (2019)[5] or any of the other studies assessing HV.[4,10,12,20] Similarly, positive findings from studies assessing cerebral infarcts, LIs, CMBs and other indicators of cerebrovascular health (indicative of pathology in prediabetes) were inconsistent. Comparatively, some consistencies were found across structural connectivity studies, as both dMRI studies measuring FA showed lower levels in prediabetics compared to those with normoglycemia.[22,24] Thus, it may be the case that some changes in brain microstructure (e.g., FA) are present in prediabetes prior to measurable macro-level changes such as reduced WMV.

Surprisingly, one volumetric study found that prediabetics had larger TBV, GMV, and WMV compared to those with normoglycemia (this was mediated by brain volume size).[18] Regardless of brain size, increased brain volume in IFG may be the result of neuroinflammation as an initial effect of hyperglycemia.[5,6] To note, this study also did not provide a power calculation or sample size calculation, and thus the validity of their statistical findings may be questioned. In a separate study, prediabetes but not T2D was associated with smaller TBV.[5] However, whether T2D is associated with smaller TBV remains controversial, as other studies have shown that this association exists.[3,12] Another surprising finding was that in one study, RD values were shown to be lower in prediabetics compared to those with normoglycemia, suggesting that prediabetics may experience less myelin abnormalities than healthy controls.[22] While some research has shown that RD is positively correlated with dysmyelination or demyelination,[29] other research has suggested that alterations in white matter microintegrity may instead be derived from glial cell alterations.[30] Evidently, it currently remains unknown as to what RD values represent, thus RD results must be interpreted with caution. Furthermore, as suggested by the authors, more research on RD and the causes of variation is needed.[22]

A more general finding from our review is that blood glucose levels may correlate with brain decline regardless of clinical definitions of diabetic status. The majority of studies in our review that assessed correlational evidence of blood glucose levels and brain health decline found a positive relationship between the two.[4,5,6,10,12,13,16,17,21,22,25] Moreover, even those with normoglycemic status may begin to experience some brain deficits with increases in blood glucose.[10,21] As previously mentioned, a fundamental mechanism that may explain the association between elevated glucose and deficits in brain health is cardiovascular comorbidities such as hypercholesterolemia and hypertension, which may lead to microvascular changes, endothelial dysfunction, and atherosclerosis.[17,31] Studies have shown that elevated glucose levels, even in the normal range, lead to the production of advanced glycation end products (AGEs) and promote oxidative stress, which may lead to neuronal

dysfunction and cell death.[17,32,33] Thus, brain deficits may occur in any scenario in which there are increases in blood glucose levels as a result of micro-level changes.

Importantly, one possible explanation for inconsistencies across study findings in our review is varying diagnostic measures used and definitions of prediabetes. For example, the oral glucose tolerance test (OGTT) used to produce 2-h PG levels has been shown to have low reproducibility,[34,35] yet may have superior sensitivity compared to FPG.[36] The majority of studies in our review that used FPG or OGTT also only collected single-measurements of glucose which may lead to low accuracy in diagnoses. Additionally, whether HbA1c is an appropriate diagnostic tool for diabetes remains controversial. Currently, the WHO does not consider HbA1c to be a suitable diagnostic test for diabetes,[8] however the ADA argues that it is a reliable measure of chronic glycemia,[9] as it correlates well with long-term diabetes complications.[37] As such, the accuracy and reliability of diagnostic measures used in included studies may be questioned, and could have resulted in misdiagnoses and/or false or missed results. Furthermore, some studies in our review that directly compared diagnostic measures[16,17,25] found significant differences in results between tests, highlighting the need for a more standardized diagnostic measure.

Aside from diagnostic variability, there are several other limitations of the included studies that should be addressed. First, no studies considered the duration of prediabetes diagnosis in their sample. One study, for example, showed that duration of T2D is correlated with greater brain deficits,[12] and this may also be the case in prediabetes. Second, some studies that had three groups (T2D, prediabetes, normoglycemia) ran omnibus testing without additional post-hoc testing, thus it was not clear where differences between groups existed and made it difficult to assess the relationship of prediabetes and T2D. Third, there was a wide variation in study methodologies, including setting, inclusion/exclusion criteria, adjusted covariates in analyses, and MRI scanners used. As such, the heterogeneity between studies makes it difficult to compare between them and make concrete conclusions, and could be the reasoning behind inconsistent findings. Most studies in this review also did not conduct a

power calculation or provide a sample size justification, and thus the validity of findings may be questionable.

Another large limitation is that the majority of studies did not provide effect sizes of significant findings, particularly those pertaining to between-group differences. Thus, we were unable to appropriately gauge the magnitude of results seen in prediabetes, nor determine whether non-significant results were due to inadequate power to detect differences. In addition, most studies had age ranges that included both middle and older adults, thus we cannot comment on the results of these two groups separately, and how age may have affected results. Typically, glucose levels increase with age,[38] and thus older adult groups may have experienced more brain deficits compared to younger adults as a result of the natural aging process. Lastly, one limitation to our review is that cross-sectional and longitudinal studies do not allow us to infer causal relationships between variables, hence we cannot conclude that prediabetes causes brain deficits.

Future studies assessing prediabetes and brain health should use more consistent diagnostic tools and procedures to be able to produce replicable results. Moreover, more longitudinal studies are needed to assess the relationship between changes in glucose levels and brain health over time. More research evaluating structural connectivity changes is also needed to provide stronger evidence for its relationship to prediabetes and its potential for further structural decline. Additionally, one study in our review explicitly provided evidence that prediabetes is progressive in nature,[6] such that greater neural decline occurs as normoglycemia progresses to prediabetes and eventually T2D. As such, more studies examining direct comparisons between prediabetes and diabetes are needed in order to shed light on this possible progression of the disease.

Finally, as our review focused mainly on structural deficits in prediabetes, future studies should also examine functional activation patterns and connectivity in this population. Currently, there are only two known studies that have examined this. One study by Liu and colleagues (2019) assessed functional connectivity in the default mode network in

prediabetics and found no differences compared to healthy normoglycemic controls.[39] Another study by van Bussel et al. (2016) found that prediabetics display altered functional brain networks compared to controls.[40] Evidently, more research on brain function in prediabetics is needed.

In conclusion, this systematic review presents some evidence that prediabetics may experience deficits in brain volume, structural connectivity, and cerebrovascular health compared to non-diabetics. However, more cross-sectional and longitudinal studies that use standardized protocols are needed to allow for more direct comparisons between studies. Ultimately, understanding micro- and macro-level changes in the brain that may occur in prediabetes can help inform future intervention work in this population.

Summary

This chapter reported findings from a systematic review of cross-sectional and longitudinal studies that examined brain deficits in prediabetic adults using MRI. Results show that deficits in structural connectivity may be present in prediabetes, however mixed results were shown for volumetric measures and cerebrovascular health. These findings suggest that changes in brain microstructure may be present in prediabetes prior to measurable macro-level changes. Additionally, blood glucose levels were positively correlated with brain deficits regardless of diabetes status (e.g., even in normoglycemia). A mechanism that may explain this association is cardiovascular comorbidities that often occur in prediabetes, including hypertension.

One possible explanation for the inconsistencies across study findings is the use of varying diagnostic measures and definitions of prediabetes, highlighting the need for more standardized measures and classifications. Future studies should consider using multiple measurements of glucose to increase accuracy, and it is suggested that HbA1c be measured for a better indication of chronic glycemia levels.

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Chapter 3

3 Scientific outcomes: Cognitive changes following 26 weeks of resistance exercise in older adults at risk for diabetes

This chapter will explore the cognitive changes in older adults at risk for diabetes following a 26-week pilot randomized controlled trial of resistance exercise. A manuscript for the reported findings is currently in preparation.

Some content in Chapter 3 is from the following published protocol manuscript:

Furlano JA, Nagamatsu LS. Feasibility of a 6-month pilot randomised controlled trial of resistance training on cognition and brain health in Canadian older adults at-risk for diabetes: study protocol. *BMJ Open.* 2019;9(10),e032047. doi:10.1136/bmjopen-2019-032047

3.1 Introduction

Dementia, including Alzheimer's disease, affects approximately 55 million people worldwide,[1] and is a major cause of disability among older adults.[2] One of the largest modifiable risk factors for dementia is T2D,[3] characterized by high blood glucose levels. In fact, individuals with T2D are at a 50% or greater risk of developing dementia compared to those without T2D.[4,5] Furthermore, there is increasing evidence that T2D is associated with deficits in a variety of cognitive domains. In a meta-analysis, it was shown that adults and older adults with T2D experience deficits in all evaluated cognitive abilities, including processing and motor speed, attention, non-verbal reasoning, and memory, when compared to diabetes-free individuals.[6]

Importantly, older adults with prediabetes (i.e., those with elevated blood glucose levels that are below the T2D cutoff) already show evidence of cognitive decline. In one cross-sectional study, prediabetes in adults and older adults was found to be related to some deficits in global cognition, processing speed, and executive function compared to normal glucose tolerance.[7]

Similarly, Marseglia and colleagues (2016) found that older adults with prediabetes perform significantly worse on cognitive tasks assessing memory, perceptual speed, and category fluency compared to healthy age-matched controls.[8] Within the same data set, prediabetes was also found to be associated with faster cognitive decline over nine years compared to diabetes-free status.[9] Moreover, glucose regulation has been shown to be inversely related to cognitive function. This was demonstrated, for example, in a study by Convit and colleagues (2003) where a negative correlation was found between glucose levels and delayed memory recall even in healthy middle-aged and older adults.[10]

Another risk factor for T2D is obesity, a common comorbidity of prediabetes. Like prediabetics, overweight (BMI 25–29.9) or obese (BMI 30 and above) individuals already experience some cognitive dysfunction that is associated with T2D. One review and meta-analysis found that those with obesity showed impairments in executive function (response inhibition, cognitive flexibility, working memory), while overweight participants showed deficits in inhibition and working memory specifically.[11] In another review assessing the relationship between executive function and excessive body weight, most included studies found that overweight or obese individuals have impaired inhibitory control, working memory, and cognitive flexibility compared to those with in the normal weight range (BMI < 25).[12] Taken together, it appears that older adults at risk for T2D experience cognitive deficits that may worsen as the progression to T2D occurs, and intervention strategies aimed at improving cognitive function in this at-risk group may represent an ideal time point to prevent or delay future decline.

One promising lifestyle intervention that may improve cognitive function is exercise. Baker and colleagues (2010) assessed the effects of aerobic training in sedentary older adults with prediabetes or newly diagnosed T2D (the majority of participants were prediabetic).[13] Participants were randomly assigned to an aerobic training or stretching control group, in which they completed their respective exercise four times per week for six months.[13] Results showed that compared to the control group, those in the aerobic training group improved on tasks of executive function including selective and divided attention, cognitive flexibility,

and working memory.[13] Despite the majority of research on exercise and cognition focusing on aerobic training, there are other forms of exercise that may also be beneficial for older adults. Specifically, resistance training has been shown to improve cognitive function and brain health in several populations of older adults. One study in sedentary women with mild cognitive impairment found improvements in executive function and associative memory following six months of progressive resistance training.[14] Another study showed that six months of moderate-to-high intensity resistance exercise improved short- and long-term memory, attention, and executive function in older men.[15] Furthermore, resistance training has additional benefits for older adults, such as improving muscle function and reducing sarcopenia,[16] and may be useful for older adults who may suffer from some physical or mobility limitations and cannot perform aerobic training. As most older adults can perform some form of resistance training, it therefore provides older adults with an alternative form of exercise that may benefit cognition.

Further benefits of resistance training are highlighted in animal and human research focused on neural mechanisms. Research in rats have shown that resistance training may increase IGF-1,[17,18] known to have neuroprotective abilities associated with improved cognitive function.[19] Other research has shown that low levels of IGF-1 are associated with IGT and a higher risk for T2D in humans. For example, Friedrich and colleagues (2012) found that low levels of IGF-1 serum concentrations are associated with insulin resistance in adults of various ages.[20] Schneider et al (2011) measured IGF-1 levels in non-diabetic individuals and assessed incident diabetes during follow-up, and found that patients with low IGF-1 levels were at an increased risk for glucose intolerance and developing diabetes.[21] Based on these combined findings, resistance training may be particularly useful in not only improving insulin resistance and reducing one's risk of developing T2D, but also improving cognitive function in our study population.

To our knowledge, this is the first study to examine the effects of resistance training on cognition in older adults at risk for diabetes (i.e., those with prediabetes and/or obesity). To address whether resistance training may benefit cognitive function in this population, a large-

scale RCT is needed. However, we first conducted a pilot RCT to assess the feasibility and efficacy of this training program in this at-risk group. Although the primary outcome measure of this study was feasibility of the exercise program, here we will present preliminary efficacy findings on cognition. Specifically, we hypothesized that 26 weeks of thrice-weekly resistance training would lead to improvements in attention, executive function, and memory in older adults at risk for T2D when compared to balance and stretching exercises.

3.2 Methods

3.2.1 Study overview

We conducted a single-blinded pilot RCT of thrice-weekly resistance exercise for 26 weeks in older adults at risk for T2D. Data was collected from November 2017 to August 2019. Cognitive and physical assessments were conducted at baseline, midpoint (13 weeks), and trial completion (26 weeks), and were conducted on Western University campus in London, Ontario, along with all exercise sessions. To assess changes in brain structure and function, MRI was done at baseline and trial completion at the Centre for Functional and Metabolic Mapping at Robarts Research Institute; MRI findings are described in Chapter 4. Ethics approval was obtained from the Health Sciences Research Ethics Board at Western University, and our trial was registered at clinicaltrials.gov (ID NCT03254381; released August 3, 2017). Written informed consent was obtained from all participants. The Standard Protocol Items: Recommendations for Interventional Trials and Consolidated Standards of Reporting Trials checklists were completed.

Initial screening of participants was conducted via telephone, and interested participants were invited to come into the lab for three testing sessions on separate days to confirm eligibility and collect baseline measures. Session 1 consisted of MRI screening and baseline cognitive and physical testing (1.5 hours), while session 2 consisted of collecting FPG (which required participants to fast eight hours prior to testing) and completing descriptive questionnaires (30 minutes). Assessments were divided into two days to avoid participants having to complete

cognitively and physically demanding tests while fasting. Individuals who were deemed eligible at the end of session 2 then completed an MRI scan during session 3 (1.5 hours; described in Chapter 4). After baseline assessments were complete, participants were randomized (randomisation.com; random block sizes of two, four and six) into either the resistance training group or balance and tone (control) group by the Primary Investigator. Participants were informed of their group allocation in order to obtain their personal physicians' approval to exercise, however they did not have direct contact with the other exercise groups nor were they made aware of our hypotheses. All assessment staff were blinded to group allocation.

3.2.2 Recruitment and Sample size

We recruited participants from the city of London, Ontario (urban community) on a rolling basis via posters in community centres, short presentations at community seminars, word-of-mouth, and advertisements in the Villager Publications Community Magazine (print) and Kijiji (online). We chose these recruitment methods based on the recommendation of researchers at Western University whom have had success in recruiting older adults for similar studies. Enrolment in the study was ongoing until we reached our target sample size (10 participants per arm). This was the recommended size for a pilot study in which the full-scale trial would have an anticipated medium effect size ($0.3 \leq d < 0.7$) and power of 0.80.[22]

3.2.3 Inclusion and exclusion criteria

To be included in our study, individuals had to: (1) be community-dwelling, (2) be aged 60-80 years, (3) be 'at risk' for T2D, where they have BMI $\geq$ 25 and/or FPG 6.1 to 6.9 mmol/l; the glucose range is based on the WHO's classification of prediabetes,[23] (4) score >24/30 on Mini-Mental State Examination (MMSE)[24], (5) score >6/8 on the Lawton and Brody Instrumental Activities of Daily Living (IADL) Scale,[25] (6) have visual acuity of at least 20/40 with or without corrective lenses, (7) speak and understand English fluently, and (8) complete the Physical Activity Readiness Questionnaire and obtain their physician's clearance to start a supervised exercise program.[26]

We excluded those who: (1) had a medical condition for which exercise was contraindicated, (2) had participated regularly (>1/week) in structured resistance or aerobic exercise within six months, (3) had been diagnosed with neurodegenerative disease (including dementia or Parkinson's disease), (4) had experienced a vascular incident (including stroke or myocardial infarction), (5) had been diagnosed with a psychiatric condition, (6) had untreated depression, (7) was on hormone replacement therapy, (8) had clinically significant peripheral neuropathy or severe musculoskeletal or joint disease, (9) was taking psychotropic medications, or (10) was unable to participate in MRI (had metal or electronic implants or was claustrophobic).

3.2.4 Descriptive measures

To describe our sample and/or assess eligibility, we collected the following measures: (1) demographic information (age, sex, education, income), (2) medication use, (3) falls history, (4) sleep quantity and quality using a monthly questionnaire, (5) number and type of comorbidities using the Functional Comorbidity Index,[27] (6) ability to perform daily tasks using the IADL, (7) depression screening using the Geriatric Depression Scale (GDS),[28] and (8) global cognitive impairment using the MMSE and Montreal Cognitive Assessment (MoCA).[29] FPG and BMI measures are described in section 3.2.8 below.

3.2.5 Feasibility outcomes

Our primary outcome measure of feasibility was assessed mainly via participant recruitment, adherence, and retention rates. These outcomes will be presented in Chapter 5.

3.2.6 Cognitive outcomes

All standardized tests used to measure cognition were chosen based on their use within the resistance exercise literature.

3.2.6.1 Executive function

Selective attention and conflict resolution was measured via the Stroop Test.[30] This test features three conditions, in which participants are instructed to read words as quickly as possible. For the first condition (A), participants read out words (names of colours) printed in blank ink (e.g., 'RED'). For the second condition (B), participants read out the colour of the X's that appear on the sheet (e.g., XXX printed in red ink, with the correct response being 'red'). For the third condition (C), participants name the colour of the words (e.g., RED printed in blue ink, with the correct response being 'blue'), thus ignoring the written word itself. Each condition has 80 trials, in which time to complete all trials (in seconds) is recorded for each condition. We calculated the difference between time to complete conditions C and B of the task, with lower scores indicating better cognitive performance.

Additionally, task-switching was measured via the TMT (Parts A and B).[30] For this test, participants are instructed to connect a set of 25 dots as quickly and accurately as possible, and time to complete the task (in seconds) is recorded. In Part A, participants connect encircled numbers (1 to 24) in sequential order. In Part B, participants connect encircled numbers (1 to 12) and encircled letters (A to L) in alternating fashion (i.e., 1-A-2-B-3-C, etc.). The time difference for completing Part B minus Part A was calculated, with lower scores indicating better performance.

To assess working memory, we used the Digit Span Test (Forward and Backward).[31] Both conditions consist of seven pairs of random number sequences that are read out loud by the assessor (one number per second), with each pair containing the same number of three or more digits. The digits are increased by one across pairs of sequences (up to nine). For the Forward test, participants repeat each sequence as it is read, while in the Backward test participants repeat the sequence in reverse order. Testing ceases when the participant fails to recollect both sequences within one pair. Scores range from 1 to 14 (one point is given for each correct sequence). To measure the central executive component of working memory, we

calculated Forward minus Backward scores, with lower scores indicating better working memory.

3.2.6.2 Other

Participants completed the Rey Auditory Verbal Learning Test (RAVLT) to assess auditory-verbal memory.[32] For this test, assessors read out a list of 15 random words (one per second) over five trials and instruct participants to recall as many words as possible after each trial. The assessor then presents a separate list of 15 unrelated words to participants, who are instructed to recall as many words as possible from the new list. Immediately following this, participants are instructed to recall as many words as possible from the original list. Following a 20 minute delay, participants again are asked to recall as many words as possible from the original list (out of 15). Performance on the last task (20 minute delay recall) was used to determine long-term memory ability, with higher scores indicating better memory.

Finally, the Alzheimer's Disease Assessment Scale–Cognitive 12 (ADAS-Cog 12) was used to assess various cognitive functions (e.g., language, constructional praxis, orientation) associated with risk for Alzheimer's disease.[33] For this test, participants complete several tasks including naming the fingers of their dominant hand, naming a set of 12 common objects, drawing geometric shapes, identifying their location and date, and recalling words. The maximum score on this test is 80, with lower scores indicating better performance.

3.2.7 MRI outcomes

Brain structure and function were assessed via MRI in a 3 Tesla Siemens scanner. MRI outcomes are discussed in Chapter 4.

3.2.8 Physical outcomes

One repetition maximum (1RM; which is a physical measure of an individual's maximum muscle strength during a single movement repetition) for the quadricep muscles was recorded for both resistance training and balance and tone groups. One repetition maximum for

additional muscle groups (latissimus (lat) dorsi, hamstrings, pectoralis major, biceps, triceps, deltoids, trapezius muscles) was also recorded for the resistance training group for the purpose of determining progressive resistance loads. In addition, balance and mobility were measured using the Short Physical Performance Battery (SPPB; administered monthly)[34] and the Timed Up and Go (TUG) Test.[35] For the SPPB, participants perform a side-by-side, semi-tandem, and tandem stand (each for 10 seconds). In this test, participants also perform a four meter walk (timed) and a five-time chair stand (timed). A higher total score (out of 14) on the SPPB indicates better performance. For the TUG, participants are instructed to stand up from a chair, walk three meters at their usual pace, turn around and walk back to the chair and sit down in it (timed), where a lower score indicates better performance. Finally, participants completed the Six Minute Walk Test which is an aerobic test that measures the distance an individual can walk in six minutes at a self-determined pace.[36]

Other physical measures included: (1) BMI calculated via height and weight, (2) FPG using a glucometer following participant fasting, (3) hip and waist circumference, and (4) monthly levels of leisure, household, and occupational physical activity using the Physical Activity Scale for the Elderly (PASE) questionnaire, where a higher score (out of 793) indicates greater physical activity levels.[37]

3.2.9 Exercise intervention

Participants in both groups completed 60 minutes of exercise (including 10 minutes of warm-up and 10 minutes of cool-down) three times per week on non-consecutive days for 26 weeks. Exercise protocols were adapted from those developed by Dr. Teresa Liu-Ambrose and used successfully in similar interventions.[14,38,39] Classes were made up of 2-4 participants (based the exercise room's available capacity) and were led by 1-2 trained fitness leaders who were undergraduate students in the School of Kinesiology at Western University. All participants were asked not to engage in structured exercise outside of the study's exercise program, and to maintain their usual diet and sleeping patterns when possible.

3.2.9.1 Resistance exercise

Participants in this group underwent progressive resistance training (i.e., loading was increased over time). Participants used seven programmable pressurized air weight machines (leg press, lat pulldown, leg curl, chest press, bicep curl, tricep curl, seated row) and completed body weight exercises to target primary muscle groups as listed in section 3.2.8 of this Chapter. The number of sets completed and the weight lifted for each exercise was recorded at every class for all participants. Warm-up and cool-down sessions consisted of walking on a treadmill or using an elliptical machine at a light pace (based on participant preference). The exercise protocol was individualized to meet each participant's physical needs.

The first three weeks of the exercise program was used to introduce participants to the weights and machines, and allow them to become familiar with the machines' set-up. Participants exercised using a light and easy resistance during this time and were monitored for proper form by instructors. At the end of week 3, 1RM was calculated on all exercise machines. Since calculating a true 1RM may be impractical for older adults due to their fragility, we instead calculated *predicted 1RM* using the following validated formula:

$$\text{Weight} \div (1.0278 - (0.0278 \times \text{Number of repetitions})),$$

which takes into account both the weight being applied and the number of repetitions comfortably possible.[40] This formula is more accurate the closer the repetitions are to one and becomes unreliable beyond ten.[40] Therefore, assessors needed to first take an educated guess as to what weight the participant would be able to lift that would not exceed ten repetitions (this was adjusted if it became apparent that the weight was far too light). Participants were closely monitored to prevent discomfort or injury.

For weeks 4 and 5, applied weight was based on increasing percentages of predicted 1RM (**Table 3.1**). Weight gradually increased (and number of reps decreased) until participants were able to complete two sets of 6-8 reps at 80% of predicted 1RM. Participants reached

this target by the end of week 5. After this, training stimulus was increased in increments of 1kg using the 7RM method—when two sets of 6-8 reps were completed with proper form and without discomfort. In addition, participants completed two sets of 6-8 mini-squats, mini-lunges, and lunge walks at each class. To increase load for squats and lunges over time, participants used hand-weights (starting with five pounds and increasing by 2-5 pounds) beginning at week 4.

Table 3.1: Resistance exercise protocol.

Week	Exercise load
1-3	Light load, 10-15 reps, 1-2 sets
4	1RM testing (day 1) 55% 1RM, 15 reps, 2 sets (day 2) 61% 1RM, 13 reps, 2 sets (day 3)
5	67% 1RM, 11 reps, 2 sets (day 1) 73% 1RM, 10 reps, 2 sets (day 2) 80% 1RM, 8 reps, 2 sets (day 3)
6-26	80% 1RM, 6-8 reps, 2 sets (with added resistance)

1RM = one repetition maximum (predicted).

3.2.9.2 Balance and tone exercise

Participants in the control group engaged in light exercises including balance and stretching exercises; only bodyweight was applied (i.e., no additional loading). These specific balance and tone exercises have not been shown to significantly improve cognitive function in previous research.[41] Warm-up and cool-down sessions consisted of stretching as a group, and the exercise protocol was individualized as needed. The control group served to control for confounding variables in the study such as socialization, commitment to the program, and any lifestyle changes associated with completing the program.

3.2.10 Monitoring

While this study was low risk, adverse events associated with exercise or physical testing were possible, such as pain, discomfort, shortness of breath, or injury. All participants were monitored closely by instructors for symptoms of these occurrences during exercise sessions.

3.2.11 Data analysis

Means (standard deviations (SD)) and percentages by group were used to describe baseline characteristics of our sample. Since pilot studies are used to estimate possible effects rather than formally testing hypotheses,[42,43] we focused on descriptive statistics and estimation (means, standard errors (SEs), medians, confidence intervals (CIs)) to infer the possible size and direction of effects, and did not report p-values. Thus, cognitive and physical results are presented as means and SE at baseline, midpoint, and trial completion, and change over time is presented as means and 95% CIs. This method of presenting data has been used previously in pilot trials, including a similar pilot exercise study in diabetic older adults.[44] Lastly, bivariate Spearman correlation coefficients were used to examine the possible magnitude and direction of associations between change in characteristics across the trial (trial completion relative to baseline), namely BMI and FPG with cognitive outcomes. Quality assessment of data was performed and discussed by two researchers to identify scores that were unreliable

(i.e., not plausible). However, since this was a pilot study, potential outliers that were deemed possible were included in analyses.

3.3 Results

Screening, recruitment, and study retention is summarized in **Figure 3.1** (further details will be provided in Chapter 5). Twenty-four participants were included in our trial, with 13 participants being randomized to the resistance training group and eleven to the balance and tone group. One balance and tone participant dropped out of the study at week ten due to health issues, therefore only their baseline data was used in our analyses in line with the intent-to-treat principle.[45] To note, some participant data is missing for outcome measures due to: assessor errors (e.g., incorrect timing on tests), unreliability (i.e., scores that were not plausible), or purposefully not collected (e.g., one balance and tone participant did not complete quadricep 1RM testing at midpoint due to joint discomfort).

3.3.1 Descriptive measures

Baseline characteristics of participants are described in **Table 3.2**. The mean age of participants (n = 24) was 68.7 years ± 5.7 (50% female). At baseline, all participants were overweight or obese (mean BMI 31.4 ± 5.0 kg/m^2), while four participants (16.7%) had prediabetes (mean FPG for all participants was 5.3 ± 0.8 mmol/l). Two participants with prediabetes were randomized to the resistance training group, and two to the balance and tone group.

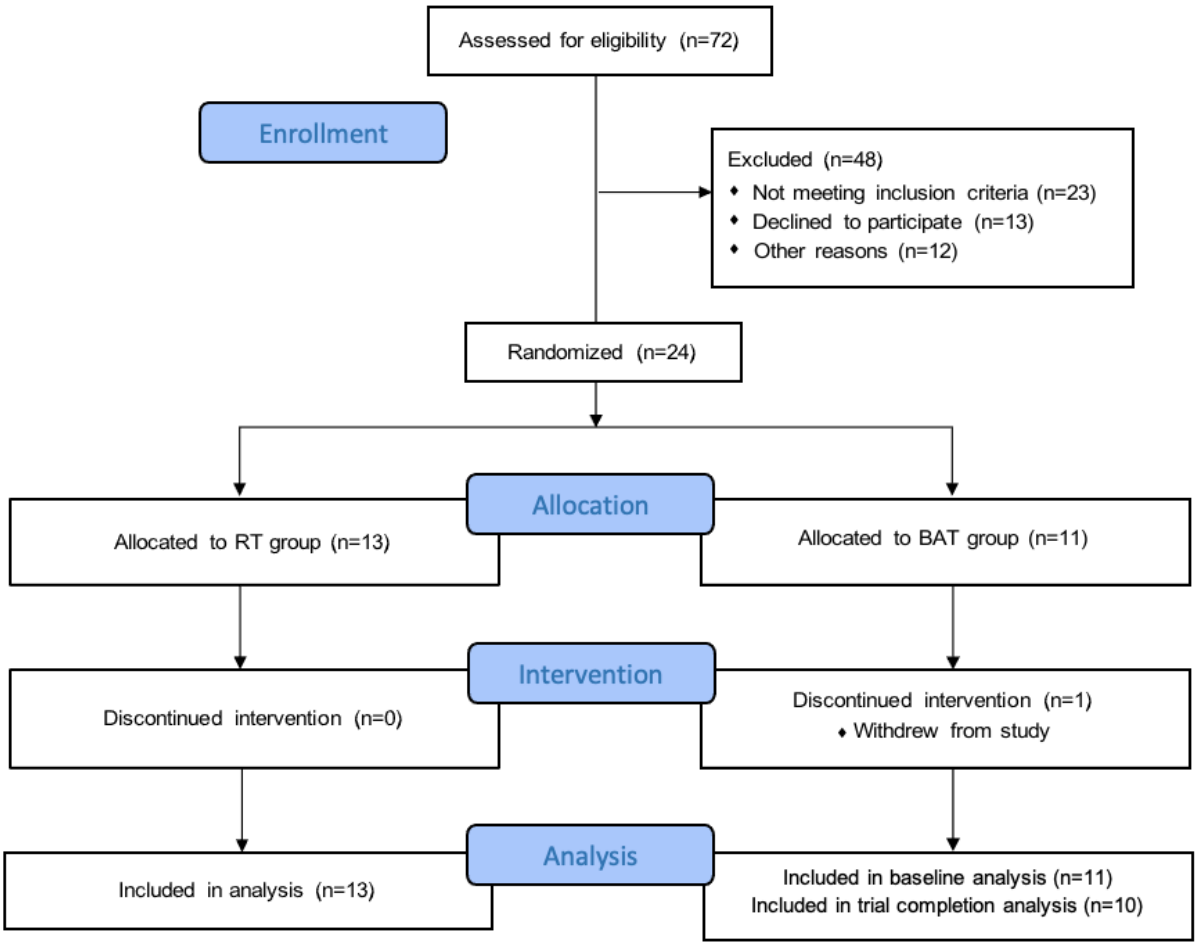

Figure 3.1: Recruitment flow diagram.

Table 3.2: Baseline characteristics of participants.

Variable	Total (*n* = 24)	RT (*n* = 13)	BAT (*n* = 11)
Age, years	68.7 ± 5.7	68.2 ± 6.0	69.3 ± 5.6
Female – n (%)	12 (50)	6 (46.2)	6 (54.5)
Education – n (%)			
High school diploma	2 (8.3)	2 (15.4)	0 (0)
Some college	6 (25.0)	3 (23.1)	3 (27.3)
College/trade degree	3 (12.5)	2 (15.4)	1 (9.1)
Bachelor's degree	8 (33.3)	4 (30.8)	4 (36.4)
Graduate degree	5 (20.8)	2 (15.4)	3 (27.3)
Annual income			
Over $20,000	4 (16.7)	3 (23.1)	1 (9.1)
Under $20,000	20 (83.3)	10 (76.9)	10 (90.9)
BMI, kg/m^2	31.4 ± 5.0	30.9 ± 3.0	31.9 ± 6.7
FPG, mmol/l	5.3 ± 0.8	5.2 ± 0.9	5.3 ± 0.8
Sleep per night, hours	6.9 ± 1.1	6.8 ± 0.9	7.0 ± 1.3
FCI, max. 18 pts	1.5 ± 1.3	0.8 ± 0.7	2.5 ± 1.3
IADL, max. 8 pts	7.8 ± 0.5	7.9 ± 0.3	7.7 ± 0.6
GDS, max. 15 pts	2.3 ± 2.5	1.8 ± 2.1	2.9 ± 3.0
MMSE, max. 30 pts	27.5 ± 1.8	27. 5 ± 2.1	27.5 ± 1.5
MoCA, max. 30 pts	24.9 ± 2.9	25.0 ± 2.1	24.8 ± 3.7

Note: All data expressed as mean ± standard deviation unless otherwise indicated.
BMI = body mass index; FPG = fasting plasma glucose; FCI = Functional Comorbidity Index; IADL = Lawton and Brody Instrumental Activities of Daily Living; GDS = Geriatric Depression Scale; MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; RT = resistance training group; BAT = balance and tone group.

3.3.2 Cognitive outcomes

Changes in cognitive outcomes by group over the 26-week intervention are shown in **Table 3.3** (midpoint > baseline, and trial completion > baseline) and are presented visually via box plots in **Figure 3.2** (trial completion > baseline). Note, when presenting means, SEs, and medians at each timepoint in **Table 3.3**, we used all available data; however when calculating mean and CIs for change over time (midpoint > baseline, or trial completion > baseline), we only included participants who had data from both timepoints (i.e., had no missing data).

3.3.2.1 Executive function

Compared to those in the balance and tone group, participants in the resistance training group showed sizable improvements in TMT at trial completion relative to baseline (**Table 3.3, Figure 3.2**). At midpoint, improvements on the TMT were already apparent in the resistance training group (**Table 3.3**). Interestingly, however, those in the balance and tone group showed improvements on the TMT at midpoint but had worse performance at trial completion (**Table 3.3**).

Both groups had comparable improvements in selective attention and conflict resolution (Stroop Test) at midpoint relative to baseline, but the resistance training group had greater improvements at trial completion compared to the balance and tone group (**Table 3.3, Figure 3.2**). Surprisingly, the balance and tone group but not the resistance training group improved in working memory (Digit Span) at trial completion relative to baseline (**Table 3.3, Figure 3.2**); at midpoint, however, both groups had improvements, but these were very small for the resistance training group (**Table 3.3**). To note, there was more variability in the resistance training group scores than the balance and tone group scores in these measures (**Figure 3.2**).

3.3.2.2 Other

Relative to baseline, the balance and tone group improved more than the resistance training group at trial completion in long-term memory (RAVLT, 20 minute delay condition), with some improvements also seen at midpoint for both groups (**Table 3.3, Figure 3.2**). In

addition, both groups improved on the ADAS-Cog 12 at both timepoints relative to baseline (**Table 3.3, Figure 3.2**), but these changes are not considered clinically significant in the literature.[46]

Table 3.3: Cognitive outcomes by group.

Variable	Baseline		Midpoint		Trial completion		Δ Baseline to midpoint		Δ Baseline to trial completion	
	Mean (SE)	Median	Mean (SE)	Median	Mean (SE)	Median	Mean (95% CI)	Median	Mean (95% CI)	Median
RT										
Stroop (C-B)	44.1 (7.2)	43.5	40.2 (4.0)	36.9	36.9 (3.8)	33.4	-3.8 (-18.7, 11.0)	-8.9	-7.2 (-23.5, 9.8)	-9.7
TMT (B-A)	[b]33.7 (5.0)	[b]35.3	[b]25.3 (3.8)	[b]19.4	[e]23.1 (3.6)	[e]23.6	-11.9 (-19.6, -4.1)	-12.3	-9.6 (-21.8, 2.5)	-3.2
Digit Span (F-B)	2.5 (1.1)	3.0	2.2 (0.8)	2.0	3.5 (0.7)	4.0	-0.3 (-3.1, 2.5)	-1.0	1.1 (-1.2, 3.4)	0.0
RAVLT (20 minute delay)	[b]7.0 (1.2)	[b]7.5	8.5 (1.2)	9.0	[e]9.0 (1.6)	[e]10.5	1.2 (-0.9, 3.2)	2.0	1.7 (-0.5, 3.8)	2.0
ADAS-Cog 12	7.1 (1.1)	6.3	5.0 (0.7)	4.5	5.6 (0.9)	4.7	-2.0 (-3.5, -0.5)	-1.7	-1.4 (-2.9, 0.1)	-1.7
BAT										
Stroop (C-B)	52.4 (6.1)	49.6	[a]43.6 (6.7)	[a]50.7	[a]41.6 (2.8)	[a]41.4	-3.8 (-20.6, 12.9)	-3.3	-5.8 (-13.4, 1.7)	-7.5
TMT (B-A)	40.9 (11.8)	24.0	[a]27.4 (4.0)	[a]28.7	[d]41.5 (6.0)	[d]41.2	-2.4 (-14.4, 9.6)	-0.4	11.0 (-2.6, 24.5)	13.1
Digit Span (F-B)	1.9 (0.7)	2.0	[a]-0.2 (0.4)	[a]0.0	[a]1.0 (0.7)	[a]1.0	-2.3 (-3.9, -0.7)	-1.5	-1.1 (-3.0, 0.8)	-0.5
RAVLT (20 minute delay)	[b]7.0 (1.5)	[b]5.0	[c]12.1 (1.5)	[c]14.0	[d]12.5 (1.1)	[d]14.0	4.3 (0.1, 8.4)	4.5	5.3 (2.1, 8.5)	5.0
ADAS-Cog 12	5.3 (1.1)	5.7	[a]4.1 (0.8)	[a]3.5	[a]3.1 (0.4)	[a]3.2	-0.6 (-2.6, 1.5)	0.0	-1.5 (-3.3, 0.4)	-1.5

Stroop (C-B) = Stroop Test condition C minus condition B; TMT (B-A) = Trail Making Test part B minus part A; Digit Span (F-B) = Digit Span Test Forward minus Backward; RAVLT (20 minute delay) = Rey Auditory Verbal Learning Test 20 minute delay condition; ADAS-Cog 12 = Alzheimer's Disease Assessment Scale–Cognitive 12; RT = resistance training group; BAT = balance and tone group; SE = standard error; CI = confidence interval.

[a] Missing data for *n* = 1 (dropout).
[b] Missing data for *n* = 1 (data collection error).
[c] Missing data for *n* = 2 (1 dropout, 1 data collection error).
[d] Missing data for *n* = 3 (1 dropout, 2 data collection errors).
[e] Missing data for *n* = 3 (3 data collection errors).

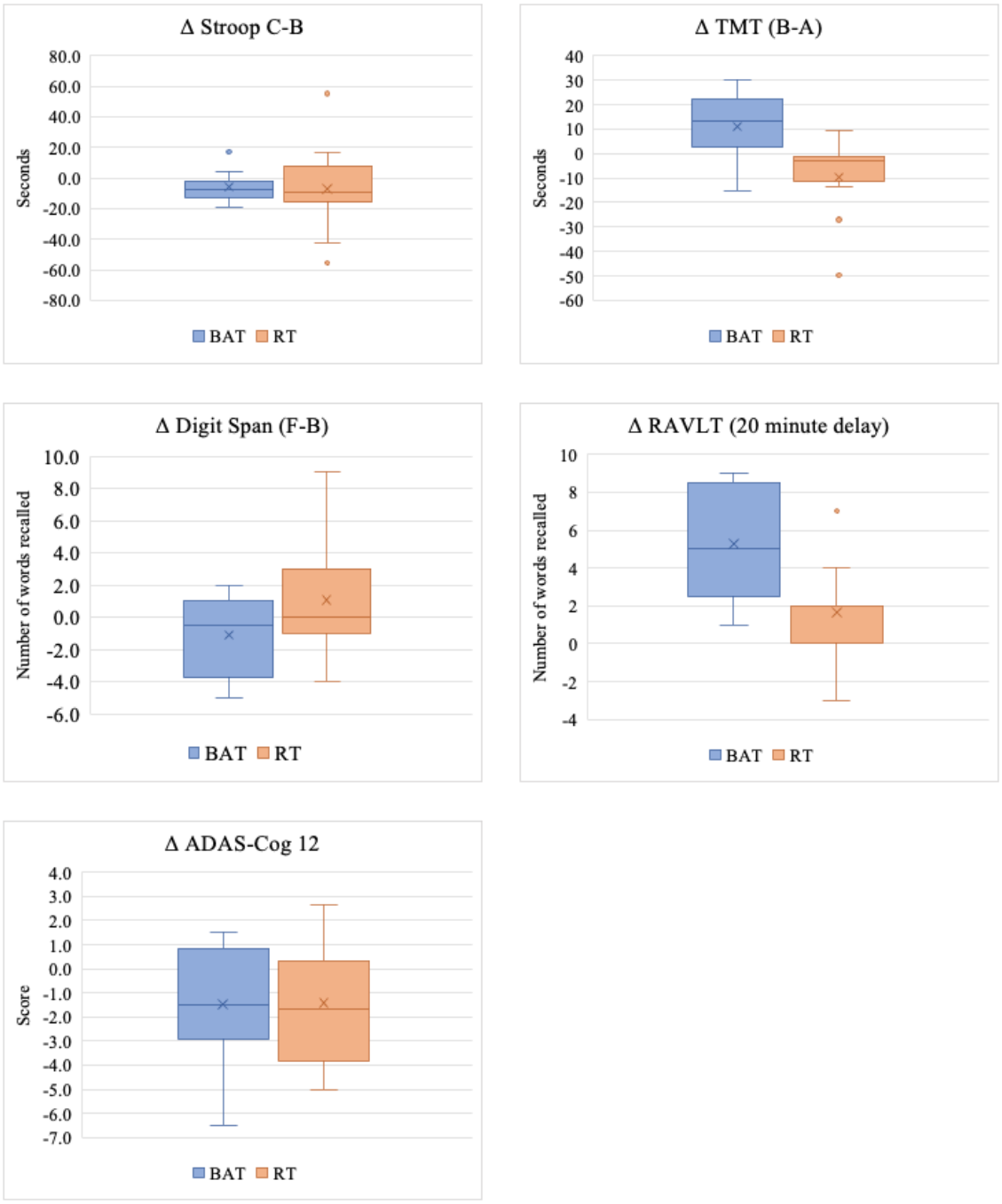

Figure 3.2: Mean change in scores on cognitive tests (trial completion > baseline).
Note: the box represents the interquartile range, where the bottom line of the box represents quartile 1 (25th percentile) and the top line represents quartile 3 (75th percentile); the whiskers

represent the minimum and maximum values excluding outliers; ‘X’ represents the mean; and the middle line of the box represents the median.
Stroop C-B = Stroop Test condition C minus condition B; TMT B-A = Trail Making Test part B minus part A; Digit Span F-B = Digit Span Test Forward minus Backward; RAVLT (20 minute delay) = Rey Auditory Verbal Learning Test 20 minute delay condition; ADAS-Cog 12 = Alzheimer’s Disease Assessment Scale–Cognitive 12; RT = resistance training group; BAT = balance and tone group.

3.3.3 Physical outcomes

Change in physical measures by group across the 26 weeks are presented in **Table 3.4**. A larger increase in 1RM was seen for the resistance training group compared to the balance and tone group (**Table 3.4, Figure 3.3**), and this was gradual from midpoint to trial completion. Across the trial, most changes in other physical measures were small and comparable for both resistance training and balance and tone groups, including FPG and BMI (**Table 3.4**). However, the resistance training group had larger increases in PASE scores at both midpoint and trial completion compared the balance and tone group, as well as larger improvements on the six minute walk test at both time points (**Table 3.4**).

Table 3.4: Physical outcomes by group.

Variable	Baseline		Midpoint		Trial completion		Δ Baseline to midpoint		Δ Baseline to trial completion	
	Mean (SE)	Median	Mean (SE)	Median	Mean (SE)	Median	Mean (95% CI)	Median	Mean (95% CI)	Median
RT										
1RM, kg	49.5 (3.9)	50.0	61.5 (4.9)	64.0	70.7 (3.5)	69.0	12.0 (4.9, 18.9)	9.0	21.2 (15.8, 26.5)	22.0
BMI, kg/m^2	30.9 (0.8)	30.7	30.7 (0.9)	31.3	30.3 (1.1)	30.5	-0.2 (-1.0, 0.6)	0.2	-0.6 (-1.8, 0.7)	0.1
FPG, mmol/l	5.2 (0.3)	5.1	5.3 (0.2)	5.1	5.5 (0.2)	5.4	0.1 (-0.3, 0.5)	0.0	0.2 (-0.3, 0.8)	0.3
Hip circumference, cm	110.2 (3.0)	111.0	110.9 (2.8)	110.5	[h]112.5 (3.0)	[h]111.0	0.7 (-4.4, 5.8)	0.0	4.2 (-1.3, 9.8)	3.0
Waist circumference, cm	108.1 (3.3)	104.1	108.5 (3.4)	108.0	[h]107.4 (3.9)	[h]105.5	0.4 (-1.6, 2.4)	0.0	0.2 (-2.4, 2.8)	-0.1
PASE	[b]109.5 (10.2)	[b]101.0	135.9 (17.6)	136.7	144.8 (19.0)	138.0	28.0 (-17.0, 73.0)	12.7	35.9 (4.7, 67.1)	37.5
SPPB	10.2 (0.4)	10.0	10.5 (0.3)	11.0	10.5 (0.4)	10.0	0.3 (-0.4, 1.0)	0.0	0.3 (-0.7, 1.3)	0.0
TUG, s	8.8 (0.6)	8.8	8.3 (0.4)	8.2	8.8 (0.5)	8.5	-0.6 (-1.7, 0.5)	-0.2	0.0 (-1.5, 1.4)	-0.2
Six minute walk test, m	478.9 (11.9)	465.0	503.0 (20.7)	507.0	513.3 (16.0)	510.0	24.1 (-21.1, 69.3)	32.0	34.4 (-6.7, 75.5)	48.0
BAT										
1RM, kg	[b]50.4 (6.2)	[b]51.5	[f]64.2 (6.2)	[f]72.0	[f]66.4 (6.8)	[f]64.0	9.1 (-2.6, 20.8)	13.0	9.1 (-3.2, 21.4)	8.0
BMI, kg/m^2	31.9 (2.0)	29.9	[g]32.0 (2.8)	[g]30.4	[a]32.3 (2.4)	[a]30.7	0.4 (-0.7, 1.5)	0.1	0.0 (-1.2, 1.2)	0.0
FPG, mmol/l	5.3 (0.2)	5.6	[d]5.1 (0.2)	[d]5.2	[a]5.6 (0.2)	[a]5.8	0 (-0.5, 0.5)	-0.1	0.3 (-0.3, 0.9)	0.4
Hip	[c]113.4	[c]112.0	[e]116.2	[e]113.0	[e]118.7 (5.6)	[e]112.0	2.7 (-3.9, 9.2)	-0.5	5.2 (-0.4, 10.7)	2.2

circumference, cm	(5.7)		(6.8)							
Waist circumference, cm	[c]114.4 (5.9)	[c]111.0	[e]110.2 (6.4)	[e]113.0	[e]111.0 (6.5)	[e]113.0	-4.6 (-11.4, 2.1)	-3.0	-3.8 (-10.5, 2.9)	-1.0
PASE	[b]115.9 (15.2)	[b]133.9	[a]97.5 (11.0)	[a]92.3	[d]117.9 (12.0)	[d]116.0	-10.1 (-59.4, 39.1)	15.0	5.2 (-25.2, 35.7)	-4.4
SPPB	9.5 (0.4)	9.0	[a]10.9 (0.3)	[a]11.0	[a]9.9 (0.5)	[a]10.0	1.3 (0.2, 2.4)	1.5	0.3 (-1.0, 1.6)	-0.5
TUG, s	8.6 (0.3)	8.6	[d]8.1 (0.4)	[d]7.4	[a]9.3 (0.9)	[a]9.2	-0.5 (-1.3, 0.2)	-0.6	0.6 (-1.3, 2.5)	0.3
Six minute walk test, m	468.8 (25.0)	485.0	[d]454.3 (21.5)	[d]480.0	[a]474.4 (21.7)	[a]484.5	1.2 (-56.5, 58.9)	-5.0	7.4 (-52.6, 67.3)	9.5

1RM = one repetition maximum (predicted) – quadricep; BMI = body mass index; FPG = fasting plasma glucose; PASE = Physical Activity Scale for the Elderly; SPPB = Short Physical Performance Battery; TUG = Timed Up and Go Test; RT = resistance training group; BAT = balance and tone group; SE = standard error; CI = confidence interval.

[a] Missing data for n = 1 (dropout).

[b] Missing data for n = 1 (data collection error).

[c] Missing data for n = 1 (1 identified as unreliable).

[d] Missing data for n = 2 (1 dropout, 1 data collection error).

[e] Missing data for n = 2 (1 dropout, 1 identified as unreliable).

[f] Missing data for n = 2 (1 dropout, 1 data not collected due to physical discomfort).

[g] Missing data for n = 3 (1 dropout, 2 data collection errors).

[h] Missing data for n = 4 (4 data collection errors).

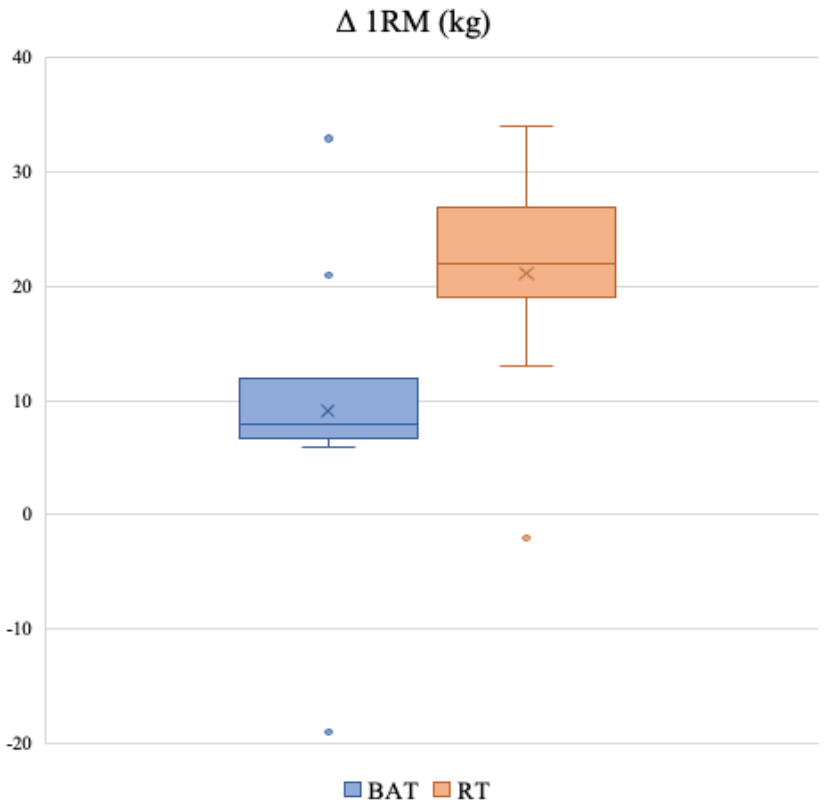

Figure 3.3: Mean change in 1RM (trial completion > baseline).

Note: the box represents the interquartile range, where the bottom line of the box represents quartile 1 (25th percentile) and the top line represents quartile 3 (75th percentile); the whiskers represent the minimum and maximum values excluding outliers; 'X' represents the mean; and the middle line of the box represents the median.
1RM = one repetition maximum (predicted) – quadricep; RT = resistance training group; BAT = balance and tone group.

3.3.4 Correlations

Table 3.5 shows correlations between change in BMI, FPG, and cognitive outcome measures at trial completion relative to baseline. Interestingly, increased 1RM strength was moderately correlated with reduced RAVLT scores. In addition, a weak-to-moderate positive correlation was found for 1RM and Digit Span scores (i.e., increased 1RM was related to a decline in performance on the Digit Span Test). Increased BMI had a weak-to-moderate association with improved ADAS-Cog 12 scores, which was also surprising. Finally, increased FPG levels was related to improved performance on the TMT (weak-to-moderate correlation). All other correlations were weak in strength.

Table 3.5: Spearman correlations for cognitive and physical outcomes (trial completion > baseline).

	Stroop (C-B)	TMT (B-A)	Digit Span (F-B)	RAVLT (20 minute delay)	ADAS-Cog 12
1RM, kg	-.098	-.112	.393	-.571	-.021
BMI, kg/m^2	.007	.098	-.076	.124	-.331
FPG, mmol/l	-.067	-.356	-.059	.010	-.181

1RM = one repetition maximum (predicted) – quadricep; BMI = body mass index; FPG = fasting plasma glucose; Stroop (C-B) = Stroop Test condition C minus condition B; TMT (B-A) = Trail Making Test part B minus part A; Digit Span (F-B) = Digit Span Test Forward minus Backward; RAVLT (20 minute delay) = Rey Auditory Verbal Learning Test 20 minute delay condition; ADAS-Cog 12 = Alzheimer's Disease Assessment Scale–Cognitive 12.

3.4 Discussion

Results from the current study suggest that 26 weeks of thrice-weekly resistance training may benefit certain cognitive domains in older adults at risk for diabetes. This is in line with previous research that has shown that positive effects of resistance training on cognitive function in older adults may be selective.[38,47] In our study, the largest improvement in cognition as a result of resistance training was seen in task-switching performance, as measured by the TMT. The ability to switch between tasks is a higher-order function shown to decline naturally with age,[48] with greater impairment seen in many chronic illnesses including hyperglycemia and obesity.[49,50] Previous study findings have shown that endurance exercise positively affects task-switching in older adults,[51] as demonstrated in our study. Moreover, the size of improvements seen in our study is similar to what has been statistically found in another resistance training intervention in older adults;[38] based on this, we can infer that we would see similar cognitive improvements in large-scale resistance training trials in our target population.

Another positive finding from our study–that resistance training improves selective attention and conflict resolution–also corroborates previous work in older adults. Liu-Ambrose et al. (2010) found that older adults who performed resistance exercise twice per week for 12 months significantly improved in selective attention and conflict resolution as measured by the Stroop Test.[38] Comparatively, our study found even greater improvements on the Stroop task than this study did after progressive resistance training, however our frequency/duration of exercise differed. Additionally, an important finding that emerged from the 12-month study data set was that Stroop performance during the trial predicted maintenance of physical activity post-intervention, such that those with greater improvements on the Stroop Test remained more physically active than those with poorer scores.[52] Improvements in selective attention and conflict resolution along with other measures of executive function, also have important implications to everyday living for older adults. For example, such executive functions are known to be essential to balance, postural maintenance, ambulation, and the prevention of falls.[53] Furthermore, many studies show that executive functioning is positively

correlated with basic activities of daily living, including preparing meals, handling finances, driving, and shopping, among others.[54]

Notably, improvements in cognitive function (task-switching, selective attention, conflict resolution) in response to resistance training in our study were already apparent to some degree at trial midpoint. In line with this, previous studies have shown that improvements in cognition can be evident after short-term resistance training. An RCT by Santos et al. (2020) assessed the effects of resistance training on cognition after only 12 weeks of thrice-weekly resistance training in community-dwelling older adults.[55] At trial completion, the authors found significant improvements in selective attention, conflict resolution, working memory, and verbal fluency.[55] However, the extent to which short-term resistance training such as this has lasting effects on cognition is not well understood, thus more exercise studies with follow-ups are needed. Moreover, cognitive improvements seen in our population early on in the trial may be the result of the degree of impairment at baseline. Other clinical populations of older adults (e.g., those with MCI) have been shown to experience cognitive benefits from resistance training faster than healthy older adults,[14,38] and this may be due to having worse baseline cognition and therefore greater room for improvements. Future correlational studies assessing cognitive abilities in our population versus healthy age-matched controls are needed.

One possible explanation for why resistance training led to improvements in executive function but not memory in our study is the use of higher-order cognitive functions to perform the resistance training exercises. It may be that resistance exercise, compared to other forms of exercise including aerobic training, is more cognitively stimulating and demanding. Resistance training often requires learning new equipment as well as attention and concentration while performing the exercises themselves (to ensure proper form, to count repetitions, etc.). Thus, execution functioning is perhaps being strengthened in this manner during resistance training. Additionally, findings on whether resistance training improves memory remain fairly inconsistent in the literature, while more consistent research demonstrates the positive relationship between resistance training and executive function.

Liu-Ambrose and colleagues (2010) found no improvements in memory as measured by the Digit Span Test, but did find improvements in executive function, following a progressive resistance training intervention in older adults.[38] Moreover, a systematic review by Loprinzi et al. (2018) found that only three of eight studies provided some evidence of a positive effect of resistance training on memory (episodic memory).[56] Evidently, more RCTs assessing the effects of resistance training on memory are needed.

An unexpected finding in the current trial was that balance and tone participants showed some improvements in cognitive function. This differs from a previous resistance training study in older adults that used a similar balance and tone protocol but found much smaller or no improvements in cognitive function (e.g., on the Stroop and Digit Span tests) for control participants.[38] Given that our study only measured quadricep muscle strength and included no other measure of muscle function in the balance and tone group, it is possible that this group improved in muscle strength in an undetected way. Studies have shown that balance and stretching exercises can in fact improve muscle strength[57,58] that may be positively related to cognition.[59] As such, future trials may benefit from including additional tests of muscle function, perhaps lean body mass measures for example, as well as further exploring the potential physical and cognitive benefits that balance and tone exercise may have in older adults at risk for diabetes. Other possible explanations for this unexpected finding, including differences in socialization between the two groups, are discussed in Chapter 5. In addition, some unexpected findings were seen in our correlational data. For example, it appears that increased muscle strength may actually be associated with reduced scores on selective cognitive tests, and increased BMI and FPG may be associated with better performance on some tests. Since we did not assess statistical significance of measured correlations, nor did we control for certain variables, future trials with a larger sample size are needed to better examine the potential relationships between physical and cognitive outcomes in response to resistance training.

While resistance training did lead to some improvements in cognition, it did not result in improvements in most physical measures including BMI or FPG. In line with this, some

studies have found that resistance training does not improve weight or glycemic control like aerobic exercise does.[60,61] However, a review and meta-analysis showed that resistance training can lead to improvements in HbA1c levels, but high-intensity training leads to much greater improvements than low-intensity training;[62] this may be the result of greater glucose uptake in skeletal muscle during high-intensity exercises.[63] This is important as the majority of insulin-stimulated glucose uptake occurs in skeletal muscle.[64] Based on this, it is possible that the resistance training group in our study did not exercise at a high enough intensity to allow for increased glucose uptake. Although our trial participants did exercise at 80% of their predicted 1RM, it has been shown that predicted 1RM may underestimate true 1RM values in older adults,[65] and thus participants may have been exercising at a lower intensity than intended. Interestingly, though, participants in the resistance training group did improve in aerobic function (walking ability) as measured by the six minute walk test. Future trials with additional tests of aerobic function may help shed light on the relationship between resistance training and aerobic function, and should examine the possible differences between resistance training and aerobic training (as well as resistance training combined with aerobic training) on physical and cognitive function in older adults at risk for diabetes.

When interpreting results, it is important to consider the potential clinical significance of cognitive changes that occur in response to exercise. For example, changes seen in ADAS-Cog 12 for both groups are considered non-clinically significant given that they were below the literature-informed minimal clinically important difference (MCID) of three.[46] Minimal clinically important difference is defined as the smallest difference in a disease score that a patient would benefit from and would lead to a change in the patient's management plan.[66] To our knowledge, MCIDs have yet to be established for many commonly used neuropsychological tests such as the Stroop Test and TMT. Thus, large-scale prospective population-based studies are needed to determine the usefulness of such tools in a clinical context. Until this is achieved, one previously proposed way to measure meaningful change from RCTs is the use of the Quality Adjusted Life Year (QALY), an internationally-recognized tool which assesses both quality and quantity of life.[66] Future trials may benefit

from incorporating this tool or similar measures of disease burden to determine how cognitive changes as a result of resistance training may benefit health long-term.

Importantly, there are several limitations to the current study that need be to addressed. Firstly, given that this was an underpowered pilot study, it is important that results are interpreted with caution. Furthermore, as we did not run inferential statistics, we cannot conclude that trends (both between-group and across timepoints) are significant, nor were we able to control for any variables that may affect results such as differences in baseline characteristics between groups. Based on our findings, it may have been beneficial to control for PASE performance in analyses had that been possible, as the resistance training group had increased PASE scores over time compared to the balance and tone group. This suggests that those in the resistance training group could have benefitted from additional leisure, occupational, or household physical activity outside of the exercise program, which may have affected results. While we did collect information on leisure physical activity and sleep, it may also be advantageous to collect information on diet and other lifestyle behaviours that could affect results.

Additionally, there were a number of errors in assessment delivery which resulted in missing data. At times, assessors forgot to administer parts of the psychological questionnaires (e.g., the 20 minute delay recall test for the RAVLT) or mis-timed the completion of tasks such as the TMT. Further supervision and check-ins may help to avoid this issue in the future and is discussed further in Chapter 5. Other recommendations for future research include examining how resistance training may affect individuals with hyperglycemia who have normal BMI compared to those who are overweight but have normoglycemia. As our sample size was small, and we were only able to recruit a very limited number of people with prediabetes (who were all overweight or obese), we were unable to effectively test this. However, we speculate that both groups would experience improvements in cognition following resistance training, as individuals with hyperglycemia or obesity are known to experience cognitive deficits and have been shown to benefit from other exercise types.[13,67] Similarly, future studies should assess potential differences between those who are overweight versus obese,

since these groups are known to have some differing cognitive abilities.[12] It would also be interesting to examine potential sex differences, as women, in general, have been shown to benefit more cognitively from exercise compared to men (which may be a result of differences in hormones, body composition, etc.).[68]

Future studies should also assess the underlying neuropsychological mechanisms that may explain the benefits of resistance training on cognition. For example, at the molecular and cellular level, resistance training leads to the release of neurochemicals (including IGF-1) that stimulate the growth of new neurons and blood vessels, as well as the strengthening of neuronal connections.[69] Resistance training has also been shown to lead to increased cytokines such as interleukin-6, which reduces beta-amyloid levels in the brain that disrupts brain cell function, and increased lactate levels that can lead to improved brain metabolism.[70,71] Understanding these mechanisms may also help link changes in cognition to structural and functional brain changes as a result of resistance training. Finally, an interesting future component to our trial would be to examine whether changes in cognition that may result from our intervention last beyond the trial, as previous studies have shown that positive effects on cognition from resistance training may persist at least one year after study completion.[52]

In conclusion, our pilot study demonstrates the preliminary efficacy of a 26-week resistance training program improving cognition in older adults at risk for diabetes. Resistance training led to some improvements in cognitive function, mainly in attention and executive functions that are important to everyday function in older adults. Based on our findings, there may also be some benefits from balance and tone exercises in this population. In the future, large-scale powered trials are needed to further explore our preliminary findings.

Summary

This chapter assessed cognitive changes following 26 weeks of thrice-weekly progressive resistance training in older adults at risk for diabetes. Compared to balance and tone exercise, resistance training led to a larger increase in 1RM quadricep strength, which provides evidence toward the effectiveness of the resistance training program in increasing muscle mass as intended. For both groups, very small changes were seen in FPG and BMI across the trial. When assessing cognition, those in the resistance training group improved in task-switching, selective attention, and conflict resolution, whereas those in the balance and tone group improved on two memory tasks. Based on these findings, it appears that resistance training may improve select cognitive functions over others, and that there may be unexpected benefits of balance and tone exercise. It is possible that the unexpected improvements in the latter group may be a result of other factors (such as socialization) outside the physical exercise itself. Considerations of ways to improve the study protocol and reduce possible confounding variables that may account for these findings are discussed in Chapter 5.

Having examined cognitive changes, we can gain a deeper understanding of the possible effects of the resistance training intervention by investigating underlying changes to neurological mechanisms in our target population. Moreover, exploring changes to brain volume and functional activation patterns may provide insight into whether changes at the structural and functional levels may be related to behavioural changes. In this regard, Chapter 4 examines structural and functional brain changes using MRI following the 26-week resistance training intervention in older adults at risk for diabetes.

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Chapter 4

4 Scientific outcomes: Structural and functional brain changes following 26 weeks of resistance exercise in older adults at risk for diabetes

This chapter will explore the structural and functional brain changes in older adults at risk for diabetes using MRI following a 26-week randomized controlled trial of resistance exercise. A manuscript for the reported findings is currently in preparation.

Some content in Chapter 4 is from the following published protocol manuscript:

Furlano JA, Nagamatsu LS. Feasibility of a 6-month pilot randomised controlled trial of resistance training on cognition and brain health in Canadian older adults at-risk for diabetes: study protocol. *BMJ Open.* 2019;9(10),e032047. doi: 10.1136/bmjopen-2019-032047

4.1 Introduction

Diabetes is associated with several anatomical and functional brain abnormalities. Cross-sectional MRI work has demonstrated that individuals with T2D exhibit smaller brain volumes, including TBV and regional volumes (e.g., HV), compared to healthy controls.[1] Research assessing functional brain patterns have also shown that diabetics experience reduced levels of brain activation associated with impaired cognitive function. One study by Chen and colleagues (2014) found that those with T2D had reduced activation in the superior and middle frontal gyri during a working memory task compared to healthy controls, and this was correlated with worse memory performance.[2] Taken together, this evidence suggests that diabetics experience deficits in brain health and, consequently, are at an increased risk for dementia.

Two major risk factors for T2D are prediabetes (the precursor stage of T2D) and obesity. Statistically, up to 70% of individuals with prediabetes will develop T2D,[3] and it has been reported that roughly 30% of people who are overweight also have T2D.[4] Compared to early

life, these comorbidities occur more frequently in old age when the brain undergoes neurodegenerative changes due to aging.[5] Furthermore, given the evidence that diabetics experience various structural and functional brain deficits, prediabetics and overweight/obese individuals, especially in late life, are at high risk for brain dysfunction. However, whether these individuals already experience deficits in brain health remains under investigation.

Based on findings from the systematic review presented in Chapter 2, it appears that prediabetic adults and older adults may experience some deficits in brain structure. Marseglia and colleagues (2019) showed that prediabetes is associated with smaller TBV, particularly WMV.[6] Similarly, Cui et al. (2019) found that prediabetics have reduced GMV in the left hippocampus compared to healthy controls.[7] Continuous hyperglycemia (measured via FPG) has also been shown to be associated with lower WMV and GMV.[8] In this study, structural brain abnormalities observed in prediabetics were comparable to 2.1 years of brain aging, suggesting that prediabetes accelerates brain health declines seen in natural aging.[8] Despite this evidence, findings are inconsistent across studies, and may be the result of varying diagnostic measures and other methodological flaws as highlighted in Chapter 2.

Similar to prediabetes, obesity has also been shown to accelerate brain decline associated with aging. Compared to normal weight people, the brains of overweight individuals (BMI 25-29) appear 8 years older, while the brains of obese individuals (BMI 30+) appear 16 years older.[9] More specifically, studies have shown that higher BMI is associated with lower brain volumes, including HV, in overweight and obese older adults.[10,11] One study in individuals with both T2D and high BMI found a reduction in WMV compared to healthy controls.[12] In fMRI work, regions implicated in memory, including the hippocampus and dorsolateral prefrontal cortex, have reduced activation in obese participants compared to healthy weight participants.[13]

There are several potential mechanisms that may explain the association between prediabetes and obesity with brain health dysfunction. In prediabetes, hyperglycemia may cause the production of glycotoxins and promote oxidative stress,[14] which can in turn lead to neuronal

cell toxicity and death.[15] Further, hyperglycemia is associated with cerebral endothelial dysfunction,[16] and ultimately cerebral perfusion and brain tissue ischemia.[17] In obesity, high BMI is linked to systemic inflammation, inefficient leptin signaling, and decreased cerebral blood flow, all of which have been associated with brain dysfunction.[18,19] Reduced cerebral blood flow, in particular, is one of the top predictors of developing Alzheimer's,[20] and studies have shown that areas of the brain vulnerable to Alzheimer's disease, including the hippocampus, have reduced blood flow as BMI increases.[21]

Evidently, there is a need for targeted interventions to improve brain health in individuals with prediabetes and obesity. Moreover, these disorders provide a window of opportunity for the prevention of further brain dysfunction seen in T2D. Exercise is one behavioural strategy that is known to improve brain structure and function. Higher fitness levels are associated with larger brain volumes, [22] and this may be the result of released neurotrophic factors such as BDNF and IGF-1 that stimulate neurogenesis and preserve neuronal health.[23] While most exercise interventions to improve brain health focus on aerobic exercise, resistance training has more recently been shown to have its own neurocognitive benefits, and is often more widely accessible for older adults, as previously discussed. A recent systematic review showed that resistance exercise interventions, ranging in weeks to several months in duration, led to substantial functional brain changes accompanied by improvements in cognition, as well as a reduction in brain atrophy, specifically white matter.[24] Furthermore, these improvements appear to hold true across several populations, including healthy and cognitively impaired adults.[24]

To date, research has not yet examined whether resistance training may improve brain structure and function in older adults at risk for T2D. To accomplish this, we first conducted a pilot RCT to evaluate preliminary efficacy. Cognitive changes measured in this study via neuropsychological tests were previously discussed in Chapter 3, thus this Chapter will focus on MRI outcomes. Importantly, brain atrophy and other changes in brain health may be detectable via MRI even before cognitive impairment is evident,[25] and thus measuring brain changes may help us further understand the potential benefits of resistance training. Based on

what is known in the literature, we hypothesized that 26 weeks of resistance training in older adults at risk for diabetes would lead to increased brain volumes, including TBV and HV, as well as increased functional activation in memory-related areas during an associative memory task.

As highlighted in Chapter 1, associative memory (the ability to memorize unrelated items in conjunction) is one cognitive function that declines with age and neurodegenerative disease. Areas of the brain implicated in learning associations include the occipital association cortex, lingual and fusiform gyri, inferior temporal gyrus, inferior pre- and postcentral gyri, orbitofrontal cortex, and precuneus.[26] Additionally, hippocampal function has been shown to be correlated with associative memory performance, as demonstrated in animal research assessing neuronal firing patterns.[27] Studies on the effects of resistance training on associative memory have shown a positive causal relationship in older adults. For example, one study found that six months of twice-weekly resistance training, compared to balance and tone exercise, improves associative memory in older adults with MCI.[28] In this study, resistance training also led to increased activation in brain regions involved in memorizing associations including the right lingual and occipital-fusiform gyri and the right frontal pole.[28] Therefore, in addition to increased functional activation in memory-related areas, we hypothesized that 26 weeks of resistance training would lead to improved associative memory performance in our study population.

4.2 Methods

4.2.1 Study design

We conducted a single-blinded pilot RCT to examine the preliminary effects of a 26-week, thrice-weekly resistance exercise program on brain structure and function in older adults at risk for T2D. Magnetic resonance imaging was completed at baseline and trial completion (26 weeks) and was 1.5 hours long per session. Further details of our study design have been reported in Chapter 3.

4.2.2 Participants

Older adults (aged 60-80) who were overweight or obese (BMI ≥ 25) and/or prediabetic (FPG 6.1 to 6.9 mmol/l) were recruited from the community in London, Ontario, Canada. Details of recruitment and inclusion/exclusion criteria can be found in Chapter 3.

4.2.3 Exercise intervention

Participants were randomized into either the resistance training or balance and tone (control) group. Exercise classes were one hour in length and were instructor-led. Classes were made up of 2-4 participants and were held three times per week on non-consecutive days for 26 weeks. Participants in the resistance training group underwent progressive resistance training (i.e., loading was increased over time based on predicted 1RM), while participants in the balance and tone group completed balance and stretching exercises. Study methods have been described in detail in Chapter 3.

4.2.4 Outcome measures

4.2.4.1 Structural MRI outcomes

T1-weighted images (TR=2300, TE=2.98, voxel size=1x1x1 mm) were used to measure whole brain and regional volumes. Percent brain volume change (PBVC) was calculated using SIENA (Structural Image Evaluation, using Normalization, of Atrophy) in the FMRIB (Functional Magnetic Resonance Imaging of the Brain) Software Library (FSL; Version 5.0.10), specifically within FAST (FMRIB's Automated Segmentation Tool).[29] SIENA is an automated method for measuring brain change across multiple time points, and has been shown to have an error rate of 0.2%.[30] SIENA starts by extracting non-brain tissue from both time-point whole-head input images, and registers the two brains using the skull images to keep the scaling constant.[29] It then estimates brain change between the two time points based on mean edge displacement.[29] Although fully automated, visual checks of output were performed to minimize error during brain extraction, spatial alignment, and tissue segmentation. SIENA was run for all participants, and PBVC by group was reported.

SIENAX (an adaptation of SIENA to measure brain volume at a single time point) was used to estimate GMV and WMV at both time points (as SIENA does not provide tissue type calculations).[29] Like SIENA, SIENAX first performs non-brain tissue extraction and estimates the outer skull surface.[29] The brain image is then registered to MNI152 (MNI = Montreal Neurological Institute) standard space using the skull image to determine the registration scaling, allowing for normalization of subject skull size.[29] Next, tissue-type segmentation is carried out in order to calculate volume estimation of grey and white matter separately.[29] Volumes for each participant at both baseline and trial completion were recorded, and average volume change overtime by group was calculated.

Left and right HVs were calculated via FIRST (FMRIB's Integrated Registration and Segmentation Tool), which is FSL's tool for automatic segmentation of subcortical structures.[31] It uses default settings for each structure which have been empirically determined.[31] FIRST was run for all participants at both time points, and left and right values were added together to produce total HVs. Average change in total HV by group across the trial was then reported.

4.2.4.2 Behavioural MRI outcomes

Performance on an associative memory task during fMRI was measured, where both associative and item memory were assessed. The memory task was a mixed block/event-related design that had been used in a previous study of resistance exercise in older adults.[32] The task required participants to view a series of photos of faces superimposed onto sceneries, in which participants encoded and recalled items separately (face or scenery; measure of item memory) and items in conjunction (face paired with scenery; measure of associative memory) (**Figure 4.1**). The task featured six conditions: face encoding, face recognition, scenery encoding, scenery recognition, face–scenery encoding, and face–scenery recognition (**Figure 4.1**). Participants completed three blocks (runs), each comprised of the six conditions with the order of conditions counterbalanced in pairs (encoding plus recognition; e.g., scenery coding with scenery recognition). Each condition featured 12

separate photos; each of the 12 photos appeared for three seconds, separated by a fixation cross appearing for six seconds.

While performing the task inside the MRI scanner, participants used a two-button response pad. During the encoding conditions, participants were asked to indicate one of the following: (1) if the face shown was male or female (to help direct participants to memorizing faces only; in this case, the scenery remained constant across photos), (2) if the scenery contained liquid water (to help direct participants to memorizing scenery only; in this case, the face remained constant across photos), or (3) if the face 'fit well' with the scenery (to direct participants to memorizing the face with the scenery; there was no correct answer to this question). Following each encoding condition, participants, in the recognition condition, were asked to indicate whether they had previously seen each of the images during the encoding sequence. Each recognition block contained six photos from the encoding condition and six distractor photos. At the beginning of each condition (encoding or recognition), instructions appeared on screen for 10 seconds to inform participants of what their specific task was (e.g., to decide if the face is male or female (encoding), to indicate whether they had seen the image previously (recognition)). Participants completed several practice trials of each condition prior to completing the task in the scanner.

Task performance was determined using Signal Detection Theory, a method of measuring the ability to differentiate between information under conditions of uncertainty.[33] According to this theory, there are four possible outcomes for the recognition conditions in the memory task (**Figure 4.2**): (1) 'hit' – when a participant says they saw the image previously and they actually had (correct); (2) 'miss' – when a participant says they did not see the image previously but they had (incorrect); (3) 'false alarm' – when a participant says they saw the image previously but they had not (incorrect); and (4) 'correct rejection' – when a participant says they did not see the image previously and they had not (correct).[33] Using hit and false alarm data, d prime was calculated, which is a measure of signal detection that accounts for response bias (i.e., participants are more likely to report that they did see an image versus

reporting that they did not see an image).[33] D prime is calculated using the following formula:

$$\text{d prime} = z(H) - z(F)$$

where ‘H’ represents hits and ‘F’ represents false alarms.[33] D prime values typically range from 0 to 4.65, with larger values indicating better memory performance (i.e., more accurate responses).[34] D prime was calculated for both associative and item memory performance at baseline and trial completion, and change in d prime over time by group was then reported.

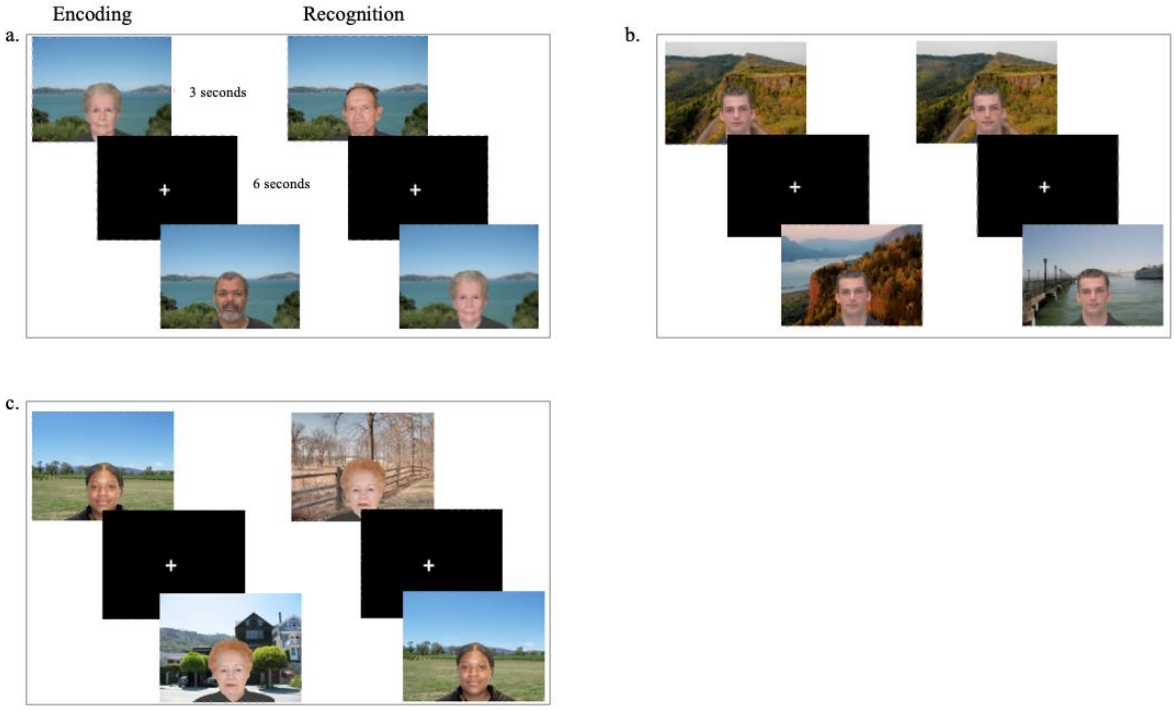

Figure 4.1: Associative memory task.
a) Item memory (face) condition; b) Item memory (scenery) condition; c) Associative memory (face-scenery) condition.

	Participant responds ‘yes’	Participant responds ‘no’
Saw image	**Hit**	**Miss**
Did not see image	**False Alarm**	**Correct Rejection**

Figure 4.2: Possible outcomes for the recognition conditions of the associative memory task.

4.2.4.3 Functional MRI outcomes

Functional MRI was used to assess changes in activation over time. Participants completed the associative memory task (previously described) during BOLD imaging (TR=1000, TE=30, slice thickness=2.5 mm). Using the correct response data (hits and correct rejections) from the task, first-level fMRI analysis was performed in FSL's FEAT (FMRIB's Expert Analysis Tool) to create signal contrasts during a single task run.[35] The data modelling which FEAT uses is based on general linear modelling (GLM).[35] With this, a model is created to fit the data, identifying where brain activation has occurred in response to a stimuli.[35] The six signal contrasts of interest were as follows: item (face or scenery) encoding, item recognition, associative (face-scenery) encoding, associative recognition, associative > item encoding, associative > item recognition. Pre-statistics processing included motion correction using MCFLIRT (Motion Correction using FMRIB's Linear Image Registration Tool),[36] brain extraction using BET (Brain Extraction Tool),[37] spatial smoothing using a Gaussian kernel FWHM (full-width at half-maximum) of 5 mm, and registration and normalization using a 2 mm MNI152 standard space image. Results were analyzed at a cluster threshold of $Z > 1.65$, $p = 0.05$. Two researchers independently reviewed the output data to determine final suitability for inclusion in analyses; a motion cut-off of 3 mm was used (i.e., participants with motion values above this were automatically excluded from analyses).

Higher-level analyses using fixed effects were then run to (1) create an average contrast over the three runs for each participant at both time points, and (2) create a contrast across the time points for each participant (trial completion > baseline).[35] Following this, a multi-subject higher-level analysis using mixed effects was done to create group contrasts.[38] All higher-level results were also analyzed at a cluster threshold of $Z > 1.65$, $p = 0.05$. The multi-subject analysis produced clusters that showed significant change in activation for each of the six signal contrasts (item encoding, item recognition, associative encoding, associative recognition, associative > item encoding, associative > item recognition). Regions of interest (ROIs) were then created based on identified clusters, and percent signal change (PSC) was

calculated via FSL's Featquery for each participant.[35] From this, average PSC over time by group was calculated and compared.

4.2.5 Data analysis

Behavioural outcomes are presented as means and SEs at baseline, midpoint, and trial completion, and change over time is presented as percent change (average) and 95% CIs by group. Structural and functional analysis was done in FSL, and these outcomes are also presented as means and SEs at baseline and trial completion. Change overtime for sMRI outcomes is presented as percent change and 95% CIs, while fMRI outcomes are presented as change in PSC and 95% CIs. Quality assessment of data was performed and discussed by two researchers. Potential outliers were included in analyses, as in Chapter 3, however some fMRI data was excluded due to excess motion (described in section 4.3.4 of this Chapter). Bivariate Spearman correlation coefficients were also used to examine the possible magnitude and direction of associations between change (across the trial) in brain and physical outcomes, as well as brain and cognitive outcomes from Chapter 3.

4.3 Results

4.3.1 Descriptive measures

Baseline characteristics of participants are described in **Table 3.2** of Chapter 3. Briefly, A total of 24 participants were randomized into our trial (13 into the resistance training group and 11 in the balance and tone group). Participants were 68.7 ± 5.7 years old on average and were 50% female. All participants were overweight or obese based on BMI, and four were also prediabetic based on FPG.

Twenty-three participants completed both baseline and trial completion MRI scans, while one participant (from the balance and tone group) only completed the baseline MRI due to dropping out of the study after 10 weeks. This individual's baseline behavioural and sMRI data was used in analyses (except in PBVC calculations which requires input from two timepoints), however their baseline fMRI data was excluded from analyses.

4.3.2 Structural MRI outcomes

Structural MRI outcomes are presented in **Table 4.1** and **Figure 4.3**, where percent change across the trial is reported. Results show that the resistance training group had less of a decline in TBV (presented as PBVC; -0.13%) compared to the balance and tone control group (-0.37%). Similarly, less hippocampal atrophy was found in the resistance training group (-1.24%) compared to the control group (-1.74%). However, the control group increased in GMV and WMV (0.29% and 0.15%, respectively) compared to the resistance training group who had a 1.18% decrease in GMV and a 0.91% decrease in WMV.

Table 4.1: Structural outcomes by group.

Variable	Baseline	Trial completion	Δ Baseline to trial completion
	[a]Mean (SE)	[a]Mean (SE)	Percent change (95% CI)
RT			
PBVC	N/A	N/A	-0.13 (-0.58, 0.32)
GMV	754939.81 (10206.60)	746013.50 (11272.60)	-1.18 (-2.80, 0.44)
WMV	626335.00 (10483.75)	620351.896 (10442.01)	-0.91 (-2.95, 1.13)
HV	7170.31 (215.56)	7082.39 (225.45)	-1.24 (-3.41, 0.93)
BAT			
PBVC	N/A	N/A	-0.37 (-0.83, 0.08)
GMV	757173.07 (18523.49)	759611.69 (19958.85)	0.29 (-0.92, 1.50)
WMV	653713.39 (17636.66)	653591.58 (14274.20)	0.15 (-2.45, 2.75)
HV	6968.00 (194.61)	6889.00 (216.81)	-1.74 (-4.73, 1.25)

[a]Note: Volumes are in mm^3.
PBVC = precent brain volume change (total brain volume); GMV = grey matter volume; WMV = white matter volume; HV = hippocampal volume; RT = resistance training; BAT = balance and tone group; SE = standard error; CI = confidence interval.

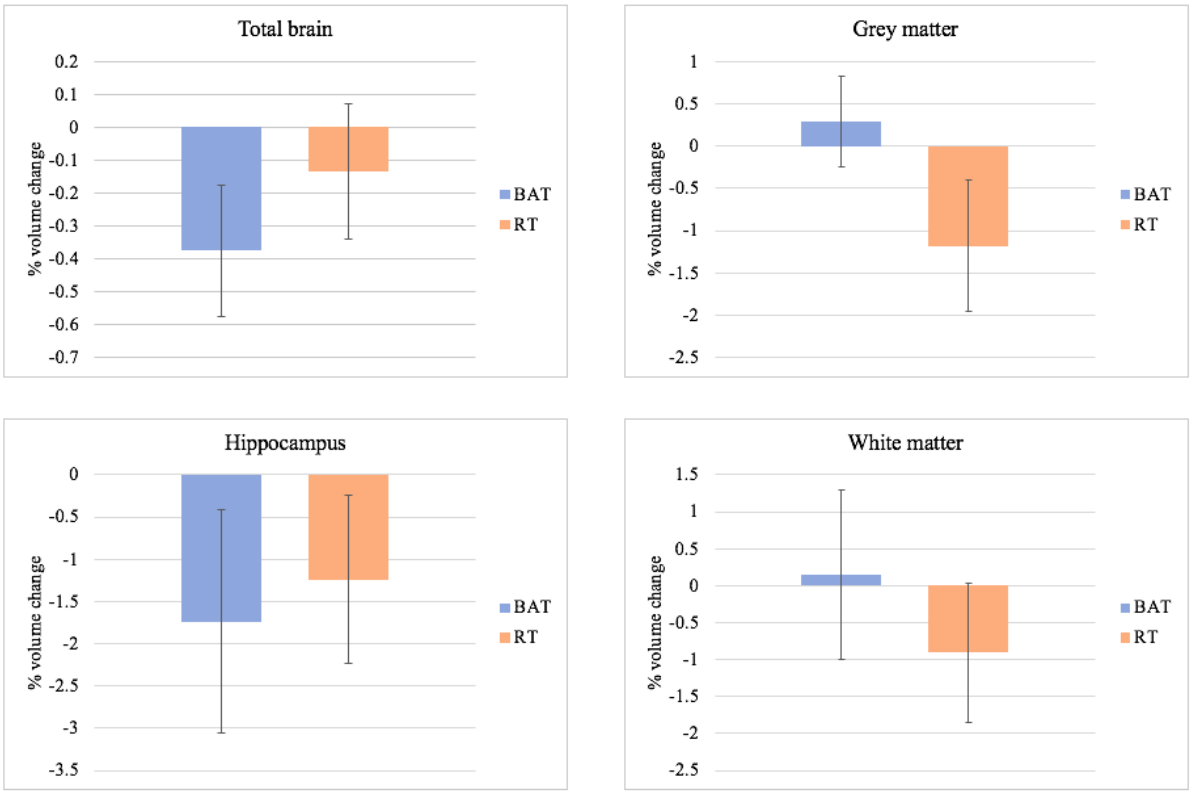

Figure 4.3: Percent volume change for brain measures (trial completion > baseline).

Note: the bars represent standard errors.
RT = resistance training group; BAT = balance and tone group.

4.3.3 Behavioural MRI outcomes

At baseline, nine participants were missing partial associative memory task data (i.e., partial conditions from 1-2 task runs). Data from three participants was missing due to task or fMRI issues, five due to participant withdrawal (i.e., participants requested to only complete 2/3 task runs due to discomfort in the scanner), and one due to the participant being late to the scan and therefore unable to complete all three runs in the allotted scanning time. At trial completion, seven participants had partial behavioural data missing, in which data from four participants was missing due to task/fMRI issues, and three due to participant withdrawal.

When assessing d prime results, participants in the resistance training group improved slightly in item memory (i.e., increased d prime) across the trial when compared to the balance and tone group (**Table 4.2**, **Figure 4.4**). In addition, both groups had small, comparable decreases in associative memory over time (**Table 4.2**, **Figure 4.4**).

Table 4.2: Behavioural outcomes by group.

Variable	Baseline	Trial completion	Δ Baseline to trial completion
	Mean (SE)	Mean (SE)	Percent change (95% CI)
RT			
d prime (associative)	2.0 (0.2)	1.8 (0.2)	-0.2 (-1.0, 0.5)
d prime (item)	1.5 (0.2)	1.7 (0.3)	0.2 (-0.2, 0.7)
BAT			
d prime (associative)	2.5 (0.8)	2.3 (0.5)	-0.3 (-2.0, 1.3)
d prime (item)	1.0 (0.1)	1.0 (0.1)	-0.1 (-0.4, 0.2)

RT = resistance training; BAT = balance and tone group; SE = standard error; CI = confidence interval.

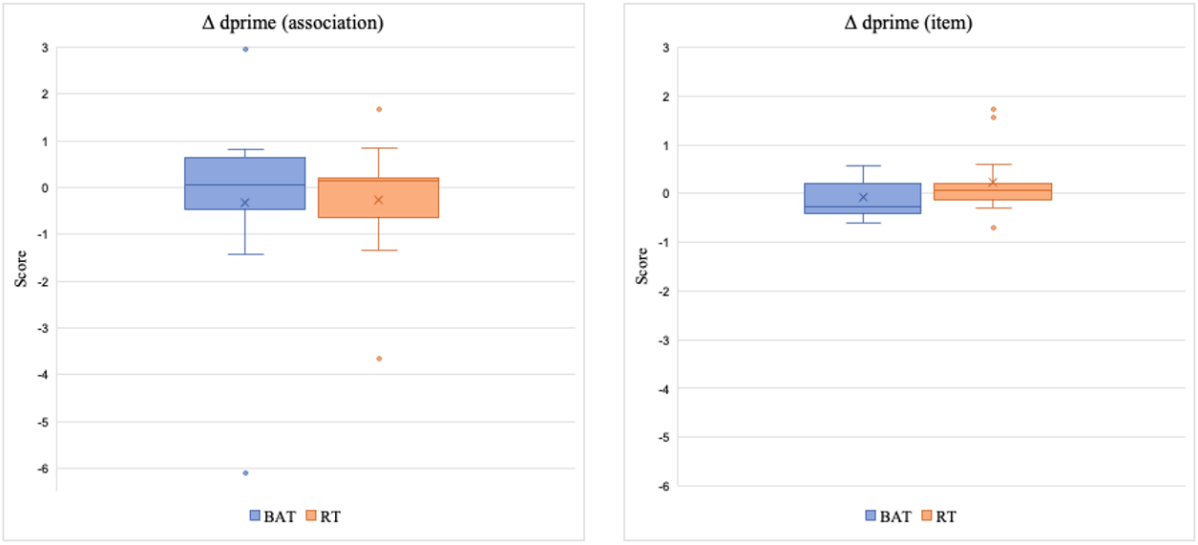

Figure 4.4: Mean change in scores on the associative memory task (trial completion > baseline).

Note: the box represents the interquartile range, where the bottom line of the box represents quartile 1 (25th percentile) and the top line represents quartile 3 (75th percentile); the whiskers represent the minimum and maximum values excluding outliers; 'X' represents the mean; and the middle line of the box represents the median.

RT = resistance training group; BAT = balance and tone group.

4.3.4 Functional MRI outcomes

In addition to missing associative memory data described in section 4.3.3 of this Chapter, additional task data was excluded for fMRI analyses. One participant was excluded from both baseline and trial completion analyses due to excess head motion (i.e., > 3mm). At baseline, two participants also had 1/3 memory task runs excluded, while an additional participant had 2/3 runs excluded, all due to excess motion. At trial completion, one participant had 2/3 runs excluded also due to motion. Altogether, we analyzed fMRI data from 22 participants at baseline (19 with full data, three with partial data) and 22 at endpoint (21 with full data, one with partial data). Since this is a pilot study, we included participants who had at least one run of the task deemed usable in analyses at either time points.

We identified brain areas showing significant changes in hemodynamic activity between groups at trial completion relative to baseline. The identified ROIs are presented in **Table 4.3**, **Table 4.4**, and **Table 4.5**. Across the trial, the resistance training group had a 0.11% increase in activation in the postcentral gyrus during associative > item encoding compared to the balance and tone group (**Table 4.6, Figure 4.5**). In addition, those in the resistance training group had a 0.13% increase in activation in the precentral gyrus and a 0.11% increase in the middle temporal gyrus (posterior) during associative > item recognition compared to the balance and tone group (**Table 4.6, Figure 4.5**). Comparatively, those in the balance and tone group had an increase in activation overtime in the anterior supramarginal gyrus (by 0.18%) and juxtapositional lobule cortex (by 0.12%) during associative > item encoding compared to the resistance training group (**Table 4.6, Figure 4.5**). No other areas were identified as having significant between-group differences in activation for any of the remaining four contrasts (item encoding, item recognition, associative encoding, associative recognition) at trial completion relative to baseline.

Table 4.3: Clusters identified as being significantly more active for associative > item encoding in the resistance training group at trial completion compared with baseline.

Hemisphere	Region	Cluster size[a]	Max Z[b]	MNI coordinates[c]		
				X	Y	Z
Left	Postcentral gyrus	1539	3.17	-34	-38	40
Left	Postcentral gyrus		2.95	-38	-38	48
Left	Postcentral gyrus		2.76	-32	-26	68
Left	Supramarginal gyrus (anterior)		2.68	-52	-34	38
Left	Postcentral gyrus		2.67	-44	-20	56
Left	Superior parietal lobule		2.64	-28	-44	48

[a] Cluster size = size of maximum cluster in voxels.

[b] Max Z = maximum Z statistic for the cluster.

[c] MNI coordinates = location of the cluster maxima in Montreal Neurological Institute standard space.

Table 4.4: Clusters identified as being significantly more active for associative > item recognition in the resistance training group at trial completion compared with baseline.

Hemisphere	Region	Cluster size[a]	Max Z[b]	MNI coordinates[c]		
				X	Y	Z
Left	Precentral gyrus	6593	3.02	-38	-4	46
Left	Precuneus cortex		2.99	-4	-56	34
Left	Middle temporal gyrus (posterior)		2.88	-72	-28	-10
Left	Postcentral gyrus		2.84	-42	-12	28
Left	Superior temporal gyrus (posterior)		2.81	-58	-34	4
Left	Inferior temporal gyrus (posterior)		2.79	-46	-36	-22
Right	Middle temporal gyrus (posterior)	5853	3.14	46	-36	0
Right	Supramarginal gyrus (posterior)		3.13	56	-40	6
Right	Thalamus		2.86	18	-24	14
Right	Middle temporal gyrus (posterior)		2.84	50	-24	-10
Right	Precentral gyrus		2.83	30	-22	48
Right	Central opercular cortex		2.83	42	10	2

[a] Cluster size = size of maximum cluster in voxels.

[b] Max Z = maximum Z statistic for the cluster.

[c] MNI coordinates = location of the cluster maxima in Montreal Neurological Institute standard space.

Table 4.5: Clusters identified as being significantly more active for associative > item encoding in the balance and tone group at trial completion compared with baseline.

Hemisphere	Region	Cluster size[a]	Max Z[b]	MNI coordinates[c]		
				X	Y	Z
Left	Supramarginal gyrus (anterior)	3413	3.13	-62	-30	42
Left	Supramarginal gyrus (anterior)		3.08	-56	-30	42
Left	Precentral gyrus		3.06	-50	2	46
Left	Supramarginal gyrus (anterior)		2.99	-64	-28	38
Left	Inferior frontal gyrus (pars opercularis)		2.81	-52	12	16
Left	Middle frontal gyrus		2.79	-40	8	48
Left	Juxtapositional lobule cortex	1206	3.1	-4	0	60
Left	Juxtapositional lobule cortex		3.04	-6	4	58
Left	Superior frontal gyrus		2.84	-2	18	60
Left	Paracingular gyrus		2.83	-4	24	40
Left	Superior frontal gyrus		2.56	-2	32	48
Left	Superior frontal gyrus		2.49	-8	14	56

[a] Cluster size = size of maximum cluster in voxels.

[b] Max Z = maximum Z statistic for the cluster.

[c] MNI coordinates = location of the cluster maxima in Montreal Neurological Institute standard space.

Table 4.6: Percent signal change in brain regions identified as having significant activation.

Variable	Baseline	Trial completion	Δ Baseline to trial completion
	Mean (SE)	Mean (SE)	Change in PSC (95% CI)
RT			
[a]PoCG	-0.08 (0.02)	0.03 (0.03)	0.11 (0.04, 0.18)
[b]PreCG	-0.08 (0.03)	0.05 (0.03)	0.13 (0.04, 0.22)
[b]MTGp	-0.06 (0.02)	0.04 (0.02)	0.11 (0.03, 0.19)
BAT			
[a]SMGa	-0.27 (0.07)	-0.08 (0.04)	0.18 (0.00, 0.36)
[a]JPC	-0.06 (0.05)	0.06 (0.02)	0.12 (0.01)

[a]Encoding conditions

[b]Recognition conditions

PoCG = postcentral gyrus; PreCG = precentral gyrus; MTGp = middle temporal gyrus (posterior); SMGa = supramarginal gyrus (anterior); JPC = juxtapositional lobule cortex; PSC = percent signal change; RT = resistance training; BAT = balance and tone group; SE = standard error; CI = confidence interval.

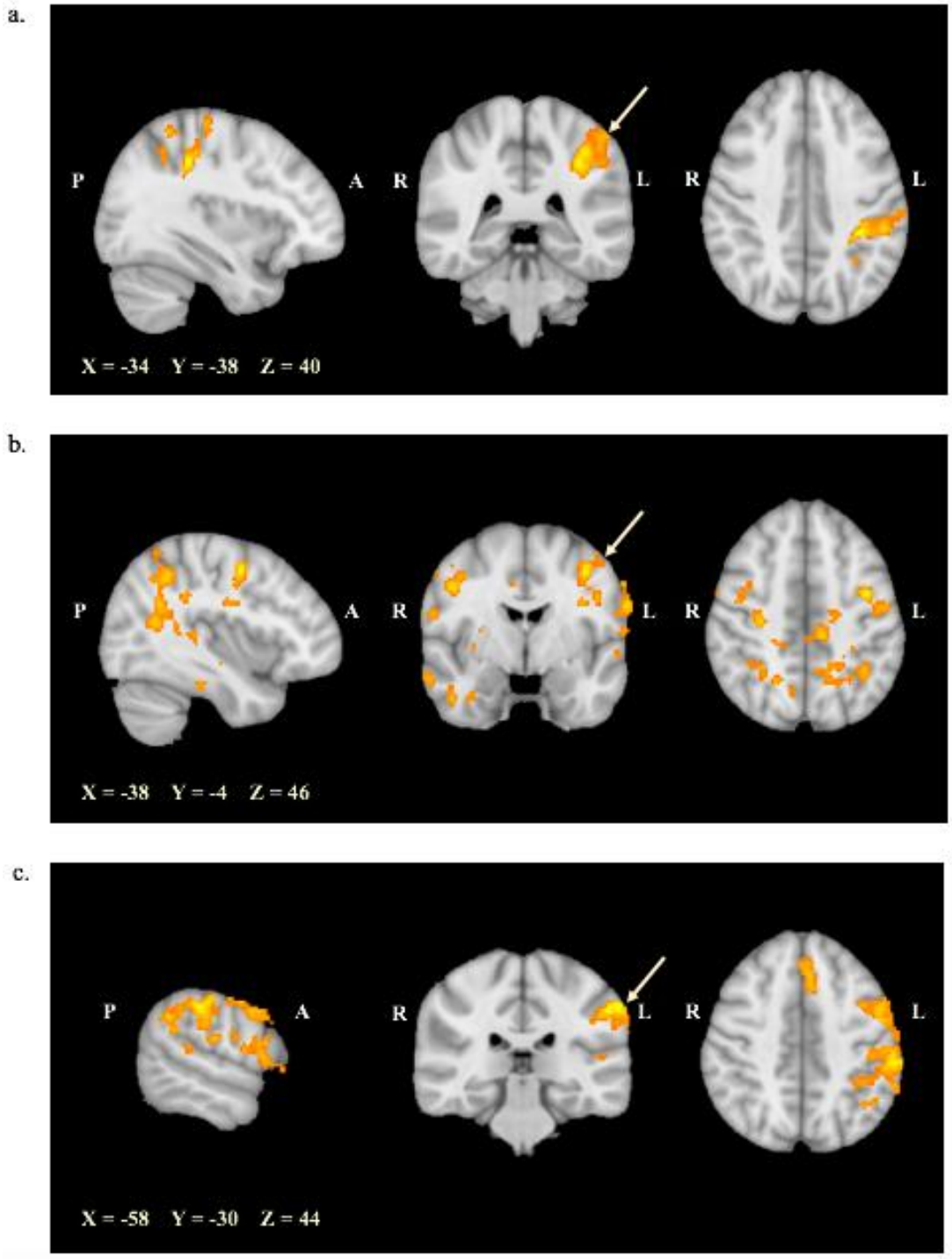

Figure 4.5: Significant changes in activation during the associative memory task (trial completion > baseline).

a. Resistance training group, associative > item encoding; main activation is found in the left postcentral gyrus (arrow).
b. Resistance training group, associative > item recognition; main activation is found in the left precentral gyrus. (arrow).
c. Balance and tone group, associative > item encoding; main activation is found in the left anterior supramarginal gyrus (arrow).

4.3.5 Correlations

Table 4.7 shows correlations between change in brain and physical/cognitive measures (Chapter 3) at trial completion relative to baseline. For brain and physical outcomes, most associations were weak, however, there were some surprising correlations including (1) a moderate negative association between PBVC and 1RM (i.e., increased brain volume was related to decreased 1RM), (2) a weak-to-moderate positive association between PBVC and FPG (i.e., increased brain volume was related to increased FPG levels), and (3) a weak-to-moderate positive association between WMV and BMI (i.e., increased volume was related to increased BMI).

For brain and cognitive outcomes, increased PBVC was moderately related to improved ADAS-Cog 12 scores. Unexpectedly, however, increased PBVC was associated with a decline in TMT performance, although this association was weak-to-moderate in strength. Similarly, a weak-to-moderate positive association was found between GMV and TMT scores as well as Digit Span scores (i.e., increased volume was related to a decline in performance on both tests). For WMV, a weak-to-moderate positive correlation was found with TMT scores and a weak-to-moderate negative correlation with RAVLT scores, as well as a moderate positive correlation with Stroop scores; for all three correlations, increased volume was associated with a decline in cognitive performance. A moderate negative correlation was also found between WMV and ADAS-Cog 12 scores (i.e., increased volume was related to improved scores). Finally, increased HV was moderately related to a decline in Digit Span performance. All other associations were weak.

Table 4.7: Spearman correlations between brain and physical/cognitive outcomes (trial completion > baseline).

	PBVC	GMV	WMV	HV
1RM, kg	-.433	.151	-.070	.106
BMI, kg/m^2	.031	-1.48	.259	-.125
FPG, mmol/l	.344	.000	-.037	-.193
Stroop (C-B)	-.005	.093	.410	.007
TMT (B-A)	.278	.252	.320	.136
Digit Span (F-B)	-.128	.294	.156	.466
RAVLT (20 minute delay)	-.016	-.086	-.222	.030
ADAS-Cog 12	-.570	.161	-.414	.045

1RM = one repetition maximum (predicted) – quadricep; BMI = body mass index; FPG = fasting plasma glucose; Stroop (C-B) = Stroop Test condition C minus condition B; TMT (B-A) = Trail Making Test part B minus part A; Digit Span (F-B) = Digit Span Test Forward minus Backward; RAVLT (20 minute delay) = Rey Auditory Verbal Learning Test 20 minute delay condition; ADAS-Cog 12 = Alzheimer's Disease Assessment Scale–Cognitive 12; PBVC = percent brain volume change (total brain volume); GMV = grey matter volume; WMV = white matter volume; HV = hippocampal volume.

4.4 Discussion

This chapter examined the effects of a 26-week resistance training program on sMRI and fMRI outcomes in older adults at risk for diabetes. Results from our pilot study demonstrate that resistance training may preserve whole brain volume decline associated with aging. Specifically, we found an average TBV decline of 0.13% in the resistance training group and 0.37% in the balance and tone group. The latter rate of decline is fairly consistent with what has been shown to occur in age-related atrophy. For example, a longitudinal study in healthy older adults aged 60-80 found an average rate of whole brain atrophy of ~0.5% per year.[39] Similarly, another study found that nondemented older adults had a 0.45% annual decline in TBV, while rates in those with early stages of dementia were double this.[40]

Contrary to our finding, a previous study in older adults found that twice-weekly resistance training led to more TBV atrophy (-0.43%) when compared to balance and tone exercise.[41] However, the authors of this study noted that this unexpected decline may be due to the removal of beta-amyloid in the brain as a result of resistance training, and with it, cerebral fluid shifts that could account for whole brain volume reductions.[41] Strengthening this argument, this study found improvements in cognitive function in response to resistance training despite showing a decrease in TBV.[41] Beyond this study, however, there is a lack of RCTs examining the effects of resistance training on TBV in older adults. This is surprising given that older adults are prone to whole brain atrophy as a result of aging, and this is associated with cognitive deficits in important domains (e.g., memory, global cognition) as well as an increased risk for dementia.[42] Given our positive findings, more trials assessing the effects of resistance exercise on brain volume in older adult populations who are at risk of brain and cognitive decline should be prioritized.

Although our results show that the resistance training group had less TBV atrophy than the control group, those in the resistance exercise group showed more GMV and WMV atrophy overtime. These differing findings may be the result of the analysis tools used within FSL to assess longitudinal changes. While SIENA is known to have a low error rate (0.2%),

SIENAX has been shown to have a higher error rate of 1% and may not be the most appropriate measure of longitudinal change (its main purpose is to be used in cross-sectional analyses).[42] Therefore, future trials should consider using additional analysis tools beyond FSL to measure change in GMV and WMV, which would also allow for a direct comparison to FSL's output. Our study also showed less decline in HV following resistance exercise; however, whether these changes are statistically significant cannot be concluded. In comparison to our findings, a similarly designed study in older women with MCI found that six months of resistance exercise led to a HV decrease of 2.17% (compared to a decrease of 1.75% in their balance and tone control group).[43] However, these differences were not statistically significant.[43] Interestingly, the amount of HV atrophy seen in both groups in our study is comparable to other clinical populations of older adults, such as those with Alzheimer's disease. For example, multiple longitudinal studies have shown that Alzheimer's disease patients have an annual HV loss of 3.5-3.98%.[44,45] Evidently, more cross-sectional studies are needed in older adults at risk for diabetes to better understand possible HV impairment in this population.

One surprising finding in our study was that resistance exercise did not improve associative memory performance. This contrasts a previous study which found that six months of twice-weekly resistance training, compared to balance and tone exercise, improved associative memory in older adults.[32] However, this study, compared to ours, involved individuals with MCI.[32] Given that deficits in associative memory have been shown to occur in mild dementia,[46] it might be the case that those with MCI experience greater deficits in associative memory compared to our target population (and thus may benefit more from exercise). Cross-sectional studies examining associative memory ability in our target population compared to both healthy older adults and other clinical populations could help shed light on potential group differences in brain health and cognition. Further, while we did not see an improvement in associative memory, we did see an improvement in item memory in response to resistance training, however these changes were very small. Future large-scale resistance exercise trials are needed to examine these possible effects more closely.

Interestingly, we did not see significant changes in activation in cortical areas that have been previously implicated in associative memory and have shown to positively respond to resistance training, such as the lingual and occipital-fusiform gyri.[32] However, when comparing trial completion relative to baseline (associative > item), those in the resistance training group did have increased activation in the postcentral gyrus during encoding and in the precentral gyrus and middle temporal gyrus during recognition when compared to the balance and tone group. Previous research examining differences in brain function in young versus older adults have found greater activation in these areas in younger adults.[47] Similarly, one study showed that greater activation in the precentral gyrus during a memory task was evident in healthy controls versus Alzheimer's disease patients.[48] Based on these findings, it appears that patterns of increased activation in our resistance training group may reflect that of younger, healthy adults. On the contrary, individuals in the balance and tone group, when compared to the resistance training group, had increased activation overtime in the supramarginal gyrus and juxtapositional lobule cortex during encoding conditions. Activation in the supramarginal gyrus has previously been implicated in the use of rehearsal strategies during working memory encoding,[49] and thus those in the balance and tone group may have used this specific strategy to memorize images. Finally, impairments in working memory have been shown to be associated with less activation in the juxtapositional lobule cortex,[50] therefore it is possible that balance and tone exercise selectively improves memory function. This is also in line with findings from Chapter 3, in which balance and tone exercise was shown to improve working memory.

Given that those in the resistance training group did improve slightly in item memory during the fMRI task, but not in other measures of memory as described in Chapter 3, it appears that resistance training may improve certain types of short-term memory over others, namely visual-item memory but not auditory-verbal memory. These findings may be the result of participants using varying strategies for memorization depending on the type of memory task (e.g., for visual but not auditory memory tasks, participants may have created categorical representations or used visual traces). Coupled with the finding of increased activation

patterns in the juxtapositional lobule cortex for the balance and tone group, future trials may benefit from collecting self-reported data on the type of memory strategy employed by participants to remember pictures.

A large limitation to the current study is the amount of participant data that was missing or excluded in analyses. When collecting fMRI task data, we experienced multiple issues running our memory task during the scan which required on-the-spot troubleshooting; this was especially difficult given that MRI scans are on a strict time schedule. As a result, several participants had partial memory task data excluded. Additionally, many participants experienced discomfort while in the scanner and requested to not complete the full memory task. Future trials should consider cutting down imaging time where possible, and developing improved methods of task troubleshooting prior to scanning. Further suggestions on how to improve these in the future are examined in Chapter 5. Moreover, it may be interesting to assess participant performance on the associative memory task while outside of the scanner to further assess behaviour outcomes and avoid any issues that occurred with use of the scanner.

In addition, similar to Chapter 3 limitations, we are unable to make definite conclusions on the effect of resistance training on brain structure and function in older adults at risk for diabetes due to this being an underpowered study. As also previously highlighted, future studies are needed to examine the underlying mechanisms (e.g., release of neurotrophic factors, increased levels of neurotransmitters) by which resistance training may improve brain structure and function, as well as the possible relationship between improvement in brain health and cognitive function in our target population. In our study, we briefly explored the relationship between change in brain health and cognitive/physical measures via correlational analyses, which showed that there may be unexpected relationships between outcomes (e.g., improved GMV was related to a decline in task-switching and working memory performance). However, there is a need to explore our correlational findings further as they were not statistically measured. Finally, future studies may also examine how quickly

the positive effects of resistance training on brain structure and function may occur (e.g., < six months) as well as their potential lasting effects.

To sum, resistance exercise appears to slow down total age-related brain atrophy and possibly regional atrophy (HV) in older adults at risk for diabetes. Additionally, it was found that increased activation patterns as a result of resistance training may lead to functionally healthier brains in this clinical population. However, negative effects of resistance training were found for GMV and WMV which may be the result of analysis methods used, and resistance training did not improve associative memory performance as anticipated.

Summary

This chapter assessed structural and functional brain changes following 26 weeks of thrice-weekly progressive resistance training in older adults at risk for diabetes. Those in the resistance training group showed less age-related TBV decline and HV atrophy compared to the balance and tone group, however they did experience greater GMV and WMV decline which may be the result of the analysis tool used for tissue type segmentation. When assessing functional activation patterns during the memory task (associative > item), resistance training led to increased activation during the encoding and retrieval phases that mimics patterns of younger adults and healthy older adults. These findings suggest that resistance training may lead to a functionally 'younger' and healthier brain. In comparison, during the encoding phase, those in the balance and tone group experienced an increase in activation in areas implicated in working memory and rehearsal memory, the latter of which may indicate use of specific memory strategies in this group. Moreover, these activation patterns may explain the improvements in short-term memory tasks seen in the balance and tone group in Chapter 3. No other significant between-group activation patterns were found in our fMRI analysis. Finally, despite activation patterns found in the resistance training group, they did not improve in associative memory performance.

While our pilot MRI findings are promising, powered RCTs are needed in this population to further assess these possible effects. In Chapter 5, the feasibility of conducting a large-scale study in older adults at risk for diabetes is examined.

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Chapter 5

5 Process outcomes: Feasibility of conducting a large-scale resistance training randomized controlled trial in older adults at risk for diabetes

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Some of the published content has been edited for this thesis.

5.1 Introduction

Over three million Canadians are living with T2D,[1] and this number continues to steadily increase each year.[2] While T2D affects people of all ages, older adults are particularly at high risk for this disease. Studies show that older adults with T2D experience deficits in cognitive function (e.g., executive function, processing speed, memory) and brain health (structure and function).[3,4] Importantly, both overweight/obese individuals and those with prediabetes (i.e., those at risk for T2D) already show some evidence of such decline.[5-7] Therefore, intervention strategies aimed at improving cognitive and brain health in this at-risk group is imperative, as it may help prevent or delay future decline.

One lifestyle intervention strategy known to improve neurocognitive function is exercise. For example, six months of structured aerobic training has been shown to improve memory and executive function in older adults at risk for T2D.[8] However, whether other types of exercise may benefit this specific population, such as resistance training, is unknown. In other populations of older adults, however, resistance exercise has been shown to improve both cognitive and brain health. Nagamatsu et al. (2012) showed that six months of resistance training leads to improved selective attention, conflict resolution, and associative memory, as well as increased hemodynamic activity in associative memory-related areas (e.g., right

lingual gyrus) in older adults with probable MCI.[9] In another study, older adults with MCI exhibited improved global cognition and increased cortical thickness of grey matter in the posterior cingulate gyrus after 26 weeks of resistance training.[10] In studies in healthy older adults, resistance training has led to reduced cortical white matter atrophy,[11] reduced WMLs,[12] and increased HV.[13] These changes may be caused by the release of neurotrophic factors through resistance training, in particular IGF-1 associated with neuroplasticity (e.g., angiogenesis, axon growth, etc.) and neuronal survival.[14,15] Additionally, changes in response to resistance training may be due to improved metabolic risk factors and reduced adiposity via muscle mass development,[16] and with this increased insulin-mediated glucose uptake in muscles as well as improved insulin sensitivity.[17,18]

To address whether resistance training may benefit cognitive function and brain health in older adults at risk for T2D, a powered RCT is needed. However, prior to conducting a large-scale trial, there is first a need to assess the feasibility of conducting a resistance exercise intervention in this population, to ultimately determine the accessibility of the program and the ability to recruit this specific population. Prior to our study, we expected that recruiting this population may be difficult, as these individuals may have low motivation to exercise, low energy levels, and/or physical limitations that prevent them from being physically active. In addition to this, prediabetes may go unnoticed and undiagnosed, as its symptoms (i.e., having elevated blood glucose levels beyond the normal range) may not be obvious.

To assess feasibility in our pilot study, we aimed to (1) examine recruitment, adherence, and retention rates of program participants, and (2) assess delivery of the intervention and barriers for study participation from the perspective of both program participants and research assistants (RAs; i.e., exercise instructors) through feedback questionnaires. We hypothesized that adherence and retention rates would be high, while recruitment rates would be low. Ultimately, this study aimed to provide unique insight into strategies for working with an at-risk population that has been relatively understudied to date, and to provide methodological recommendations to implement into future trials.

5.2 Methods

5.2.1 Study design

Details of our study design have been reported in depth in Chapter 3. Briefly, we conducted a single-blinded pilot RCT to examine the feasibility of a 26-week, thrice-weekly resistance training intervention in older adults at risk for T2D.

5.2.2 Participants

Participants were community-dwelling older adults aged 60-80 who were at risk for diabetes (had BMI ≥ 25 and/or FPG 6.1 to 6.9 mmol/l). As previously mentioned, participants were recruited through posters in community centers, short presentations at community seminars, word-of-mouth and ads in the Villager Publications' community magazine (print) and Kijiji (online classified advertisement). Further details on inclusion/exclusion criteria can be found in Chapter 3.

5.2.3 Exercise intervention

Following baseline assessments, participants were randomized into a thrice-weekly resistance training or balance and tone (control) group for 26 weeks. Participants exercised in small groups of 2-4 and all classes were led by 1-2 instructors (RAs). Timing of classes differed per group depending on participant availability (ranged from morning to evening). Participants in the resistance training group completed exercises using programmable resistance machines and body weight/hand weights, while participants in the balance and tone group completed balance and stretching exercises (as a group). Warm-up and cool down time for the resistance training group consisted of walking on a treadmill or using an elliptical machine, while participants in the balance and tone group performed stretches together. Study methods have been described in further detail in Chapter 3.

5.2.4 Primary feasibility outcome measures

5.2.4.1 Recruitment

Time and number of individuals screened to enroll 10 program participants per group was recorded. Recruitment strategies (type, time of year) were also examined.

5.2.4.2 Adherence

Adherence to the exercise program, calculated by [(number of classes attended/78 classes maximum) x 100%)], was recorded for both exercise groups. Our target adherence rate was 70%+, based on other exercise trials with similar populations of older adults.[19,20] If participants missed sessions, we followed-up with them via phone and offered make-up sessions when possible. To promote adherence, participants were entered into a monthly gift card draw based on number of classes attended, and were given a $50 honorarium for each completed assessment timepoint (baseline, midpoint, trial completion). We also allowed partners/friends (i.e., “support exercisers”) to participate in the exercise classes.

5.2.4.3 Retention

Number of program participants that completed the full exercise program by group was recorded. Our target retention rate was 70%+, based on other exercise trials with similar populations of older adults.[19,20]

5.2.4.4 Safety

The number and description of adverse events by exercise group was recorded.

5.2.4.5 Fidelity

To ensure consistency across exercise classes and help identify any potential program issues, a questionnaire was completed by a non-study affiliate once per month in which s/he attended and evaluated a randomly selected resistance training and balance and tone session.

S/he assessed the structure of the class, including the delivery of the exercises by the RAs and instructor-participant engagement.

5.2.5 Secondary feasibility outcome measures

5.2.5.1 Feedback questionnaires

5.2.5.1.1 Program participants

We administered an anonymous Qualtrics questionnaire via e-mail to all exercising individuals at study completion. The 11-question mixed methods survey assessed perceived successful elements of the exercise intervention, potential areas for program improvement, and overall participant enjoyment and satisfaction with the study. The questionnaire featured 5-point Likert-scale questions (response options were “strongly disagree”, “disagree”, “neutral”, “agree”, and “strongly agree”) and open-ended questions. The purpose of this questionnaire was to gather further information regarding the feasibility of our intervention and identify key strategies to working with this population for future full-scale RCTs.

5.2.5.1.2 Research assistants

We also administered a separate questionnaire to the RAs to complement the information from program participants on how to improve future exercise interventions. This anonymous Qualtrics questionnaire was sent via e-mail to all RAs when their volunteer roles ended. The 16-question mixed methods survey aimed to assess overall enjoyment as an RA, delivery of the program, and any potential challenges faced/areas for improvement from the RA perspective. Similar to the program participant questionnaire, the RA questionnaire included both 5-point Likert-scale and open-ended questions.

5.2.5.1.3 Questionnaire analysis

Likert-scale questions featured both positive and reverse-coded negative statements. For Likert-scale data, we calculated frequencies (percentages of responses), and collapsed positive (“strongly agree” and “agree”) and negative (“strongly disagree” and “disagree”)

responses. For each open-ended question, responses were grouped into categories based on content similarities, and percentages of responses per category (out of total responses for that question) were reported. Individually-based responses that could not be placed into existing categories were not reported in the results unless we believed them to be especially important for future trials. To describe overall findings, we grouped our results into four themes for program participants (motivation to participate, perceived positive outcomes, constructive feedback, and future exercise participation) and three themes for RAs (perceived positive outcomes, constructive feedback and recommendations for future trials [program participants], and constructive feedback and recommendations for future trials [RAs]).

5.3 Results

5.3.1 Descriptive statistics

Descriptive statistics of participants are presented in **Table 3.2** of Chapter 3. The average age of participants was 68.7 years ± 5.7 with 50% being female. All 24 participants were overweight or obese and four were also prediabetic.

5.3.2 Feasibility

Figure 3.2 of Chapter 3 provides the CONSORT (Consolidated Standards of Reporting Trials) diagram to show the flow of participants through our study. Ongoing recruitment of program participants occurred over 17 months (October 2017 to February 2019), where a total of 72 older adults were recruited (48 of which were ineligible or no longer interested in participating in the study). Reasons for ineligibility included: low FPG and BMI, Parkinson's disease, T2D, untreated depression, stroke, metal implants preventing MRI, psychotropics, hip injury preventing exercise, hormone replacement therapy, regular exerciser, and physician advisory not to exercise. Reasons for no longer being interested in participating after recruitment included MRIs, driving to the exercise lab in the Winter, and the time commitment required for the study.

Of the 72 people recruited, 58.3% were by newspaper ads, 15.3% by presentations at community seminars, 12.5% by Kijiji ads, 8.3% by word-of-mouth, and 5.6% by community posters (**Figure 5.1**). For participants who enrolled in the study and were randomized (*n* = 24), the majority were also recruited through newspaper ads (66.7%), with some being recruited through Kijiji ads (12.5%), at community seminars (12.5%), and by word-of-mouth (8.3%). Recruitment was highest during Fall and Winter months (i.e., October, January), but depended highly on when newspaper ads were used. A summary of recommended recruitment strategies, along with other items for optimization in future trials, is listed in **Table 5.1**. In addition to the 24 eligible participants in our study, we had 3 support exercisers also complete the exercise program.

We maintained a 95.8% retention rate of program participants in our study, with only one balance and tone participant dropping out at week 10 due to health issues. Program participant attendance averaged 84.4%, with a slightly higher attendance rate for the resistance training groups (85.5%) compared to the balance and tone groups (83.3%). Six participants completed between 2-13 make-up sessions due to missed classes. Missed classes occurred most in the Winter and Summer months, and were mainly due to illness, vacation time, and scheduling conflicts. The number of participants who completed MRI analysis, including those with missing data, have been described in Chapter 4.

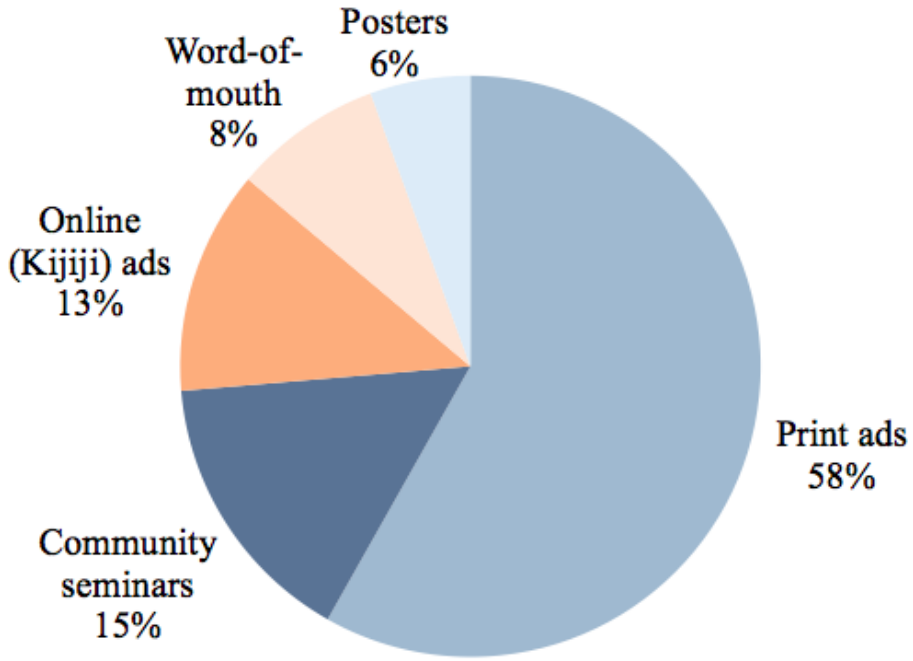

Figure 5.1: **Study recruitment methods.**

Table 5.1: Items for optimization in future RCTs.

Item	Description of Current Study	Optimization for Future Studies
Recruitment	- Low recruitment rate; some months unsuccessful - Newspaper ads, Kijiji ads, presentations at community seminars successful - Posters less successful	- Use of newspaper ads, Kijiji ads, presentations at community seminars - Recruit in early Fall & Winter - Ads emphasize that the program is free and instructor-led, with the option to bring a friend
Participant Blinding	- Program participants not blinded to group allocation	- Physician added to the research team if possible - Program participants blinded to group allocation
Exercise Program	- BAT exercises reportedly too repetitive - Possibility that BAT groups socialized more than RT groups (due to group warm-ups/cool-downs) - Exercise sessions held mostly in the evening - Varying class size	- Diversity of exercises for BAT - Warm-up/cool-down protocol the same between groups - Variety of class times - Classes held during early day when possible
Study Protocol	- MRIs reported as unenjoyable part of the study - No formal RA training manual or handouts - More RA practice sessions requested	- Better inform program participants of MRI procedures - Cut down MRI scanning time when possible - RA training manual (covering training steps, work expectations, troubleshooting procedures, etc.) developed - Hold more RA practice sessions
Program Participant Performance Feedback	- More program participant check-ins requested - More performance feedback of program participants requested	- Program participants receive bi-weekly one-on-one check-ins to review progress

MRI = magnetic resonance imaging; RA = research assistant; RCT = randomized, controlled trial; BAT = balance and tone group.

5.3.3 Safety

We observed no significant adverse events during the course of this study.

5.3.4 Fidelity

Assessors reported high consistency between exercise classes (i.e., RAs closely followed protocols, performed adequate equipment demonstrations, engaged with participants, and successfully answered participant questions). No issues were reported.

5.3.5 Feedback questionnaires

5.3.5.1 Program participant questionnaire

Twenty individuals, out of 27 total (24 participants plus 3 support exercisers), completed this questionnaire following completion of the study.

5.3.5.1.1 Motivation to participate

5.3.5.1.1.1 Open-ended responses

The largest motivating factor to participate in this study was identified as becoming more active and improving physical fitness (48.1% of responses for this question). Other reasons for participating included wanting to contribute to research (18.5% of responses), having an interest in the research topic (14.8%), and the desire to improve their memory (7.4%).

5.3.5.1.2 Perceived positive outcomes

5.3.5.1.2.1 Likert-scale responses

Based on Likert-scale responses, 90% of participants reportedly enjoyed their participation in the study. In addition, the majority of participants felt that they received sufficient information about the study prior to participation (70%) and had adequate support from research personnel throughout the study (90%).

5.3.5.1.2.2 Open-ended responses

Participants reported that their favorite component of the study was socializing with instructors and other participants (65.7% of responses) and improving their physical health (20%). Similarly, in a separate question, the 2 most commonly reported benefits of study participation were increased strength/mobility and fitness (53.3% of responses) and the ability to socialize with others (16.7%). Other less reported benefits included receiving instructor-led exercise sessions at no cost (6.7% of responses) and being shown correct exercise techniques (3.3%).

5.3.5.1.3 Constructive feedback

5.3.5.1.3.1 Open-ended responses

The least favorite component of the study for participants was identified as timing of sessions (27.3% of responses) and completing MRIs (22.7%). Other responses included the drive to campus (13.6% of responses) and the repetitiveness and simplicity of balance and tone exercises (9.1%). Similarly, in a separate question, the most difficult component of the study was said to be timing of sessions (30% of responses) and MRIs (20%). One individual also said staying motivated to exercise (5% of responses) was particularly challenging.

5.3.5.1.4 Future exercise participation

5.3.5.1.4.1 Likert-scale responses

Eighty-five percent of participants reported feeling more motivated to remain physically active after participating in this study. Additionally, 70% of participants said that they would participate in this program or a similar program in the future and 90% said they would tell a friend to participate.

5.3.5.2 Research assistant questionnaire

RA feedback was provided by 28 RAs (73.7% of total RAs involved in this study).

5.3.5.2.1 Perceived positive outcomes

5.3.5.2.1.1 Likert-scale responses

Assessing overall RA experience, it was reported that 100% of RAs enjoyed their involvement. In addition, 100% of RAs said that they enjoyed running exercise sessions, 81.2% felt that the study was well-organized, and 92.6% said they would be an RA in this study or a similar study again. For training and research support, 85.2% of RAs felt they had received sufficient training for the position, 85.2% felt confident in their ability to address program participant questions, and 77.8% said they received adequate support from research personnel throughout the study.

5.3.5.2.1.2 Open-ended responses

RAs reported that their favourite component of being involved in the study was working with participants (58.1% of responses). Other responses included gaining first-hand experience in research (14% of responses), helping older adults (9.3%), and administering cognitive assessments (4.7%) as this was another opportunity for one-on-one time with participants.

5.3.5.3 Constructive feedback and recommendations for future trials (program participants)

5.3.5.3.1 Open-ended responses

The majority of RAs had no recommendations for improving the participant experience in future trials (41.2% of responses), however some suggested developing faster ways for participant sign-in at exercise classes (11.8%), having more diverse exercises (11.8%), providing clearer instructions for participants at the beginning of the study (5.9%), and offering frequent participant feedback throughout the study (5.9%).

5.3.5.4 Constructive feedback and recommendations for future trials (research assistants)

5.3.5.4.1 Open-ended responses

RAs reported that the most challenging aspects of the study were having to modify balance and tone exercises due to lack of available equipment or altered group size (10.3% of responses), keeping participants in the balance and tone group motivated (6.9%), troubleshooting laboratory equipment (6.9%), ensuring that all participants followed the protocol (3.4%), and handling participant complaints (3.4%).

While the majority of RAs said that there were no ways in which research personnel could have improved their experience (40% of responses), a suggestion was having more balance and tone exercises (5%) as participants tended to complete these sessions quickly. To improve RA training, suggestions included having more RA practice sessions with one another (28.6% of responses) and providing handouts that highlight example exercises and RA expectations (21.4%), among others.

5.4 Discussion

To our knowledge, this pilot study is the first to assess the feasibility of conducting an RCT of resistance training to improve cognitive and brain function in older adults at risk for T2D. Results show that recruitment of this population is difficult as expected, however once enrolled in our study, participants thoroughly enjoyed it and remained committed to the exercise program as evident by high retention and adherence rates. Based on these findings, a large-scale study was deemed feasible, and we identified key research strategies that may improve future trials with this population.

Despite the challenge of recruiting participants, we were able to identify ways to optimize recruitment rates for future studies. For example, it is recommended to recruit this population in the Fall and Winter months, as this appears to be when older adults may have more time to commit to a 26-week-long research study. Additionally, recruiting through newspaper ads,

Kijiji ads, and community seminars (where research personnel can engage potential participants directly) was shown to be effective. For recruitment ads, emphasizing the benefits of study participation, such as receiving free instructor-led exercise sessions and socializing with others, is highly recommended. To recruit prediabetic individuals in the future, it may be helpful to collaborate directly with family physicians who can help identify people who are at risk for T2D, as well as diabetes clinics.

In addition to recruitment methods, we also identified general strategies to working with this population. For example, it is recommended to have regular check-ins with participants and to offer frequent feedback on performance. Additionally, creating opportunities for more socialization throughout the program may be helpful, and may lead to increased overall enjoyment of and adherence to the exercise program, as shown in previous studies.[21,22] Some studies have even shown that offering social activities (e.g., coffee sessions) after each exercise session helps improve program adherence in older adults,[23] thus this could be something to implement in the future. Other ways to increase program adherence include allowing participants to bring a partner/friend to exercise alongside, and offering incentives such as gift card draws based on number of classes attended.

Overall, both program participants and RAs expressed a high level of study enjoyment and satisfaction. For example, a program participant said “It is wonderful for me to be able to engage with positive, encouraging, energetic, knowledgeable, and fun volunteers. They gave me more than exercise but confidence that the future might be better than I can imagine”. While the majority of feedback from program participants was indeed positive, some general recommendations for future studies included offering more diverse exercises and developing ways to further keep participants, particularly those in the balance and tone groups, motivated. Lastly, since MRIs were reported as a least enjoyable component of the study, future trials should aim to better inform participants of MRI procedures (e.g., expectations, scan length, the possibility of discomfort due to noise and tight space) and should consider ways to cut down scanning time when possible.

We acknowledge that there are several limitations to this study. First, the program participant questionnaire did not collect information on group allocation, and as a result we were unable to compare between-group differences. Similarly, since the questionnaire was completed by all program participants (participants and non-participant partners) we were unable to separate out responses from actual participants in the study. Additionally, our questionnaire also included several open-ended questions which may have led to reduced completion rates.

Other study limitations included program participants not being blinded to group allocation (due to needing individual physician approval to exercise), balance and tone groups possibly socializing more than resistance training groups due to having group (versus individual) warm-up and cool-down exercises, and limited exercise lab availability which led to having mostly late-afternoon and evening classes. To remedy these in the future, it is recommended to have a physician on staff if possible so that group allocation can be blinded as described in Chapter 3 (or to directly contact each participant's physician to privately inform them of group allocation), to have similar warm-up and cool-down exercises for both balance and tone and resistance training groups to increase consistency across groups, and to offer more choices for timing of exercise sessions when possible.

Based on our findings, a large-scale study assessing the effects of resistance training on cognitive and brain health in older adults at risk for T2D is feasible, provided that recruitment challenges are addressed in the future. In order to properly analyze between-groups differences, future studies will require larger sample sizes to determine whether resistance training can improve cognitive and brain health over time for those at risk for T2D. As there are several challenges to working with this at-risk population, we hope that our study will inform future trials of best practices.

Summary

This chapter assessed the feasibility of a large-scale RCT examining the effects of resistance exercise on cognitive and brain health in older adults at risk for diabetes. Based on previous feasibility studies in similar populations, a large-scale study was deemed feasible from our results. Program participants reported high program enjoyment and satisfaction, and offered minor recommendations for future studies (e.g., more diverse exercises particularly for the balance and tone group, regular check-ins with participants, cutting down MRI scanning time when possible). Moreover, program adherence, retention, and fidelity were high in this pilot study, though recruitment was challenging. In our published manuscript, we identified key strategies to improve recruitment in future trials including recruiting through community seminars where research personnel can directly engage with potential participants, and highlighting the social benefits of participation as this appears to be an attractive element to the program. Strategies for study improvement that were identified in this feasibility trial will be implemented into future large-scale trials.

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Chapter 6

6 Thesis discussion

6.1 Thesis summary

Broadly, this thesis aimed to assess the feasibility and preliminary effects of a resistance training program to improve neurocognition in sedentary older adults at risk for diabetes (i.e., those with prediabetes and/or obesity). This population was targeted as these individuals are known to experience some cognitive and brain deficits and are at risk of further decline related to T2D. An additional aim of this thesis was to identify the type of brain deficits that are associated with prediabetes based on the literature. Specifically, a systematic review (Chapter 2) reported on current evidence of the structural and cerebrovascular brain impairments experienced in prediabetes, as this appears to be less understood in this disease compared to obesity. Subsequent chapters reported on the cognitive findings (Chapter 3) and brain health outcomes (Chapter 4) from a 26-week resistance training pilot RCT in older adults at risk for diabetes, as well as the feasibility of conducting a large-scale powered trial (Chapter 5).

6.2 Findings and interpretations

6.2.1 Systematic review

The systematic review revealed that prediabetics may experience dysfunction in structural connectivity compared to healthy age-matched individuals; such deficits included a lower number of white matter connections and weaker localized connectivity. This is in line with other DTI research showing that those with T2D exhibit white matter impairments (e.g., lower regional FA values)[1] and is evidence that prediabetics already experience deficits exhibited in T2D. Furthermore, the finding that prediabetics experience structural connectivity deficits, coupled with research showing that resistance exercise benefits the brain structurally (e.g., results in reduced cortical WMLs),[2] highlights the need for studies to

examine how resistance training may benefit DTI outcomes in older adults at risk for diabetes.

An additional finding of the systematic review was that volumetric and cerebrovascular outcomes in prediabetes were inconsistent across studies. As discussed in Chapter 2, this may be the result of varying T2D diagnostic measures used in these studies. Given that the WHO and ADA –two well-known health organizations– have conflicting definitions of prediabetes to some degree, more research should focus on examining how they differ in terms of patient health outcomes as well as developing a more standardized diagnostic criteria for prediabetes. Clinically, differences in diagnostic criteria may result in incorrect diagnoses, which may lead to some people being unnecessarily treated while others do not receive treatment that is needed. In addition, despite varying study results, one consistent finding in studies included in the systematic review was that increased blood glucose levels were correlated with greater neural decline, independent of diabetes status. Importantly, this was even evident in normoglycemia, suggesting that strategies to improve blood glucose across all populations should be a health priority.

6.2.2 Pilot randomized controlled trial

Findings from the pilot RCT of resistance training in older adults at risk for diabetes showed that resistance exercise may improve selective neurocognitive functions. Specifically, it was found that 26 weeks of progressive resistance exercise may improve task-switching, selective attention and conflict resolution, and item memory. This is an important finding as executive function, attention, and memory have all been shown to be impaired in T2D,[3] and prediabetics and/or those who are overweight or obese are at high risk of such impairment. Moreover, these functions are known to decline with age and are associated with the ability to perform everyday tasks in old age,[4,5] thus preserving them is important to promoting independent living in later years. Despite these positive findings, however, more studies are needed to determine the clinical relevance of these potential cognitive improvements, as this is an area of research that is currently lacking.

Our pilot study also found that balance and tone training may result in improvements in some cognitive domains (e.g., working memory) in older adults at risk for diabetes, and thus future research is needed to explore this possible relationship. As discussed in Chapter 5, one explanatory theory is that socialization in the balance and tone group may have played an important, and initially underestimated, role in promoting and improving cognitive abilities. One study assessing socialization levels in individuals with age-related cognitive impairments found that social engagement benefits cognition independent of other nonpharmacological treatments including physical activity and intellectual stimulation.[4] The benefit of socialization was further demonstrated in our study via participant feedback questionnaires, in which participants expressed that interacting with instructors and fellow participants was the most enjoyable aspect of the exercise program. Based on these combined findings, future exercise studies and other lifestyle intervention trials should include a large social engagement component when possible. Research could also explore the differences between exercise and exercise plus socialization in older adults at risk for diabetes, in order to gain a deeper understanding of the possible effects of socialization on the brain in this population.

In addition to cognitive changes, resistance exercise led to less total brain shrinkage that occurs with age, and was shown to have a potentially positive effect on HV such that it may slow down atrophy related to the disease of this clinical population. However, more studies using inferential statistical measures are needed to confirm these results, as, for example, previous research has found similar HV results that were not statistically significant.[6] Resistance exercise in our trial also resulted in functional activation patterns during an associative memory task that are seen in healthy populations and may indicate healthier brains. While these results are promising and mimic previous studies described in Chapter 4, we are unable to make conclusions about the underlying mechanisms of these findings. For example, it is currently unknown whether resistance training improves beta-amyloid or IGF-1 levels in older adults at risk for diabetes, both of which are known to occur as a result of resistance exercise in other populations including healthy older adults.[7,8] Evidently, more

human and animal trials measuring neurotrophic factors and molecular compounds in older adults at risk for diabetes are warranted. Based on our pilot cognitive findings, future trials are also needed to examine regional brain volumes in areas that support functions such as task-switching, selective attention and conflict resolution, including the prefrontal cortex. Conducting an executive function task during fMRI may also shed light on functional activation patterns in related areas.

Overall, our pilot findings demonstrate that resistance exercise may benefit a clinical population of older adults. Importantly, there are several benefits of resistance training that other types of exercise, mainly aerobic, may not provide older adults. Firstly, as demonstrated in our study, resistance training improves muscle abilities, and this is known to promote neurocognition.[9] A review showed that changes in muscle function (strength) and structure (size) were positively linked to changes in brain structure.[10] It has also been found that increased quadricep strength is linked to better performance in global cognition and executive function in older adults.[11,12] Secondly, resistance training is accessible in that most older adults can perform some form of it. For example, older adults who have lower limb dysfunction can still participate in upper body strengthening exercises, but may be limited in aerobic exercise options. Thirdly, resistance exercise is often cognitively challenging during the learning and performing of exercises, which is often not the case for aerobic exercises (e.g., running, swimming). Lastly, resistance exercise has been shown to reduce sarcopenia, which affects up to 40% of older adults worldwide,[13] in ways that aerobic exercise does not (e.g., through improved muscle function).[14]

Nevertheless, countless studies have found that combining resistance and aerobic exercise to promote neurocognition is more effective than the use of only one exercise modality. For example, an RCT in older adults found that a combined training program (high intensity aerobic and resistance exercise) led to greater benefits in immediate and delayed memory when compared to aerobic exercise only.[15] This may be due to aerobic and resistance exercise improving cognition and brain health via distinct underlying mechanisms. Studies have shown that resistance training may improve neural communication, reduce associative

inflammatory markers, increase IGF-1 levels, and increase peripheral BDNF production.[16] Aerobic exercise, however, is known to increase hippocampal levels of BDNF and TrkB (Tropomyosin receptor kinase B; a receptor of BDNF) and glutamatergic proteins (glutamate is an important neurotransmitter related to brain function).[16] As such, future trials should assess the effects of a combined aerobic and resistance exercise program on the brain in older adults at risk for diabetes, and further examine these differing mechanisms.

6.2.2.1 Feasibility

While our pilot study provided important information on the preliminary effects of resistance exercise on the brain, large-scale RCTs are needed to further explore these findings. As such, we assessed the feasibility of conducting a large-scale trial in older adults at risk for diabetes. Our findings showed high attendance and program retention rates, which were even higher than a previous exercise trial in older adults with T2D (that our study was largely modelled after).[17] In our trial, we allowed participants to exercise with a friend or family member since previous studies have shown that a lack of social support is a key barrier to physical activity,[18] and this may have led to high participation. Regardless, high adherence and retention rates, as well as positive feedback received from study participants, is evidence of the success of the exercise program in our target population. However, recruitment in older adults at risk for diabetes, particularly those who are prediabetic, was challenging as expected. Given that many people with prediabetes may be unaware of their diagnosis, working with medical clinics and physicians in future trials may optimize study recruitment.

6.2.2.2 Applications and implications

Based on our pilot RCT findings, prediabetes and obesity may represent a window of opportunity to improve neurocognition through a lifestyle intervention, and prevent further decline associated with T2D. Compared to pharmacological interventions which are often costly and can have negative side effects, exercise is an excellent cost-efficient and widely available tool to improve neurocognitive and physical health related to diabetes. For example, a systematic review and meta-analysis found that exercise was superior to

pharmacological interventions in reducing visceral adiposity.[19] Exercise has also been found to be better at regulating blood lipid levels and lowering blood pressure compared to drug interventions.[20] Further, these changes in physical function are known to be positively related to neurocognitive abilities.[21,22] Taken together, these findings demonstrate the effectiveness of exercise as a disease prevention and treatment tool, particularly in T2D and related complications. Our study findings add to this literature by demonstrating that resistance exercise, as an alternative to aerobic exercise in older adults, may improve the brain in a population of older adults who are experiencing decline and are at risk for further decline. Ultimately, our findings have the potential to help prevent diabetes-related complications and dementia, and in turn help reduce the global burden that these diseases have.

6.2.2.3 Limitations

It is important to note that our pilot study has several overarching limitations. Firstly, the use of a single measurement of FPG to diagnose prediabetes is a large study limitation, and may not be an effective measure of change in glucose overtime (i.e., may have resulted in seeing no changes in glucose levels following resistance exercise in our trial). Although convenient, it is instead recommended to use two or more measurements to increase reliability and/or to collect HbA1c which has been shown to be a better indicator of chronic hyperglycemia.[23] However, this would require additional laboratory visits and/or a nurse on staff to draw blood. Future large-scale studies should incorporate these changes into the study design when possible. Future trials could also assess whether findings differ if the ADA's classification of prediabetes, which has a lower FPG threshold than that of the WHO, is instead used. In addition, the use of BMI as a measure of obesity has its own limitations. Despite being a widely used tool, BMI does not take into consideration factors such as muscle mass and bone density which may affect calculations, and therefore may not be reflective of true body fat levels. Other measures of body fat that may be more reliable include bioelectrical impedance and dual-energy x-ray absorptiometry that measures body composition, although these methods are more costly and resource-demanding. Future trials may consider using more than one measure of obesity.

Another study limitation previously described is that participants were not blinded to group allocation. Allocation concealment helps reduce performance and ascertainment bias, as knowledge of group assignment can affect trial behaviour and responses to outcomes.[24] In the future, having a physician on staff if possible to provide medical clearance would allow for double blinding. Additionally, more physical health measures, such as insulin and lipid levels, may also help shed light on the effects of resistance exercise on functions that are known to decline in diabetes. Future trials could also assess self-reported barriers to exercise in older adults at risk for diabetes, as this may help inform recruitment strategies as well as overall strategies to promote participation in exercise. In line with this, future trials should consider strategies to promote exercise use after completion of study programs, as it has been shown that levels of physical activity often drop following the cessation of an exercise trial in older adult groups.[25] Lastly, as discussed in Chapter 3, our pilot results need to be interpreted with caution as our study was underpowered and did not include the use of inferential statistics.

6.3 Future directions

In addition to the future studies already proposed throughout this Chapter, research is needed on the optimal levels, frequency, and type of resistance exercise to achieve positive health outcomes, as these would help inform exercise guidelines and prescription use. Currently, the WHO guidelines for resistance exercise are very broad, and merely suggest that adults and older adults participate in muscle strengthening exercises two days per week.[26] Unlike aerobic exercise that has very specific guidelines, there are no further details as to what resistance training should entail. This may be especially problematic for adults who are non-exercisers or are unfamiliar with resistance exercise, as they may struggle to incorporate this type of exercise into their health regimes. Moreover, more research on resistance training is needed to examine the best dose-response relationship. In our study, we were unable to decipher the differences between the effects of the specific individual exercises used and the major muscle groups that were targeted. Further, the majority of exercises were completed with the use of exercise equipment that may not be accessible to all older adults. Thus, future

trials should examine the effects of different exercises with emphasis on ones that can be completed with limited or no equipment.

Based on the findings of our pilot trial, next steps in this research will be to conduct a large-scale trial in older adults at risk for diabetes. In line with our pilot sample size calculation, the recommended size for a main trial with a medium effect size of .80 is at least 34 participants per exercise group.[27] Strategies discussed in Chapter 5 will be implemented to improve recruitment methods as well as exercise study protocols in this larger trial. These include, but are not limited to, ensuring more consistency in program delivery across groups where possible to limit confounding variables, introducing the use of an additional blood glucose measure (HbA1c) and potentially an additional obesity measure, collaborating with medical health professionals where possible to improve recruitment, incorporating a measure of disease burden such as QALY, and possibly introducing an executive function task to be completed during fMRI. In addition, we will consider adding an aerobic exercise training group to this trial to directly compare the effects of resistance versus aerobic exercise in older adults at risk for diabetes. Finally, we are currently working to examine the effects of resistance exercise on DTI measures in older adults at risk for diabetes.

6.4 Conclusion

In conclusion, this thesis demonstrates that 26 weeks of progressive resistance training may lead to some improvements in cognition and brain health in older adults at risk for diabetes. Important recommendations for future large-scale trials were provided and will be used to further assess the effects seen in our pilot study. This thesis also showed that more studies with standardized diagnostic criteria are needed to assess brain deficits in prediabetes. In addition to already showing some neurocognitive impairment, individuals at risk for diabetes are at high risk for both diabetes-related impairments and dementia, and thus more cross-sectional and longitudinal research should be conducted in this understudied population. Finally, given the usefulness of exercise as a brain and cognitive preservation tool, studies

should focus on incorporating exercise into daily life in a way that is meaningful for older adults at risk for diabetes as well as other clinical populations of older adults.

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Appendices

Appendix A: Ethics Approval

Western Research

Date: 14 August 2018

To: Lindsay Nagamatsu

Project ID: 109379

Study Title: The effect of aerobic versus resistance training on cognitive function and brain health in older adults at-risk for diabetes: A feasibility pilot study

Application Type: Continuing Ethics Review (CER) Form

Review Type: Delegated

REB Meeting Date: 04/Aug/2018

Date Approval Issued: 14/Aug/2018

REB Approval Expiry Date: 18/Aug/2019

Dear Lindsay Nagamatsu,

The Western University Research Ethics Board has reviewed the application. This study, including all currently approved documents, has been re-approved until the expiry date noted above.

REB members involved in the research project do not participate in the review, discussion or decision.

Western University REB operates in compliance with, and is constituted in accordance with, the requirements of the TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The REB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

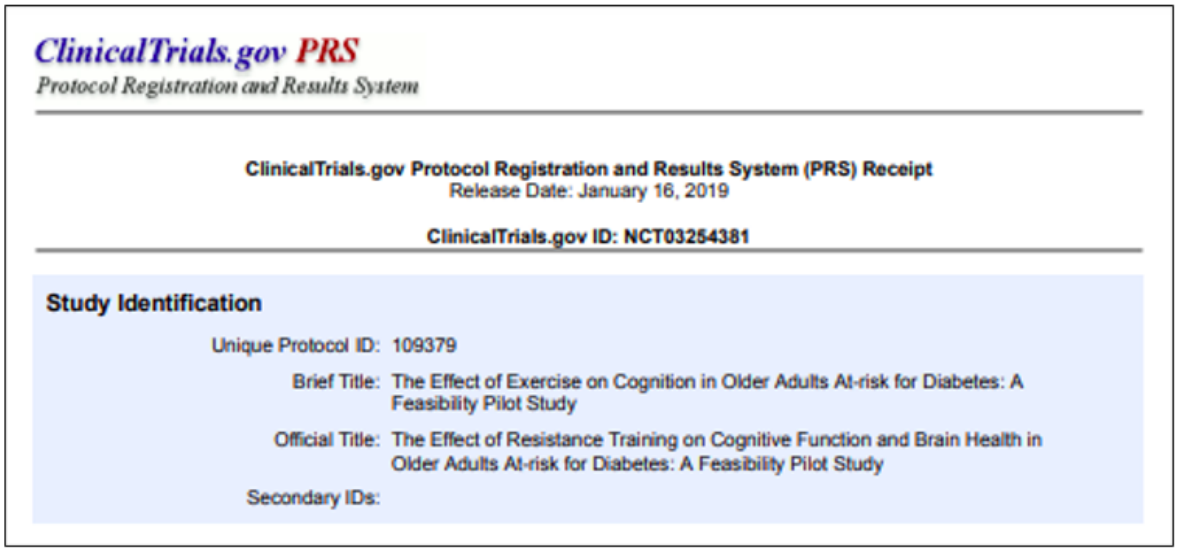
Please do not hesitate to contact us if you have any questions.

Sincerely,

[redacted]

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).

Appendix B: Clinical Trials Registration



ClinicalTrials.gov PRS
Protocol Registration and Results System

ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: January 16, 2019

ClinicalTrials.gov ID: NCT03254381

Study Identification

Unique Protocol ID:	109379
Brief Title:	The Effect of Exercise on Cognition in Older Adults At-risk for Diabetes: A Feasibility Pilot Study
Official Title:	The Effect of Resistance Training on Cognitive Function and Brain Health in Older Adults At-risk for Diabetes: A Feasibility Pilot Study
Secondary IDs:	

Appendix C: Letter of Information and Consent

Western
UNIVERSITY · CANADA

Letter of Information and Consent

Project Title: The effect of aerobic versus resistance training on cognitive function and brain health in older adults at-risk for diabetes: A feasibility pilot study

Principal Investigator:

Dr. Lindsay Nagamatsu, PhD School of Kinesiology | Faculty of Health Sciences
[redacted]

Invitation to Participate: You are being invited to consider participating in this research study about how exercise affects brain health and cognitive processing in older adults.

You are being invited because you are aged 60-80, meet our initial health criteria, and do not currently exercise but are able to do so.

Introduction: Older adults are at high-risk for developing type 2 diabetes, which is associated with cognitive decline. One promising lifestyle intervention to prevent or delay the onset of such decline is exercise, which has been found to improve cognitive function (mental abilities used to perform simple and complex tasks) and brain health (structure and function). However, research has not yet looked at the effects of exercise on neurocognitive health in older adults who are at-risk for diabetes. Before we can examine this, we need to first conduct a feasibility pilot study to determine whether a larger-scale trial would be viable.

Inclusion/Exclusion Criteria: To be eligible to participate in our study, you must: 1) be community-dwelling, 2) be aged 60-80 years, 3) read, write, and speak English fluently, 4) have not participated regularly (more than once per week) in resistance or aerobic training in the last 6 months, 5) not currently have a medical condition for which exercise is contraindicated, 6) have not been diagnosed with neurodegenerative disease, 7) have normal or corrected-to-normal visual acuity, 8) have not experienced a stroke or myocardial infarction, 9) not have untreated depression, 10) not be currently on hormone replacement therapy,11) not have clinically significant peripheral neuropathy or severe musculoskeletal or joint disease, 12) not be currently taking psychotropic medications, 13) have your physicians approval, 14) be "at-risk" for diabetes based on your glucose level, weight, or risk score on a questionnaire, and 15) must be able to participate in MRI (cannot have metal or electronic implants, and should not be claustrophobic).

Study Length: This study requires your participation for 6 months. You will attend a one-hour exercise session three times per week in addition to assessment visits at

baseline, 3, and 6 months. Assessment at baseline will take approximately 3.5 hours divided into two sessions. Assessment at 3 months will take approximately 2 hours, and at 6 months approximately 3.5 hours divided into 2 sessions.

Procedure: See below for a summary chart.

Session 1: Confirm eligibility, consent and study information, baseline assessments (demographic and health questionnaires, cognitive tests, physical tests, glucose test). The glucose test will involve a simple, small prick to your finger. If you are not comfortable completing any of these measures, you can choose not to complete them. Session 1 will take approximately 2.5 hours.

- Following session 1, you will be required to obtain permission from your physician to participate in a moderate-intensity exercise program before beginning the next session.

Session 2: Baseline assessment: Magnetic Resonance Imaging (MRI). This will occur at Robarts Research Institute on campus. MRI involves the use of magnetic waves to take pictures of the inside of your body. In this study, it will be used to examine brain structure and function. You will be required to lie still in the MRI scanner for approximately 1 hour, and you will be asked to perform a memory task where you will view pictures for approximately 45 minutes of this time. While in the scanner, you will be able to speak with someone at all times. Researchers will answer any questions you may have about this procedure.

- After session 2 is complete, you will be randomly assigned to one of three exercise groups (aerobic training, resistance training, balance and tone exercises). Since this is a randomized control trial, you have an equal chance of being assigned to each of the three groups. Aerobic training will consist of a walking program; resistance training will include the use of weight machines and free-weights; and balance and tone exercises will include stretching, range of motion exercises, balance exercises, and relaxation techniques. Exercise classes will be held on campus (at Arthur and Sonia Labatt Health Sciences Building) three times per week and will be 60 minutes each in length. Free parking will be provided at the building during your exercise classes.

- You will also be required to complete a physical activity questionnaire (to monitor exercise outside of the program) and falls calendar (to monitor falls) monthly during the 6-month intervention.

Session 3: At the 3-month mark of the exercise intervention, you will again undergo cognitive testing, physical testing, and glucose testing, as done in session 1. This will take approximately 2 hours.

Session 4: After 6-months of the exercise intervention, you will again undergo cognitive testing, physical testing, and glucose testing, as done previously, for a final time. This will take approximately 2.5 hours.

Session 5: MRI. This will take approximately 1 hour. The procedure will be the same as

during baseline assessments. After MRI is complete, your participation in this study will be completed.

Summary Chart

Session #	Procedures	Timeframe
Session 1 (baseline)	- Provide consent - Demographic and health questionnaires - Cognitive tests - Physical tests - Glucose test	2.5 hours
Obtain permission from physician to participate in the exercise program		
Session 2 (baseline)	- MRI	1 hour
Begin the exercise program (participants randomly assigned to aerobic training, resistance training, or balance/tone group)		1 hour, *three times per week* for *6 months*
Complete physical activity questionnaire and falls calendar		*Monthly* for 6 months
Session 3 (after 3 months)	- Cognitive tests - Physical tests - Glucose test	2 hours
Session 4 (after 6 months)	- Cognitive tests - Physical tests - Glucose test	2.5 hours
Session 5 (after 6 months)	- MRI	1 hour
Study participation complete		

Benefits: You may or may not benefit from study participation.

Risks: Adverse events associated with exercise or physical testing may occur during this study. You will be monitored closely by instructors for symptoms of pain, discomfort, and shortness of breath during exercise classes. Any adverse effects will be recorded and reported immediately. Possible risks of MRI include hazards due to unsafe

procedures during scanning. To prevent this from occurring, scanning will be guided by highly qualified and trained MRI technicians and safety procedures will be followed closely. Another possible risk of MRI includes experiencing claustrophobia. You will be able to communicate with research personnel at all times during scanning and scanning can be stopped at any point at your request.

Withdrawing: You have the right to withdraw from the study at any point without any consequences, and you will be compensated for your participation up to the point of withdrawal. If you decide to withdraw from the study, the information that was collected prior to you leaving the study will still be used to answer the research questions with your permission. However, data already collected may be withdrawn upon your request. No new information will be collected without your permission.

Confidentiality: Your personal information will remain private and confidential. Only the Principal Investigator and research personnel will have access to the data. We will not share your data with anyone outside the study unless required by law. Representatives of The University of Western Ontario Health Sciences Research Ethics Board may require access to your study-related records to monitor the conduct of the research. Your personal information (age – provided as part of the inclusion criteria, and name – provided as contact information) will remain private and confidential. During your participation in this study, you will be identified using only a study ID number.

While we do our best to protect your information, there is no guarantee that we will be able to do so. We will keep any personal information about you in a secure and confidential location for a minimum of five years. A list linking your study ID number with your name will be kept by the researcher in a secure place, separate from your study file. If the results of the study are published, your name will not be used.

Compensation: You will receive a $50 honorarium for each assessment time point completed (baseline, 3 months, and 6 months). In addition, each time you attend an exercise class, your name will be placed in a lottery for a weekly draw for a $10 gift card.

Rights of Participants: Your participation in this study is voluntary. You may decide not to be in this study. Even if you consent to participate you have the right to not answer individual questions or to withdraw from the study at any time. If you choose not to participate or to leave the study at any time it will have no consequences for you.

We will provide you with any new information that is learned during the study that might affect your decision to stay in the study.

If you are harmed as a direct result of taking part in this study, all necessary medical treatment will be made available to you at no cost. You do not waive any legal right by signing this consent form.

Questions? If you have any questions about this research study please contact Dr. Lindsay Nagamatsu, PhD, [redacted]

[redacted]

If you have any questions about your rights as a research participant or the conduct of this study, you may contact The Office of Research Ethics [redacted]

You will be given a copy of this Letter of Information once it has been signed.

Consent:

Project Title: The effect of aerobic versus resistance training on cognitive function and brain health in older adults at-risk for diabetes: A feasibility pilot study

Principal Investigator: Dr. Lindsay Nagamatsu, [redacted]

I have read the Letter of Information, have had the nature of the study explained to me and I agree to participate. All questions have been answered to my satisfaction.

_____	_____	_____
Print Name of Participant	Signature	Date (DD-MM-YYYY)
_____	_____	_____
Print Name of Researcher	Signature	Date (DD-MM-YYYY)

Appendix D: Permission to Reproduce Published Materials

Chapter 2 (published systematic review): Prior permission from the *Journal of Neuroscience Research* is not required if the purpose of the reproduction is for inclusion in a thesis dissertation.

Chapters 3 and 4 (published protocol paper): Prior permission from *BMJ Open* is not required if the purpose of the reproduction is for inclusion in a thesis dissertation.

Chapter 5 (published feasibility manuscript): Prior permission from the *Canadian Journal of Diabetes* is not required if the purpose of the reproduction is for inclusion in a thesis dissertation.

Curriculum Vitae

Name:	Joyla Furlano
Post-secondary Education and Degrees:	University of Toronto Toronto, Ontario, Canada 2009-2013 B.Sc. Psychology The University of Western Ontario London, Ontario, Canada 2016-2021 Ph.D. Neuroscience
Honours and Awards (select)	AGE-WELL and McMaster Institute for Research on Aging Postdoctoral Award in Technology ($50,000) 2021-2022 Head and Heart Indigenous Graduate Research Fellowship ($9,100) The University of Western Ontario 2021 Province of Ontario Graduate Scholarship ($15,000) The University of Western Ontario 2020-2021 Head and Heart Indigenous Graduate Research Fellowship ($9,100) The University of Western Ontario 2020 Canadian Consortium on Neurodegeneration in Aging 2020 Training and Capacity Building for Indigenous Dementia Research Award ($4,000) 2020 Province of Ontario Graduate Scholarship ($15,000) The University of Western Ontario 2019-2020
Related Work Experience (select)	Sessional Instructor The University of Western Ontario, Faculty of Psychology 2021-2022 Teaching Assistant

The University of Western Ontario, School of Kinesiology
2020-2021

Sessional Instructor
The University of Western Ontario, School of Kinesiology
2019

Teaching Assistant
The University of Western Ontario, School of Kinesiology
2016-2019

Publications (Published or Accepted):

Furlano JA, Morava A, Wong MYS, Bray NW, Sui W, Munn J, Prapavessis H. (in press). Exercise Behaviours and Exercise Resource Use Among Graduate Students at a Canadian University. Journal of American College Health.

Furlano JA*, Ford SD*, Speechley M. (accepted with minor revisions). The Perceived Benefits of a Social and Knowledge-sharing Community Program for Older Adults. Canadian Journal on Aging.

Horst BR, **Furlano JA**, Wong MYS, Ford SD, Han BB, Nagamatsu LS. (2021). Identification of Demographic Variables Influencing Dementia Literacy and Risk Perception Through a Global Survey. Frontiers in Public Health, 9:711. DOI: 10.3389/fpubh.2021.660600.

Furlano JA, Horst BR, Nagamatsu LS. (2021). Brain Deficits in Prediabetic Adults: A Systematic Review. Journal of Neuroscience Research, 00:1-19. DOI: 10.1002/jnr.24830.

Furlano JA, Nagamatsu LS. (2020). Feasibility of a 26-week Exercise Program to Improve Brain Health in Older Adults At-risk for Diabetes: A Pilot Study. Canadian Journal of Obesity. DOI: 10.1016/j.jcjd.2020.11.001.

Furlano JA, Morava A. (2020). The Benefits and Challenges of Staying Physically Active During the COVID-19 Pandemic. Health Science Inquiry, 11(1).

Furlano JA, Nagamatsu LS. (2019). Feasibility of a 6-month Pilot Randomised Controlled Trial of Resistance Training on Cognition and Brain Health in Canadian Older Adults At-risk for Diabetes: Study Protocol. BMJ Open, 9(10):e032047. DOI: 10.1136/bmjopen-2019-032047.

Nagamatsu LS, **Furlano JA**. (2017). Improving Executive Function for Better Diabetes Management. Advances in Obesity Weight Management & Control, 7(5):00213. DOI: 10.15406/aowmc.2017.07.00213.