THE EFFECT OF AEROBIC EXERCISE ON CEREBROVASCULAR FUNCTION AND COGNITION IN OLDER ADULTS

A Thesis submitted by

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ABSTRACT

Dementia prevalence is expected to treble over the next 30 years. This is only partly explained by the fact that the global population is ageing. Cerebrovascular function and cognitive decline throughout ageing which is exacerbated by reduced cardiometabolic health status, as this promotes chronic low-grade inflammation and oxidative stress, thus impairing endothelial function. This reduces the ability of the cerebrovasculature to respond to the metabolic demands of the brain, as well as maintain the integrity of the blood-brain-barrier, both of which have a substantial impact on cognitive function. Modifiable lifestyle factors, such as physical inactivity, that cause a decline in cardiometabolic health leading to conditions such as obesity, exacerbate these changes beyond those that are associated with normal ageing. A large population of older adults globally are both sedentary and obese thus predisposing them to the development of a neurodegenerative disease, such as dementia. Therefore, it is vital that cost-effective evidence-based strategies are implemented to improve both cerebrovascular function and cognition in order to slow or prevent the normal age-related decline and dementia. The aim of this thesis was to investigate the effects of aerobic exercise training (AT) on cerebrovascular function and cognition in older adults.

The purpose of Chapter 3 was to examine cerebrovascular, cognitive and neuroanatomical adaptations to ageing and the potential benefits of exercise training on these outcomes in adults 50 years or older. Cross-sectional or intervention studies that included exercise (aerobic, resistance or multimodal) and its effect on cerebrovascular function, cognition and neuroanatomical adaptations in this age demographic were systematically searched for, tabulated and described narratively. There were limited studies identified that described effects of resistance exercise training and multimodal training on cerebrovascular function and cognition, while AT was the predominant focus of the studies identified. Collectively, the evidence indicated that exercise irrespective of type could improve cerebrovascular function, cognition and/or neuroplasticity through areas of the brain associated with cognition in adults 50 years or older, irrespective of their health status. It was also determined from this chapter that AT could be a promising and inexpensive strategy in

improving overall brain health. However, the effects of AT on both cerebrovascular function and cognition are poorly described, as too is the amount of AT needed to improve both of these functions.

Chapter 4 determined the differences in cerebrovascular and cognitive function between aerobic exercise trained, older adults and sedentary, untrained, older adults. This was achieved by using transcranial Doppler ultrasonography (TCD) to determine the cerebrovascular responsiveness (CVR) to physiological (hypercapnia, 5% carbon dioxide) and cognitive stimuli (battery of individually administered cognitive tests). Anthropometric, cardiovascular, exercise performance, and strength measurements, and a blood collection were used to determine the differences in cardiometabolic health between each group. Correlation analyses were performed to determine if cerebrovascular function and cognition were interrelated. The trained group (*n=13*) had a higher CVR to hypercapnia (80.3 ± 7.2 vs 35.1 ± 6.7%, $P < 0.001$), higher CVR to cognitive stimuli (30.1 ± 2.9 vs 17.8 ± 1.4%, $P = 0.001$) and a higher overall cognitive capacity (117 ± 2 vs 98 ± 4, $P < 0.001$) than the untrained, sedentary group (*n=13*). Once these parameters were adjusted for covariates (cardiometabolic markers and education), no statistical difference was observed between the groups. Both CVR to hypercapnia and CVR to cognitive stimuli were positively correlated to cognition, indicating the interrelatedness between cerebrovascular function and cognition in older adults. It was concluded that an interaction between AT, cardiometabolic factors and education may exist that directly influence cerebrovascular function and cognition, whereby AT mediates the improvements in these functions in older adults.

Chapter 5 investigated the effects of 16 weeks AT on cerebrovascular and cognitive function in sedentary, obese, older adults. Participants were randomly assigned to either an AT group (*n=14*) or control group (*n=13*). Before and after the intervention, TCD was used to measure the CVR to physiological and cognitive stimuli. Following 16 weeks of AT, CVR to hypercapnia (98.5 ± 10.3% vs 58.0 ± 12.1%, $P = 0.021$), CVR to cognitive stimuli (25.9 ± 1.7% vs 16.4 ± 1.6%, $P <$

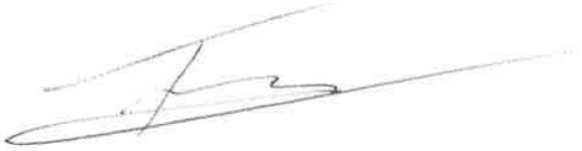
0.001) and total cognitive capacity (111 ± 4 vs 104 ± 4, $P = 0.004$) increased in the AT group compared with the control group. A very strong relationship was observed between the number of exercise sessions completed and CVR to cognitive stimuli ($r = 0.878, P < 0.001$), but not for CVR to hypercapnia ($r = 0.246, P = 0.397$) or total composite cognitive score ($r = 0.213, P = 0.465$). Cerebrovascular function and cognition improved following 16 weeks of AT, with CVR to cognitive stimuli dependent on the amount of exercise undertaken.

My thesis concludes that AT has a positive effect on brain health by improving both cerebrovascular function and cognition in older adults, particularly in those who are sedentary, untrained and obese. Further studies are warranted to determine if a minimum dose of AT is required to improve brain health and if the improvements can occur at any age throughout the lifespan.

Keywords: Cerebrovascular function, cognition, ageing, exercise

CERTIFICATION OF THESIS

This Thesis is the work of **Edward Spencer Bliss** except where otherwise acknowledged, with the majority of the authorship of the papers presented as a Thesis by Publication undertaken by the Student. The work is original and has not previously been submitted for any other award, except where acknowledged.



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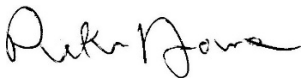

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Chapter 5: The Effects of Aerobic Exercise Training on Cerebrovascular and Cognitive Function in Sedentary, Obese, Older Adults. ***Edward S. Bliss***, Rachel H. X. Wong, Peter R. C. Howe and Dean E. Mills.

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LIST OF ABBREVIATIONS

6MWT	6 minute walk test
ACC	Anterior cingulate cortex
ACE	Addenbrooke's Cognitive Examination
ADAS-COG	Alzheimer Disease Assessment Scale – Cognitive Subscale
ANCOVA	Analysis of co-variance
ANOVA	Analysis of variance
ANZCTR	Australian and New Zealand Clinical Trial Registry
ASL	Arterial spin labelling
AT	Aerobic exercise training
BBB	Blood-brain-barrier
BDNF	Brain-derived neurotrophic factor
BHB	beta-hydroxybutyrate
BMI	Body mass index
Ca^{2+}	Calcium
CBF	Cerebral blood flow
CBF_V	Cerebral blood flow velocity
cGMP	Cyclic guanosine monophosphate
CHO	Total cholesterol
CO_2	Carbon dioxide
CPI	Cerebral pulsatility index
CT	Combined exercise training
CVR	Cerebrovascular responsiveness
eNOS	Endothelial nitric oxide synthase
fMRI	Functional magnetic resonance imaging
GC	Guanylate cyclase
GH	Growth hormone
GTP	Guanosine triphosphate
HCAR1	Hydroxycarboxylic acid receptor 1
HDL	High-density lipoprotein
HOMA-IR	Homeostatic model assessment of insulin resistance
hs-CRP	High-sensitivity C-reactive protein
IGF1	Insulin-like growth factor-1
iNOS	Inducible nitric oxide synthase

LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LPAQ	Lifetime Physical Activity Questionnaire
MCA	Middle cerebral artery
MCI	Mild cognitive impairment
MLCP	Myosin light chain phosphatase
MMSE	Mini Mental State Examination
MRI	Magnetic resonance imaging
NIH	National Institutes of Health
nNOS	Neuronal nitric oxide synthase
NO	Nitric oxide
NVC	Neurovascular coupling
PCO_2	Partial pressure of carbon dioxide
$P_{ET}CO_2$	End-tidal partial pressures of carbon dioxide
PGC-1α	Peroxisome proliferator-activated receptor gamma coactivator 1-alpha
PKG	Protein kinase G
POMS	Profile of mood states
RAVLT	Rey's auditory verbal learning test
ROS	Reactive oxygen species
RT	Resistance exercise training
SDMT	Symbol digit modalities test
SEM	Standard error of the mean
SPECT-CBF	Single photon emission computed tomography cerebral blood flow
TCD	Transcranial Doppler ultrasonography
TG	Triglycerides
VEGF	Vascular endothelial growth factor
$\dot{V}O_2$	Oxygen uptake
$\dot{V}O_2max$	Maximal oxygen uptake
$\dot{V}O_2peak$	Peak oxygen uptake
VSMC	Vascular smooth muscle cells
YPAS	Yale Physical Activity Survey

CHAPTER 1: GENERAL INTRODUCTION

Chapter 2 will briefly outline the changes associated with ageing, the dementia burden using Australia as an example, and define cerebrovascular and endothelial function. The chapter will also highlight that currently ageing, physical inactivity and obesity are on an upward trajectory in countries such as Australia, thus reducing cardiometabolic health, cerebrovascular function and cognition, and potentially contributing to dementia burden. This chapter provides the reader an overview of this area before cerebrovascular dysfunction and changes associated with ageing are discussed in detail in Chapter 3: Benefits of exercise training on cerebrovascular and cognitive function in ageing. Chapter 2 will also identify the methods that can be used to measure cognition and cerebrovascular function, particularly transcranial Doppler ultrasonography (TCD), as this will be the primary method used to determine the primary outcomes of the studies conducted (discussed in Chapters 4 and 5).

Chapter 3 will then report that there are limited studies that have examined the effects of exercise training on cerebrovascular function and its association with cognitive function in middle-aged and older adults. The chapter primarily examines the benefits of exercise training on cerebrovascular and cognitive function in ageing. This is achieved by firstly, reviewing the impact of ageing on cerebrovascular function, cognition and structural changes within the brain. Secondly, the effects of aerobic exercise training (AT) and resistance exercise training (RT), alone and in combination (CT), on structural adaptations, cerebral blood flow (CBF) and cognition in middle-aged and older adults are discussed. Thirdly, I have determined if there are any published randomised control trials examining the association between CBF and cognition function in this cohort. Finally, I have discussed why cerebrovascular structure and function and cognition may change following exercise training.

The conclusions and gaps of knowledge identified in Chapter 3 resulted in a cross-sectional study comparing adults who have undertaken regular AT over a large majority of their lifespan with older adults who are untrained and sedentary (Chapter 4). It highlights significant differences in cardiometabolic health status between both

groups. Chapter 4 also discusses the significant differences between cerebrovascular function and cognition between these groups. It notes that the sedentary older group were in fact obese and had reduced cardiometabolic status, thus highlighting that these older adults are suitable targets for an intervention study to investigate the effect of AT on cerebrovascular function and cognition.

Chapter 5 reports the effects of AT undertaken to four days per week for 16 weeks on cerebrovascular and cognitive function in sedentary, obese, older adults in a randomised control trial. This chapter also attempts to resolve a current gap in knowledge by determining if a minimum amount of AT is required to elicit a positive response in cerebrovascular function or cognition (i.e. determine if a dose-response relationship exists between the amount of AT undertaken and changes in overall brain health). Finally, Chapter 6 will summarise and discuss the findings from these studies and draw conclusions regarding the effect of AT on cerebrovascular function and cognition in older adults, as well as suggests the future directions

1.1 Research aims, objectives and hypotheses

The overall aim of this research was to investigate the effects of regular AT on cerebrovascular function and cognition in older adults. To achieve this objective three research studies were undertaken:

Study 1 (Chapter 3): Systematic literature review that was written narratively that aimed to examine the benefits of exercise training on cerebrovascular and cognitive function in ageing.

Study 2 (Chapter 4): Cross-sectional study that aimed to investigate cerebrovascular function and cognition in aerobic exercise trained and untrained older adults. It was hypothesised that cerebrovascular function and cognition would be higher in aerobic exercise trained compared to untrained older adults.

Study 3 (Chapter 5): Randomised control trial that aimed to determine whether mixed-intensity AT for 16 weeks could improve cerebrovascular function and cognition in a sedentary, older, overweight or obese cohort who are at risk of

cognitive decline and dementia. It was hypothesised that AT would improve both cognition and cerebrovascular function. It was also hypothesised that the greater the dose of AT, the greater the improvements in cerebrovascular and cognitive function.

CHAPTER 2: LITERATURE REVIEW

2.1 Ageing

Ageing is typically associated with the gradual decline of various physiological and psychological processes. Older adults are more likely to develop chronic diseases and have a propensity towards hypertension, cardiovascular diseases and impaired glucose utilisation, obesity, reduced kidney function, and cognitive function (Paterson, Jones & Rice 2007; Taylor 2014). This may be due to the chronic low-grade inflammatory state associated with ageing, as well as the decline in endothelial function – both of which are described as the primary phenotypes associated with senescence (Woods et al. 2011; Toda 2012). Ageing is also associated with the gradual decline in lean mass (sarcopenia), cardiorespiratory fitness and cognitive performance, as well muscle strength, endurance, flexibility and mobility (Paterson, Jones & Rice 2007; Taylor 2014). As these decline (particularly if this is accelerated due to a chronic condition such as dementia), the ability of an individual to perform general tasks associated with daily life becomes more challenging and their overall health and wellbeing deteriorates (Paterson, Jones & Rice 2007; Taylor 2014).

Of the changes described above, it is potentially the ability to maintain adequate cognitive function throughout the lifespan that is most vital in maintaining our quality of life. This is because cognitive function plays a large part in our overall health and wellbeing and quality of life as we age, especially since a decrease in this is related to a reduction in psychological health, particularly mood and behaviour (AIHW 2012; Iadecola 2013; Brown, Hansnata & La 2017). Specifically, a decline in our cognitive ability can reduce our ability to make decisions on a regular basis and problem-solve, interact socially, maintain work performance and employment, perform necessary activities of daily living and maintain independence, as well as others – all of which may reduce sense of self-worth, health and wellbeing and quality of life (Salthouse 2012). In any case, as we age and these processes decline collectively, an individual may eventually lose the ability to function independently and socially, thus resulting in increased care and, eventually, institutionalisation (AIHW 2018a). Hence, it is imperative to find and implement strategies that can provide a positive impact on a person's quality of life and assist in reducing the burden associated with the loss of independence on healthcare systems.

The need to find and implement strategies that can improve a person's quality of life as they age is vital. This is because the global population is ageing, particularly in countries such as Australia (WHO 2018; ABS 2019). Over the last 20 years, there has been a steady increase in the proportion of Australians who are classified as older (i.e. 65 years or older) (ABS 2019). In 2000, the percentage of the Australian population who were classified as older was approximately 12% (ABS 2019). This percentage has now increased to approximately 17% of the entire population (ABS 2019). Additionally, the rate of those who are classified as older in Australia is expected to grow steadily in the future (ABS 2019). The increased rate of ageing in Australia is also occurring in conjunction with an increased rate of both physical inactivity and cardiometabolic diseases, such as obesity (Figure 2.1)

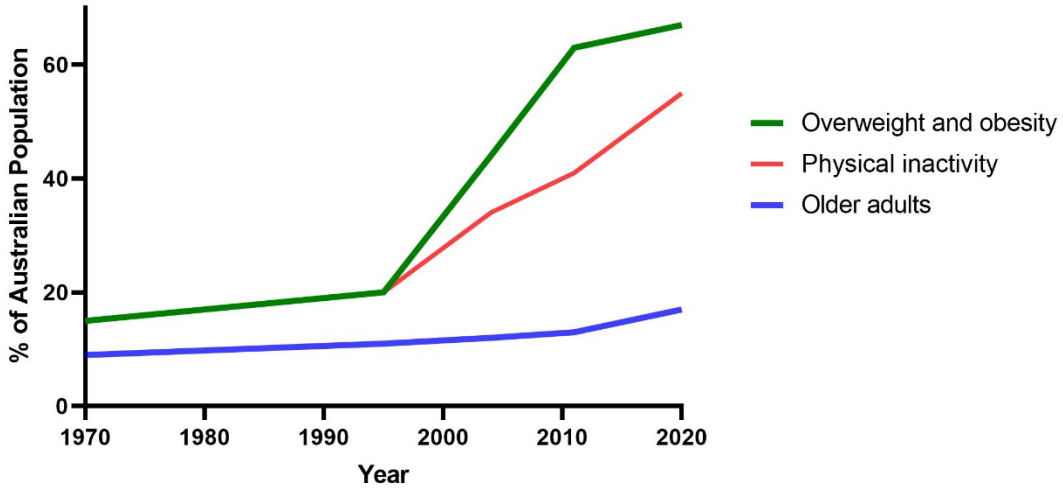

Figure 2.1: The increase in the rates of overweight and obesity, physical inactivity and ageing over the last 50 years in Australia. It is evident from the figure that all three are increasing as time progresses. Data sourced for this figure was obtained from AIHW (2018a, 2018b); ABS (2019); AIHW (2020a, 2020b).

2.2 Obesity

Overweight and obesity are defined predominantly by body mass index (BMI). A BMI of between 25 and 30 kg/m^2 indicates that an individual is overweight and a

BMI of more than 30 kg/m^2 would classify that individual as obese (AIHW 2020b). These classifications have guided the current data that has been generated internationally. The data indicates that obesity is an emergent epidemic that is burdening global public-health systems, especially in high-income countries, such as Australia. For example, in the 1970s fewer than 15% of Australians were classified as overweight and obese with the rate increasing to 20% by 1995 (Hayes et al. 2017). Currently, Australia possesses one of the highest incidences of overweight and obesity globally, affecting 67% of adults (ABS 2019; AIHW 2020b). Further, approximately 84% of men aged between 55 and 85 and approximately 73% of females of the same age are classified as overweight and obese (ABS 2019; AIHW 2020b). These statistics are also less favourable for those living in non-metropolitan areas of Australia, such as the Toowoomba and Ipswich regions (collectively the Darling Downs and West Moreton region), as well as the South-West Queensland region. In these areas the rate of obese adults over 18 years increases to over 72% (AIHW 2020b). The progress towards reducing this target in both metropolitan and non-metropolitan Australia is poor and there are no signs that this trend is starting to lessen (Tolhurst et al. 2016; AIHW 2020b).

The poor progress in reducing obesity globally is an issue because obesity is a pathogenic condition. It is a cardiometabolic disease. In simplistic terms obesity results when there is an energy imbalance, where intake exceeds output resulting in increased adiposity (Bliss & Whiteside 2018). However, obesity is not a simple matter of failing to maintain energy homeostasis. It is a consequence of complex interactions among genetic, environmental, socioeconomic, psychological and dietary factors, which manifest physically as increased adiposity, chronic low-grade inflammation, dysbiosis, increased neurogenic tone and hormonal imbalances (Bliss & Whiteside 2018). These obesogenic factors promote the development of comorbidities including cardiovascular diseases and mental illnesses such as depression, anxiety and dementia and increase morbidity and mortality (Table 2.1). Obesity both exacerbates these conditions and promotes the pathogenesis of these diseases, thus demonstrating that obesity is a central condition that promotes and exacerbates chronic disease development and complications (Bliss & Whiteside

2018). Hence any strategies that improve obesity outcomes and reduce the complications associated with obesity are needed. Given that obesity in simplistic terms is defined as disproportion of energy status, it would be logical to explore the efficacy of exercise and physical activity (i.e. energy output) in improving these outcomes and obesity-related comorbidities.

Table 2.1: Overweight and obesity comorbidities in different physiological systems.

Physiological system	Comorbidities	References
Cardiovascular	Stroke Myocardial infarction Angina Coronary heart disease Cardiac failure Hypertension Deep vein thrombosis Pulmonary embolism Dyslipidaemia	(Wilson et al. 2002; Stein, Matta & Goldman 2011; Lu et al. 2014; Writing Group et al. 2014; Klovaite, Benn & Nordestgaard 2015; Aune et al. 2016)
Gastrointestinal	Non-alcoholic fatty liver disease Gallbladder and pancreatic disease Gastro-oesophageal reflux disease Liver, colorectal, oesophageal, gallbladder and pancreatic cancers	(Chen, Xiong & Wu 2012; Eslick 2012; Stinton & Shaffer 2012; DiBaise & Foxx-Orenstein 2013)
Endocrine	Non-insulin dependent diabetes mellitus Gestational diabetes mellitus Polycystic ovary syndrome	(Flegal et al. 2007; Arendas, Qiu & Gruslin 2008; Yang et al. 2008)
Genitourinary	Chronic kidney disease/chronic renal failure Kidney stones Renal and prostate cancers Urinary incontinence Erectile dysfunction Buried penis	(Bump et al. 1992; Esposito et al. 2004; Ejerblad et al. 2006; Flegal et al. 2007; Polednak 2008; Munkhaugen et al. 2009; Pestana et al. 2009; Stinton & Shaffer 2012; Grima & Dixon 2013)
Pulmonary	Obstructive sleep apnoea Obesity hypoventilation syndrome Asthma Chronic obstructive pulmonary disease	(Guerra et al. 2002; Steuten et al. 2006; Eisner et al. 2007; O'Donnell, Ciavaglia & Neder 2014)
Musculoskeletal	Osteoarthritis Spinal disc disorders and lower back pain Tendons, fascia and cartilage disorders Foot pain Impaired mobility	(Molenaar et al. 2008; Tukker, Visscher & Picavet 2009; McAdams DeMarco et al. 2011; Grima & Dixon 2013)
Reproductive	Menstrual disorders	(Bianchini, Kaaks & Vainio 2002; Arendas,

	Pregnancy complications, such as miscarriage and intrauterine foetal death Birth defects Infertility Breast (post-menopause), endometrial and ovarian cancers	Qiu & Gruslin 2008; Polednak 2008; Grima & Dixon 2013)
Mental/Psychological	Dementia Depression Eating disorders Reduced health-related quality of life Psychosocial stigma and poor self esteem	(Beydoun, Beydoun & Wang 2008; Molenaar et al. 2008; Grima & Dixon 2013; Hilbert et al. 2014)
Integumentary	Increased sweat gland activity Impaired epidermal barrier repair Striae Cellulitis Hyperpigmentation Intertrigo Lymphoedema	(Löffler, Aramaki & Effendy 2002; Yosipovitch et al. 2004; Yosipovitch, DeVore & Dawn 2007)
Immune	Disruption of lymphoid tissue integrity Changes in leukocyte development, phenotypes and activity Decreased immunity from infection Decreased efficacy of vaccines Increased pro-inflammatory markers, such as IL6 and TNFα	(Ghanim et al. 2004; Bremer et al. 2011; Kanneganti & Dixit 2012; Sheridan et al. 2012)

Reference: Bliss and Whiteside (2018).

2.3 Physical inactivity

Insufficient physical activity is described as not meeting the recommended physical activity guidelines outlined by a governing body, such as the Australian Department of Health. The current Australian physical activity guidelines recommend that those who are 65 years or older participate in at least 30 minutes of moderate activity daily and incorporate muscle strengthening activities (AIHW 2020a). Adults aged between 18 and 64 years are recommended to participate in at least 150 minutes of moderate to vigorous intensity exercise per week and incorporate muscle strengthening activates twice per week (AIHW 2020a).

Physical inactivity is also associated with chronic diseases (Table 2.2). One-third of the burden due to physical inactivity in Australia in 2011 was due to coronary

heart disease (39,262 disability-adjusted life years), which was followed by dementia (18% of total physical inactivity burden), diabetes (16%), bowel cancer (13%) and stroke (12%) (AIHW 2017).

Table 2.2: Burden (disability-adjusted life years) due to physical inactivity by disease.

Disease	Number	%
Coronary heart disease	39,262	33.6
Dementia	20,752	17.8
Diabetes	19,065	16.3
Bowel cancer	15,003	12.9
Stroke	13,555	11.6
Breast cancer	7,813	6.7
Uterine cancer	1,226	1.1

Reference: AIHW (2017).

There is a tendency toward participating less in physical activity as we age, whether that be structured exercise training or incidental physical activity (Taylor 2014; Bennie et al. 2016; AIHW 2018a). Younger generations in developed countries, such as Australia, are exercising less than previous generations, which is of growing concern given we are an ageing population (AIHW 2018a). There are nearly 4 million older Australians aged over 65 years and of these over 69% are classified as insufficiently physically active (ABS 2019; AIHW 2020a). Further, the rate of physical inactivity of those living in non-metropolitan areas of Australia, such as the Darling Downs and West Moreton region, as well South-West Queensland, also increases when compared with metropolitan areas (AIHW 2020a). This is an issue because not only is exercise and physical activity important to reduce the risk of developing obesity, but because they have also been associated with a decreased risk of developing chronic cardiometabolic health conditions, such as hypertension, diabetes and obesity (Taylor 2014; Lin et al. 2015; Piercy et al. 2018; Seals, Nagy & Moreau 2019; Ashton et al. 2020). A recent systematic review also determined that being physically active in our older years, reduces the risk not only of cardiovascular mortality, but also cancers of the prostate and breast, fractures, disability,

psychological diseases such as depression and cognitive decline including the development of dementia (Cunningham et al. 2020). These findings highlight that there is also overlap between being physical activity and how they may lessen the impact of overweight and obesity comorbidities that are shown in Table 2.1

The evidence gathered around improvements in cardiometabolic health that exercise can induce are well described (Lin et al. 2015; Seals, Nagy & Moreau 2019; Ashton et al. 2020). Exercise is fundamental in maintaining lean mass and cardiorespiratory fitness, as well as muscle strength, endurance, flexibility and mobility which are required to maintain quality of life (Paterson, Jones & Rice 2007; Taylor 2014; Piercy et al. 2018). Hence, exercise training and physical activity may an inexpensive and effective treatment and lifestyle intervention option that can favourably impact our overall health and wellbeing.

Our overall health and wellbeing and quality of life is also fundamentally associated with our ability to maintain our brain health (AIHW 2012). Two important factors that are associated with maintaining overall brain health throughout the lifespan are cerebrovascular function and cognition (Salthouse 2012; Bangen et al. 2014; Toth et al. 2017). While physical activity and exercise have been shown to improve cardiometabolic health, the evidence and impact around the effects of exercise and physical activity on cerebrovascular and cognitive functions and their decline, is not as well defined. It is important to determine the effect of lifestyle factors, such as participating in physical activity, on cerebrovascular function and cognition, because a decline in either of these functions can predispose an individual to developing a neurodegenerative disease, such as dementia.

2.4 Dementia

Dementia is a cluster of irreversible conditions resulting in the gradual decline of cognitive function and psychological health, which is determined clinically using a wide range of screening tools (AIHW 2012; Iadecola 2013; Brown, Hansnata & La

2017). These tools include the Mini-Mental State Examination, the 7-minute screen, the International Statistical Classification of Diseases and Related Health Problems and the Diagnostic and Statistical Manual of Mental Disorders (AIHW 2012; Iadecola 2013; Brown, Hansnata & La 2017). Over 100 different types of dementia based on different underlying pathologies are described however the three most common dementia types are Alzheimer's disease, vascular dementia and Lewy body dementia (AIHW 2018a). While each dementia type has distinctive end-stage features, it is the initial preceding events, such as the decline in cerebrovascular function, that may manifest into dementia that is of interest. This is because there is a large degree of overlap between dementia types and because it has been demonstrated that other than unmodifiable risk factors (age and a familial predisposition), cardiometabolic risk factors (Table 2.3) increase the likelihood of developing dementia in general (Gorelick et al. 2011; Iadecola 2013; Jellinger 2013).

Research into this area is of great importance given that the current worldwide incidence of dementia is more than 50 million people and is expected to treble in the next 30 years (WHO 2018; Nichols et al. 2019). Further, in developed countries such as Australia, the burden of dementia is increasing, where it is the first and second leading cause of total disease burden in Australian women and men respectively, as well as the second leading cause of death overall (Brown, Hansnata & La 2017; AIHW 2018a) (Table 2.4). While there are various unmodifiable factors that can lead to dementia (particularly age) it is not clear why dementia is becoming more prevalent. It has been shown that a causal relationship exists between the development of dementia and chronic health conditions that are associated with modifiable lifestyle factors, such as overweight and obesity, diabetes and physical inactivity, contributing to the development of cardiovascular disease, stroke and type 2 diabetes (Kokmen et al. 1996; Kalmijn et al. 2002; Prins et al. 2002; Seliger et al. 2004; Kuller et al. 2005; Scarmeas et al. 2009; Solomon et al. 2009; Ahtiluoto et al. 2010; Bunch et al. 2010; Anstey et al. 2014; AIHW 2018a; Sabia et al. 2018). All of these studies were population-based prospective cohort studies from Europe or the United States of America. Solomon et al. (2009) reported that raised total cholesterol concentrations, which can used to determine risk of cardiovascular disease, in midlife

were strongly associated with an increased dementia risk, where the higher the cholesterol the greater the risk of dementia. Bunch et al. (2010) investigated the risk of cardiovascular disease and dementia incidence directly rather than through the use of cholesterol as a marker and reported that cardiovascular disease, particularly atrial fibrillation, was significantly associated with dementia development in over 37,000 participants. Further, Bunch et al. (2010) concluded that atrial fibrillation also increased the risk of dementia-related death in individuals who suffered from dementia. Cardiovascular disease and increased cholesterol concentrations also place an individual at an increased risk of developing stroke. Kokmen et al. (1996) reported that within 12 months of suffering from an initial cerebral infarct the risk of developing dementia increased by nine times compared with the general population. Additionally, if dementia did not result within the first year, then those who had suffered from a stroke had a 50% increased risk of developing dementia than the general community thereafter. This was supported by Kuller et al. (2005) who reported that those with vascular disease stroke were likely to develop dementia. Ahtiluoto et al. (2010) reported that those who suffered from diabetes at the start of the study, had doubled the incidence of dementia and that this was mostly associated with a cerebral infarct following vascular pathology. The authors of this study also examined autopsies of those that died during follow-up, which was approximately 50% of the cohort. They indicated that those with diabetes had extensive vascular pathology and that this led to dementia. Further, the authors noted that vascular pathology alone was also associated with the development of dementia even in the absence of diabetes. Finally, Seliger et al. (2004) demonstrated that moderate renal impairment, which is a common complication associated with both cardiovascular diseases and diabetes, was associated with an excess risk of developing dementia and that this risk increased as renal impairment increased. These studies collectively demonstrate the impact cardiovascular diseases has on the development of dementia.

Cardiovascular diseases and their complications are largely associated with lifestyle choices and conditions that result from these choices such as obesity and diabetes. One of the earliest studies assessing the association between cigarette smoking and cognitive decline reported smoking during midlife was inversely proportional to cognitive performance and linked to cognitive decline in later life (Kalmijn et al. 2002). This was supported Anstey et al. (2014) who reported that reductions in

smoking reduced the risk of cognitive impairment and increased longevity. Further, Anstey et al. (2014) also demonstrated the same also was valid with regard to being sedentary and obese, in that reductions in obesity and improvements in exercise participation reduced the risk of cognitive impairment. Scarmeas et al. (2009) also reported that higher adherence higher levels of physical activity reduced dementia risk in older adults, as too did an adherence to Mediterranean-type diets. This also highlights the importance of diet on cognitive function and in an earlier study, Prins et al. (2002) reported that elevated homocysteine concentrations, which is an established marker for vascular disease and thromboses resulting from poor nutrition, vitamin deficiency, drug use and/or kidney disease, were strongly associated with decreased cognitive performance and global cognition in older patients independent of any neural structural changes. This suggests that cognitive decline may not only be due structural changes, but rather changes in vascular health. Finally, Sabia et al. (2018) reported that dementia risk was significantly increased in individuals who drink excessively in midlife as well as those who completely abstained from alcohol in midlife. Hence, it is clear from these studies that lifestyle choices have a major impact on overall brain health as we age and that these are largely associated with an increased risk of developing a cardiovascular disease.

These modifiable risk factors listed above have two major characteristics in common, endothelial dysfunction and chronic low-grade inflammation (Hadi, Carr & Al Suwaidi 2005), which is described in the section below as well as in Chapter 3. In any case, there are currently no successful clinical and/or curative treatments, and this has led to increased research aimed at improving modifiable lifestyle factors that may prevent or reduce its occurrence. Accordingly, there is an urgent need for evidence-based interventions to prevent and reduce the risk of developing dementia, particularly by focusing on improving parameters such as cerebrovascular function – a decline of which can predispose an individual to developing dementia (Toth et al. 2017).

Table 2.3: Cardiometabolic risk factors associated with the occurrence of dementia.

Risk factor	Example	Reference
Behavioural	Sedentary lifestyle Smoking Alcohol abstinence during midlife Excessive alcohol intake (>14 standard drinks/week)	(Kalmijn et al. 2002; Scarmeas et al. 2009; Sabia et al. 2018)
Metabolic	Obesity Hypertension Dyslipidaemia Homocysteinaemia	(Prins et al. 2002; Kuller et al. 2005; Solomon et al. 2009; Anstey et al. 2014)
Vascular diseases	Stroke Diabetes Atrial fibrillation Chronic renal disease	(Kokmen et al. 1996; Seliger et al. 2004; Ahtiluoto et al. 2010; Bunch et al. 2010)

Table 2.4: Summary of Australian dementia statistics.

Present	2025	2056	References
~ 400 000 diagnosed with dementia ~ 55:45 female: male ratio	~ 550 000 to be diagnosed with dementia ~ 55:45 female: male ratio	~ 1.12 million to be diagnosed with dementia ~ 60:40 female: male ratio	(Brown, Hansnata & La 2017; AIHW 2018a)
~ 250 people/day are diagnosed with dementia	~ 318 people/day to be diagnosed with dementia	~ 650 people/day to diagnosed with dementia	(Brown, Hansnata & La 2017; AIHW 2018a)
~ 27 000 diagnosed with younger onset dementia	~ 29 000 to be diagnosed with younger onset dementia	~ 42 000 to be diagnosed with younger onset dementia	(Brown, Hansnata & La 2017; AIHW 2018a)
• 2nd leading cause of death • Leading cause of death in females • ~ 64% of dementia-related deaths are female • Accounts for 11% of mortality in females • 2nd leading cause of death in males • Accounts for 5.4% of mortality in males	Unknown	Unknown	(Brown, Hansnata & La 2017; AIHW 2018a)
Costs ~ $9 billion to the government annually	Expected to cost ~ $18 billion to the government annually	Expected to cost ~ $36 billion to the government annually	(Brown, Hansnata & La 2017; AIHW 2018a)
Leading cause of disability in those over 65 years	No change	No change	(Brown, Hansnata & La 2017; AIHW 2018a)
3rd leading cause of disability overall	Unknown	Unknown	(Brown, Hansnata & La 2017; AIHW 2018a)

2.5 Cerebrovascular function

In simple terms, cerebrovascular function describes the ability of the blood vessels to perfuse the brain with blood, respond to increased cerebral metabolism and environmental changes, as well as ensure that this supply of blood is adequately regulated at all times (Smith & Greenberg 2009; Duchemin et al. 2012; Toth et al. 2017). This section will extend from this simplistic definition to describe what cerebrovascular function is and why it is of importance.

The brain does not store energy and, therefore, requires a constant supply of blood to function. The brain is one of the most metabolically active organs in the body and receives approximately 15% of the total cardiac output at rest (Xing et al. 2017). The supply of arterial blood to the brain via the cerebral circulation (Figure 2.2) is referred to as cerebral blood flow (CBF), which is tightly regulated and varies according to metabolic demands. CBF can be determined by blood viscosity, the degree of vasodilation and cerebral perfusion pressure, and it is regulated by both autoregulation (macrovascular function) or neurovascular coupling (NVC; microvascular function) (Duchemin et al. 2012). The vasculature supplying certain highly active and metabolically demanding regions of the brain are typically dilated to ensure that these demands are met (Mohr, Lazar & Marshall 2011). For example, the middle cerebral artery (MCA), which is an intracranial vessel that supplies blood to the majority of the lateral surfaces of each hemisphere, the lateroinferior frontal lobe, lateral temporal lobe and the basal ganglia and capsules, is maximally dilated and changes minimally in response to altered concentrations of carbon dioxide (CO_2) (Serrador et al. 2000; Mohr, Lazar & Marshall 2011). The dilatation of the MCA is a controversial and unclear topic. A previous study, which directly measured changes in MCA diameter during hyperventilation using magnetic resonance imaging, indicated that the diameter did not change, thus suggesting that it is maximally dilated (Valdueza et al. 1997). This was supported by a later study, which reported no change in MCA diameter during CO_2 manipulation (Serrador et al. 2000). However, more recent evidence suggests that MCA diameter changes are complex, as it does not change during ramping (i.e. gradually increasing CO2) but did so minimally (< 2.0%) during steady-state hypercapnia in young adults aged 19 – 25

years (Al-Khazraji et al. 2021). In any case if the MCA does dilate it is only minimally. This is because the MCA is a conduit vessel that bifurcates from the internal carotid artery which is an extracranial vessel supplying the intracranial vessels with blood, thus any change in CBF velocity (CBF_V) reflects changes in the flow rate of the microvasculature downstream of the MCA. Hence, the MCA is the easiest and an ideal vessel to locate with ultrasonography and assess when measuring cerebrovascular responsiveness (CVR) to stimuli such as hypercapnia (increased partial pressure of carbon dioxide (PCO_2) in the blood) and cognitive tasks resulting in increased neuronal metabolism, particularly since blood flow is only anterograde (i.e. toward the insonation probe) and not retrograde like other vessels that bifurcate from the extracranial vessel (Serrador et al. 2000).

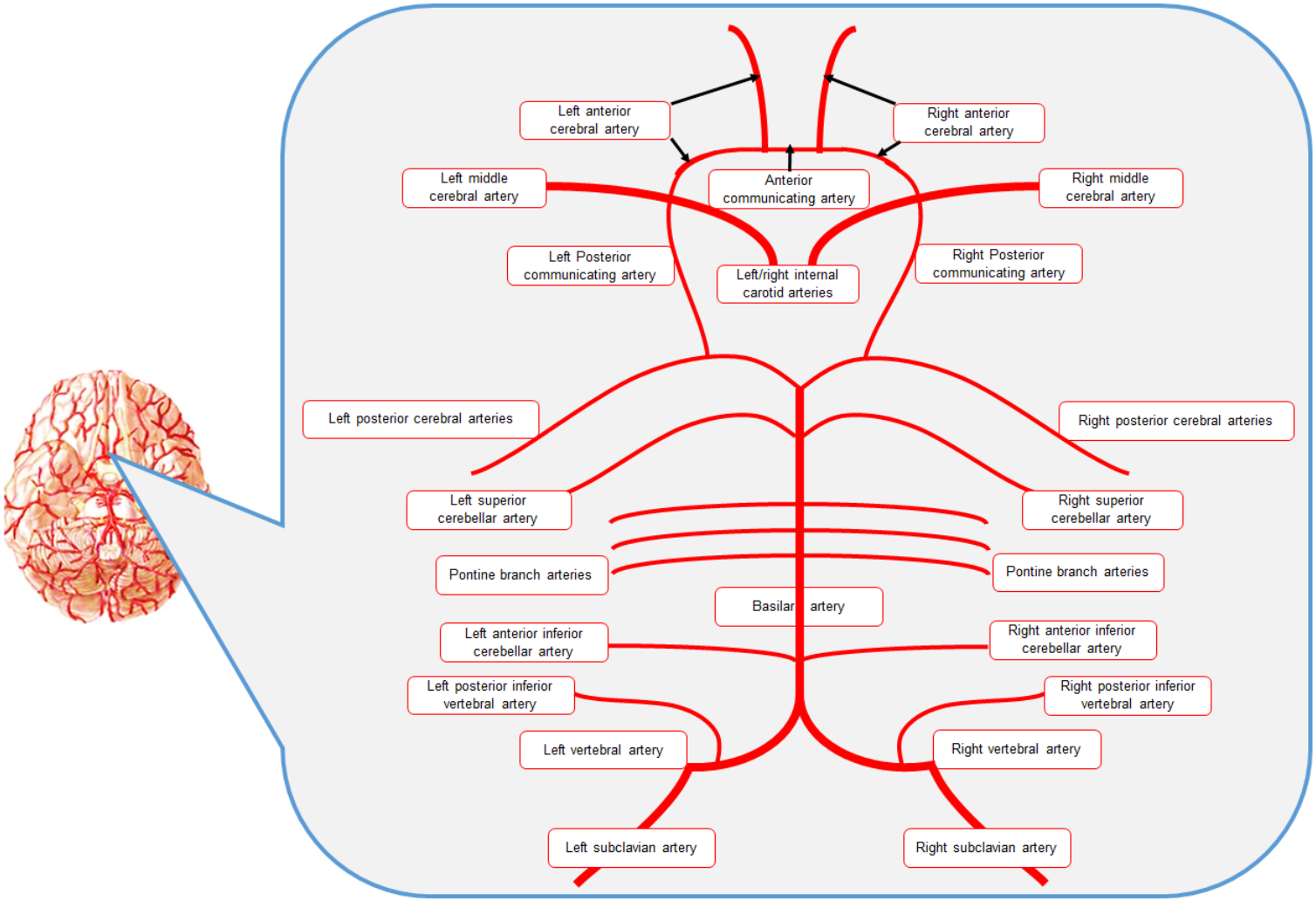

Figure 2.2: The cerebral circulation. Blood enters the brain via the anterior or the posterior circulation. Both areas meet at the Circle of Willis, which consists of the posterior cerebral arteries, the anterior and posterior communicating arteries, the anterior cerebral arteries and the internal carotid arteries. These arteries are interconnected in order to alleviate any occlusions, blockages or decreases in blood flow that may occur, thus ensuring adequate blood flow to cerebral regions and preventing an ischaemic event.

The physiological mechanism that ensures that CBF is maintained and kept constant during changes in systemic blood pressure is referred to as cerebrovascular autoregulation (Duchemin et al. 2012). This is stimulated by chemical and mechanical stimuli, which induce a myriad of molecular pathways that result in modulating the vascular resistance applied to the cerebral macrovasculature and, therefore, the CBF (Duchemin et al. 2012; Toth et al. 2017). Further, NVC is the complex interaction between neuronal metabolic demands and local haemodynamic changes, which ensures that metabolic demands are met by the microvasculature (Duchemin et al. 2012; Toth et al. 2017). The increase in metabolism needs to be supported by an increased availability of nutrients and oxygen short-term and an increased availability of growth factors and other chemical messengers to aid in neurogenesis, synaptogenesis, interneural signal transduction and overall anatomical maintenance. These are supplied by the cerebral circulation, thus indicating that any decline in microvascular function would limit these processes, essentially due to failure of the cerebrovasculature to meet the metabolic needs of the brain. Finally, the mechanisms that lead to the regulation of CBF, which allow for the prevention of both ischaemia and hyperaemia at any time, are extremely complex and yet to be fully elucidated. It is known though that the upregulation of endothelial nitric oxide synthase (eNOS) and the subsequent synthesis and release of nitric oxide (NO) from the endothelium is a fundamental component involved in both cerebrovascular autoregulation and NVC (Duchemin et al. 2012; Toth et al. 2017).

The endothelium plays an important role in maintaining vascular homeostasis and maintaining cardiovascular health, primarily due to its location and the functional capacity of the endothelial cells to respond to different stimuli within its environment (Behrendt & Ganz 2002). In particular, the endothelium is pivotal in the acute regulation of vasomotor tone and, therefore, systemic blood flow and blood pressure, as well as long-term blood vessel haemostasis, inflammation, angiogenesis, and a myriad of other functions (Behrendt & Ganz 2002; Rossman et al. 2018). This is achieved largely through the release of NO, which is a vasoprotective molecule and one of the most potent vasodilators within the human body (Rossman et al. 2018).

Endothelium-dependent dilation is mediated primarily by the synthesis of NO by eNOS and its release onto juxtaposed vascular smooth muscle (Toda 2012; Rossman et al. 2018) (Figure 2.3). The consequent smooth muscle relaxation results in vasodilation and increased blood flow (Toda 2012; Rossman et al. 2018). The endothelium is also vital for maintaining cerebrovascular function and health. It has been demonstrated that endothelial-derived NO prevents reductions in CBF, CBF_V and cerebral hypoperfusion (Hylland & Nilsson 1995; DeWitt et al. 1997; Hortobágyi et al. 2007; Toth et al. 2017). However, as we age, the endothelium's ability to produce adequate concentrations of NO to maintain vascular health diminishes (Toth et al. 2017). Further, the decline in endothelial function contributes to a 0.38 – 0.45% reduction in CBF per year from midlife onwards in healthy individuals, thus indicating that ageing is the primary risk factor associated with cognitive impairment and that endothelial dysfunction is one of the primary phenotypes associated with senescence (Parkes et al. 2004; Chen, Rosas & Salat 2011; Toda 2012; Joris et al. 2018). This indicates the importance of ensuring both endothelial health and NO bioavailability within the cerebral circulation are maintained throughout the lifespan.

2.6 Methods used to determine cerebrovascular function

Regional and global CBF to assess cerebrovascular function can be measured either directly or indirectly. Direct methods include single-photon emission computerised tomography, positron emission tomography, magnetic resonance imaging and arterial spin labelling. These are accurate and precise, but can be invasive, expensive, time-consuming, require specific timeframes between recurrent testing to reduce radiation exposure from radiotracers, and require the installation of dedicated medical imaging technology units (Willie et al. 2011; Joris et al. 2018; Miyazawa et al. 2018). In contrast, transcranial Doppler ultrasonography (TCD) (Figure 2.4), which is an indirect method to assess cerebrovascular function, as it is not able to directly measure cerebral perfusion and the blood delivered to a particular brain region, does not require exposure to ionising radiation, provides high temporal resolution, is non-invasive, quick, portable, and relatively inexpensive (Willie et al. 2011; Joris et al. 2018; Miyazawa et al. 2018). TCD is also routinely use clinically as a tool to quickly

assess for conditions such as ischaemia stroke, subarachnoid haemorrhage and brain death. TCD, however, does require an experienced operator, in comparison to the direct methods which are largely automated (Willie et al. 2011). TCD has been validated for assessing cerebrovascular function; there are good correlations between measurements and conclusions from this technique when compared to the direct methods listed above (Figure 2.5) (Serrador et al. 2000; Miyazawa et al. 2018). Specifically, CBF_V through the MCA correlated significantly with total CBF and perfusion of specific brain segments measured by single-photon emission computerised tomography (a direct method) (Miyazawa et al. 2018). The association between total CBF and CBF_V through the MCA was greater when a TCD could measure and determine the cross-sectional area of MCA as well as CBF_V through the MCA (Miyazawa et al. 2018). Finally, single-photon emission computerised tomography measurements of CBF in the temporal and frontal lobes correlated strongly with CBF_V through the MCA, thus indicating that the MCA is a suitable target to determine differences in cognitive stimuli that are associated with these regions of the brain (Miyazawa et al. 2018). The correlations performed by Miyazawa et al. (2018) also indicated that TCD is most useful for assessing regional CBF rather than total CBF, although it could potentially be estimated if the MCA diameter could be determined. In any case, the findings of this study indicate that the TCD is an appropriate and validated tool used to measure cerebrovascular function in the absence of an expensive and direct method.

TCD provides a continuous reading of CBF_V through the larger cerebral arteries, such as the MCA (Figure 2.4), by using a transcranial ultrasound probe positioned over the thinner areas of the skull (Willie et al. 2011). In order to obtain the ideal insonation angle to view the MCA and accurately assess CBF_V through the MCA, the probe is placed over either the anterior, middle or posterior transtemporal window (Willie et al. 2011). Once in position, basal CBF_V in the MCA is determined followed by CVR, i.e. the increase in CBF_V which occurs during a physiological (e.g. hypercapnia) or psychological (e.g. cognitive battery) challenge, the latter being a measure of NVC (Serrador et al. 2000; Willie et al. 2011). The MCA, being a large conduit vessel, dilates minimally during hypercapnia or a cognitive challenge. Hence, the increase in CBF_V is primarily attributable to dilation of the microvasculature downstream of the MCA in response to local chemical changes

induced by the physiological or psychological challenge (Serrador et al. 2000; Willie et al. 2011). Simply put, CVR is a quantitative measure of the potential of the cerebral microcirculation to dilate in response to physical or chemical stimuli and is a surrogate measure of local endothelial function. How this can be visualised using TCD is summarised in Figure 2.4. Hence, TCD is a valid technique that can be employed to assess cerebrovascular function in both clinical and research settings. In the latter, it can be used to quantitate potential improvements in response to interventions administered to populations at risk of accelerated cognitive decline. Finally, it is also a valid technique to measure the response of the cerebrovasculature when the brain is required to work and increases its metabolism. Simply, it is an invaluable tool that allows us to measure NVC. This is of importance because both cerebrovascular and cognitive function should be interpreted together, where possible, and not as separate functions (Bangen et al. 2014).

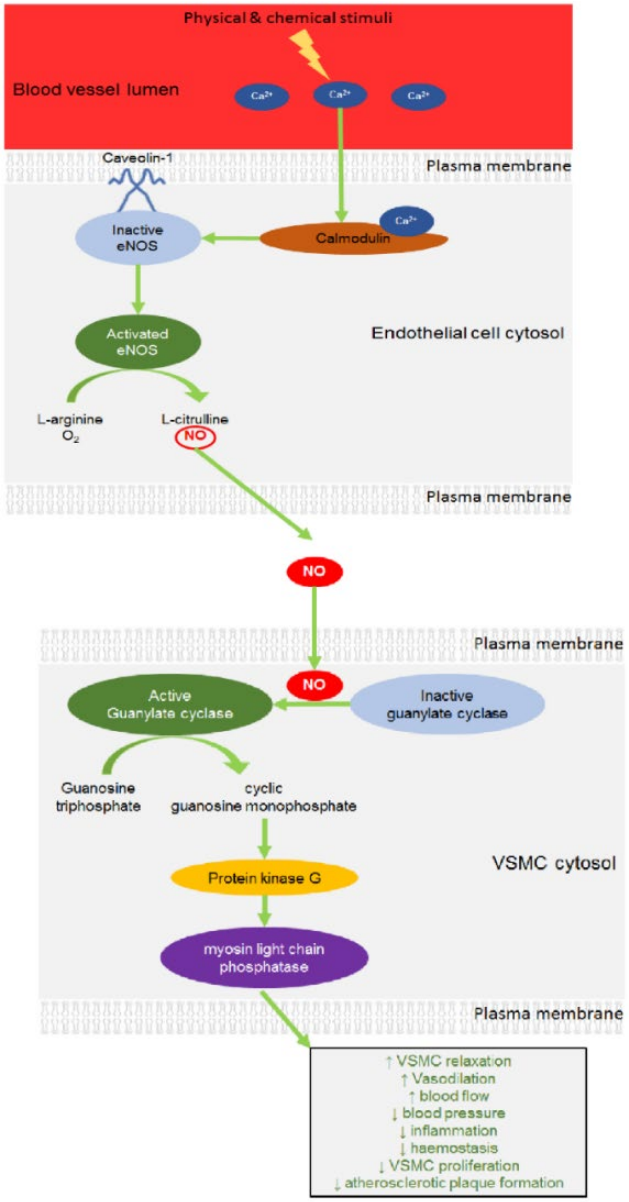

Figure 2.3: The mechanism and effects of endothelial nitric oxide synthase (eNOS) derived nitric oxide (NO). NO is synthesised and released by nitric oxide synthases (NOS) of which there are three isoforms, inducible NOS (iNOS), neuronal NOS (nNOS) and endothelial NOS (eNOS). These enzymes produce NO when they catalyse the transformation of L-arginine and oxygen to L-citrulline, in the presence of oxygen and various cofactors, such as calmodulin (Toda 2012; Rossman et al. 2018). However, only eNOS is present in the endothelium and is, therefore, associated with endothelium-dependent dilation (Toda 2012; Rossman et al. 2018). Inactive eNOS is membrane-bound to caveolin-1, but as cytosolic calcium (Ca^{2+}) increases in response to physical (e.g. shear stress) and chemical (e.g. cytokine-induced) stimuli, calmodulin becomes activated and signals eNOS to migrate to the cytosol and synthesise NO (Toda 2012). NO then diffuses from the endothelium to the neighbouring vascular smooth muscle cells (VSMC), where it signals guanylate cyclase (GC) to convert guanosine triphosphate (GTP) into cyclic guanosine monophosphate (cGMP), which subsequently activates protein kinase G (PKG) and, in turn, stimulates myosin light chain phosphatase (MLCP) to induce VSMC relaxation (Toda 2012). Additionally, this results in enhanced vasodilation, improved blood flow and decreased blood pressure, as well as the regulation of haemostasis, inflammation and VSMC proliferation and phenotype-switching, thus preventing atherosclerotic plaque formation (Toda 2012; Rossman et al. 2018).

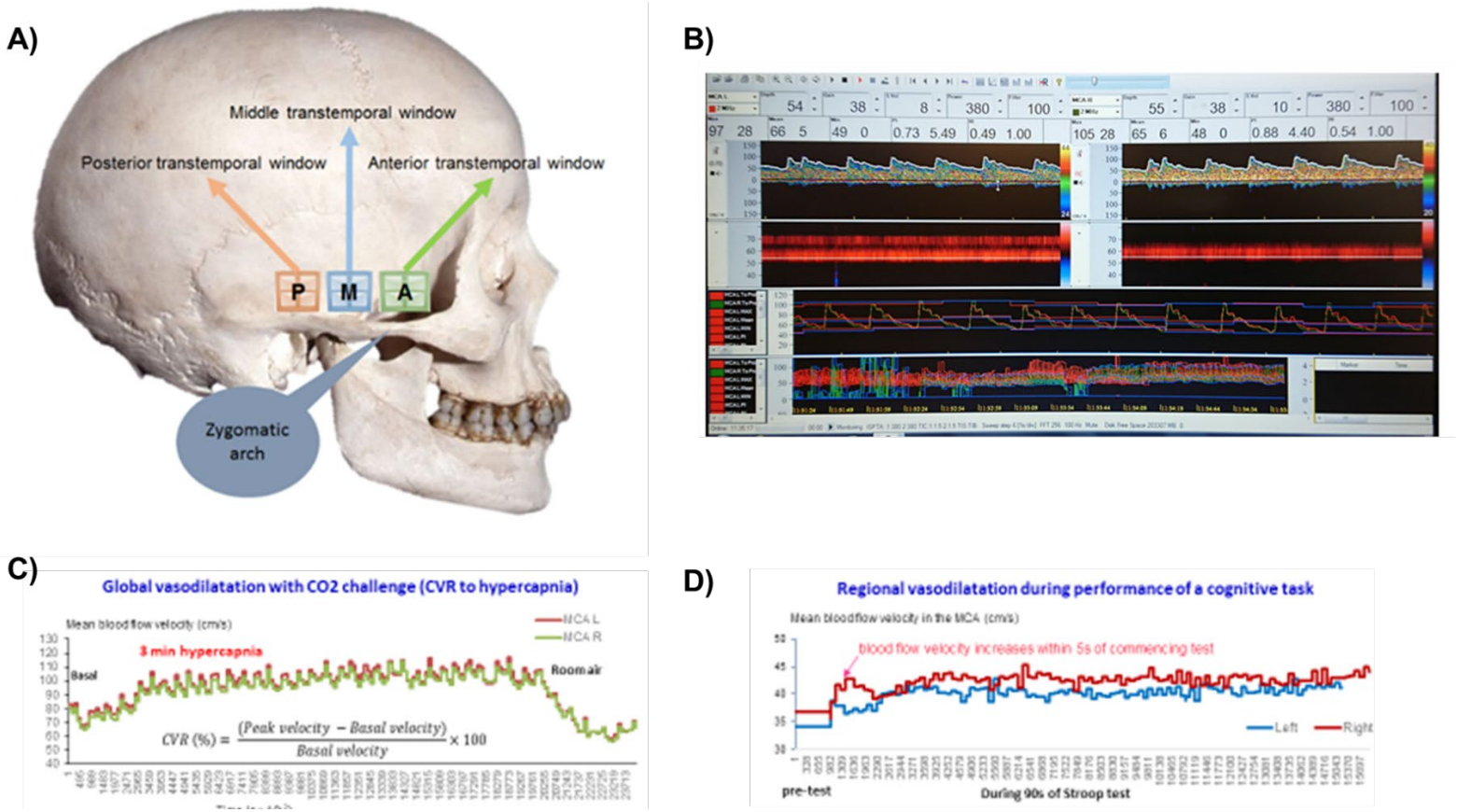

Figure 2.4: The location of the transtemporal windows (A), a transcranial Doppler ultrasonography recording of cerebrovascular blood flow velocity (CBF_V) (B), and visualisations of a complete data set reflecting cerebrovascular responsiveness (CVR) to hypercapnia (C) and cognitive stimuli (D). All three windows shown in (A) lie superior to the zygomatic arch. The anterior transtemporal window is immediately superior to the anterior process of the arch and the posterior lies anterior to the ear toward the posterior end of the arch, while the middle transtemporal window is located between them (Willie et al. 2011). The transcranial Doppler ultrasonography recording shown in (B) shows the depth of the middle cerebral artery (MCA), the minimum, maximum and mean CBF_V, the cerebral pulsatility index, the resistive index, wave analysis and the flow of blood toward the probes, as well as a second-by-second wave analysis and graph plot of the minimum and maximum CBF_V. The data sets demonstrate the increase CBF_V in the MCA following application of a stimulus which reflects the ability of the cerebral microvasculature vasodilate in response to either a physiological (C) or cognitive stimulus (D), which reflects the ability of the microvasculature to respond to increased neuronal metabolism. These changes are reflected by an increased in CBF_V in the MCA

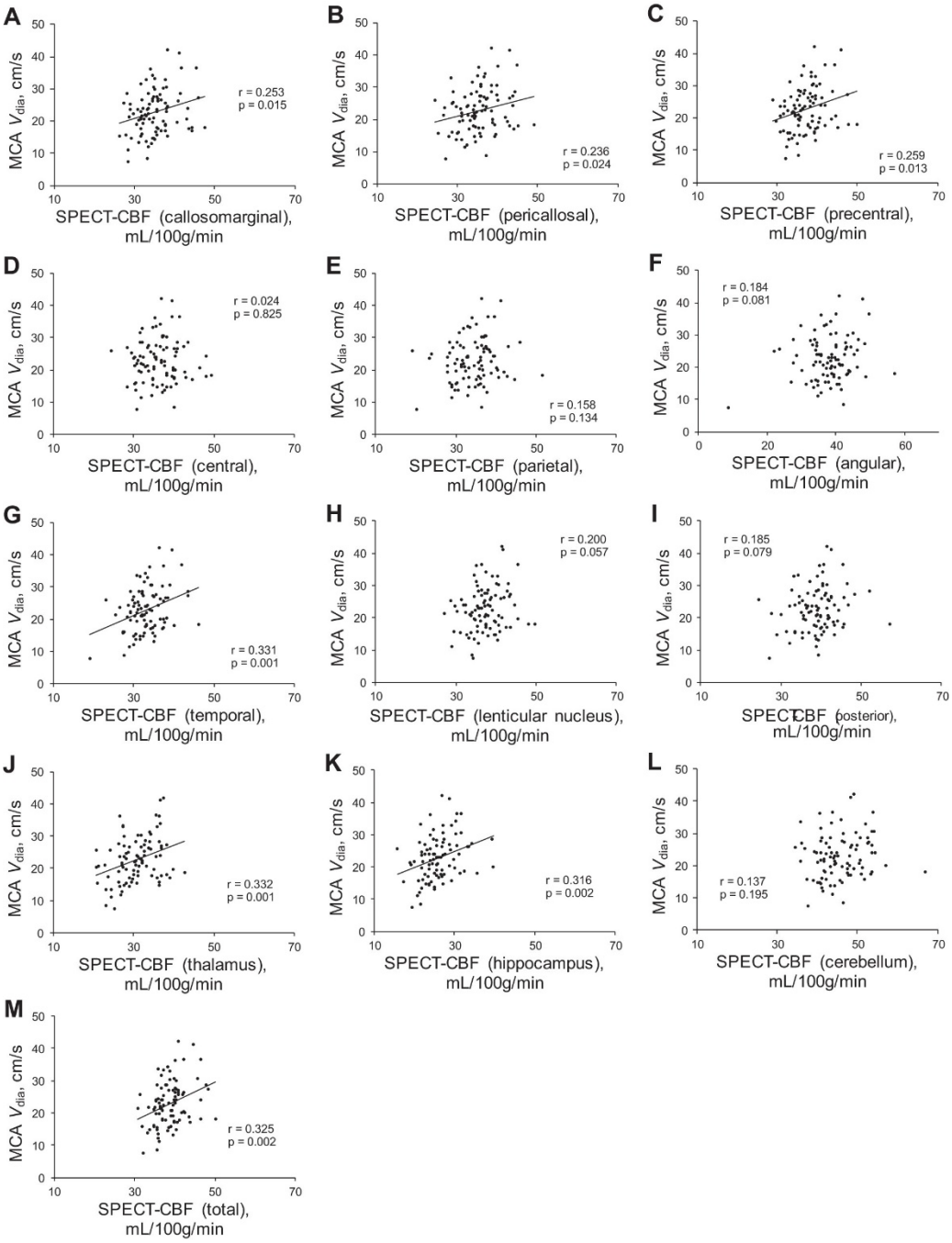

Figure 2.5: Relationships between middle cerebral artery cerebral blood flow velocity (MCA CBF_V) and single photon emission computed tomography cerebral blood flow (SPECT-CBF) at different regions of the brain (A, callosomarginal; B, pericallosal; C, precentral; D, central; E, parietal; F, angular; G, temporal; H, lenticular nucleus; I, posterior; J, thalamus; K, hippocampus; L, cerebellum) and total brain blood flow (M). The regression line represents significant correlation ($P < 0.05$) between the two measures of CBF. SPECT-CBF (x-axis) directly measures the CBF rate per 100g of tissue at every minute. MCA CBF_V (y-axis) is measured by transcranial Doppler ultrasonography. It is an indirect measure of cerebral perfusion as it measures the rate of CBF_V through the MCA. This changes in response to vasodilatation of the cerebral microvasculature downstream of the MCA and, as such, is a global of CBF. It is evident that there are strong correlations between the two different techniques at the regions of the brain that control cognitive and executive functions, such as the hippocampus, as well as total brain blood flow. Reference: Miyazawa et al. (2018).

2.7 Cognition

Cognition underpins or describes the mental processes of the brain and should not be considered a static function and is one of the most highly ordered and complex functions of the brain (Harada, Natelson Love & Triebel 2013; Harvey 2019). In essence, cognition reflects the ability of the brain to acquire information multimodally (e.g. visual, auditory, lived experiences and emotions), process and integrate this information and then guide behaviour and actions (Harada, Natelson Love & Triebel 2013; Harvey 2019). Intact cognition is to required so that individuals can make decisions, communicate, think, analyse and move on a daily basis (Salthouse 2012).

Cognitive function is complex and reflects an array of mental processes. However, it can be summarised as being either crystallised or fluidic (Harada, Natelson Love & Triebel 2013; Harvey 2019). Crystallised cognition can be described as acquired and well-established knowledge that is frequently practiced (Harada, Natelson Love & Triebel 2013; Harvey 2019). Fluid cognition essentially describes our ability to respond to novel situations. It requires a great deal of flexibility and reasoning, which is typically based on an individual's processing speed, attention, memory, language, executive function, visuospatial ability, and visual construction proficiency (Harada, Natelson Love & Triebel 2013; Harvey 2019). All of these processes, whether considered crystallised or fluid, are underpinned by the complex function and connections of specific neuronal circuits and interactions within specific sections of the brain (Harada, Natelson Love & Triebel 2013; Harvey 2019). Hence, each mental or psychological process is linked to a specific neurological process (or processes) in the brain (Figure 2.6). These processes can be subdivided into specific domains and subdomains and it is these processes, both specific and overall, that are regularly assessed in cognitive studies to determine cognitive capacity and function, as well as changes that may be evident as we age (Salthouse 2012). A summary of the cognitive changes observed throughout the ageing process and consequences of decreased cognitive function are described in detail in Chapter 3: Benefits of exercise training on cerebrovascular and cognitive function in ageing (for a succinct summary please see Table 3.1).

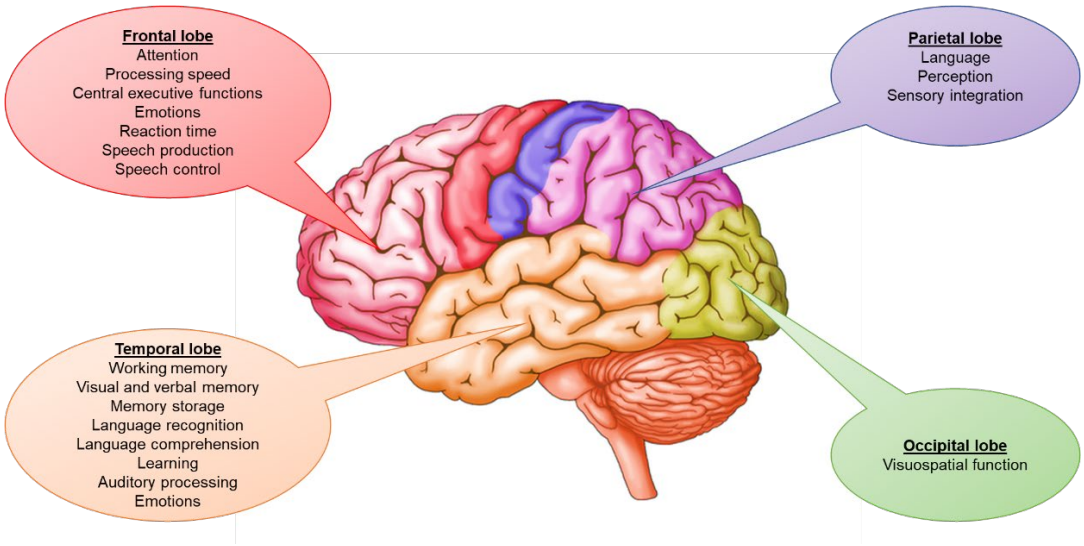

Figure 2.6: A summary of the cognitive domains typically measured in neuropsychology and the associated cerebral structures.

2.8 Methods used to determine cognition

Cognition can be measured with an array of tools, whether they are paper, computer or virtual reality based (Jin, Pilozzi & Huang 2020). Defining or listing every test is outside the scope of this thesis, as is describing the advantages and disadvantages of each of these tests and mode of administration. Detailed reviews (both systematic and narrative) have been conducted (Zygouris & Tsolaki 2015; Aslam et al. 2018; Jin, Pilozzi & Huang 2020). However, it is important to describe the tools and tests used for this thesis. Individual cognitive tests were utilised to comprise the cognitive battery that assessed neuropsychological function. These tests were both computer and paper based and included the Trail Making Task Parts A and B, Spatial Span Test (Corsi-block tapping test) and the National Institutes of Health (NIH) Toolbox, comprising a battery of individual cognitive examinations. The tests used, as well as the domains each test examined and the administration method of the test can be seen in Table 2.5. These tests were also used in the experimental chapters of this thesis and constituted a battery that covered all cognitive domains. The Trail Making Task used in this thesis was selected as a simple and effective means of measuring central executive function that had been validated both for clinical and research purposes for the demographic being tested in this study (Senior, Piovesana &

Beaumont 2018). The Spatial Span Test was incorporated into this cognitive battery, as it is the most widely used task in neuropsychology that assesses visuospatial short-term working memory (Brunetti, Del Gatto & Delogu 2014). A computerised version of the Spatial Span Test was used because it is simple to set-up and administer in comparison to the physical board, as well as offering increased accuracy and automatic computerised measures to remove examiner bias (Brunetti, Del Gatto & Delogu 2014). The NIH Toolbox has been extensively validated for its use as a tool for assessing neurological and behavioural function (i.e. cognition) in adults (Slotkin et al. 2012; Heaton et al. 2014; Weintraub et al. 2014; Thaung Zaw, Howe & Wong 2021). The validity data has been independently scrutinised using test–retest reliability measures and the effects of its administration (i.e. practice effects) (Slotkin et al. 2012; Heaton et al. 2014; Weintraub et al. 2014; Thaung Zaw, Howe & Wong 2021). Further, comparisons of all raw scores for each individual test within the NIH Toolbox has been performed, validated and established against other tests that are considered to be the gold standard for each individual cognitive domain. These validity studies have also considered the effects of age, sex, education and ethnicity and, as such, have accounted for these parameters when final normalised scores are calculated for both fluid and crystallised intelligence indicated above (Slotkin et al. 2012; Heaton et al. 2014; Weintraub et al. 2014; Thaung Zaw, Howe & Wong 2021). Finally, the total composite cognitive score has been validated as a highly reliable score that represents an overall summation of general cognitive function and indicates general cognitive ability based on normalised scores (Slotkin et al. 2012; Heaton et al. 2014; Weintraub et al. 2014).

The advantage that the NIH Toolbox test scores offer over traditional methods of assessing the comparative individual cognitive domains is that they are automatically computed within the program to control for examiner bias, as well as being simple to set-up and administer (Slotkin et al. 2012; Heaton et al. 2014; Weintraub et al. 2014). A detailed review outlining the advantages of all computerised cognitive batteries over paper based or traditional based methods has been compiled previously (Jin, Pilozzi & Huang 2020). In any case, it can be observed that a validated tool was

utilised to comprehensively ascertain cognitive function in the demographic included in this thesis.

Table 2.5: Summary of the cognitive tests used in this thesis, including domain assessment and method of administration.

Test	Domain	Administration method	Reference
Trail Making Task (Parts A and B)	Central executive function	Paper	(Senior, Piovesana & Beaumont 2018; Thaung Zaw, Howe & Wong 2021)
Spatial Span Test	Visuospatial short-term working memory	Computer	(Thaung Zaw, Howe & Wong 2021)
National Institute of Health Toolbox			
Dimensional Change Card Sort Test	Cognitive flexibility Attention	Computer	(Slotkin et al. 2012; Heaton et al. 2014; Weintraub et al. 2014)
Picture Vocabulary Test	Language Crystallised cognition	Computer	(Slotkin et al. 2012; Heaton et al. 2014; Weintraub et al. 2014)
List Sorting Working Memory Test	Working memory	Computer	(Slotkin et al. 2012; Heaton et al. 2014; Weintraub et al. 2014)
Oral Reading Recognition Test	Language Crystallised cognition	Computer	(Slotkin et al. 2012; Heaton et al. 2014; Weintraub et al. 2014)
Flanker Inhibitory Control and Attention Test	Attention Inhibitory control	Computer	(Slotkin et al. 2012; Heaton et al. 2014; Weintraub et al. 2014)
Picture Sequence Memory Test	Episodic memory	Computer	(Slotkin et al. 2012; Heaton et al. 2014; Weintraub et al. 2014)
Pattern Comparison Processing Speed Test	Processing speed	Computer	(Slotkin et al. 2012; Heaton et al. 2014; Weintraub et al. 2014)
Total composite cognitive score	General cognitive function General cognitive ability	Computer	(Slotkin et al. 2012; Heaton et al. 2014; Weintraub et al. 2014)

2.9 Cerebrovascular and cognitive function in ageing

Chapter 3 describes the age-related changes in cognition, neural structure and cerebrovascular function in detail. Briefly, these will be summarised here.

Ageing is associated with a decline in fluid intelligence, which describes our ability to respond to novel situations (Harada et al. 2013). This includes a decline in processing speed, attention, memory, language, executive functions and visuospatial ability, and visual construction proficiency. Crystallised intelligence, which describes acquired knowledge, does not generally change with ageing (Harada et al. 2013). Whether these functional changes are associated with specific structural changes in the brain remains relatively undefined. This is due to individual, group and population variations, as well as disease states, modifiable and unmodifiable changes (Bliss et al. 2020).

Functional (cognitive) changes may be delayed compared with when a neuroanatomical change occurs, which also causes complications when studying structural and functional brain changes simultaneously (Kennedy & Raz 2015). However, it is evident that the grey matter of the brain declines with age while simultaneous expansion of the cerebral ventricles occurs, thus leading to cortical thinning (Cole 2018). The prefrontal, medial, temporal and parietal cortices are considered vulnerable structures in relation to ageing, probably because neuronal death and reduced plasticity due to decreases in synaptic density take place throughout the ageing process (Harada et al. 2013). It has also been suggested that white matter probably decreases with age (Harada et al. 2013). These changes are not described in detail by the literature, primarily because the primary objectives of more recent studies have been focused on the changes associated with functional connectivity, of which, has been shown to reduce in the default mode network (Cabeza et al. 2018; Damoiseaux 2017). Finally, anatomical changes have also been associated with reduced blood-brain-barrier (BBB) integrity and cerebrovascular pathology in post-mortem examinations (Cole 2018). It has also been reported that those with Alzheimer's have reduced functional connectivity and unfavourable neuroanatomical changes that are associated with reduced cerebral perfusion and neuronal metabolism (i.e. cerebrovascular function) (Chen et al. 2011). The findings associated with reduced BBB integrity and cerebrovascular function highlight the importance that maintaining endothelial function and cerebrovascular health have on

the ageing brain and preventing further cognitive decline beyond what is considered to be normal age-related decline (Bliss et al. 2020).

The senescent phenotype is described as having hormonal imbalances, increased low-grade systemic inflammation, increased reactive oxygen species (ROS) production and reduced endothelial function (Chang, Flavahan & Flavahan 2018; Rossman et al 2018). These processes are intertwined as described in Figure 1 of Chapter 3. To summarise, endothelial dysfunction results, as chronically raised ROS and inflammatory mediators result in the uncoupling of eNOS, thus reducing NO (Berkowitz et al. 2003; Pikula et al. 2009; Deer & Stallone 2016; Chang, Flavahan & Flavahan 2018). When NO production decreases it promotes decreased vasodilator tone, increased arterial stiffness, platelet aggregation, vascular smooth muscle cell proliferation and inflammation (Rossman et al. 2018). This cycle continues as we age thus leading to endothelial dysfunction. This decline is not limited to just the systemic vasculature but also to the cerebrovasculature. Centrally, this process ultimately results in a decline of cerebral perfusion and a reduction in perfusion regulatory mechanisms (Bangen et al., 2014; Toth et al. 2018). The reduction in both cerebral perfusion and these regulatory mechanisms, results in hypoperfusion, which subsequently manifests as local ischaemia and micro-haemorrhages in the microvasculature, leading to reductions in capillary density and BBB function (i.e. reduced cerebrovascular function) (Zlokovic 2011; Raz et al. 2012; Bangen et al. 2014; Tzeng & Ainslie 2014; Asai et al. 2015; Di Marco et al. 2015; Schipke et al. 2018). These changes are exacerbated by increased extracranial and intracranial conduit artery stiffness (e.g. MCA), which then diffuses to the cerebral microvasculature (Webb et al. 2012). Subsequently the cerebral microvasculature pulsatility becomes increased, which then reduces cerebral perfusion and promotes local ischaemia (Bliss et al. 2020). The reduction in perfusion and BBB integrity, along with the increased concentration of ROS and inflammatory mediators promotes unfavourable neuroanatomical changes, reduces neuronal metabolism, reduces connectivity and reduces cognitive function (Zlokovic 2011; Raz et al. 2012; Bangen et al. 2014; Tzeng & Ainslie 2014; Asai et al. 2015; Di Marco et al. 2015; Schipke et al. 2018). If these are exacerbated or continue to be exacerbated,

particularly by other cardiometabolic conditions that promote chronic low-grade inflammation and reduced vascular health, such as obesity, then cerebral dysfunction will follow resulting in cognitive impairment (See Figure 1 Chapter 3).

2.10 Cerebrovascular and cognitive function in obesity

The effects of obesity, as well as its comorbidities are well defined. This is highlighted in Table 2.1. Obesity has been demonstrated to have a negative effect on cognition. These effects have been documented in a detail in a systematic review (Bischof & Park 2015). Global cognitive function has been demonstrated to be significantly reduced in older obese patients, while specific cognitive domains (single or multiple) have been reported to be reduced in obese individuals throughout the lifespan (Gunstad et al. 2007; Benito-León et al. 2013; Bischof & Park 2015). Interestingly, obesity during middle-age, appears to significantly reduce cognitive function more than when obesity occurs in the older years of life (Whitmer et al. 2005; Sabia et al. 2009; Xu et al. 2011). Mid-life obesity, when continued into later life, has been described to significantly increase the risk of further cognitive decline and dementia (Whitmer et al. 2005; Sabia et al. 2009; Xu et al. 2011). Further, obese individuals have been reported to have lower brain volume, particularly grey matter volume, as well as decreased anterior cingulate cortex, hippocampal and thalamic volume (Enzinger et al. 2005; Raji et al. 2010; Brooks et al. 2013). Maintenance of the obesogenic state into later life has also been associated with increased risk of dorsolateral prefrontal cortex atrophy (Brooks et al. 2013). Finally, white matter hyperintensities and reduced connectivity in the default mode network have been reported to be evident in older obese adults and that these unfavourable changes are more severe in those who have a higher BMI compared with those who have a lower BMI (Jagust et al. 2005; Bettcher et al. 2015; Bischof & Park 2015).

The mechanisms as to why obesity reduces cognitive function and promotes unfavourable neuroanatomical changes is complex and poorly defined. Obesity is a cardiometabolic disease. It reduces cardiovascular function by a number of mechanisms. One of the most fundamental mechanisms in which it reduces

cardiovascular function is by promoting a reduction in endothelial function and health. This is predominantly because it is a chronic low-grade inflammatory disease that induces significant hormonal imbalances (see Bliss & Whiteside 2018 for a detailed review of hormone imbalances and the effect of this on the gut-brain axis). For example, obesity reduces adiponectin and increases cortisol production, which promotes the development of chronic low-grade systemic inflammation and oxidative stress (Nigro et al. 2014; Dye et al. 2017; Bliss & Whiteside 2018). This is in addition to the adipokines that are secreted by central adipose stores that also promote the chronic low-grade systemic inflammatory state and oxidative stress (Bischof & Park 2015; Dye et al. 2017; Bliss & Whiteside 2018). This subsequently exacerbates the decline in endothelial function leading to endothelial dysfunction, resulting in the events that are described in both 2.9 Cerebrovascular and cognitive function in ageing and Chapter 3 Ageing and cerebrovascular function (i.e. it reduces cerebrovascular function leading to reduced cerebral perfusion). This is supported by studies that have reported decreases in CBF in obese individuals, whereby there is a negative association between CBF and BMI (Willeumier, Taylor & Amen 2011). Further, it has been recently reported that CBF was lower in older obese adults than those adults who were not obese and of the same age. The same study also indicated that for every 1 cm increase in waist circumference (i.e. increased central adiposity) there was a further decrease in CBF beyond that of normal ageing (Knight et al. 2021). This suggests that obesity exacerbates the age-related changes associated with a reduction in cerebrovascular function and cognition. If obesity in maintained in later life and no intervention is prescribed, such as physical activity, then this will exacerbate these changes beyond normal ageing, thus promoting the development of a neurodegenerative disease such as dementia.

2.11 Summary of the effect of exercise on cerebrovascular function and cognition

Currently there are no curative treatments available for dementia, thus indicating that most treatment options are around maintaining health and wellbeing and quality of life and/or symptomatic treatments (AIHW 2018a). Prevention is also more favourable than a cure. Given that cerebrovascular function and cognition decline as

we age and are exacerbated by cardiometabolic conditions thus promoting the development of dementia, treatments or interventions that focus on improving these outcomes may reduce dementia burden. These treatments should be inexpensive and simply to administer or participate in. Hence, exercise may be a promising cost-effective non-pharmacological treatment that may improve these outcomes.

There is increasing evidence that exercise training, particularly aerobic exercise training (AT), may assist in maintaining optimal cerebrovascular function and, therefore, prevent or slow the progression of the development of cognitive impairment and, ultimately, neurodegenerative disorders, such as dementia (Cassilhas et al. 2007; Ainslie et al. 2008; Lautenschlager et al. 2008; Baker et al. 2010; Brown et al. 2010; Liu-Ambrose et al. 2010; Erickson et al. 2011; Ivey et al. 2011; Anderson-Hanley et al. 2012; Liu-Ambrose et al. 2012; Nagamatsu et al. 2012; Vicente-Campos et al. 2012; Vreugdenhil et al. 2012; Chapman et al. 2013; Smith et al. 2013; Suzuki et al. 2013; Fiatarone Singh et al. 2014; Maass et al. 2014; Moore et al. 2014; Nyberg et al. 2014; Bolandzadeh et al. 2015; Bossers et al. 2015; Nishiguchi et al. 2015; ten Brinke et al. 2015; Anazodo et al. 2016; Hoffmann et al. 2016; Sobol et al. 2016; Chirles et al. 2017; Akazawa et al. 2018). This will be discussed in more detail in Chapter 3: Benefits of exercise training on cerebrovascular and cognitive function in ageing. The rationale for this review was that there were no reviews conducted that systemically searched for evidence on the effects of exercise training on cerebrovascular function and cognition. This meant that the gaps in the knowledge and the current state of research was limited. Hence, this reviewed assisted in identifying gaps in the current knowledge and future directions for research. The following summarises the primary findings associated with the literature:

- AT can improve both cognition and cerebrovascular functions, however it is not known how little exercise and/or what intensity of AT is required or preferable to elicit a positive response (i.e. a dose-response relationship and intensity scale in middle-aged to older adults has not been determined);
- RT can improve cognition, but it remains largely unknown what effect this has on cerebrovascular function, which may be primarily due to the lack of

studies performed exploring the effect of RT on both cognition and cerebrovascular function;

- CT may improve cognition and cerebrovascular function, particularly in those with a diagnosed condition, such as stroke, however very few studies have been conducted that explore both cognition and cerebrovascular function;
- The mechanisms associated with improvements in cognition and cerebrovascular function are poorly defined, with animal models providing the most assistance in ascertaining why exercise may induce positive effects on cerebrovascular function and cognition; and
- Very few studies, if any, have performed correlation analyses between cognition and cerebrovascular function when exercise is used as an intervention in middle-aged to older adults to improve both parameters. This may largely be due to the fact that limited studies have been performed in this area in this cohort that measure both cerebrovascular function and cognition simultaneously irrespective of the exercise modality used.

2.12 Summary

In summary, the global population is ageing. In countries such as Australia, there are increased rates of older who are both obese and physically inactive than previous years. Additionally, the rate and cost of dementia is increasing and will continue to do so. The increased dementia burden is not only associated with ageing. Rather it is also associated with increased rates of cardiometabolic diseases, such as obesity, and lifestyle factors, such as not participating in physical activity. These can further promote and exacerbate the normal rate of decline of both cerebrovascular function and cognition. Both of these parameters when reduced beyond that of normal ageing can ultimately eventuate to cerebral pathologies and development of dementia. However, in order to reduce this burden an understanding of both cerebrovascular function and cognition are necessary to ensure appropriate treatment or intervention strategies are employed to counter this decline.

The brain requires a constant and controlled supply of blood to cater for its metabolic needs and CBF is tightly regulated. CBF increases concurrently with neuronal activity and metabolism and can be measured using TCD which does not require exposure to ionising radiation, provides high temporal resolution, is non-invasive, quick, portable, and relatively inexpensive. The endothelium plays a fundamental role in regulating CBF, by upregulating eNOS, which subsequently synthesises and releases the potent vasodilatory and vasoprotective hormone NO. Therefore, endothelial-derived NO assists in regulating vasculature tone and thereby systemic blood flow and blood pressure, as well as the ability of the microvasculature to respond to the metabolic demands of the brain. However, the ability of the endothelium to synthesise and release NO decreases with age. Conditions associated with chronic low-grade inflammation, such as obesity, intensify the development of endothelial dysfunction, which reduces the ability of the cerebrovasculature to respond to the metabolic demands of the brain, as well as maintaining the integrity of the BBB. When there is reduced cerebrovascular function and the brain's metabolic demands are not met, then the brain cannot perform its functions, particularly cognition, efficiently or effectively. This can result in cognitive decline and cognitive impairment, thus indicating a relationship between cerebrovascular function and cognition.

Therefore, treatments or lifestyle interventions, such as physical activity, which promote cardiovascular health and limits adiposity may be beneficial in improving endothelial function, CBF and, consequently, preventing or slowing the progress of cognitive impairment and, eventually, dementia. AT may improve cognition and local cerebral perfusion of brain regions associated with executive function, such as the hippocampus, and neuroplasticity in older adults. The improvement in cerebrovascular function and cognition may act to prevent or slow the progress of developing cognitive impairment and ultimately dementia. However, there is no current literature that has systematically reviewed the research conducted on the effects of exercise training on cerebrovascular function and cognition. No studies have specifically compared cerebrovascular function and cognition in aerobic endurance trained and sedentary, untrained older adults and determined if there is a relationship between these two functions in older adults. As indicated above, no

study has determined if a dose-response relationship and improvements in brain health exists in middle-aged to older adults has not been determined. Importantly, to address dose-response, a description of dose needs to be outline for the remainder of the thesis, particularly for Chapter 5. Quantification of exercise exposure is typically accomplished using the concept of exercise dose (Wasfy & Baggish 2016). At the most basic conceptual level, exercise dose is determined by three discrete variables: 1) duration, 2) frequency, and 3) intensity, and in aggregate, exercise dose can be described as the product of these three parameters (Wasfy & Baggish 2016). Hence, the remainder of this thesis addresses these current gaps in knowledge.

CHAPTER 3: BENEFITS OF EXERCISE TRAINING ON CEREBROVASCULAR AND COGNITIVE FUNCTION IN AGEING

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Benefits of exercise training on cerebrovascular and cognitive function in ageing

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Abstract

Derangements in cerebrovascular structure and function can impair cognitive performance throughout ageing and in cardiometabolic disease states, thus increasing dementia risk. Modifiable lifestyle factors that cause a decline in cardiometabolic health, such as physical inactivity, exacerbate these changes beyond those that are associated with normal ageing. The purpose of this review was to examine cerebrovascular, cognitive and neuroanatomical adaptations to ageing and the potential benefits of exercise training on these outcomes in adults 50 years or older. We systematically searched for cross-sectional or intervention studies that included exercise (aerobic, resistance or multimodal) and its effect on cerebrovascular function, cognition and neuroanatomical adaptations in this age demographic. The included studies were tabulated and described narratively. Aerobic exercise training was the predominant focus of the studies identified; there were limited studies exploring the effects of resistance exercise training and multimodal training on cerebrovascular function and cognition. Collectively, the evidence indicated that exercise can improve cerebrovascular function, cognition and neuroplasticity through areas of the brain associated with executive function and memory in adults 50 years or older, irrespective of their health status. However, more research is required to ascertain the mechanisms of action.

Keywords

Dementia, exercise training, cerebrovascular function, cognition, ageing

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Introduction

The current worldwide incidence of dementia is more than 50 million people and is expected to treble in the next 30 years.[1,2] Dementia is associated with adverse changes in cerebrovascular structure and function, which contribute to a decline in cognition.[3–5] The greatest risk factor for developing dementia is advanced age.[1] However, there are various modifiable risks factors that lead to impaired vascular function and contribute to dementia. These include behavioural risk factors (limited educational engagement, physical inactivity and excessive alcohol consumption), metabolic risk factors (obesity, hypertension, dyslipidaemia, hyperglycaemia and homocysteinaemia) and cardiovascular diseases (coronary heart disease, heart failure, arrhythmia, stroke, diabetes and renal disease).[6–16] Of these, low-level educational engagement, chronic renal disease, diabetes mellitus, hypertension and physical inactivity account for the largest degree of dementia burden globally, particularly in developed countries such as Australia.[2,17] These modifiable risk factors are associated with and characterised by endothelial

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dysfunction,[18] which can impair cerebrovascular function. This, in turn, may promote the development of cerebral dysfunction, cerebral pathology, impaired cognition (in addition to the age-related decline) and eventually a neurodegenerative disease state such as dementia (Figure 1).[18]

There is increasing evidence that exercise training may help to maintain optimal cerebrovascular function and thereby prevent or slow the development of cognitive impairment.[19–47] Currently, there are limited randomised controlled studies examining the effects of exercise training on cerebrovascular function and its

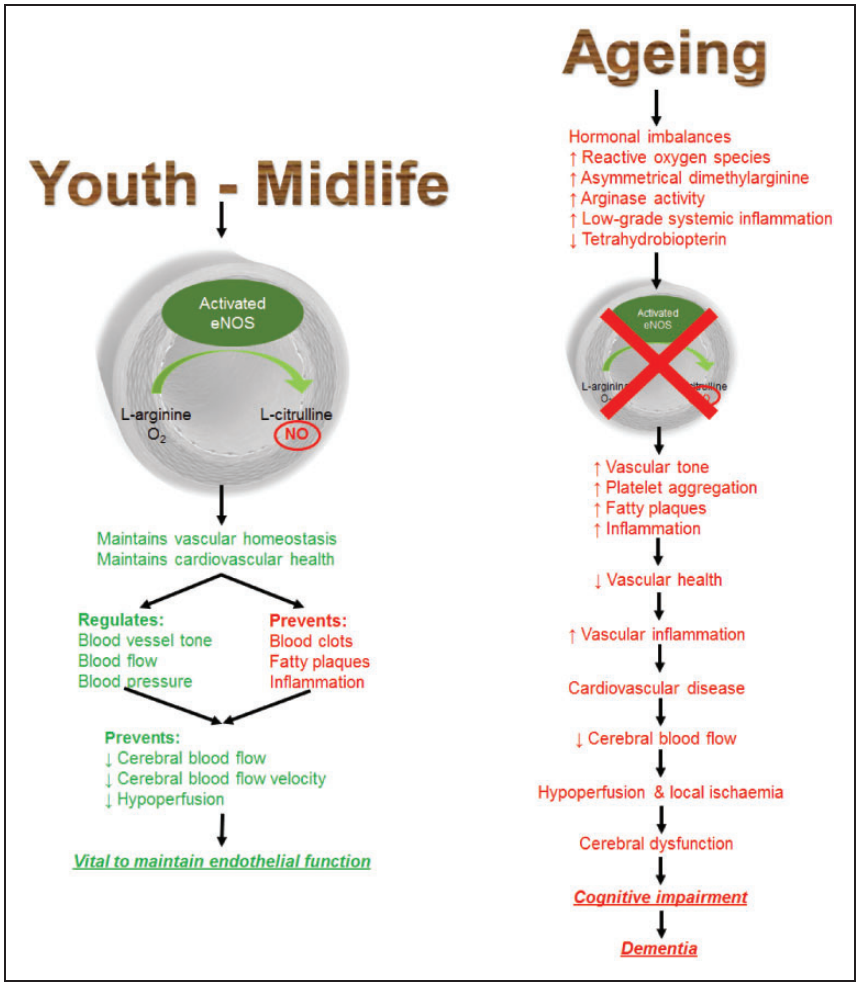

Figure 1. Ageing is associated with hormonal imbalances and increased low-grade systemic inflammation. It is also associated with the increased production of reactive oxygen species (ROS), which may be due to diminished nuclear regulation factor 2 and superoxide dismutase expression and increased expression of nicotinamide adenine dinucleotide phosphate oxidase complexes, resulting in increased mitochondrial superoxide production.[120] Uncoupled endothelial nitric oxide (NO) synthase (eNOS) increases superoxide production by catalysing nicotinamide adenine dinucleotide phosphate, instead of synthesising NO. Increased arginase activity reduces L-arginine supply, thus promoting the uncoupling of eNOS.[69,70] This may also be associated with diminished tetrahydrobiopterin availability and increased asymmetrical dimethylarginine concentrations, which subsequently acts as a competitive inhibitor of eNOS, thus reducing NO biosynthesis.[71] These promote and lead to endothelial dysfunction, which subsequently manifests as local ischemia and micro-haemorrhages in the microvasculature, leading to reductions in capillary density and BBB function (i.e. reduced cerebrovascular function).[121,122] It may also be a result of increased conduit artery stiffness, which then diffuses to the cerebral circulation and increases pulsatility of the cerebral microvasculature, reducing CBF and promoting ischaemic-induced leukoaraiosis.[123] Nevertheless, increased inflammation and oxidative stress, hypoperfusion and decreased BBB integrity are potentiated by these events.[3,121,124–128] This subsequently promotes increased microglial activity, amyloid-β production and decreased amyloid-β clearance, which may act as a trigger for enhanced S100B and glial fibrillary acidic protein secretion to form astrocytes, thus promoting the inflammatory cycle and the continued accumulation of neurotoxic products.[3,121,124–128] Further, the increase in amyloid-β accumulation in the brain can further compromise cerebrovascular function that manifests into neurodegeneration and further structural and functional changes within the brain.[129]

association with cognitive function in middle-aged and older adults, as both should be interpreted together and not as separate functions. The purpose of this review is to examine the benefits of exercise training on cerebrovascular and cognitive function in ageing. Firstly, we will review the impact of ageing on cerebrovascular function, cognition and structural changes within the brain. Secondly, the effects of aerobic exercise training (AT) and resistance exercise training (RT), alone and in combination, on structural adaptations, cerebral blood flow (CBF) and cognition in middle-aged and older adults will be discussed. Thirdly, we will determine if there are any published randomised control trials examining the association between CBF and cognition function in this cohort. Finally, we will discuss why cerebrovascular structure and function and cognition may change following exercise training.

Methods

This review implemented the procedures and following the guidelines outlined in the Peer Review of Electronic Search Strategies: 2015 Guideline Statement. Appropriate literature was searched for systematically using seven databases (PubMed, CINAHL, Cochrane, Science Direct, Web of Science, Scopus and MEDLINE) to explicitly find, select, evaluate and interpret relevant research, as well as Google Scholar as a method to ensure completeness.[48] The inclusion criteria were that original articles must be written in English, peer-reviewed, describe a cross-sectional study or an intervention trial in middle-aged or older adults ($\geq$50 years old) and include the use of exercise (aerobic, resistance or multimodal). In this review, we defined AT as training performed over months and years, which comprises repeated bouts of exercise that primarily utilise energy produced via aerobic respiration, such as running, cycling and swimming. RT is defined as repeated bouts of muscle contraction against an applied force or resistance, which primarily aims to improve muscular strength, endurance, size and definition. Multimodal or combined exercise training (CT) is defined as the combination of at least two different forms of exercise training, such as AT and RT. The search terms used were: exercise (including physical activity or exercise training), ageing, blood–brain barrier (BBB), CBF, CBF velocity (CBF_v), cerebral perfusion, cerebral volume (whole brain and specific regions such as the hippocampus), neuroplasticity, cognition, transcranial Doppler (TCD) ultrasonography, magnetic resonance imaging (MRI) and arterial spin labelling (ASL).

The search was completed by April 2019 and included all studies conducted up until this period. An updated search was performed prior to submission of the article in February 2020, with limited results being returned other than those who have published method papers with results still pending. Additionally, a search was performed on the International Clinical Trials Registry Platform. It was found that there were over 34 registered trials in this field of research, which were about to commence, are ongoing or due to be completed by the end of 2020.

After removing duplicates, those identified were screened initially by title then abstract and, if deemed suitable, were read in full and included in the review. Further, the reference lists of suitable articles were screened to ensure completeness. The studies identified for inclusion in the review have had their primary and secondary results tabulated and their primary results described narratively. Knowledge gaps and future directions of research were identified based upon the findings of these studies.

Age-related cognitive decline and structural changes

Whilst crystallised intelligence (i.e. acquired knowledge) remains relatively unchanged, our fluid intelligence (ability to respond to novel situations), such as processing speed, attention, memory, language, executive functions and visuospatial ability, and visual construction proficiency decreases with ageing.[49] The changes in these cognitive domains in normal ageing are summarised in Table 1, which indicates that the majority of these abilities decline at some stage throughout the lifespan. The exceptions to this include certain aspects of memory (implicit memory and memory retention), language (vocabulary and visual confrontation naming), visuospatial ability and similarity association and proverb description and reasoning of familiar material (executive function domain).[49–57]

Our understanding of the anatomical and functional changes that occur within the brain during ageing is not well defined. These changes may vary between individuals and populations and are undoubtedly related to modifiable (environmental) and unmodifiable (genetic) changes. They may be affected by a variety of disease states that promote cerebrovascular dysfunction, oxidative stress and inflammation.[58–61] Further, actual cognitive changes may lag behind neuroanatomical changes by decades and, therefore, may not correlate.[60] Nonetheless, there appears to be consensus that the brain's grey matter declines with age in conjunction with expansion of the cerebral ventricles,[62] thus contributing to age-related cortical thinning. Further, the prefrontal, medial temporal and parietal cortices are some of the most vulnerable regions to senescent changes.[49,58,60] This is likely a consequence of neuronal death and reduced plasticity due to decreases in synaptic density.[49] Additionally, white matter also decreases with age, but there is limited information about

Table 1. Summary of the cognitive domain changes throughout the lifespan.

References	Cognitive domain	Stable, increases or decreases
Harada et al.,[49] Kochunov et al.[52]	Processing speed	Decreases (from third decade of life)
Harada et al.,[49] Salthouse et al.[55]	Attention *(Auditory, selective and divided attention)*	Decreases (later life)
Harada et al.,[49] Haaland et al.[51], Piolino et al.,[53] Rönnlund et al.,[54] Salthouse et al.,[55] Singh-Manoux et al.,[56] Zelinski and Burnight[57]	Memory	Decreases (episodic – throughout life; semantic – later life)
	• Explicit memory *(episodic and semantic memory)*	Stable
	• Implicit memory *(procedural)*	Decreases (throughout life)
	• Memory acquisition	Stable
	• Memory retention	Decreases (later life)
	• Memory retrieval	
Harada et al.,[49] Singh-Manoux et al.,[56] Zelinski and Burnight[57]	Language *(overall)*	Increases
	• Vocabulary	Increases (increases throughout life)
	• Visual confrontation naming	Increases (until seventh decade)/decreases (from seventh decade of life)
	• Verbal fluency	Decreases (throughout life)
Harada et al.,[49]	Visuospatial ability	Stable
	Visual construction proficiency	Decreases (throughout life)
Harada et al.,[49] De Luca and Leventer[50] Singh-Manoux et al.,[56]	Executive function	Decreases (throughout life, rapid from seventh decade of life)
	• Concept formation, abstraction and mental flexibility	Decreases (throughout life)
	• Response inhibition	Decreases (from fourth to fifth decade of life)
	• Inductive reasoning	Decreases (throughout life)
	• Reasoning *(unfamiliar material)*	Stable/increases
	• Similarity association, proverb description and reasoning *(familiar material)*	Decreases (throughout life)
	• Executive function *(associated with a speeded motor component)*	

structural changes compared with functional connectivity.[49,59] Functional connectivity is reduced within the default mode network, which is comprised of the precuneus and the post cingulate, medial prefrontal and lateral parietal cortices and has been correlated to reduced attention, memory and executive function.[58,59] In post-mortem examinations, these anatomical changes are associated with the deterioration of the BBB, thus suggesting that these changes are associated with impaired cerebrovascular function.[62] In support of this, reduced CBF and metabolism are associated with reduced functional connectivity and anatomical changes in healthy individuals and are exacerbated in those with Alzheimer's disease.[63] Since poor cardiometabolic status intensifies endothelial dysfunction, cerebrovascular dysfunction and cognitive decline, interventions that improve cardiometabolic health, such as regular exercise, may be beneficial in preventing or slowing the progress of the chain of events leading to dementia.[5,64]

Ageing and cerebrovascular function

As we age, the endothelium's ability to produce adequate concentrations of nitric oxide (NO) to maintain optimal vascular health and cerebrovascular function decreases.[5] Even in healthy individuals, CBF is estimated to be continually reduced by 0.38–0.45% annually from midlife onwards until age 80 years, after which the trajectory is unknown.[19]

The mechanisms that lead to age-related endothelial dysfunction and diminished NO concentrations are complex and are not fully understood. What is clear is that the senescent phenotype favours decreased vasodilator tone, platelet aggregation, vascular smooth muscle cell proliferation and inflammation, which is probably associated with elevated oxidative stress caused by an increase in reactive oxygen species (ROS) production.[65] In animal models, ROS production has been demonstrated to be a key factor leading to endothelial dysfunction, cerebrovascular dysfunction and cognitive impairment.[66–68] Further, there is increased uncoupling of endothelial nitric oxide synthase (eNOS) in ageing, resulting from a diminished L-arginine supply,[69,70] and increased concentrations of asymmetrical dimethylarginine, which acts as a competitive inhibitor of eNOS, thus reducing NO biosynthesis.[71]

Endothelial dysfunction may also be induced by hormonal imbalances and increased angiotensin

activity. Both of these are associated with the senescent phenotype and promote vascular inflammation and ROS production. They may also promote increased endothelial expression of endothelin-1, which induces vasoconstriction while suppressing the effects of NO.[70,72,73] Additionally, adiposity from mid-to-late life reduces systemic adiponectin concentrations, which may have a role in maintaining cerebrovascular function and reducing vascular inflammation via upregulating eNOS activity.[74,75] In any case, NO bioavailability becomes diminished as it reacts with superoxide, resulting in peroxynitrite formation and continuation of the inflammatory cycle leading to endothelial cell dysfunction and the promotion of atherosclerosis and cardiovascular diseases.[5] Ultimately, this impairs or causes a decline in the effectiveness of CBF regulatory mechanisms. The resulting decline in CBF leads to cerebral hypoperfusion, cerebral dysfunction and the development of cognitive impairment, as well as the potential development of leukoaraiosis (i.e. white matter lesions resulting from small blood vessel damage frequently observed as white matter hyperintensities on MRI) and increased amyloid-β production that is characteristic of dementia.[3,5]

Why exercise training might improve cerebrovascular and cognitive function – evidence from animal studies

Acutely, CBF increases concurrently with cardiac output and oxygen uptake ($\dot{V}O_2$) during incremental exercise, probably due to vasodilatation caused by shear stress and the increased demand for the endothelial-derived NO to maintain this vasodilatory state. However, increased neuronal metabolic demand in regions of the brain that control motor function and the autonomic nervous system activities also increases during exercise.[76] Increased neuronal metabolism results in increased carbon dioxide and metabolite production, triggering vasodilatation of the cerebral microvasculature and increased CBF and local perfusion, which permits for adequate removal of these waste products via the venous network.[76] The venous network also dilates in response to increased blood flow through the arterial network during exercise. It would be presumed that this chronic adaptation would be partly due to increased efficiency of this process.

Exercise training promotes angiogenesis within areas of the brain that were previously ischaemic, via the upregulation of eNOS and endothelial progenitor cell production in mice and Sprague–Dawley rats.[77,78] The reduction in endothelial expressed low-density lipoprotein (LDL) receptor-related protein 1 that occurs during ageing has been linked to decreased cerebral perfusion in animals, and exercise training has been demonstrated to reverse this process, thereby improving cerebrovascular function.[75,79,80] These findings suggest that exercise training may improve endothelial function, which would possibly increase cerebrovascular function, which is related to cognition.

In support of this, it was reported that in middle-aged female mice, AT improved cerebrovascular function, peripheral endothelial function as well as favourable neuroanatomical changes, such as decreased hippocampal astrocyte hypertrophy.[81] This was in contrast to the sedentary group who had increased hippocampal astrocyte hypertrophy, reduced vascular and cerebrovascular function and myelin dysregulation.[81] Additionally aged Wistar rats that underwent swimming training for 1 h per weekday for eight weeks demonstrated significantly increased CBF and brain capillary vascularity, in addition to increased brain microvessel vascular endothelial growth factor (VEGF) and eNOS concentrations and reduced plasma malondialdehyde concentration, compared to aged sedentary rats and rats immersed in water for leisure.[82] However, these were still below to be lower than young sedentary rats, thus supporting the notion that CBF decreases with age and that exercise training can improve these outcomes possibly by upregulating VEGF and eNOS and reducing oxidative stress.

In aged animals, there are a lack of studies that directly test the effects of exercise on CBF and cognition. One study using a mouse model of Alzheimer's disease reported improvements in both CBF and cognition using a pharmaceutical intervention, while another demonstrated that exercise improved neurogenesis and cognition in aged mice.[83,84] This suggests that exercise, which can improve both CBF and cognition in animals, may result in improved outcomes associated with the ageing brain. In support of this was another study that reported middle-aged to older female cynomolgus monkeys that underwent AT had improved cognition (determined by the Wisconsin General Testing Apparatus) and vascular volume within the cerebral cortex compared to aged-matched sedentary controls.[85] However, these findings were found to be abolished following a three-month period of physical inactivity, which also suggest exercise is a vital component in maintaining neurovascular function throughout the ageing process.

In summary, these novel animal studies highlight that exercise training improves cerebrovascular function and cognition by improving vascular health, specifically endothelial function. These few novel studies provide insight as to why exercise may improve cerebrovascular and cognitive function in humans, as they improve parameters that are associated with ageing, such as decreased endothelial function leading to

reduced cerebrovascular function, BBB integrity and ROS formation.

Results of studies

The effects of exercise training on cerebrovascular function and structure

The studies that have been included in the results have measured and reported cerebrovascular function slightly different from each other or have at least focused on one aspect of cerebrovascular function. Hence, it is important to address terms used throughout the text here. Cerebrovascular responsiveness (CVR) is the ability of the vasculature to respond to cognitive or physiological stimuli.[86,87] Specifically, the response of smaller healthy vessels to a stimulus is to dilate, which results in an increase in CBF.[86,87] The physiological mechanism that ensures that CBF is maintained and kept constant during changes in systemic blood pressure is referred to as cerebrovascular autoregulation (i.e. cerebrovascular conductance).[5,26] This is stimulated by chemical and mechanical stimuli, which induce a myriad of molecular pathways, including those described above, which result in modulating the vascular resistance applied to the cerebral vasculature and, therefore, the CBF.[5] Further, cerebrovascular function can be described as declining if cerebral pulsatility (i.e. cerebral arterial stiffness) increases.[20] This will be observed in conjunction with a decline in CBF_V.[20] These functions can be determined by medical imaging systems (e.g. MRI and ASL) and TCD ultrasonography.

Aerobic exercise training (Table 2)

Ainslie et al.[19] measured CBF_V in the middle cerebral artery (MCA) in apparently healthy aerobic exercise trained and sedentary males. Their estimation of the annual decrease in CBF_V was 0.45%. However, CBF_V remained 17% higher in aerobic exercise-trained individuals compared to their age-matched sedentary counterparts, suggesting a difference in cerebrovascular function of 10 years between the active and sedentary individuals. A major limitation to this study was that CVR was not evaluated. Brown et al.[26] assessed whether higher aerobic fitness was associated with superior cognitive in a group of healthy aerobic exercise trained and sedentary older women. Trained females had a higher $\dot{V}O_2$max compared with the sedentary group and increased cerebrovascular conductance. Cognition was negatively correlated with age and positively correlated with maximal oxygen uptake ($\dot{V}O_{2max}$). These cross-sectional studies provide an indication that aerobically trained individuals may have superior cerebrovascular function and that aerobic fitness, cerebrovascular function and cognition are interrelated.

One of the first exercise training studies undertaken evaluated the effects of AT in healthy, sedentary and overweight older adults.[46] CBF_V in the MCA in response to breath-holding was higher in the trained group compared to the control group. Additionally, AT decreased blood pressure and improved individual lipid profiles, in addition to increasing exercise performance. This suggested that AT improved cerebral responsiveness by modulating cardiovascular markers, thus contributing to improved cardiovascular health and, consequently, improved endothelial function. This was supported by a recent interventional study that investigated the effects of AT assessing the response of cerebral pulsatility to an acute bout of exercise before and after exercise training in older sedentary adults.[20] The trained group had improvements in CBF_V and a decreased PI, as well as lower total cholesterol concentrations and increased peak oxygen uptake ($\dot{V}O_2$peak) post-intervention. However, based on the primary findings of the study, it was indicated that arterial stiffness had declined post-intervention during the acute bout of exercise and that chronic exercise training may be necessary for sustaining the improvements in systemic and cerebrovascular functions.

The benefits of regular AT are also evident in patients with established endothelial dysfunction. Anazodo et al.[21] measured changes in both resting CBF and CVR to hypercapnia in patients with coronary artery disease and healthy patients of the same age, following an AT-based program. At baseline, patients were reported to have lower CBF, reduced CVR to hypercapnia, and some atrophied brain regions compared to their healthy counterparts. Following the exercise intervention, CBF was increased in the anterior cingulate cortex (ACC) in the coronary artery disease patients. In fact, the increase in CBF to this region was equal to the shortfall measured at baseline, i.e. the difference between the exercise intervention group and the control group at baseline.

A similar improvement in cerebral perfusion was also observed in overweight adults, who suffered from a stroke and were at risk of developing mild cognitive impairment (MCI).[33] AT improved bilateral CVR to hypercapnia which were accompanied by a 19% improvement in $\dot{V}O_2$peak, compared with a 4% decline in the control group. Hence, AT can improve CVR in these stroke survivors and potentially protect against further neurological insults. However, it was noted that those using statins (58%) had higher CVR at baseline and lower training-induced elevation of CVR, indicating that statin use alone has already

Table 2 Summary of research that has examined the effects of aerobic exercise training on cerebrovascular function, cognition and neural structural adaptations.

References	Study design	Participant description	Group allocation	Primary method used to evaluate CBF/cognition	Effect of exercise on primary outcome	Effect of exercise on other outcomes
Cerebrovascular function						
Studies conducted in apparently healthy individuals						
Ainslie et al.[19]	Cross-sectional	Healthy males (17–79 years old) Endurance-trained/ sedentary	Trained ($n = 154$) Untrained ($n = 153$)	TCD	↑ MCA CBF_V (9.1 $cm \cdot s^{-1} \cdot year^{-1}$ of life)	↑ $\dot{V}O_2$ max
Akazawa et al.[20]	Non-randomised control trial 12 weeks aerobic exercise 4-6 × 30-45 min/week Moderate intensity	Healthy adults (52–66 years old) Sedentary	Exercise ($n = 10$)	TCD	↓ cerebral pulsatility index	↓ arterial stiffness ↑ $\dot{V}O_2$ max ↓CHO
Brown et al.[26]	Cross-sectional	Females (50–90 years old) Endurance trained/ sedentary	Trained ($n = 28$) Untrained ($n = 13$)	TCD	↑ cerebrovascular conductance	↓ resting mean arterial pressure ↑ $\dot{V}O_2$ max
Chapman et al.[28]	Randomised control trial 12 weeks aerobic exercise 3 × 60 min/week Moderate intensity	Healthy adults (57–75 years old) Sedentary	Exercise ($n = 18$) Control ($n = 19$)	MRI	↑ ACC blood flow ↑ hippocampal blood flow	↑ memory performance ↑ $\dot{V}O_2$max ↑ ability to perform exercise
Maass et al.[37]	Randomised control trial 12 weeks aerobic exercise 3 × 30 min/week Moderate intensity	Healthy adults (60–77 years old)	Exercise ($n = 21$) Stretching (control; $n = 19$)	MRI	↑ $\dot{V}O_{2VAT}$ correlated with ↑ hippocampal perfusion & head volume, which correlated with ↑ recognition memory & early recall	↑ hippocampal perfusion in younger participants ↓ hippocampal perfusion in older participants
Vicente-Campos et al.[46]	Randomised control trial 28 weeks aerobic exercise 3–4 × 50 min/week Moderate intensity	Health adults (60–75 years old) Sedentary	Exercise ($n = 22$) Control ($n = 21$)	TCD	↑ vasomotor reactivity ↑ MCA CBF_V	↑ waking velocity & cardiorespiratory capacity ↑ HDL ↓ CHO, LDL & TG ↓ BP
Studies conducted in those diagnosed with a cardiovascular disease						
Anazodo et al.[21]	Non-randomised control trial 24-week aerobic exercise-based cardiac rehabilitation program	Adults Coronary artery disease	Exercise ($n = 17$)	ASL	↑ ACC blood flow	↓ resting CBF and CVR to hypercapnia at baseline

(continued)

Table 2 Continued.

References	Study design	Participant description	Group allocation	Primary method used to evaluate CBF/cognition	Effect of exercise on primary outcome	Effect of exercise on other outcomes
Ivey et al.[33]	Randomised control trial 24 weeks aerobic exercise-based rehabilitation program 3 × 40 min/week Moderate intensity	Adults (>60 years old) Remote stroke (>6 months) Mild-to-moderate gait defects	Exercise ($n = 19$) Control ($n = 19$)	TCD	↑ bilateral cerebrovascular vasomotor reactivity	↑ $\dot{V}O_2$max ↑ walking speed
Cognition						
Studies conducted in those who are overweight but apparently healthy						
Anderson-Hanley et al.[22]	Randomised control trial 12 weeks aerobic exercise 5 × 45 min/week Moderate intensity	Adults (≥55 years old) Overweight	Cycle (control; $n = 41$) Cybercycle (experimental; $n = 38$)	Cognitive battery	↑ score on cognitive battery	↑ BDNF ↓ BMI, fat mass and blood glucose ↑ lean mass and insulin
Studies conducted in those with mild cognitive impairment						
Baker et al.[23]	Randomised control trial 24 weeks aerobic exercise 4 × 45–60 min/week High intensity	Adults (55–85 years old) Mild cognitive impairment Sedentary	Exercise ($n = 19$) Stretching (control; $n = 10$)	Cognitive battery	↑ cognitive scores in multiple tests (female) ↑ cognitive score in 1 test (male)	↓ CHO & LDL ↑ glucose utilisation (female) ↓ insulin, cortisol and BDNF (female) ↑ IGF1, cortisol and HOMA-IR (male)
Studies conducted in those diagnosed with Alzheimer's disease						
Hoffmann et al.[32]	Randomised control trial 16 weeks aerobic exercise 3 × 60 min/week Moderate–high intensity	Adults (50–90 years old) Mild Alzheimer's disease	Exercise ($n = 102$) Control ($n = 88$)	SDMT (cognitive testing)	No change between the two arms of the study ↑ SDMT from baseline (experimental arm)	↑ Neuropsychiatric inventory from baseline (experimental arm only)
Sobol et al.[43]	Cross-sectional	Adults (50–90 years old) Mild Alzheimer's disease	Undefined ($n = 185$)	Cognitive battery	↑ cognition correlated with ↑ 30 s chair sit-to-stand performance	↑ dual-task performance correlated with ↑ performance in the cognitive battery
Neural structural adaptations						
Studies conducted in apparently healthy individuals						
Erickson et al.[30]	Randomised control trial One-year aerobic exercise 3 × 40 min/week Moderate intensity	Healthy adults (55–80 years old) Sedentary	Exercise ($n = 60$) Stretching (control; $n = 60$)	MRI	↑ hippocampal volume	↑ spatial memory ↑ BDNF ↑ $\dot{V}O_2$max

(continued)

Table 2 Continued.

References	Study design	Participant description	Group allocation	Primary method used to evaluate CBF/cognition	Effect of exercise on primary outcome	Effect of exercise on other outcomes
Studies conducted in those with mild cognitive impairment						
Chirles et al.[29]	Non-randomised control trial 12 weeks aerobic exercise 4 × 30 min/week Low–moderate intensity	Adults (60–88 years old) Mild cognitive impairment	MCI (exercise; $n = 16$) Non-MCI (exercise; $n = 19$)	MRI	↑ right parietal lobe connectivity (MCI group) ↓ right parietal lobe connectivity (healthy group) ↑ left post central gyrus connectivity (both)	↑ neural connectivity from baseline (MCI group) No change in neural connectivity from baseline (healthy group)
Smith et al.[42]	Non-randomised control trial 12 weeks aerobic exercise 4 × 30 min/week Low–moderate intensity	Adults (60–88 years old) Mild cognitive impairment Low levels of physical activity	MCI (exercise; $n = 17$) Non-MCI (exercise; $n = 18$)	MRI Semantic memory task	↑ semantic memory ↓ neural activation post exercise	↑ $\dot{V}O_2$peak

TCD: transcranial Doppler ultrasound; ASL: arterial spin labelling; MRI: magnetic resonance imaging; CBF: cerebral blood flow; CBF_V: cerebral blood flow velocity; MCA: middle cerebral artery; ACC: anterior cingulate cortex; CVR: cerebrovascular responsiveness. SDMT: symbol digit modalities test; CHO: total cholesterol; LDL: low-density lipoprotein; TG: triglycerides; BMI: body mass index; IGF1: insulin-like growth factor-1; HOMA-IR: homeostatic model assessment of insulin resistance; BDNF: brain-derived neurotrophic factor; MCI: mild cognitive impairment.

improved CVR with less scope for further improvement. Nonetheless, this study shows that AT can improve cerebrovascular function even in individuals with established cerebrovascular dysfunction.

A larger study which assigned older sedentary adults to a one-year walking program[30] showed increased hippocampal volume, systemic brain-derived neurotrophic factor (BDNF) concentrations, spatial memory and $\dot{V}O_2$ max. The authors of the study also ran correlation analyses between hippocampal volume and $\dot{V}O_2$ max, as well as correlations between BDNF and hippocampal volume. It was reported that increases in exercise capacity and systemic BNDF concentrations were associated with increased hippocampal volume which was, in turn, positively associated with improved spatial memory. Hence, it was concluded that AT increased BDNF which reversed both senescent-related hippocampal atrophy and decline in spatial memory.

The changes elicited in regions of the brain that are responsible for cognition following AT have not been clear. A study that evaluated the effects of AT on hippocampal vascularity in healthy older adults, indicated varied results.[37] $\dot{V}O_2$ at ventilatory threshold increased by 10% after training, which correlated with the increases in hippocampal CBF perfusion and brain volume as measured by functional MRI (fMRI). Hippocampal volume and perfusion were also correlated positively to changes in recognition memory and early recall. This suggests that hippocampal vascularity decreases with age and that the effect of exercise training may attenuate this decline. A later study aimed to determine if functional connectivity of the default mode network (described above) could be improved in non-MCI and MCI older adults who took part in AT.[29] It was noted that right parietal lobe connectivity increased in the MCI group, but decreased in the non-MCI group, while left post central gyrus connectivity increased in all of the participants. It was also noted that there was increased neural connectivity in 10 regions of the brain that spanned from all major lobes of the cerebrum as well the insular lobe and the cerebellum in the MCI group. However, these changes after training were not evident in the non-MCI group, suggesting that exercise training may impart protective effects on cognition in elderly adults with MCI by increasing the plasticity in the posterior cingulate cortex and the precuneus and thereby improving neural recruitment. While mechanisms mediating these changes occurred were not proposed, it could be hypothesised that enhanced cerebrovascular function increased the availability of neural growth factors such as BDNF in these areas of the brain, resulting in synaptogenesis.[88] However, further testing is needed to support this hypothesis.

Chapman et al.[28] assigned cognitively healthy, sedentary adults to an AT program. Following training, CBF was increased at rest in the ACC, which is responsible for executive functioning and autonomic cardiovascular control. The trained group also demonstrated improved immediate and delayed memory performance, which was associated with a general increase in hippocampal perfusion. The authors suggested that exercise training could assist in diminishing the biological and cognitive consequences of the senescent phenotype in sedentary older adults by increasing neuroplasticity in both the ACC and hippocampus. However, measurements of physical volume of these brain areas were not undertaken. Hence, this study indicates that improvements in cerebrovascular function, particularly within the ACC and hippocampus, following AT are associated with improved cognitive capacity in sedentary older adults and that these changes may diminish the progression of the senescent phenotype described above.

In summary, there is strong evidence that AT improves cerebrovascular function. The studies presented indicate that improved vascular function and health and exercise capacity may be associated with these improvements as well as increased systemic BDNF concentrations.

Resistance exercise training (Table 3)

Xu et al.[89] investigated the impact of flexibility, RT and AT on cerebrovascular perfusion in older adults. It was reported that females who participated in RT had greater cerebrovascular perfusion than those who did not and that this finding remained significant after adjusting for health, educational status and the other types of exercise training performed. It was also reported that there was no association between cerebral perfusion and AT or flexibility training. While interesting, these results were based on self-reported subjective data obtained from a small sample size and did not include the intensity and duration of exercise and should be examined with caution. Additionally, the authors of this study did not offer an explanation or propose a mechanism whereby RT could improve cerebrovascular perfusion. The adaptations to RT and cardiovascular function are not well understood compared to AT. To highlight this, a recent cross-sectional study of nearly 400,000 United States residents aimed to determine whether meeting the current physical activity guidelines for moderate-to-vigorous intensity aerobic physical activity, RT or both were associated with chronic health conditions.[90] It was reported that meeting the guidelines for both forms of physical activity resulted in less risk of developing any cardiovascular disease, including stroke, and that meeting the strength

Table 3. Summary of research that has examined the effects of resistance exercise training on cerebrovascular function, cognition and neural structural adaptations.

References	Study design	Participant description	Group allocation	Primary method used to evaluate CBF/cognition	Effect of exercise on primary outcome	Effect of exercise on other outcomes
Cerebrovascular function						
Studies conducted in apparently healthy individuals						
Xu et al.[89]	Cross-sectional	Adults (57–76 years old) Sedentary Participation in one or more strength-training sessions/week Participation in aerobic exercise training	Total participants (n =59) Resistance trained (n = 31)	MRI	↑ cerebrovascular perfusion (strength-trained females)	No association between ↑ cerebral perfusion with either aerobic or flexibility training
Cognition						
Studies conducted in apparently healthy individuals or self-reported memory complaints						
Busse et al.[93]	Randomised control trial Nine months resistance exercise 2 × 60 min/week Varied intensity	Adults (62–86 years old) Sedentary Subjective memory complaints	Exercise (n = 14) Control (n = 17)	Cognitive battery	↑ memory performance	↑ muscle strength
Cassilhas et al.[27]	Randomised control trial 24 weeks resistance exercise 3 × 60 min/week Moderate or high intensity	Healthy males (65–75 years old) Sedentary	Moderate intensity (exercise; n = 19) High intensity (exercise; n = 20) Stretching without overload (control; n = 23)	Cognitive battery	↑ cognition, memory and executive function	↓ POMS score (↑ performance) ↑ IGF1 ↑ muscle strength
Studies conducted in those with mild cognitive impairment						
Fiatarone Singh et al.[31]	Randomised control trial 26 weeks resistance exercise 2–3 × 60–100 min/week Moderate–high intensity	Adults (>55 years old) MCI	Exercise + sham cognitive training (n = 22) Cognitive training + sham exercise (n = 24) Exercise + cognitive training (n = 27) Sham exercise + sham cognitive training (control; n = 27)	ADAS-cog Cognitive battery	↑ ADAS-cog performance post intervention ↑ ADAS-cog performance (participants with normal scores doubled from baseline, i.e. 24–48% one-year post-intervention)	↑ executive function ↑ executive function one year post-intervention ↑ visual memory ↑ speed/attention (all groups)
Neural structural adaptations						
Studies conducted in those with mild cognitive impairment						
Bolandzadeh et al.[24],	Randomised control trial One-year resistance	Females (65–75 years old) Community dwelling	1 × 60 min/week (exercise; n = 46)		↑ Stroop performance (↑10.9-12.6%)	↓ white matter lesions (2 sessions/week)

(continued)

Table 3. Continued.

References	Study design	Participant description	Group allocation	Primary method used to evaluate CBF/cognition	Effect of exercise on primary outcome	Effect of exercise on other outcomes
Liu-Ambrose et al.,[35] Liu-Ambrose et al.[36]	exercise 1 × 60 min/week Or 2 × 60 min/week High intensity	Not participated in resistance training in the last six months	2 × 60 min/week (exercise; $n = 47$) Balance and tone (control; $n = 42$)	MRI Cognitive battery	↑ executive function ↑ left middle temporal gyrus and left anterior insula function – improved functional plasticity of response inhibition (2 sessions/week) ↑ flanker task performance (2 session/week) ↓ whole-brain volume ↓ trail making task time (all groups)	↑ gait speed ↑ muscle power (2 session/week) ↑ muscle strength
Nagamatsu et al.[39] ten Brinke et al.[45]	Randomised control trial 26 weeks resistance exercise Or 26 weeks aerobic exercise 2 × 60 min/week Moderate–high intensity	Females (70–80 years old) Mild cognitive impairment	Aerobic exercise ($n = 30$) Resistance exercise ($n = 28$) Balance and tone (control; $n = 28$)	MRI Stroop test RAVLT Associated memory tasks	↑ Stroop test performance ↑ memory performance and conflict resolution performance (resistance exercise) ↑ right lingual and occipital-fusiform gyri and right frontal pole functional plasticity (resistance exercise) ↑ hippocampal volume by 4% (aerobic exercise)	↑ cardiovascular capacity ↑ physical function (aerobic exercise)

MRI: magnetic resonance imaging; ADAS-Cog: Alzheimer disease assessment scale–cognitive subscale; POMS: profile of mood states; RAVLT: Rey's auditory verbal learning test; IGF1: insulin-like growth factor-1; MCI: mild cognitive impairment.

component of the guidelines alone resulted in less risk of cardiovascular disease development than moderate-to-vigorous intensity aerobic physical activity. Hence, it may be plausible that strength training can reduce the incidence of systemic vascular disease and may also reduce cerebrovascular dysfunction, through an unknown and unexplored mechanism.

Other than the longitudinal data presented above, there have been no studies that examine the effect of RT on cerebrovascular function.

The effects of exercise training on cognitive function

Aerobic exercise training (Table 2). A population-based study examined the relationship between aerobic exercise-trained individuals and executive function at the start of adulthood and the risk of developing cognitive impairment in later life.[41] Over one million young Swedish males who were subject to mandatory conscription examinations between 1968 and 2005 were evaluated to ascertain the risk of developing cognitive impairment. Aerobic fitness and cognitive performance at 18 years of age was associated with an increased risk of developing cognitive impairment in later life. Specifically, those with poor aerobic fitness had a >7-fold increased risk of developing early-onset dementia and early-onset MCI, while those with poor cognitive performance had a >8-fold increased risk compared with those who did not. Another cross-sectional study, which utilised the baseline data from their AT study involving older participants with mild Alzheimer's disease, reported that a greater performance in the 30 s chair sit-to-stand test correlated with increased cognition.[43] Sobol et al.[43] concluded that there was a strong association between superior cognitive performance, physical function and the ability to carry-out dual tasks, thus suggesting that interventions that improve physical function and the ability to multi-task may impart benefits on improving cognitive outcomes and prevent further deterioration in patients with mild Alzheimer's disease. Taken together, these studies suggest that physical fitness is strongly associated with cognitive performance and that the former has a positive effect on the latter.[19,26,41,43]

Smith et al.[42] determined if AT could improve semantic memory activation during fMRI in physically inactive older adults with MCI in comparison to appropriately matched cognitively-intact individuals. $\dot{V}O_2$ peak and performance in list-learning tasks increased (indicating improved semantic memory performance), and there was a decrease in activation intensity (i.e. improved neural operating efficiency) post exercise. This study did not evaluate any cerebrovascular functions, but did suggest that the improved neural efficiency may be due to improved cerebral perfusion, even with low–moderate intensity AT.

Baker et al.[23] evaluated the impact of AT on cognitive function and biomarkers of Alzheimer's disease in older adults with amnestic MCI. After training, female participants had improved cognition, cortisol and BDNF concentrations compared to the stretching (control) group. Aerobically trained men, however, had increased insulin-like growth factor-1 (IGF1) and only performed favourably in one of the cognitive battery tests. Hence, this study concluded that AT can improve cognition and that these effects may be greater in women who are at greater risk of developing cognitive impairment than men, possibly due to an altered hypothalamic–pituitary–adrenal axis response. While this may in part be true, these findings and the increased risk of developing MCI in women may also be due to loss of the vasoprotective effects of oestrogen post-menopause.[91] Taken together, these studies[20,23,46] suggest that AT improves cognitive function and indicate that improved lipid profiles are important for maintaining vascular health and, therefore, cerebrovascular function. Further, it suggests that there may be a sex difference in responses to exercise training, which should be considered in future studies.

In another intervention study, overweight older adults participated in three-month traditional cycling or cyber-cycling (a cycle ergometer with an attached virtual reality component) training demonstrated increased cognitive performance and systemic BDNF concentrations compared to their baseline results.[22] Cyber-cycling participants had greater increases than those who underwent traditional cycling, resulting in a medium effect size improvement of cognitive performance compared to the control group. This suggested that virtual reality coupled with AT increased neuroplasticity more than standard AT and that cyber-cycling imparts a 23% relative reduction in the risk of MCI development. This study did not have a sedentary control group but relied on improvements from baseline measurements and did not provide details of potential mechanism/s by which a virtual reality component could elicit improved executive functioning, other than suggesting that increased BDNF concentrations may have elicited these results. Hence, this may provide a future direction for researchers to consider when prescribing exercise coupled with a virtual reality program.

A later and larger study evaluated the effects of AT in sedentary older adults with mild Alzheimer's disease.[32] There were no differences between the control and training groups in cognitive performance. However, participants with over 80% compliance to the exercise program and trained at 70% of their maximal heart rate or greater exhibited improvements in

cognitive performance from baseline compared to the control group, thus suggesting a dose–response relationship between AT and cognitive performance. Finally, it was reported that neuropsychiatric scores were improved from baseline in the exercise group compared to the control group, whose scores declined over the course of the program. Hence, it was concluded that AT could impede or slow the progression of neuropsychiatric symptoms and that increased adherence to AT is imperative to improve cognition in those who are already cognitively impaired.

In summary, there is evidence that AT can improve cognitive performance. Again, this appears to be related to improved exercise capacity. However, the mechanism leading to these changes is not clear, but may involve increased systemic BDNF, vascular health and hormonal changes. Further studies are required to determine the mechanism of action leading to improved cognitive performance.

Resistance exercise training (Table 3). Cassilhas et al.[27] conducted one of the first studies investigating the effects of RT on cognition in healthy, sedentary, older males. A limitation to the exercise protocol used in this study was that no progressive overload, periodisation or adjustments added or made that adjusted for intensity and conditioning to this program. The program may have been completed in this manner for simplicity, since the control group performed the same routine once per week without any overload applied. In any case, both exercise groups demonstrated improved cognition in comparison to the control group. Lean mass, systemic IGF1 concentrations and muscle strength were increased in both of the exercise groups when compared to the control group, with these changes being more prominent in the high-intensity exercise group. Additionally, IGF1 concentrations decreased in the control group suggesting IGF1 may be mediating the change in cognition. These results suggest that RT could improve cognitive function possibly by increased growth factors, which may act as mediators of neurogenic pathways within the brain.[27,92] However, no correlational results were generated from this study.

This finding was supported by a later study that investigated the effects of RT on cognitive performance and muscle strength in sedentary older adults with subjective memory complaints.[93] It was found that the exercise group, particularly the women, demonstrated improved memory performance within the cognitive battery administered and increased muscle strength compared to the control group. This finding indicates that RT may improve memory deficits in elderly participants with memory complaints.

Finally, Fiatarone Singh et al.[31] evaluated 26 weeks of either progressive RT, cognitive training or a combination of both on global cognitive function in older adults with MCI. The cognitive training incorporated the COGPACK program, which is a neuro-rehabilitation program incorporating adaptive computerised exercises of memory, executive function, attention and processing speed.[98] Upon study completion, those in the RT group demonstrated improvements to a greater extent than the other groups in the Alzheimer Disease Assessment Scale–Cognitive Subscale (ADAS-Cog), which assesses cognitive decline. In this group, the proportion of participants attaining normal ADAS-Cog scores increased from only 24% at baseline to 48% following one year of training. They also performed 74% higher in executive function testing than the other groups in a 12-month follow-up post-intervention, indicating that the improvements in executive function were sustained for at least one year. Additionally, the RT group demonstrated increased visual memory performance compared to the other groups immediately post-intervention. These findings indicate that progressive RT improves global cognitive and executive functions and that cognitive training prevents any further decreases in overall memory and cognition. Interestingly, combined training did not demonstrate an enhanced benefit compared to RT alone, possibly because it was too challenging for participants to successfully engage for a full 100 min, separating RT and cognitive training may have assisted this. Why cognition was maintained a year after RT cessation was unclear, and biomarkers such as IGF1 and BDNF were not measured.

The cognitive improvements observed by Busse et al.[93] were more evident in females than males and Xu et al.[89] reported that sex differences could account for differences in improvements of cerebral perfusion and cognition induced by RT. Two larger trials examined this finding by investigating the efficacy of chronic exercise training, particularly RT, on executive functions and cognition in elderly females with MCI.[24,35,36,39,45] The EXCEL study randomised participants to either AT or RT or to a balance and tone (control) group.[39,45] Compared to the control and AT groups, participants in the RT group increased performances in the Stroop test, memory tasks and conflict resolution, as well as enhancing functional plasticity in the right lingual and occipital–fusiform gyri and right frontal pole, assessed by fMRI. The AT group reported a 4% increase in hippocampal volume compared with the other groups but did not show improvement in memory performance to the recall tasks, as one would expect an increase in hippocampal volume to correlate with improved memory function. These findings suggest that RT improves cognitive performance and regional brain plasticity to a

greater extent than AT in elderly females at risk of further cognitive decline.

The other large-scale study aimed to determine if performing once or twice weekly RT sessions for one year could improve executive function and cognition in older females compared to balance and muscular toning exercises.[24,35,36] Both RT groups improved by 10.9–12.6% in the Stroop test compared with a control group who reported a 0.5% decrease and demonstrated improved executive function compared to the control group. However, only the participants performing two RT sessions per week had increased functional plasticity in the left middle temporal gyrus and left anterior insula, as well as superior performance in the flanker task and muscle power measurements. Additionally, MRI revealed a decrease in whole-brain volume in both groups compared with the control group. The authors of the study cautiously suggest that this may have been due to an increase in amyloid-β removal in conjunction with other neural proteins, as this had been a finding in previous studies that specifically measured and noted reductions in cerebral volume following treatments with pharmaceuticals.[94,95] This study did not measure any neurodegenerative or inflammatory biomarkers and could only speculate that this may be the case. In support of this, however, the twice per week RT group experienced a decrease in white matter lesions, which one-third of the participants were reported to possess. These findings warrant further research into the effect of exercise on cerebral volume. In any case, it was concluded that two RT sessions performed twice a week may improve cognition, executive function, selective attention and conflict resolution in older females and that this dosage of exercise could potentially convey favourable functional plasticity changes in a manner similar to AT.

Taken together, these studies indicate that RT improves cognitive performance. However, none of these studies offer an insight as to why RT appears to exert a greater effect in women than men. Future studies might benefit from measuring different hormones, such as androgens and oestrogens. It has been suggested that phytoestrogens, such as resveratrol, increase central oestrogen receptor activity, while promoting upregulation of eNOS and, therefore, NO production, thus leading to improvements in cerebrovascular function.[91] Further, these studies did not investigate possible effects of changes in body composition, as it is well known that a result of RT is increased lean mass. Any increase in tissue, whether positive or negative, demands increased capillarisation and recruitment of the existing vasculature, which is largely mediated through VEGF, a protein that promotes angiogenesis and potentiates the effects of NO. Specifically, central VEGF concentrations and increased cerebral capillarisation have been demonstrated in animal studies to be upregulated centrally via the centrally derived lactate receptor hydroxycarboxylic acid receptor 1 (HCAR1) following increased plasma lactate concentrations and shear stress.[96,97]

The effects of multimodal exercise training on cerebrovascular function, structure and/or cognition (Table 4)

One of the first intervention studies examined the effects of CT (of the participants' choice) on cognition in older participants with self-reported memory problems.[34] The rate of cognitive decline (evaluated using ADAS-Cog exam) improved by 0.26 points post-intervention, while the control group had declined by 1.04 points, both of which were considered as clinically significant. Eighteen months post-intervention, the intervention group had improved by a further 0.73 points, whilst the control group improved 0.04 points from the previous ADAS-Cog examination. The intervention group also reported a modest improvement in a word list delayed recall test and clinical dementia rating. These findings were supported by a later study that investigated the effects of CT on cognition in physically inactive older Alzheimer's disease patients.[47] It was reported that exercise training improved mini-mental state examination (MMSE) scores by 2.6 points and ADAS-Cog by 7.1 points. Taken together, these studies suggest that CT improves both cognitive and physical function in elderly individuals with either self-reported memory issues or Alzheimer's disease. However, the latter study did not define intensity, dose or progression, thus it is unknown if there was a dose–response relationship in relation to the study outcomes.

Bossers et al.[25] compared the effects of either CT or AT on cognitive and motor function in institutionalised elderly adults with dementia. Post-intervention, the CT group demonstrated increased global cognition, visual and verbal memories and executive function compared with the control group, while the AT group only demonstrated increases in executive function compared to the control group. Eighteen weeks post-intervention, there was a decline in cognitive function towards baseline values. Hence, it was concluded that a combined exercise program is more effective than AT alone in reducing cognitive and motor function decline in patients with dementia.

Suzuki et al.[44] assigned older adults with MCI to a CT program. Memory function and whole brain cortical atrophy all improved after training compared to controls. Further, lower total cholesterol and higher BDNF concentrations were associated with increased cognitive function and memory in patients with MCI at

Table 4. Summary of research that has examined the effects of multimodal exercise training on cognition and neural structural adaptations.

References	Study design	Participant description	Group allocation	Primary method used to evaluate CBF/cognition	Effect of exercise on primary outcome	Effect of exercise on other outcomes
Cerebrovascular function						
Studies conducted in those diagnosed with a cardiovascular disease						
Moore et al.[38]	Randomised control trial 19-week multimodal exercise 3 × 45–60 min/week Varied intensity	Adults (>50 years old) >6 months post stroke	Exercise ($n = 20$) Stretching (control; $n = 20$)	MRI ACE-R	↑ middle temporal lobe tissue CBF No change in grey matter tissue volume ↑ ACE score (6 points)	No change in HOMA-IR ↑ $\dot{V}O_2$peak ↑ walking speed ↑ balance ↑ physical function ↑ HDL ↓ diastolic blood pressure
Cognition						
Studies conducted in those diagnosed with a dementia						
Bossers et al. [25]	Randomised control trial Nine-week multimodal exercise 4 × 30 min/week Varied intensity Or Nine-week aerobic exercise 4 × 30 min/week Moderate–high intensity	Adults (80–90 years old) Diagnosis of dementia	Multimodal exercise ($n = 33$) Aerobic exercise ($n = 34$) Social (control; $n = 34$)	Cognitive battery	↑ global cognition, visual & verbal memories, executive function (multimodal exercise) ↑ executive function (aerobic exercise)	↑ walking endurance, muscle strength & balance (multimodal exercise) ↑ walking endurance (aerobic exercise)
Vreugdenhil et al.[47]	Randomised control trial 16 weeks multimodal exercise 10 resistance + 30 min walking Intensity and weekly session were undefined	Adults (mean 77 years old) Alzheimer's disease Lower levels of physical activity	Exercise ($n = 20$) Control ($n = 20$)	MMSE ADAS-Cog	↑ MMSE scores (2.6 points) ↑ ADAS-Cog exam performance (7.1 points)	↑ lower body strength ↓ waist-to-hip ratio ↑ mobility (2.9s faster on timed up & go test) ↑ Instrumental activities of daily living scores (1.6 points)
Studies conducted in apparently healthy individuals or self-reported memory complaints						
Lautenschlager et al.[34]	Randomised control trial 24 weeks multimodal exercise 3 × 50 min/week Moderate intensity	Healthy adults (>50 years old) Self-reported memory problems (excluding dementia)	Exercise ($n = 85$) Control ($n = 85$)	ADAS-Cog	↑ 0.26 points post-intervention ↑ 0.73 points 18 months post-intervention	↑ physical activity 18 months post intervention ↑ word list delayed recall test ↑ clinical dementia rating
Neural structural adaptations						
Studies conducted in apparently healthy individuals						
Nishiguchi et al.[40]	Randomised control trial 12 weeks multimodal exercise	Healthy adults (>60 years old)	Exercise ($n = 24$)	MRI Cognitive battery	↑ memory and executive function ↓ activation in visual	↑ average daily steps (54%) ↑ 100% adherence to program

(continued)

Table 4. Continued.

References	Study design	Participant description	Group allocation	Primary method used to evaluate CBF/cognition	Effect of exercise on primary outcome	Effect of exercise on other outcomes
	1 × 90 min/week + pedometer-based walking activity Varied intensity		Control ($n = 24$)		short-term memory centres (e.g. bilateral prefrontal cortex)	
Studies conducted in those with mild cognitive impairment						
Suzuki et al.[44]	Randomised control trial 24 weeks multimodal exercise 2 × 90 min/week Varied intensity	Adults (55–95 years old) MCI	Exercise ($n = 45$) Education (control; $n = 45$)	MRI ADAS-Cog Cognitive battery	↓ whole brain cortical atrophy ↑ cognitive battery and ADAS-Cog exam scores	↓ baseline CHO and ↑ BDNF associated with improvements in cognitive function pre-exercise

ADAS-Cog: Alzheimer disease assessment scale–cognitive subscale; MMSE: mini-mental state examination; MRI: magnetic resonance imaging; ACE: Addenbrooke's cognitive examination; CHO: total cholesterol; BDNF: brain-derived neurotrophic factor; MCI: mild cognitive impairment.

baseline than those who had higher total cholesterol and lower BDNF concentrations. However, it was not determined how having higher or lower baseline concentrations of these biomarkers impacted the results throughout the course of the study, or if participants with more favourable concentrations of these biomarkers responded better to the exercise intervention compared with those who had a less favourable profile. Interestingly, these biomarkers were not measured upon completion of the study, as this could have provided a mechanism or possibly explained the improved response to exercise. This study provides further evidence that exercise training improves cognitive function and was supported by Nishiguchi et al.[40] who evaluated the effects of CT on cognition and brain activation efficiency healthy older adults. The exercise group had improvements in memory and executive function when compared to the control group, but they had less activation in regions of the brain, such as the prefrontal cortex, that were associated with short-term and visual memory. Hence, it was concluded that the combined exercise increased the activation efficiency of the brain during cognitive tasks and that this was associated with improved memory and executive function.

Moore et al.[38] examined a CT program in older participants who had previously suffered from a stroke six months prior or longer. Medial temporal lobe tissue CBF increased in the exercise group without incidence of grey matter atrophy compared to the control group, who reported a decrease in grey matter atrophy. Further, exercise training improved cognition by 6 points. Training increased $\dot{V}O_2$peak, diastolic blood pressure, HDL and physical and cognitive function. Hence, it was suggested that CT could lead to improved short-term metabolic, cognitive and functional capacity of the brain. These results suggest a similar mechanism to AT, as markers of cardiovascular health had improved in the exercise group and provides further evidence that exercise training improves cognitive function.

In summary, there is evidence that CT improves both cerebrovascular function and cognitive performance, particularly in those that have been diagnosed with stroke, MCI or dementia. The mechanism of action is, again, not clear, but likely involves improved vascular function and health leading to increased CBF, increased exercise capacity and structural adaptations within the brain that lead to improved brain activation efficiency.

Why does cerebrovascular and cognitive function change following exercise training?

It is evident from this review that exercise training improves cerebrovascular structure and function and

cognition. It is also evident that the mechanisms that lead to these improvements in humans are poorly defined. The link, or the associations, between the two do not appear clear. Very few studies have performed correlation analyses on the results generated from their studies or undertaken perturbation studies to understand the mechanisms involved. Erickson et al.[30] analysed associations between hippocampal volume and $\dot{V}O_2$ max and BDNF and hippocampal volume. They concluded that AT increased BDNF, which, in turn reversed both senescent-related hippocampal atrophy and decline in spatial memory. Aside from this, associations can only be made based upon the observations generated from the studies described. It is quite evident that as $\dot{V}O_2$ max and/or physical function increases, so too does cerebrovascular function and cognition. However, this does not identify a direct mechanism by which exercise improves these parameters. Rather, it provides an insight into the potential mechanisms that could lead to change. $\dot{V}O_2$ max, which represents cardiorespiratory fitness, is governed by the Fick equation (cardiac output multiplied by the arterial–venous oxygen difference). For $\dot{V}O_2$ max to increase there would be one or several physiological adaptations following exercise training, which are defined elsewhere.[98–100]

Mechanistic evidence observed in animal studies

What occurs centrally after exercise training is poorly defined in humans. Centrally in mice there is an increase in oxidative enzyme synthesis, suggesting that exercise may improve central oxidative capacity.[82,98–104] Therefore, it may be plausible that some of the adaptations that are described in skeletal muscle may also occur centrally, thus leading to improvements in cerebrovascular and cognitive functions. Specifically, chronic exercise in animal enhances endothelial function, upregulates eNOS expression and activity thereby increasing NO production and reduces ROS production. These changes reduce vascular inflammation and inhibit endothelial dysfunction. Additionally, exercise training enhances mitochondrial biogenesis via upregulating transcription factors, such as peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α).[105] Specifically, PGC-1α upregulates oestrogen-related receptor alpha-α, which subsequently upregulates lactate dehydrogenase (LDH) B and indirectly inhibits LDH A, thus leading to increased lactate oxidation during exercise.[106] This process increases the oxidative capacity of skeletal muscle and improves an individual's exercise capacity, as well as contributing to reducing ROS production, chronic inflammation, angiogenesis and the loss of muscle atrophy and function that is associated with the senescent phenotype.[105,106] However, further studies are required in order to demonstrate this.

The clinical studies described indicate that specific growth factors may have a role in conferring improvements in cerebrovascular and cognitive functions in at risk populations. Acute exercise results in increased arterial shear stress, enhanced synthesis of growth hormone and NO, as well as increased β-hydroxybutyrate and lactate production, all of which either stimulate increased IGF1 synthesis, promote increased BDNF expression and synthesis and/or HCAR1-induced VEGF upregulation, respectively.[96,97,107–111] BDNF and IGF1 are expressed centrally and systemically and when produced systemically cross the BBB and augment the response of their centrally derived counterparts.[97,112] These factors promote increased neuroplasticity, neurogenesis, neural repair, synaptogenesis and angiogenesis, in addition to possibly promoting the removal of amyloid-β.[96,97,105,107,108,110–115] BDNF and IGF1 may also enhance glutamate synthesis centrally, via upregulating synapsin-1, thus contributing to improved cognition.[114] Additionally, VEGF promotes angiogenesis and potentiates the effects of NO via phosphatidylinositol-4,5-bisphosphate hydrolysis, which subsequently activates the calmodulin and protein kinase B and C pathways, thus resulting in eNOS upregulation.[82,96,110]

In older animal models, ageing increases ROS production and chronic low-grade inflammation, resulting in arterial stiffening.[82,101] Exercise training decreases inflammation and ROS production, modulates arterial structure and increases NO bioavailability, thus reducing arterial stiffness and improving endothelial function (reviewed in detail in Ref.116). This has also been suggested to occur in older physically inactive adults.[101] Hence, it would be expected that exercise-induced improvements in endothelial function, which leads to increased CBF, would also improve the ability of these neurotrophic factors to reach the smaller cerebral vessels and potentiate growth, maintenance and efficiency of the areas of the brain that are responsible for cognitive and executive functioning, such as the hippocampus. While this hypothesis seems plausible and may assist in providing an explanation as to why exercise studies note changes in brain volume, plasticity and neural efficiency, future studies are required in order to validate this.

Summary

There is evidence that AT can improve CBF, cognition and neuroplasticity through areas of the brain associated with executive function and memory in older adults but there is still much to explore regarding the effect of RT and how both of these work in concert.

This is largely due to the limited studies performed on the effects of RT on cerebrovascular function and cognition. Improvements in cognitive performance and structural adaptations have been reported with RT which, in some studies, was indicated to be superior to AT. There is some evidence that CT may be superior to AT or RT alone. While this seems logical given the systemic health benefits that CT imparts compared with a single exercise modality, more studies are needed to determine whether benefits also occur centrally. It is also evident that improved cerebrovascular function may act to prevent or slow the progress of cognitive impairment and ultimately dementia. There is currently limited literature that has researched the effects of exercise training on cognition in conjunction with cerebrovascular function, general health and well-being. There are also limited human studies that have aimed to determine the mechanisms by which exercise improves these parameters. While it appears that neurotrophic factors increase in an older population in parallel with exercise, no studies have directly attempted to measure cerebrovascular, inflammatory and metabolic markers that may act to increase their production and reduce ROS production by the potential pathways that we have summarised in Figure 2, which have been based on the current evidence and studies conducted in animal models. In any case, we can conclude that exercise training can improve CBF, cognition and neuroplasticity through areas of the brain associated with executive function and memory in older adults and this message should be promoted to the general public.

Future directions

At present, there are several significant gaps in our understanding of the benefits of exercise training on cerebrovascular and cognitive functions in ageing.

1. Few of the studies cited indicate a dose–response relationship between exercise training, in particular AT, on cerebrovascular and cognitive function in ageing. This is an important step because we do not know whether more is better or if something is better than nothing given that older adults are not meeting the current physical activity guidelines. Further, we do not know whether meeting these guidelines, especially by those who are physically inactive or sedentary, will benefit cerebrovascular and cognitive function in ageing. Randomised clinical trials that vary the frequency and/or duration of exercise would be beneficial in determining if some exercise is better than none.

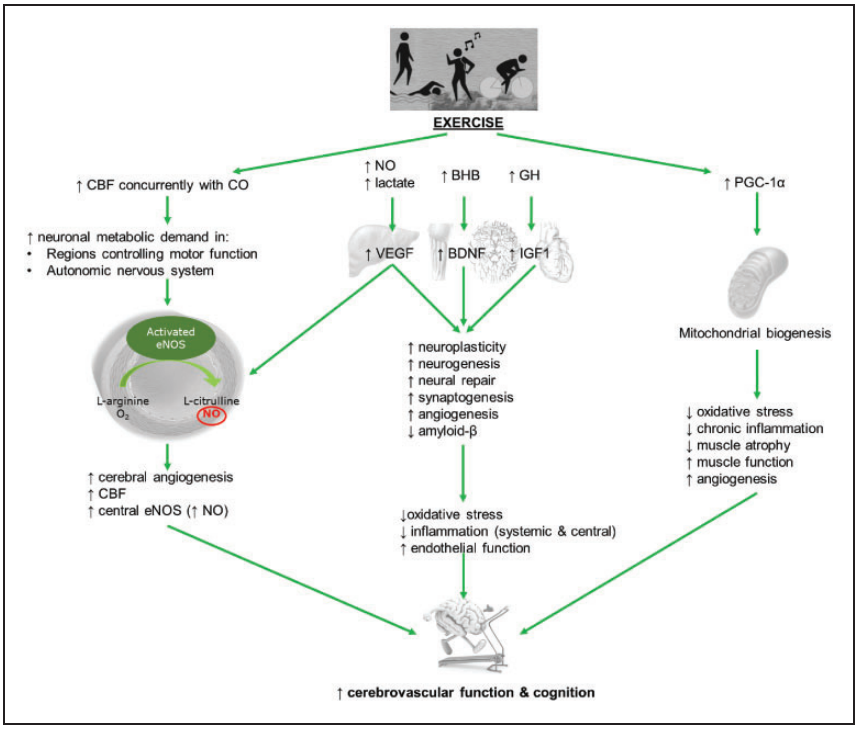

Figure 2. A summary of the potential mechanisms that may be elicited by exercise in improving cerebrovascular function and cognition. CBF: cerebral blood flow; eNOS: endothelial nitric oxide synthase, NO: nitric oxide; BHB: beta-hydroxybutyrate; GH: growth hormone; VEGF: vascular endothelial growth factor; BDNF: brain-derived neurotrophic factor; IGF1: insulin-like growth factor-1; PGC-1a: peroxisome proliferator-activated receptor gamma coactivator 1-alpha.

2. This raises the question as to whether it may be easier for the general public to participate in exercise of shorter duration, higher intensity and more frequently, especially if there are physiological benefits associated with this. High-intensity interval training has significantly grown in popularity and has numerous benefits that are either comparable to or exceed those elicited by more traditional exercise programs, such as steady-state moderate-intensity AT. These may be due to reduced perceived exertion and excess post-exercise $\dot{V}O_2$, and people suffering from chronic disease may be more compliant with this form of exercise.[117–119] Therefore, randomised control trials that focus on more vigorous exercise training performed at shorter durations would help to ascertain whether this method could produce favourable results.
3. Finally, it is currently unknown if lifelong exercise training of any kind is required to maintain cerebrovascular function and prevent the development of dementia or if participating in exercise later in life can mirror the benefits of lifelong exercise and potentially decrease the likelihood of dementia development. As indicated above, there is limited research that has longitudinally assessed data providing any an insight into the trajectory of cerebrovascular function and cognition with exercise training throughout the lifespan, as well as how the type, duration, frequency and intensity of exercise training may impact these parameters. Future studies that incorporate these aspects will undoubtedly provide novel information and assist in determining the mode, intensity and duration of exercise required to elicit benefits with regard to cerebrovascular function and cognition.

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Chapter 3 Postface

Since the time of publication of Chapter 3, one significant piece of research in the area has been published. The study was not a randomised control trial, but rather a one-armed pre-post intervention study conducted by Guadagni et al. (2020), which aimed to determine if a 6-month supervised aerobic exercise training program could improve cerebrovascular function and cognition in older, overweight, low-active adults free from chronic disease. Participants were subjected to approximately 90 minutes of moderate intensity aerobic exercise initially and progressed to approximately150 minutes of moderate intensity aerobic exercise over the 6-month period. Testing involved cognitive assessment to a broad neuropsychological battery and cerebrovascular responsiveness to hypercapnia and submaximal exercise. Interestingly, participants underwent testing 6 months prior to the intervention, again at the start of the intervention and then post-intervention. The two pre-intervention trials were used to account for learning effects when performing cognitive tasks, which may be seen as a strength of the study. The authors reported improvements in executive function, verbal memory and fluency, as well as improvements in resting cerebrovascular function (i.e. increased cerebrovascular conductance and peak cerebral blood flow velocity; reduced cerebrovascular resistance) and cardiorespiratory fitness. The authors reported a negative association between changes in cerebrovascular resistance and executive function, as well as positive association in fluency with cerebrovascular resistance during hypercapnia. The authors do not clearly suggest how these changes resulted but indicated that the observed changes in the reported cognitive domains and cerebrovascular parameters were probably due to improved cardiorespiratory fitness.

Reference

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CHAPTER 4: THE BENEFITS OF REGULAR AEROBIC EXERCISE TRAINING ON CEREBROVASCULAR FUNCTION AND COGNITION IN OLDER ADULTS

The Benefits of Regular Aerobic Exercise Training on Cerebrovascular Function and Cognition in Older Adults

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Abstract

We compared the differences in cerebrovascular and cognitive function between thirteen aerobic exercise trained, older adults (64 ± 2 years; 7 female/6 male) and thirteen age, height and sex-matched sedentary, untrained controls (66 ± 2 years; 7 female/6 male). Aerobic training was defined as consistent participation in at least 150 min of moderate-vigorous intensity aerobic exercise training, such as swimming, cycling and running, per week greater than two years. We determined whether other measures accounted for differences in cerebrovascular and cognitive function between these groups and examined the associations between these functions. Participants undertook anthropometric, mood, cardiovascular, exercise performance, strength, cerebrovascular, and cognitive measurements, and a blood collection. Transcranial Doppler ultrasonography determined cerebrovascular responsiveness (CVR) to hypercapnia and cognitive stimuli. The trained group had a higher CVR to hypercapnia (80.3 ± 7.2 vs 35.1 ± 6.7%, $P < 0.001$), CVR to cognitive stimuli (30.1 ± 2.9 vs 17.8 ± 1.4%, $P = 0.001$) and total composite cognitive score (117 ± 2 vs 98 ± 4, $P < 0.001$) than the controls, which was determined by two-way analysis of variance. These parameters no longer remained statistically different between the groups following adjustments for covariates using an analysis of co-variance. There were positive correlations between the total composite cognitive score and CVR to hypercapnia ($r = 0.474$, $P = 0.014$) and CVR to cognitive stimuli ($r = 0.685$, $P < 0.001$). We observed a relationship between cerebrovascular and cognitive function in older adults and an interaction between exercise training and cardiometabolic factors that may directly influence these functions.

Introduction

Normal ageing is accompanied by a decline in fluid cognitive ability, which is preceded by reduced cerebrovascular structure and function (Rogers et al., 1985; Ainslie et al., 2008; Barnes et al., 2012; Salthouse, 2012; Harada et al., 2013; Bangen et al., 2014; Kennedy and Raz, 2015). This reduction may be attributed to modifiable risks factors that determine cardiometabolic health, including nutrition and physical activity (Woods et al., 2011; AIHW, 2012; Toda, 2012; Bangen et al., 2014; Toth et al., 2017; Bliss et al., 2021). As cerebrovascular function and cognition decline during ageing, our ability to perform general tasks associated with daily life decreases (Paterson et al., 2007; Salthouse, 2012; Taylor, 2014; Bliss et al., 2021). Given that the population is rapidly ageing, and the costs associated with loss of independence and chronic diseases on healthcare systems are rapidly increasing (Taylor, 2014; Brown et al., 2017), it is imperative that evidence-based strategies to prevent and reduce the decline in cerebrovascular function and cognition are identified, such as aerobic exercise. Aerobic exercise defines bouts of exercise that utilise energy produced via aerobic respiration. Examples of such exercise include walking, running, swimming, cycling and rowing (ACSM, 2013; Bliss et al., 2021). An individual can be considered aerobically trained if they repeatedly perform these bouts of exercise over a period of months and years (ACSM, 2013).

Regular exercise has also been shown to help maintain cerebral perfusion in healthy ageing (Rogers et al., 1990; Ainslie et al., 2008; Bailey et al., 2013), which would be an important, simple and cost-effective treatment. For example, Ainslie et al. (2008) reported that the normal age-related decline in mean cerebral blood flow (CBF) velocity (CBF_V) in the middle cerebral artery (MCA) was 0.38-0.45% per year between the ages of 18 and 80 years. However, individuals who regularly engaged in at least 150 min of moderate-vigorous intensity aerobic exercise training for at least two years (self-reported data and objectively determined using maximal aerobic exercise capacity measurements) demonstrated a 17% higher CBF_V across the lifespan compared to age-matched sedentary counterparts (Ainslie et al., 2008). Nevertheless, a limitation to this study was that it did not measure the effects of regular physical activity and exercise on CVR. CVR is the ability to modify regional blood flow in response to specific physiological (e.g. hypercapnia) or psychological stimuli (Serrador et al., 2000; Willie et al., 2011). It is the increase in CBF_V in a conduit cerebral blood vessel which is attributable to dilatation of the microvasculature downstream in response to local chemical changes induced by physiological or psychological stimuli (Willie et al., 2011). CVR is an important measure as the cerebral vasculature is highly responsive to its environment, particularly to the partial pressure of arterial carbon dioxide, and to changes in neuronal metabolism. Further, it is the responsiveness of the cerebrovasculature that maintains both cerebral autoregulation and neurovascular coupling (NVC), and, consequently, cerebral function (Duchemin et al., 2012; Braz et al., 2017; Toth et al., 2017; Miller et al., 2018).

Cross-sectional research that has measured the difference in CVR between aerobically exercise trained and untrained individuals has shown mixed findings. Barnes et al. (2013) and Marley et al. (2020) reported that CVR to hypercapnia was positively associated with maximal aerobic exercise fitness and Bailey et al. (2013) reported a positive linear relationship between maximal aerobic exercise fitness (measured objectively using maximal exercise capacity tests), CBF_V and CVR. However, others have reported no difference in CVR between aerobically exercise trained and untrained individuals (Braz et al., 2017; Miller et al., 2018) or a lower CVR in elderly Masters athletes compared to untrained controls

(Thomas et al., 2013; Zhu et al., 2013). The difference in findings is not clear, but may be due to differences in the technique used for testing CBF (Willie et al., 2011; Braz et al., 2017; Joris et al., 2018), variation in ages and training status (Miller et al., 2018), use of subjective or objective measurements to determine exercise training status and capacity, choice of which cranial or extracranial vessel is used for testing (Willie et al., 2011; Braz et al., 2017) or difference in hypercapnia protocols and the derivatives of CVR (Miller et al., 2018).

Maintaining optimal cerebrovascular function may also delay cognitive decline (Bangen et al., 2014; Toth et al., 2017). Cognitive decline throughout the lifespan is well defined and previous research has reported that middle-aged to older adults who participate in regular physical activity and aerobic exercise training or have undertaken an aerobic exercise training intervention (either self-reported or objectively measured using exercise capacity tests) have greater cognitive capacity than sedentary individuals (Lautenschlager et al., 2008; Baker et al., 2010; Anderson-Hanley et al., 2012; Vreugdenhil et al., 2012; Bossers et al., 2015; Hoffmann et al., 2016; Sobol et al., 2016). Further, aerobic exercise intervention trials lasting between 12-24 weeks have demonstrated improvements in cerebral perfusion (Chapman et al., 2013; Maass et al., 2014), cerebral arterial stiffness (Akazawa et al., 2018) and cerebrovascular responsiveness (CVR) to hypercapnia (Vicente-Campos et al., 2012; Guadagni et al., 2020) in sedentary, older adults. Interventional studies highlight the relationship between exercise, cognition and cerebrovascular function. However, they typically only consider short-term changes that exercise may induce rather than chronic adaptations that may be associated with lifelong exercise and sedentary behaviour. This highlights a current knowledge gap between short-term changes and chronic adaptations and whether the ‘gap’ can be closed by implementing exercise training regimes. None of these studies have examined the association between cognition and cerebrovascular function.

Only two cross-sectional studies have measured and associated cognition with cerebrovascular function (Rogers et al., 1990; Brown et al., 2010). Both parameters should be measured simultaneously as they are interdependent and, therefore, should not be studied as separate functions (Bliss et al., 2021). These studies demonstrated that older adults with higher aerobic fitness had greater cerebrovascular and cognitive function compared to sedentary individuals. However, CVR to psychological stimuli (NVC) was not tested, nor were any correlation analyses between cerebrovascular and cognitive function performed. Here it would be expected that higher cognitive function would be associated with increased cerebrovascular function, while lower cognitive function would be associated with reduced cerebrovascular function This is important as it measures complex interactions between neuronal metabolic demands and local haemodynamic changes, thus ensuring that the metabolic demands of the brain are met by the vasculature (Duchemin et al., 2012; Toth et al., 2017). Further, other potential covariates including body composition, cardiovascular function, biochemistry and educational level that may also explain the differences in cerebrovascular and cognitive function between aerobic exercise trained and untrained sedentary individuals were not accounted for. These important variables may directly impact vascular, cerebrovascular and cognitive functions and may also explain the differences between aerobic exercise trained and sedentary, untrained individuals (Bliss et al., 2021). This is because ageing is associated with reductions in vascular, cerebrovascular and cognitive functions and these potential covariates along with sedentary behaviour exacerbate their decline by essentially promoting low-grade systemic inflammation, oxidative stress and reducing endothelial function (see Bliss et al. (2021) for in depth review of mechanisms) (Woods et al., 2011; Toda, 2012; Bangen et al., 2014; Toth et al., 2017).

Accordingly, the aims of our study were three-fold. Firstly, to compare the differences in cerebrovascular and cognitive function between older adults that had undertaken regular aerobic exercise training and those that were sedentary and untrained. Secondly, to determine the association between cerebrovascular and cognitive function in these individuals. Finally, to examine if other measures including body composition, cardiovascular function, biochemistry and educational level would account for the differences between trained and untrained groups.

Methods

Participants

Thirteen aerobic exercise trained older adults and thirteen age, height and sex matched sedentary, untrained controls participated in the study (Table 1). These participants were recruited from South-East Queensland, Australia, which includes metropolitan, regional and rural areas, between October 2019 and March 2021. Trained participants were defined as those who had regular participation in at least 150 min of moderate-vigorous intensity aerobic exercise training per week consistently for at least two years and untrained participants as those who were physically inactive for at least the previous two years (AIHW, 2018). The trained individuals were recruited from various sporting clubs, such as road-runner associations, cycling clubs, swimming clubs, gymnasiums, bushwalker clubs and the general public who participate in aerobic exercise but are not associated with any particular sport or club. This was to ensure that we had a mix of participants who undertook different types of aerobic exercise over the lifespan, as the purpose of the study was not to focus on a single mode or type of aerobic exercise. It should be noted that recruitment and testing were terminated earlier than anticipated due to the impacts of COVID-19 and the restrictions placed on gathering, research and travel by the Queensland and Australian Governments. The exclusion criteria were: aged under 50 years or over 80 years; cognitive impairment, current smokers; blood pressure ≥ 160/100 mmHg; prescribed insulin, hormone-replacement therapy, or oral anticoagulants; and a significant history of cardiovascular, neurological, cerebrovascular, kidney, liver disease or cancer. Participants were only included in the study if they were on a stable medication treatment plan that did not contradict the exclusion criteria. The Yale Physical Activity Survey (YPAS) (Dipietro et al., 1993), Lifetime Physical Activity Questionnaire (LPAQ) (Friedenreich et al., 1998), and a customised health and wellbeing screen were initially used to determine whether participants met the study criteria, as well as their exercise training status. The LPAQ assessed the types of and length of participation in various physical activities throughout the lifespan, while the YPAS assessed current physical activity status semi-quantitatively including energy expenditure and duration of exercise. A higher score in these surveys is considered favourable, with the exclusion of sedentary behaviours, such as the sitting index score. All study procedures were approved by the University of Southern Queensland Research Ethics Committee (H19REA015), which adheres to the Declaration of Helsinki. The study was registered with the Australian and New Zealand Clinical Trial Registry (ACTRN12619001291178). All participants provided written, informed consent prior to participation in the study.

Experimental design

The study utilised a cross-sectional design. Each participant visited the laboratory on two separate occasions, at a similar time of day, separated by a minimum of 24 h and a maximum of 7 days. Participants fasted and abstained from caffeinated stimulants for 1 h before visit 1 and 8-12 h before visit 2. They were also requested to refrain from moderate-vigorous

intensity exercise for 24 h before each visit and take their daily supplements and medication after each visit was completed. During visit 1, participants undertook anthropometric, cardiovascular, exercise performance, strength, cerebrovascular and cognitive measurements. At their second visit, participants undertook body composition measurements, blood collection and the Profile of Moods State questionnaire. The Profile of Mood States questionnaire calculated mood disturbance by adding the scores of the negative mood state scales (i.e. anger-hostility, confusion-bewilderment, depression-dejection, fatigue inertia, tension-anxiety) and subtracting the positive mood state scale (i.e. vigour-activity) (Heuchert and McNair, 2012). Lower values in the negative mood states and total mood disturbance indicates better mood, while higher values in vigour is associated with positive mood. Between visits, participants were asked to complete a nutritional questionnaire (Automated Self-Administered 24-hour Dietary Assessment Tool; National Institute of Health (NIH), Bethesda, MA, USA) to assess energy intake over a typical 24 h period (Pannucci et al., 2018).

Basal cerebral haemodynamics

Transcranial Doppler ultrasonography (TCD; DopplerBox X; Compumedics DWL, Singen, Germany) was used to measure basal cerebrovascular haemodynamics, including baseline, peak and mean values for both CBF_V and cerebral pulsatility, as well as CVR in response to hypercapnia and cognitive stimuli (Edmonds Jr et al., 2011; Barbour et al., 2017; Evans et al., 2017). Participants were seated and fitted with a headpiece which housed two 2-MHz TCD ultrasound probes that were fixed and aligned bilaterally to the left and right cranial temporal bone windows to insonate the MCA at a depth of approximately 40-65 mm. Once a suitable blood flow signal was obtained, participants were asked to sit quietly while basal measurements were recorded for 30 s.

Cerebrovascular responsiveness to hypercapnia

Participants were subsequently challenged with a hypercapnic stimulus for 3 min, as a plateau in CBF_V is obtained within this time, and monitored for another 1 min following removal of this. This process was performed in duplicate following a 5 min rest period (whilst participants breathed in room air) to ensure CBF_V returned to baseline values (Barbour et al., 2017; Evans et al., 2017). Participants breathed through a two-way non-rebreathing valve (model 2730, Hans Rudolph, Kansas City, MO, USA) whilst wearing a nose-clip. The inspiratory port of the two-way valve was connected to 1 m of wide bore tubing distal to a 100 L Douglas bag which contained carbogen gas (5% carbon dioxide and 95% oxygen; Carbogen 5; BOC, Toowoomba, QLD, Australia). Flow was measured from the expiratory port of the two-way valve using a pneumotachograph (MLT 300L; AD Instruments, Bella Vista, NSW, Australia) which was calibrated with a 3 L syringe prior to the commencement of each test. Volume was obtained by numerical integration of the flow signal. End-tidal partial pressures of carbon dioxide ($P_{ET}CO_2$) were sampled from the expiratory port of the two-way valve connected to a gas analyser (ADI ML206; AD Instruments) that was calibrated across the physiological range with known gas concentrations (BOC). Flow and $P_{ET}CO_2$ measurements were sampled at 200 Hz using a 4-channel Powerlab analog-to-digital converter (AD Instruments) interfaced with a computer and displayed in real time during testing. Data were stored for subsequent offline analysis using LabChart software (version 7.2, AD Instruments) .

Cognitive function and cerebrovascular responsiveness to cognitive stimuli

The individual cognitive tests that comprised the cognitive battery used to assess neuropsychological function included the Trail Making Task Parts A and B which assessed central executive function, Spatial Span Test (visuospatial short-term working memory) and a NIH Toolbox, which is a battery of cognitive examinations (Strauss et al., 2006; Evans et al., 2017). The NIH Toolbox is comprised of individuals tests and included the Dimensional Change Card Sort Test (cognitive flexibility and attention); Picture Vocabulary Test (language and crystallised cognition); List Sorting Working Memory Test (working memory); Oral Reading Recognition Test (language and crystallised cognition); Flanker Inhibitory Control and Attention Test (attention and inhibitory control); Picture Sequence Memory Test (episodic memory); and Pattern Comparison Processing Speed Test (processing speed) (Slotkin et al., 2012; Heaton et al., 2014). Additionally, a total composite cognitive function score, which was adjusted and controlled for age, sex, education and ethnicity and derived from all of the tests that comprise both fluid and crystallised measurements indicated above, was determined (Heaton et al., 2014). This is a validated and highly reliable score that represents an overall summation of general cognitive function and indicates general cognitive ability based on normalised scores (Slotkin et al., 2012; Heaton et al., 2014; Weintraub et al., 2014). All tests excluding the Trail Making Task were delivered using an iPad (6^{th} generation, Apple Inc, Cupertino, CA, USA). All NIH Toolbox test scores were automatically computed within the program to control for examiner bias. The outputs for all tests were normalised based on the demographics entered into the program (age, education level, familial education history, sex, ethnicity and occupation). A full description of how these tests are administered, how these scores are calculated and the validation of these tests and scores have been previously described in detail (Slotkin et al., 2012; Heaton et al., 2014; Weintraub et al., 2014). These individual cognitive tests were used for the CVR to cognitive stimuli. The CVR to cognitive stimuli was assessed individually for each cognitive task. Thirty s of baseline data was recorded before the start of each cognitive task. The total composite (overall) CVR to all cognitive stimuli was summated and averaged based on the number of tests completed. All participants had the same duration of cognitive stimuli applied – i.e. there were no differences in the cognitive tasks administered to the participants of the study.

Data capture and processing for cerebrovascular responsiveness

Beat-to-beat measurements of CBF_V were recorded from the MCA onto software (QL Reader; Compumedics DWL, Singen, Germany) sampling at 100 Hz and were stored for subsequent offline analysis. If a bilateral signal was not obtained, then analysis took place with only the side that was able to be obtained. These data were then normalised and analysed using Curve Expert Professional software (Hyams Development, Chattanooga, TE, USA) to determine resting cerebral pulsatility index (CPI), resting CBF_V and peak CBF_V (determined as the highest CBF_V during the 3 min period). CPI and CVR were calculated based on the equations [1] and [2] from previous work (Bakker et al., 2004; Wong et al., 2016c; Harris et al., 2018)

$$[1] \quad \text{CPI} = \frac{\text{peak systolic CBFv} - \text{ end diastolic CBFv}}{\text{mean CBFv during a cardiac cycle}}$$

$$[2] \quad \text{CVR (\%)} = \frac{(\text{peak CBFv} - \text{resting CBFv})}{\text{resting CBFv}} \times 100 \div \text{resting CPI}$$

Anthropometrics and body composition

Participants were instructed to wear light clothing prior to testing and subsequently asked to remove their shoes for measurements. Body mass was measured to the nearest 100 g using an electronic scale (Tanita Ultimate Scale 2000; Tanita, Tokyo, Japan) and waist and hip circumferences recorded to the nearest 1 cm using a standard tape measure as previously described (Welborn et al., 2003). Height was recorded to the nearest 1 cm using a wall-mounted telescopic stadiometer (Seca220; Vogel & Halke, Hamburg, Germany). Height, body mass and waist and hip circumference measurements were measured in duplicate and the mean of the two measurements were analysed. Body mass index (BMI) and a waist-to-hip ratio were calculated as previously described (Keys et al., 1972; Welborn et al., 2003). Dual-energy X-ray absorptiometry was measured to determine body composition of total lean mass, body fat percentage, and whole-body bone mineral content and density (Luna Corp Prodigy Advance Model GE; Madison, WI, USA).

Cardiovascular function

Systolic and diastolic blood pressure, mean arterial pressure and arterial elasticity were measured non-invasively using a HDI/Pulsewave™ CR-2000 Research Cardiovascular Profiling System (Hypertension Diagnostics, Eagan, MN, USA) (Prisant et al., 2002). Participants rested in a seated position for 10 min prior to measurements and four consecutive readings were recorded approximately 5 min apart. An automated oscillometer and an appropriately size blood pressure cuff over the left brachial artery were used to assess blood pressure and a tonometer, placed over the right radial artery, to assess pulse wave analysis, heart rate and estimated cardiac output and cardiac index (Prisant et al., 2002; Barbour et al., 2017). The first reading was discarded, and the mean of the three subsequent measurements were used for analysis.

Biochemical analyses

Approximately 20 ml of venous blood was sampled using a suitable method (either evacuated tube system or winged-infusion) from the veins of the antecubital fossa into thrombin-based clot activator serum separator tubes, 17 IU/ml lithium heparin tubes, 3.2% citrate tubes and 1.8 mg/ml K2 ethylenediaminetetraacetate tubes (BD, Macquarie Park, NSW, Australia). Following collection, blood was either left to stand for 30 min at 18-25°C (serum separator tube) prior to centrifugation at 1300 g and 18°C for 10 min, or centrifuged immediately at 1300 g and 18°C for 10 min (plasma tubes) as outlined by the tube manufacturer and the testing laboratory (BD, 2019; QML, 2019). Following centrifugation, blood was either separated as serum or plasma pending the type of tube used to collect the blood. Samples used for the general chemistry profile and high-sensitivity C-reactive protein (hs-CRP) measurements were performed on a Siemens ADVIA® Labcell® (Siemens Healthcare, Bayswater, VIC, Australia), which utilises spectrophotometric (enzymes, metabolites, proteins, lipids), turbidimetric (hs-CRP) and potentiometric (electrolytes) techniques (Healthineers, 2019). The remainder of the serum and plasma was stored at -80°C for subsequent analyses of vascular endothelial growth factor, which was measured in duplicate using an enzyme-linked immunosorbent assay according to the manufacturer's instructions (Catalogue No. KHG0111; Invitrogen, Human VEGF ELISA Kit, Vienna, Austria).

Exercise performance and handgrip strength

Exercise performance was assessed using a 6 minute walk test (6MWT) according to published guidelines (ATS, 2002). Handgrip strength was determined using hand dynamometry (Jamar Digital Plus; Lafayette Instruments, Lafayette, IN, USA) as previously described (Hillman et al., 2005). Participants were permitted three attempts with both their dominant and non-dominant hands. The first reading for each hand was discarded and was used as a familiarisation and the second and third readings for each hand were averaged for each hand and were used for analysis.

Statistical analysis

Statistical analyses were performed using SPSS for Windows (IBM, Chicago, IL, USA). An initial power calculation was performed on the basis of previous research that has investigated the differences in CVR between aerobic exercise trained and untrained participants (Wong et al., 2016a; Wong et al., 2016c; Barbour et al., 2017; Evans et al., 2017). The power analysis demonstrated that a sample size of 12 per group would be required to detect a 5% difference in CVR between trained and untrained participants (alpha = 0.05 and power = 0.8). Normality of data was assessed using a Shapiro-Wilk test. Comparisons between groups for anthropometric, body composition, cardiovascular, cognitive, exercise performance, baseline cerebrovascular, baseline respiratory, both CVR to hypercapnia and CVR to cognitive stimuli, strength and biochemical measures were determined using independent t-test or Mann-Whitney U-tests for parametric and non-parametric data, respectively. Between-group differences for raw cerebrovascular (excluding CVR) and respiratory measures were analysed using a two-way analysis of variance to determine the effects of 'group' (trained vs. untrained) and 'time' (baseline vs. peak during hypercapnia). Significant group x time interaction effects were followed by planned pairwise comparisons between groups using the Bonferroni method. Pearson's product moment correlation coefficient (parametric data) or Spearman's (non-parametric data) correlation analysis was used to examine the relationship between variables and reported cut-off points to examine these relationships were applied as previously described (Schober et al., 2018). An analysis of co-variance (ANCOVA) was performed using objective (non-self-reported) measures that demonstrated a significant relationship with the primary outcomes (covariates) as independent variables and the primary outcomes (CVR to hypercapnia; CVR to cognitive stimuli; total composite cognitive score) as dependent variables. These objective measures included years of education, 6MWT distance, large arterial compliance, serum hs-CRP concentration, waist circumference, total body fat percentage, heart rate and breathing frequency. Additionally, one measure of total body composition (total body fat percentage) and only biochemical measurements that were considered clinically significant (i.e. were outside reference ranges) were used in the ANCOVA if significant in the correlation analyses. Statistical significance was set at $P < 0.05$. Data are presented as means ± SEM.

Results

Participant characteristics

Participant characteristics are shown in Table 1. The types of aerobic exercises types that participants undertook, including duration in years, are shown in Supplemental Table 1.There were no differences between the groups for age, sex and height. The trained group had spent more time in education compared to the untrained group. The trained group had a lower body mass, hip circumference, waist circumference, total body fat and hip-to-waist ratio than the

untrained group. The trained group walked for longer during the 6MWT and had a higher total energy output, sitting index score and vigorous activity and leisurely walking index score than the untrained group. The trained group had a higher vigour score than the untrained group. There were no other differences in participant characteristics between the groups.

Biochemical analyses

Participants' general biochemistry profiles, hs-CRP and vascular endothelial growth factor are shown in Table 2. Serum sodium and high-density lipoprotein concentrations were higher in the trained compared to the untrained group. Serum glucose, triglycerides, hs-CRP, alkaline phosphatase and alanine aminotransferase concentrations were lower in the trained compared to the untrained group. There were no other differences in the general chemistry profile and vascular endothelial growth factor between the groups.

Cardiovascular function

Cardiovascular function is shown in Table 3. Heart rate, cardiac output, and systolic, diastolic and mean arterial blood pressure were lower in the trained group compared to the untrained group. Large arterial compliance was higher in the trained group compared to the untrained group. There were no other differences in cardiovascular function between the groups.

Cerebrovascular responsiveness to hypercapnia

The CVR to hypercapnia is shown in Figure 1 and Table 4. There were no differences in TCD signal laterality between the groups (untrained unilateral signal, *n=4* vs. trained unilateral signal, *n=5*; *P = 0.695*). There were no differences in CBF_V at baseline (*P = 0.406).* The CVR to hypercapnia (53% higher) and CPI were higher for the trained than the untrained group. There was an increase (main effect of time) in CBF_V, CPI, $P_{ET}CO_2$ and tidal volume in response to hypercapnia. The responses (time x group interaction) of CBF_V and CPI were also higher for the trained than the untrained group. Breathing frequency was lower for the trained compared to the untrained group, but there were no time x group interactions.

Cognitive function and cerebrovascular responsiveness to cognitive stimuli

Cognitive function and cerebrovascular responses to cognitive stimuli are shown in Figure 1 and Table 5. The trained group had higher overall cognitive function than the untrained group, which was demonstrated by a higher total cognitive composite score (17% higher). The trained group also had higher cognitive function than the untrained group in the Dimensional Change Card Sort Test (cognitive flexibility and attention), the List Sorting Working Memory Test (working memory), and Oral Reading Recognition Test (crystallised cognition). The trained group completed both sections of the Trail Making Task (executive function) in less time with fewer errors made in Part B of the task than the untrained group. The time difference between Parts B and A of the Trail Making Task was lower in the trained compared to the untrained group.

The total composite (overall) CVR to all cognitive stimuli was higher in the trained compared to the untrained group (40% higher). The trained group had a higher CVR to cognitive stimuli compared with the untrained groups during the Dimensional Change Card Sort test, Picture Vocabulary Test, Flanker Inhibitory Control and Attention Test, Picture Sequence Memory Test, List Sorting Working Memory Test, Part A of the Trail Making Task and the Spatial Span Test.

Correlations between measured variables and cerebrovascular responsiveness to hypercapnia and cognitive stimuli, and cognitive function

Significant correlations between measured variables and CVR to hypercapnia and cognitive stimuli, and cognitive function are shown in Table 6 and Figure 2. There were moderate positive correlations between CVR to hypercapnia and CVR to cognitive stimuli and the total composite cognitive score. There was a strong positive correlation between the total composite CVR to cognitive stimuli and total composite cognitive score. Both CVR to cognitive stimuli and total composite cognitive score were also strongly correlated with consistent exercise training (years).

There were moderate positive correlations between CVR to hypercapnia and the total years educated, 6MWT distance and large arterial compliance. There were moderate negative correlations between CVR to hypercapnia and serum hs-CRP concentration, waist circumference, total body fat percentage, heart rate and baseline breathing frequency.

There were moderate positive correlations between the total composite cognitive score and total years educated and, 6MWT distance. There were moderate negative correlations between the total composite cognitive score and peak breathing frequency during hypercapnia, waist circumference and heart rate. There was a moderate negative correlation between the total composite cognitive score and large arterial compliance.

There were moderate positive correlations between the total composite CVR to cognitive stimuli and total years educated and 6MWT distance. There were moderate negative correlations between the total composite CVR to cognitive stimuli and waist circumference, heart rate, and breathing frequency both at baseline and peak breathing frequency during hypercapnia.

Analysis of covariance between the primary outcomes and covariates

Objective measures that demonstrated a significant relationship with the primary outcomes (CVR to hypercapnia; CVR to cognitive stimuli; total composite cognitive score) and were considered clinically significant were used in the ANCOVA (described above; shown in Table 6). Those that demonstrated significant relationships with the primary outcomes and were clinically significant included years of education, 6MWT distance, large arterial compliance, serum hs-CRP concentration, waist circumference, total body fat percentage, heart rate and breathing frequency. Following adjustment for covariates (years of education, 6MWT distance, large arterial compliance, serum hs-CRP concentration, waist circumference, total body fat percentage, heart rate and resting breathing frequency) the ANCOVA revealed that the CVR to hypercapnia no longer remained statistically different between the groups ($P = 0.934$). The ANCOVA performed for the composite CVR to cognitive stimuli (covariates: total years educated, 6MWT distance, maximum breathing frequency during hypercapnia and at rest, waist circumference measurement and heart rate; $P = 0.343$) was also not statistically different between the groups. This was the same for the ANCOVA performed for the total composite cognitive score (covariates: total years educated, total composite CVR to cognitive stimuli, 6MWT distance, CVR to hypercapnia, maximum breathing frequency during hypercapnia, waist circumference measurement, heart rate and large arterial compliance; $P = 0.202$). Education level was also strongly correlated with the primary outcomes. When education was removed from the ANCOVA and all other significant variables listed above were left in the analysis, the results were still insignificant

(CVR to hypercapnia, *P = 0.246*; CVR to total composite of cognitive stimuli, *P = 0.193*; and total composite cognitive score, *P = 0.940*).

Discussion

Main findings

The aims of our study were three-fold. Firstly, to compare the differences in cerebrovascular and cognitive function between older adults that had undertaken regular aerobic exercise training over the last 40 years and those that were sedentary and untrained. Secondly, to determine the association between cerebrovascular and cognitive function in these individuals. Finally, to examine if other measures including body composition, cardiovascular function, biochemistry and educational level would account for the differences between trained and untrained groups. In support of our aims, the main findings were that, firstly, the trained group had undertaken 40 years of aerobic exercise training and had higher cerebrovascular and cognitive functions than the untrained group. Secondly, there were moderate positive correlations between CVR to hypercapnia and total composite cognitive score and CVR to cognitive stimuli. Finally, following adjustment for covariates, CVR to hypercapnia, total composite cognitive score and CVR to cognitive stimuli were not significantly different between the groups, thus suggesting that aerobic exercise may improve cerebrovascular function and cognition in the obese independent of any significant reduction in BMI.

Cerebrovascular responsiveness to hypercapnia

We observed that the CVR to hypercapnia was higher for the trained than the untrained group. This finding supports previous studies that have reported a higher CVR to hypercapnia in older aerobic trained individuals (Rogers et al., 1990; Brown et al., 2010; Bailey et al., 2013; Barnes et al., 2013; Marley et al., 2020), but not others that have reported no differences between trained and untrained groups (Thomas et al., 2013; Zhu et al., 2013; Braz et al., 2017; Miller et al., 2018). We found no differences in resting CBF_V between the trained and untrained groups, which contradicted previous studies who have reported a higher CBF_V in aerobic exercise trained individuals (Ainslie et al., 2008; Bailey et al., 2013). However, previous research has also reported no differences in resting CBF_V following an exercise intervention or between trained and untrained individuals, respectively (Vicente-Campos et al., 2012; Thomas et al., 2013; Braz et al., 2017). The discrepancy between our findings and others is not clear but may be due to the potential variation in aerobic fitness levels between the trained and untrained participants, the types of training others had participated in and using only a single sex for analysis. For example, Ainslie et al. (2008) only recruited men who participated in cycling or running and did not report the final maximum oxygen consumption test. However, Thomas et al. (2013) only recruited competitive and nationally ranked men and women Masters runners whose maximum oxygen consumption test was 41 mL/kg/min compared with sedentary individuals who reported a value of 23 mL/kg/min. Braz et al. (2017) recruited men who participated in any type of aerobic exercise as long as they met the definition of being aerobic exercise trained, but reported similar maximum oxygen consumption test values to Thomas in the trained group (40 mL/kg/min), but much higher values in the untrained group (31 mL/kg/min). Additionally, we also observed a higher peak CBF_V in the trained compared to the untrained group and a lower CPI both at rest and during hypercapnia, which is consistent with the literature (Bailey et al., 2013; Barnes et al., 2013; Marley et al., 2020; Mohammadi et al., 2021).

The higher CVR to hypercapnia reflects an enhanced ability of the cerebrovasculature to modify regional blood flow in response to local chemical changes (i.e. carbon dioxide) and maintain cerebral autoregulation. The finding may suggest that regular aerobic exercise training can improve the motor reactivity of the blood vessels and reduce arterial stiffness within the cerebrovasculature (Rogers et al., 1985; Miller et al., 2018). Furthermore, aerobic exercise training could be related to favourable changes in cardiovascular structure and function systemically and this is transferrable centrally (Bailey et al., 2013). For example, it was observed that the trained group had lower central adiposity, blood triglycerides and blood glucose, as well as higher blood high-density lipoprotein concentrations, and cardiovascular parameters. Additionally, hs-CRP, which is a marker of chronic low-grade systemic inflammation and predictor of risk of an acute cardiovascular or cerebrovascular event (Jialal and Devaraj, 2001), was lower in the trained group. The differences in these parameters between the groups are consistent with the benefits associated with consistent aerobic exercise training (Lin et al., 2015; Rossman et al., 2018). These results also highlight the poor cardiometabolic status of the untrained group and this may place them at greater risk of suffering from both decreased cerebrovascular function and cognitive decline (Woods et al., 2011; Toth et al., 2017; Bliss et al., 2021). The higher concentrations of biochemical markers in the untrained group may be an indication of reduced endothelial function, which may lead to oxidative stress and inflammation. This subsequently promotes decreased capillarisation and increased arterial stiffness, thus reducing blood flow and vasoreactivity (Woods et al., 2011; Toda, 2012; Bangen et al., 2014; Toth et al., 2017). The reduction in cerebrovascular function, in turn, reduces the metabolic capacity of the brain, as the brain is no longer supplied as efficiently as it once was with essential nutrients, oxygen and its metabolic waste is no longer removed as quickly as in earlier life (Bangen et al., 2014; Toth et al., 2017; Bliss et al., 2021). Therefore, our results support the notion that aerobic exercise training may modulate these changes, preventing or slowing down these processes that are also associated with ageing.

Cognitive function and cerebrovascular responsiveness to cognitive stimuli

We observed that the total composite cognitive score was higher in the trained compared to the untrained group. While we also evaluated specific cognitive measurements that utilise different cognitive domains, the total composite score evaluates a variety of cognitive domains that are used during activities of daily living (Harvey, 2019). Each cognitive domain and subtype can directly impact on another (i.e. they are interdependent) and diseases associated with cognitive decline and neurodegeneration, in general, typically do not affect a single domain, rather impacting all cognitive domains (Salthouse, 2012; Harvey, 2019). The differences in cognitive function between the groups support the current literature, which indicates that regular aerobic exercise training improves cognitive function (Lautenschlager et al., 2008; Baker et al., 2010; Anderson-Hanley et al., 2012; Vreugdenhil et al., 2012; Bossers et al., 2015; Hoffmann et al., 2016; Sobol et al., 2016). The mechanisms for how aerobic exercise training improves cognitive function in humans is poorly understood. Existing knowledge on this mechanism has been mainly drawn from animals studies (Bliss et al., 2021). Improvements in cognition may be attributed to increased brain-derived neurotrophic factor (BDNF) concentrations both systemically and centrally. BDNF acts to promotes synaptogenesis and has been associated with increased hippocampal volume and spatial memory (Erickson et al., 2011) in humans and improved cognition in animal studies (Vaynman et al., 2004). However, the exact role of BDNF in improving neuroplasticity and cognition in different disease states, such as Parkinson's disease, still remains inconclusive (Johansson et al., 2020).

We also observed that the total composite CVR to cognitive stimuli, which is referred to as NVC, was higher in the trained compared with the untrained group. NVC is the complex interaction between neuronal metabolic demands and local haemodynamic changes, which ensures that metabolic demands are met by the vasculature (Duchemin et al., 2012; Toth et al., 2017). The mechanisms that lead to the regulation of CBF, which allow for the prevention of both ischaemia and hyperaemia at any time, are extremely complex and yet to be fully elucidated. In any case, it is known that the upregulation of endothelial nitric oxide synthase and the subsequent synthesis and release of nitric oxide from the endothelium is a fundamental component involved in both cerebrovascular autoregulation and NVC (Duchemin et al., 2012; Toth et al., 2017). Only one other study that has measured NVC in older trained and untrained individuals. Fabiani et al. (2014) reported that NVC varied according to aerobic fitness level and that individuals with greater aerobic fitness had a higher NVC capacity. However, the authors of this study did not measure the CVR to cognitive stimuli, rather to visual stimuli. Hence, our study is the first study to specifically measure the CVR to individual cognitive tasks, as well as cumulatively. Further, our study is the first to determine an association between cerebrovascular and cognitive function in this particular cohort. The authors of this study suggested that the difference in the NVC responses between trained and untrained individuals were most probably associated with the cardiovascular system and noted that older participants with low aerobic fitness were also hypertensive and overweight or obese. This is similar to our findings and we also observed differences between the groups in markers of cardiometabolic health (i.e. body composition, cardiovascular function and biochemical analyses, such as hs-CRP, glucose and lipid profile). Since ageing and cardiometabolic health both directly impact endothelial function, promote arterial stiffness and chronic low-grade systemic inflammation, it would be expected that anything that favours the senescent phenotype or exacerbates endothelial dysfunction, such as obesity, would directly impact NVC and, in turn, cognition.

Correlations between cerebrovascular and cognitive function

The potential association between cerebrovascular function cognitive function is supported by our finding that total composite cognitive scores were moderately positively correlated with CVR to hypercapnia and strongly positively correlated with CVR to cognitive stimuli. Correlation studies between cerebrovascular function and cognition in trained individuals have only been reported once, in which cerebrovascular function was shown to be a positive predictor of overall cognition in older women (Brown et al., 2010). However, other studies have also reported a correlation between cerebrovascular and cognitive function in healthy post-menopausal women (Wong et al., 2016b), hypertensive older adults (Hajjar et al., 2014), Alzheimer's disease (Richiardi et al., 2015), and healthy older adults (Keage et al., 2015). It is likely that hypertensive older adults and those with Alzheimer's disease are sedentary. Therefore, it is difficult to make a conclusion based on our findings on the regular aerobic training-cerebrovascular function-cognition relationship. Further studies will need to delineate these relationships by incorporating exercise status into their studies.

The association between cognitive performance and CVR to hypercapnia may be modest as the latter measures a generalised response of the cerebrovasculature to a chemical stimulus and reflects the ability of the cerebrovasculature to respond solely to this stimulus (e.g. increased concentrations of carbon dioxide) (Bailey et al., 2013; Barnes et al., 2013). This is in contrast to NVC, which describes the mechanical response of the neurovascular unit during localised neuronal activation and exertion (i.e. response to increased neuronal metabolism and signalling) (Zlokovic, 2011). Hence, while both parameters may be important to

holistically determine cerebrovascular function, it is NVC that is most probably specifically related to cognitive function as potentially indicated by the results of this study. Further, decreased endothelial function and reduced NVC affect cognition, simply because if the haemodynamic response is blunted then there is insufficient essential nutrients and oxygen being made available to supply neurons during times of increased metabolism (Bliss et al., 2021). This essentially affects the ability of the neurons to perform work efficiently and effectively, thus contributing to decreased cognitive function, which, over time, dissipates further leading to cognitive decline.

Analysis of covariance between the primary outcomes and covariates

When we adjusted for other covariates including body composition, cardiovascular function, biochemistry and educational level that may also explain the differences in cerebrovascular and cognitive function between the trained and untrained groups, the difference between them became statistically insignificant. This finding may suggest that exercise probably modifies multiple physiological variables which have an impact on and interaction with cognitive and cerebrovascular function. It also potentially suggests that having a favourable cardiometabolic profile, which is imperative to maintaining endothelial function, may assist in maintaining the autoregulatory function of the cerebrovasculature throughout the lifespan. The finding may also indicate that exercise could positively contribute to this status by reducing central adiposity, reducing low-grade chronic systemic inflammation, improving cardiovascular structure and function and thereby potentially improving cerebrovascular function and cognition. However, no long-term follow-up studies have been performed to confirm whether improvement in cerebrovascular function will directly improve cognition, but based on empirical studies, the relationship appears to be quite clear (Bliss et al., 2021).

In support of our findings are the results of our correlation analyses. Some of the strongest associations made between our primary outcomes (CVR to physiological and psychological stimuli and cognitive function) were with exercise (years consistently performed exercise training and 6MWT distance). Other associations were made between cardiorespiratory variables, central adiposity and low-grade systemic inflammation. Aerobic exercise training reduces adiposity and the chronic low-grade systemic inflammation that is associated with increased central adiposity (You et al., 2013; Keating et al., 2015). Additionally, reductions in cerebrovascular function and structure are largely attributed to modifiable risks factors that impact on cardiometabolic health, particularly physical inactivity (Kokmen et al., 1996; Kalmijn et al., 2002; Prins et al., 2002; Seliger et al., 2004; Kuller et al., 2005; Scarmeas et al., 2009; Solomon et al., 2009; Ahtiluoto et al., 2010; Bunch et al., 2010; Anstey et al., 2014; Sabia et al., 2018). Physical inactivity, in conjunction with reduced cardiometabolic health, promotes and exacerbates the development of chronic low-grade systemic inflammation and reduced endothelial function (Woods et al., 2011; AIHW, 2012; Toda, 2012; Bangen et al., 2014; Toth et al., 2017). Since physical inactivity promotes increased adiposity and low-grade systemic inflammation, which, in turn, can drive reactive oxygen species production thus reducing endothelial function, it may further exacerbate and reduce cerebrovascular function due to a reduction in capillary density and increased arterial stiffness (i.e. reduced blood flow and vasoreactivity) (Woods et al., 2011; Toda, 2012; Bangen et al., 2014; Toth et al., 2017).

Finally, the only other variable that was strongly correlated with the primary outcomes was education. When education was removed as a covariate from the ANCOVA and all other variables mentioned used in this modelling (described above) were used as covariates (i.e. when we just removed education from the analysis), the results were still not significant

between the groups. Currently, there is limited work, if any, that has determined the effects of education level on cerebrovascular function other than in Alzheimer's disease, where it has been reported that higher regional CBF is associated with higher levels of education in these individuals (Chiu et al., 2004). However, more studies are required to determine the effect of education level on cerebrovascular function. Education duration has been correlated to increased cognitive capacity throughout the lifespan and as a potential attenuator of cognitive decline associated with ageing (Lövdén et al., 2020). Therefore, the impact of this on cognitive outcomes in this study cannot be excluded, even though an individual's level of education is considered by the NIH Toolbox's scoring algorithm (i.e. education is controlled for by the NIH Toolbox) (Slotkin et al., 2012; Heaton et al., 2014; Weintraub et al., 2014). Educational differences may also be an inherent complication with recruiting individuals for human trials, as the compliance and motivation to participate in studies appears to be higher in those who are more educated compared with those that are not (Mbuagbaw et al., 2017). This may pose a challenge to control for not only in this study but others as well, as others have highlighted education as an important that may affect clinical trials associated with neurodegenerative diseases, such as dementia (Huang et al., 2020). Interestingly, those with higher education levels also appear to progress more rapidly through the course of Alzheimer's disease compared with those with lower educational levels (Kemppainen et al., 2008), meaning that the relationship of education and cognitive decline, particularly in relation to dementias, still requires more investigation. In any case, our results suggest that, while education is a significant element in maintaining overall brain health, having a favourable cardiometabolic profile is just as important in maintaining both cerebrovascular and cognitive function and that all of these elements are probably inter-related when it comes to improving or maintaining overall brain health throughout the lifespan.

Methodological limitations

Different techniques have been used to assess cerebrovascular function, such as direct methods like magnetic resonance imaging (MRI) and indirect methods such as TCD (see (Joris et al., 2018) for detailed comparison). CVR is a quantitative measure of the potential of the cerebral microcirculation to dilate in response to physical or chemical stimuli and is a surrogate measure of local endothelial function (Joris et al., 2018; Rossman et al., 2018). It is not a direct method in determining CBF differences in specific regions of the brain in response to a stimulus such as a cognitive task. We acknowledge that CVR is a crude measure that records changes essentially in one vessel only, which in this case is the MCA. We chose to use the MCA as changes in its blood flow velocity more directly reflect changes in CBF arising from the dilatation of the downstream microvasculature supplying brain regions that are critical for cognitive function (Serrador et al., 2000; Willie et al., 2011; Braz et al., 2017). Certain responses to different tests may not have been captured using TCD and by not excluding participants on the basis laterality. TCD and the use of the MCA only may not explain the magnitude differences in one test compared to another in specific brain regions (Joris et al., 2018). This may be seen as a limitation of the technique and by the fact we included participants who had either a bilateral or unilateral signal. Since we averaged the left- and right-side measures we may be reporting a reduced CVR in certain tasks. However, we captured the change in CVR without the exclusion of unilaterality, and, therefore, may not be a limitation, because this may have underestimated the associations between primary outcomes and the covariates. Additionally, it would not be expected that training status influences changes unilaterality, rather globally. More highly localised and direct processes could be used in future studies, if available, and these may give more definitive results. However, it is unlikely that this should be a limiting factor given that correlations between

direct methods of CBF determination and TCD have been positively associated and validated (Willie et al., 2011; Miyazawa et al., 2018).

What was interesting in this study and has already been highlighted as a potential limitation above, is that the trained group had a higher level of education than the untrained. While others have reported this previously (Dishman et al., 1985; Lawrence, 2017), there is also conjecture if this is limited to major metropolitan areas and extends to regionals areas. In Australia, particularly Queensland, metropolitan areas tend to be both more educated and physically active (QHealth, 2020). It may be that educational level is a mediator of performing exercise, as education may be an important mediator of motivation to perform exercise (Dishman et al., 1985; Lawrence, 2017). Alternatively, it may be that participating in exercise promotes or motivates individuals to further their education (Dishman et al., 1985) However, this differs regionally and rurally, where those in regional areas may be more educated than some areas but are less physically active than areas of lower education (QHealth, 2020). In these areas, education level may not mediate exercise participation. This may account for why there were differences in education level in our participants, as we recruited a mix of people from metropolitan and regional areas. Determining sociodemographic differences were outside the scope of this study but may be an opportunity for future studies to perform these analyses within a single location and compare the differences between metropolitan, regional and rural centres.

A greater adiposity may contribute to a reduced cerebrovascular and cognitive function, independent of exercise training status (Woods et al., 2011; Toda, 2012; Bangen et al., 2014; Toth et al., 2017). Obesity and sedentary behaviour rates are growing and may lead to the development of comorbidities, including cognitive decline and dementia (Beydoun et al., 2008; Taylor, 2014; Brown et al., 2017). The untrained group in our study had a higher body mass, hip circumference, waist circumference, total body fat and hip-to-waist ratio than the trained group. We did not match the groups by body mass, BMI, waist circumference or body composition which is different from previous studies that reported no differences in BMI between the trained and untrained groups (Ainslie et al., 2008; Barnes et al., 2013; Zhu et al., 2013; Braz et al., 2017; Miller et al., 2018). We chose to not undertake this because our aim was to compare differences between older adults that had undertaken regular aerobic exercise training and those that were sedentary and untrained. As a result, the sedentary and untrained individuals had a higher a central adiposity and this was reflective of sedentary individuals in the regional areas of Australia where they were recruited. Given the high rates of physical inactivity and obesity globally, our aim was to replicate the real-world scenario and replicate this by comparing the two groups used in this study (OECD, 2020). Additionally, there are variations in hypercapnia protocols, including breath-holding and manual manipulation, step-wised induction against non-stepwise induction and variation in baseline breathing (Rogers et al., 1985; Rogers et al., 1990; Ainslie et al., 2008; Brown et al., 2010; Barnes et al., 2012; Barnes et al., 2013; Zhu et al., 2013; Braz et al., 2017; Miller et al., 2018; Marley et al., 2020). We chose to use 5% carbon dioxide to induce hypercapnia, as this is a reliable challenge that we have undertaken previously (Wong et al., 2016a; Wong et al., 2016b; Wong et al., 2016c; Evans et al., 2017). Finally, we acknowledge that our data may be confounded by other sources of variation such as diet and sex differences between participants. However, we attempted to minimise the latter by matching each group with an equal number of men and women.

Conclusion

In conclusion, older adults that had undertaken regular aerobic exercise training over the past 40 years had higher cerebrovascular and cognitive functions than age and sex matched, untrained and sedentary adults and their overall cognitive performance correlated moderately with their CVR to hypercapnia and strongly with their CVR to cognitive stimuli. However, following adjustment for covariates, CVR to hypercapnia, CVR to cognitive stimuli and total composite cognitive score did not differ significantly between trained and untrained groups. Our novel data demonstrate that there is a relationship between cerebrovascular and cognitive function in older adults and that there is an interaction between exercise training and cardiometabolic factors that may directly influence cerebrovascular and cognitive functions. Future studies are needed to examine the specific role of each these variables and how they are modulated by exercise to maintain cerebrovascular and cognitive function in older adults.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author contributions

ESB and DEM conceptualised and designed the study protocol. RHXW, PRCH, ESB and DEM designed the experiments. ESB and SMB collected the data. ESB and SMB analysed the data. ESB and DEM performed statistical analysis, with all authors contributing to data interpretation. ESB, SMB, RHXW, PRCH and DEM contributed to revisions of intellectual content. All authors approved the final manuscript.

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Tables

Table 1. Participant demographics, anthropometrics, body composition, grip strength, exercise performance, nutritional intake, exercise performance and mood for the untrained and trained groups. Values are means ± SEM.

Variable	Untrained (n=13)	Trained (n=13)	P value
Demographics			
Age (years)	66 ± 2	64 ± 2	0.471
Sex (Male/Female)	6 / 7	6 / 7	-
Education (years)	16 ± 1	21 ± 1	**0.002**
Retired (Yes/No)	8 / 5	8 / 5	-
Consistent exercise training (years)	0	40 ± 4	**< 0.001**
Anthropometrics			
Body mass (kg)	99.3 ± 4.9	70.1 ± 4.7	**< 0.001**
Height (m)	1.69 ± 0.02	1.70 ± 0.03	0.830
Body mass index (kg/m^2)	34.6 ± 1.5	24.0 ± 1.2	**< 0.001**
Hip circumference (cm)	124 ± 4	101 ± 3	**< 0.001**
Waist circumference (cm)	115 ± 3	86 ± 3	**< 0.001**
Hip-to-waist ratio	0.93 ± 0.02	0.86 ± 0.01	**0.003**
Body composition			
Total lean mass (kg)	52.8 ± 3.0	47.2 ± 3.0	0.212
Total body fat (%)	45 ± 2	28 ± 3	**< 0.001**
Total bone mineral density (g/cm^2**)**	1.31 ± 0.03	1.26 ± 0.05	0.335
Total bone mineral content (g/cm)	2876 ± 158	2690 ± 186	0.457
Grip strength			
Dominant hand (kg)	32.0 ± 3.0	32.3 ± 2.8	0.801
Non-dominant hand (kg)	30.0 ± 2.5	30.2 ± 2.5	0.949
Exercise performance			
6-minute walk test distance (m)	487 ± 19	630 ± 21	**< 0.001**
Nutritional intake			
Total energy intake (kcal)	2538 ± 250	2735 ± 272	0.600
Physical activity levels			
Energy expenditure (kcal/min)	73.5 ± 11.4	135.7 ± 30.4	**0.041**
Vigorous activity index	1 ± 1	33 ± 6	**< 0.001**
Leisurely walking index	5 ± 2	23 ± 3	**< 0.001**
Moving index	8 ± 1	9 ± 1	0.466
Standing index	4 ± 1	5 ± 1	0.188
Sitting index	4 ± 0	3 ± 0	**0.041**
Flights of stairs climber per day	2 ± 1	5 ± 2	0.146
Seasonal adjustment score	1 ± 0	1 ± 0	0.437
Mood			
Tension	6 ± 1	5 ± 1	0.290
Depression	8 ± 3	4 ± 2	0.806
Anger	6 ± 2	5 ± 1	0.992
Fatigue	7 ± 2	5 ± 1	0.518
Confusion	7 ± 2	6 ± 1	0.394
Vigour	14 ± 2	20 ± 2	**0.037**
Total mood disturbance	20 ± 10	5 ± 6	0.157

Table 2. Biochemical analyses for the untrained and trained groups. Values are means ± SEM.

Variable	Untrained (n=13)	Trained (n=12)	P value
Sodium (mmol/L)	139 ± 1	142 ± 1	**0.006**
Potassium (mmol/L)	4.7 ± 0.1	4.4 ± 0.1	0.078
Chloride (mmol/L)	105 ± 1	106 ± 1	0.206
Bicarbonate (mmol/L)	25 ± 1	25 ± 1	0.405
Glucose (mmol/L)	5.8 ± 0.4	4.9 ± 0.2	**0.022**
Urea (mmol/L)	5.9 ± 0.4	6.3 ± 0.7	0.910
Creatinine (mmol/L)	77 ± 5	77 ± 4	0.971
Estimated glomerular filtration rate (ml/min)	80 ± 4	79 ± 3	0.364
Urate (mmol/L)	0.34 ± 0.01	0.32 ± 0.02	0.354
Total bilirubin (µmol/L)	10 ± 1	12 ± 1	0.111
Alkaline phosphatase (U/L)	91 ± 7	63 ± 6	**0.008**
Gamma-glutamyl transferase (U/L)	37 ± 6	27 ± 4	0.190
Alanine aminotransferase (U/L)	36 ± 5	24 ± 4	**0.003**
Aspartate aminotransferase (U/L)	33 ± 4	27 ± 3	0.258
Lactate dehydrogenase (U/L)	216 ± 16	216 ± 17	0.870
Calcium (mmol/L)	2.32 ± 0.02	2.36 ± 0.04	0.172
Corrected calcium (mmol/L)	2.38 ± 0.03	2.37 ± 0.03	0.587
Phosphate (mmol/L)	1.1 ± 0.0	1.2 ± 0.0	0.271
Total protein (g/L)	69 ± 1	69 ± 1	0.877
Albumin (g/L)	41 ± 1	42 ± 1	0.601
Globulins (g/L)	28 ± 1	27 ± 1	0.440
Total cholesterol (mmol/L)	5.2 ± 0.3	5.3 ± 0.2	0.329
Triglycerides (mmol/L)	1.7 ± 0.2	1.1 ± 0.1	**0.042**
High-density lipoprotein (mmol/L)	1.37 ± 0.08	1.63 ± 0.10	**0.047**
Low-density lipoprotein (mmol/L)	2.83 ± 0.24	2.86 ± 0.19	0.970
Total cholesterol-to-high-density lipoprotein ratio	3.9 ± 0.3	3.4 ± 0.2	0.139
High-sensitivity C-reactive protein (mg/L)	4.3 ± 1.0	1.0 ± 0.4	**0.002**
Vascular endothelial growth factor (pg/mL)	273.3 ± 42.5	205.8 ± 34.3	0.241

Table 3. Cardiovascular function for the untrained and trained groups. Values are means ± SEM.

Variable	Untrained (n=13)	Trained (n=13)	P value
Heart rate (beats/min)	76 ± 3	56 ± 2	**< 0.001**
Cardiac output (L/min)	5.3 ± 0.3	4.4 ± 0.2	**0.024**
Cardiac index (L/min/m^2)	2.5 ± 0.1	2.5 ± 0.1	0.583
Systolic blood pressure (mmHg)	143 ± 3	126 ± 4	**0.003**
Diastolic blood pressure (mmHg)	78 ± 2	69 ± 2	**0.014**
Mean arterial pressure (mmHg)	104 ± 3	93 ± 2	**0.009**
Large arterial compliance (ml/mmHg x 10)	9.3 ± 1.0	13.6 ± 1.1	**0.008**
Small arterial compliance (ml/mmHg x 10)	4.7 ± 0.6	3.9 ± 0.4	0.659
Systemic vascular resistance (dyne/sec/cm^{-s})	1560 ± 75	1710 ± 85	0.200
Total vascular impedance (dyne/sec/cm^{-s})	180 ± 12	178 ± 12	0.911

Table 4. Cerebrovascular responsiveness to hypercapnia for the untrained and trained groups. Values are means ± SEM.

Variable	Untrained (n=13)		Trained (n=13)		P value		
	Baseline	**Peak**	**Baseline**	**Peak**	**Time**	**Group**	**Time x Group**
CBF_V (cm/s)	33.1 ± 2.8	45.4 ± 4.0	36.5 ± 2.9	60.1 ± 4.0	**< 0.001**	0.068	**< 0.001**
$CBF_V/P_{ET}CO_2$ (cm/s/mmHg)	1.2 ± 0.1	1.5 ± 0.1	1.1 ± 0.1	1.6 ± 0.1	**< 0.001**	0.795	0.065
Cerebral pulsatility index	1.28 ± 0.08	0.95 ± 0.05	0.91 ± 0.03	0.80 ± 0.03	**< 0.001**	**0.001**	**0.004**
$P_{ET}CO_2$ (mmHg)	30.7 ± 2.2	35.1 ± 1.9	32.4 ± 0.9	38.3 ± 0.9	**< 0.001**	0.207	0.191
Tidal volume (L)	0.69 ± 0.09	0.95 ± 0.12	1.11 ± 0.19	1.40 ± 0.19	**< 0.001**	0.080	0.697
Breathing frequency (breaths/min)	19 ± 2	20 ± 3	11 ± 1	11 ± 1	0.645	**0.001**	0.579
Minute ventilation (L/min)	12.9 ± 1.7	17.6 ± 3.2	12.5 ± 2.5	13.1 ± 1.7	0.065	0.430	0.157

Abbreviations = CBF_V, cerebral blood flow velocity; $P_{ET}CO_2$, partial pressure of end tidal carbon dioxide.

Table 5. Cognitive function and cerebrovascular responsiveness to cognitive stimuli for the untrained and trained groups. Values are means ± SEM.

Variable	Untrained (n=13)	Trained (n=13)	P value
Cognitive function			
Dimensional change card sort*	7.26 ± 0.57	8.46 ± 0.15	**0.048**
Pattern comparison processing speed*	43 ± 3	50 ± 3	0.220
Picture vocabulary test*	5.77 ± 0.65	6.62 ± 0.52	0.149
Flanker inhibitory control and attention*	7.89 ± 0.15	8.12 ± 0.11	0.317
Picture sequence memory*	-0.93 ± 0.25	-0.41 ± 0.24	0.136
List sorting working memory*	15 ± 1	20 ± 0	**< 0.001**
Oral reading recognition*	4.17 ± 0.80	8.12 ± 0.34	**0.001**
Trail making task (Part A)			
Time (s)	38.4 ± 3.9	27.0 ± 1.6	**0.044**
Errors made	0.8 ± 0.3	0.2 ± 0.1	0.081
Trail making task (Part B)			
Time (s)	89.9 ± 15.1	48.0 ± 3.4	**0.001**
Errors made	2.6 ± 0.6	0.6 ± 0.4	**0.020**
Part B – Part A time difference	51.5 ± 11.7	21.0 ± 3.9	**0.006**
Spatial Span Test			
Time (s)	104 ± 8	116 ± 6	0.277
Total spans completed	5.1 ± 0.4	5.8 ± 0.2	0.186
Cerebrovascular responses to cognitive stimuli (%)			
Dimensional change card sort test	15.8 ± 2.9	26.0 ± 3.1	**0.027**
Pattern comparison processing speed test	19.6 ± 2.2	28.0 ± 3.1	0.085
Picture vocabulary test	20.7 ± 2.7	32.0 ± 3.0	**0.032**
Flanker inhibitory control and attention test	11.9 ± 2.2	25.7 ± 3.1	**0.003**
Picture sequence memory test	19.2 ± 2.3	35.8 ± 4.0	**0.006**
List sorting working memory test	18.7 ± 1.7	32.7 ± 5.3	**0.049**
Oral reading recognition test	15.3 ± 2.0	23.7 ± 3.8	0.146
Trail making task (Part A)	19.8 ± 2.9	38.6 ± 5.9	**0.038**
Trail making task (Part B)	18.5 ± 2.2	31.8 ± 4.1	0.080
Spatial Span Test	17.2 ± 2.2	31.4 ± 3.7	**0.012**

*Normalised, computed and standardised automatically by NIH Toolbox, based on validated measures (Slotkin et al., 2012).

Table 6. Correlations between measured variables and cerebrovascular responsiveness (CVR) to hypercapnia and cognitive stimuli, and cognitive function **(total composite cognitive score)**.

Variable	CVR to hypercapnia		CVR to cognitive stimuli		Cognitive function	
	***r* value**	***P* value**	***r* value**	***P* value**	***r* value**	***P* value**
Education (years)	0.620	0.001	0.590	0.002	0.611	0.003
Consistent exercise training (years)	0.503	0.009	0.643	<0.001	0.682	<0.001
Body mass (kg)	-0.398	0.044	-0.538	0.005	-0.456	0.033
Height (m)	-0.482	0.013	-0.550	0.004	-0.477	0.025
Hip circumference (cm)	-0.568	0.002	-0.532	0.005	-0.421	0.051
Waist circumference (cm)	-0.509	0.008	-0.631	0.001	-0.574	0.005
Hip-to-waist circumference ratio	-0.301	0.135	-0.538	0.002	-0.532	0.011
Total body fat (%)	-0.575	0.003	-0.396	0.050	-0.353	0.116
6-minute walk test distance (m)	0.483	0.012	0.551	0.004	0.566	0.006
High-sensitivity C-reactive protein (mg/L)	-0.687	<0.001	-0.403	0.051	-0.241	0.306
Heart rate (beats/min)	-0.573	0.002	-0.606	0.001	-0.533	0.011
Large arterial compliance (ml/mmHg x 10)	0.397	0.045	0.434	0.027	0.321	0.145
Baseline breathing frequency (breaths/min)	-0.585	0.003	-0.541	0.008	-0.561	0.012
Peak breathing frequency (breaths/min)	-0.400	0.058	-0.666	0.001	-0.575	0.010
CVR to hypercapnia (%)	-	-	0.553	0.008	0.474	0.014
CVR to cognitive stimuli (%)	0.553	0.008	-	-	0.685	<0.001
Total composite cognitive score	0.474	0.014	0.716	<0.001	-	-

Figure Legends

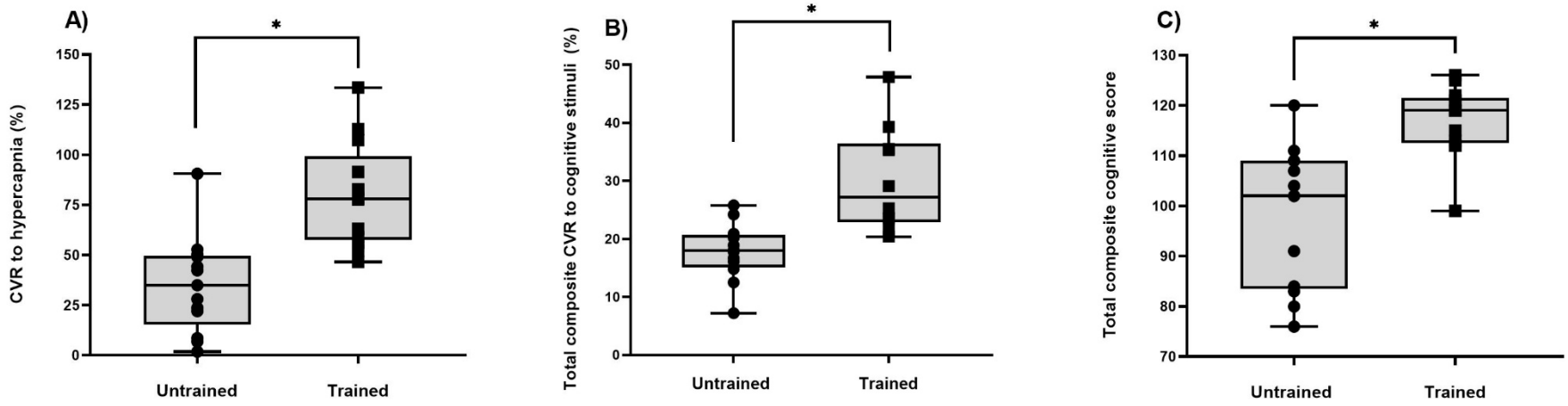

Figure 1. Cerebrovascular responsiveness (CVR) to hypercapnia (A), CVR to total composite of cognitive stimuli (B) and total composite cognitive score (C) for untrained and trained groups. *Significant difference between groups ($P < 0.001$).

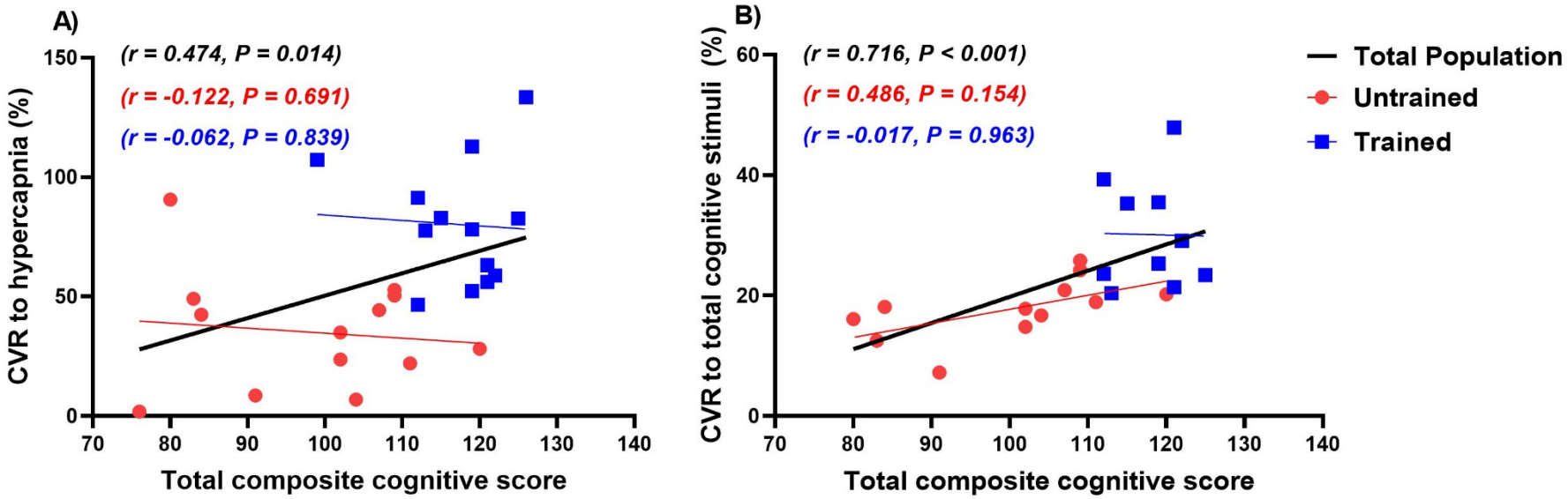

Figure 2. Correlations between cerebrovascular responsiveness (CVR) to hypercapnia (A), total composite CVR to cognitive stimuli (B) and total composite cognitive score.

CHAPTER 5: THE EFFECTS OF AEROBIC EXERCISE TRAINING ON CEREBROVASCULAR AND COGNITIVE FUNCTION IN SEDENTARY, OBESE, OLDER ADULTS

The Effects of Aerobic Exercise Training on Cerebrovascular and Cognitive Function in Sedentary, Obese, Older Adults

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Running headline

Exercise Training on Cerebrovascular and Cognitive Function

Abstract

Cerebrovascular function and cognition decline with age and are further exacerbated by obesity and physical inactivity. This decline may be offset by aerobic exercise training (AT). We investigated the effects of 16 weeks AT on cerebrovascular and cognitive function in sedentary, obese, older adults. Twenty-eight participants were randomly allocated to AT or a control group. Before and after the intervention, transcranial Doppler ultrasonography was used to measure the cerebrovascular responsiveness (CVR) to physiological (hypercapnia, 5%carbon dioxide) and cognitive stimuli. AT increased the CVR to hypercapnia (98.5 ± 10.3% vs 58.0 ± 12.1%, *P = 0.021*), CVR to cognitive stimuli (25.9 ± 1.7% vs 16.4 ± 1.6%, *P < 0.001*) and total composite cognitive score (111 ± 4 vs 104 ± 4, *P = 0.004*) compared with the control group. A very strong relationship was observed between the number of exercise sessions completed and CVR to cognitive stimuli (*r = 0.878, P < 0.001*), but not for CVR to hypercapnia (*r = 0.246, P = 0.397*) or total composite cognitive score (*r = 0.213, P = 0.465*). Cerebrovascular function and cognition improved following 16 weeks of AT and a dose-response relationship exists between the amount of exercise sessions performed and CVR to cognitive stimuli.

Keywords

Aerobic exercise training, cerebrovascular function, cognition, ageing, obesity

Introduction

Ageing is associated with the development of cognitive decline which may be preceded by reduced cerebrovascular function and unfavourable neuroanatomical changes (Bangen *et al.*, 2014; Toth *et al.*, 2017). There is also increased chronic low-grade systemic inflammation and reactive oxygen species production with ageing, which promotes endothelial dysfunction and reduced cerebrovascular function and cognition (Pikula *et al.*, 2009; Toth *et al.*, 2017; Chang *et al.*, 2018; Rossman *et al.*, 2018; Bliss *et al.*, 2021). Both cerebrovascular function and cognition are exacerbated in sedentary and obese individuals because physical inactivity and obesity promote oxidative stress, which increases the chronic low-grade inflammation, resulting in uncoupling of endothelial nitric oxide synthase which further promotes oxidative stress and inflammation leading to endothelial dysfunction (Pikula *et al.*, 2009; Toth *et al.*, 2017; Chang *et al.*, 2018; Rossman *et al.*, 2018; Bliss *et al.*, 2021). Hence, sedentary behaviour and obesity further impair cerebrovascular function, due to a reduction in capillary density and increased arterial stiffness (i.e. reduced blood flow and vasoreactivity due to decreased endothelial function) (Woods *et al.*, 2011; Toda, 2012; Bangen *et al.*, 2014; Toth *et al.*, 2017). These changes diminish the metabolic capacity of the brain, as the brain is no longer supplied as efficiently as it once was with essential nutrients and oxygen and its metabolic waste is no longer removed as efficiently as in earlier adulthood. If cerebrovascular function is further reduced, the development of cerebral pathologies, cerebral dysfunction and, eventually, a neurodegenerative disease, such as dementia, can ensue as severely reduced cerebrovascular function is associated neurodegenerative changes, including tauopathies and β-amyloid deposition (Kearney-Schwartz *et al.*, 2009; Smith & Greenberg, 2009; Bliss *et al.*, 2021).

The population of older adults who are sedentary and obese is growing and this can lead to the development of comorbidities, including dementia (Beydoun *et al.*, 2008; Taylor, 2014; Brown *et al.*, 2017). The prevalence of dementia is expected to treble over the next 30 years to 150 million people globally (AIHW, 2012; Nichols *et al.*, 2019). Thus, it is important to find and implement cost-effective and evidence-based strategies that promote improvements in cerebrovascular function and cognition

which can slow or prevent the normal age-related decline and dementia. One such intervention is aerobic exercise training (AT), which has been shown to maintain cerebral perfusion and cognitive capacity in healthy ageing and potentially reduce the risk of individuals developing dementia (Rogers *et al.*, 1990; Ainslie *et al.*, 2008; Bailey *et al.*, 2013).

Previous research has demonstrated that moderate intensity AT interventions between 12-24 weeks improve cognition in middle-aged to older adults who were sedentary (Lautenschlager *et al.*, 2008; Erickson *et al.*, 2011; Anderson-Hanley *et al.*, 2012; Chapman *et al.*, 2013; Guadagni *et al.*, 2020), suffer from mild cognitive impairment (Baker *et al.*, 2010), or had a diagnosis of a dementia (Hoffmann *et al.*, 2016; Sobol *et al.*, 2016). Improvements in cerebral perfusion have also been reported in sedentary older adults who participated in 12 weeks of moderate intensity AT (Chapman *et al.*, 2013; Maass *et al.*, 2014) and in older adults with coronary artery disease following 24 weeks of AT (Anazodo *et al.*, 2016). Cerebral pulsatility index (CPI), which determines arterial resistance and compliance of a vessel's ability to stretch and recoil following left ventricular ejection, provides an estimation of arterial stiffness. CPI increases as compliance decreases and resistance increases, thus reflecting structural changes in the arterial walls (i.e. less elasticity) and reduced ability to adequately perfuse the area in which the vessel in supplying (Afkhami *et al.*, 2021). CPI has been reported to decrease in middle-aged to older sedentary adults who undertook a 12 week moderate intensity AT (Akazawa *et al.*, 2018) and following 6 months of moderate intensity AT, the cerebrovascular responsiveness (CVR) to hypercapnia increased in older, sedentary adults (Vicente-Campos *et al.*, 2012; Kleinloog *et al.*, 2019; Guadagni *et al.*, 2020) and stroke patients (Ivey *et al.*, 2011).

There are several important limitations to these studies. Firstly, the effects of AT on both cerebrovascular function and cognition are not as well defined particularly in older obese and sedentary adults who are at greater risk of developing impaired cognitive function (Beydoun *et al.*, 2008; Pikula *et al.*, 2009; Woods *et al.*, 2011;

Toda, 2012; Bangen *et al.*, 2014; Toth *et al.*, 2017; Chang *et al.*, 2018; Rossman *et al.*, 2018; Bliss *et al.*, 2021). Secondly, studies have not typically measured cerebrovascular and cognitive function together. Since these functions are interrelated and contribute to overall brain health, both should be measured together to determine the effect these combined parameters exert (Bliss *et al.*, 2021). Thirdly, no study has performed measurements of CVR to cognitive stimuli (i.e. neurovascular coupling, NVC). This is of importance because CVR to both physiological and cognitive stimuli are imperative to maintaining cerebral function because both reflect the ability of the microvasculature to maintain cerebral autoregulation and NVC (Duchemin *et al.*, 2012; Toth *et al.*, 2017; Miller *et al.*, 2018). The measurement of both parameters in conjunction with cognition is essential to holistically determine the effects of AT on overall brain health. Finally, few of the studies cited have deviated from the recommended physical activity guideline of 150-300 min of moderate intensity exercise. Many older adults are not meeting these guidelines and are not participating in exercise (AIHW, 2018a; Piercy *et al.*, 2018; Guadagni *et al.*, 2020). The evaluation of the dose response relationship between AT and cerebrovascular and cognition function is important, as we currently do not know how much AT is required to elicit improvements in cerebrovascular and cognitive function in older adults. It may be that some exercise is better than none at delaying or preventing further cerebrovascular and cognitive decline. This may also encourage sedentary adults to exercise with a future goal of reaching the recommended physical activity guidelines.

Accordingly, the aim of the study was to evaluate the effects of 16 weeks AT performed for two to four days per week on cerebrovascular and cognitive function in sedentary, obese, older adults. We hypothesised that compared with control participants: 1) AT would improve both cognition and cerebrovascular function determined by the CVR to physiological and cognitive stimuli; 2) the greater the dose of AT, the greater the improvements in cerebrovascular and cognitive function.

Methods

Participants

Participants were recruited from the Ipswich Region, Australia between April 2019 and March 2021 via an approved media campaign that incorporated physical advertisement via media releases (flyers and newspaper articles), social media and a radio interview. Inclusion criteria were: age between 50 and 80 years; were physically inactive based on classed as physically inactive based on the physical activity guidelines of 150 min of moderate-vigorous intensity aerobic exercise per week (AIHW, 2018b); and had a body mass index (BMI) of >25 kg/m^2 . The exclusion criteria were: current smoker; blood pressure ≥160/100 mmHg; prescribed insulin, hormone-replacement therapy, or oral anticoagulants; had a significant history of cardiovascular, cerebrovascular, kidney, liver disease or cancer; and had a diagnosis of cognitive impairment and/or a neurodegenerative disease. Participants were only included in the study if they were on a stable medication treatment plan that did not contradict the exclusion criteria. The Yale Physical Activity Survey (Dipietro *et al.*, 1993), the Exercise and Sports Science Australia Adult Pre-exercise Screening System (Norton & Norton, 2011), and a customised health and wellbeing screen were used to determine whether participants met the inclusion and/or exclusion criteria, as well as their physical activity status and exercise behaviours. All study procedures were approved by the University of Southern Queensland Research Ethics Committee (H19REA007), which adheres to the Declaration of Helsinki. The study was registered with the Australian and New Zealand Clinical Trial Registry (ACTRN12619000988156). Participants provided written, informed consent.

Experimental design

The study adopted a randomised control design. The intervention lasted 16 weeks. Before and at the end of the intervention, participants visited the laboratory on two occasions, at a similar time of day, separated by a minimum of 24 h and a maximum of 7 days. Participants fasted and abstained from coffee, tea and other stimulants for 1 h before visit 1 and 8-12 h before visit 2. They were also requested to refrain from

moderate-vigorous intensity exercise for 24 h before each visit and to take their daily supplements and medication after each visit was completed. During visit 1, participants undertook anthropometric, cardiovascular, exercise performance, strength, cerebrovascular and cognitive measurements. During visit 2, participants undertook body composition measurements, blood collection and the Profile of Moods State questionnaire. The Profile of Mood States questionnaire calculated mood disturbance by adding the scores of the negative mood state scales (i.e. anger-hostility, confusion-bewilderment, depression-dejection, fatigue inertia, tension-anxiety) and subtracting the positive mood state scale (i.e. vigour-activity) (Heuchert & McNair, 2012). Lower values in the negative mood states and total mood disturbance indicated better mood, while higher values in the positive mood state portion of the questionnaire are associated with positive mood. Between visits 1 and 2, participants were asked to complete a nutritional questionnaire (Automated Self-Administered 24 h Dietary Assessment Tool; National Institute of Health, Bethesda, MA, USA) to estimate energy intake over a typical 24 h period (Pannucci *et al.*, 2018).

Exercise intervention

Participants were then randomly allocated to one of two arms of the study using Altman's minimisation method (prioritising BMI and sex) to ensure that the groups were balanced (Altman & Bland, 2005). The two arms of the study included a control group, which did not participate in any exercise training, and an exercise group. Participants allocated to the exercise group were asked to participate in AT for between two to four days per week (i.e., they could participate in either two, three or four sessions per week). These sessions were conducted as group classes supervised by a clinical exercise physiologist. Table 1 provides an overview of the exercise session content. All sessions lasted for approximately 40-45 min and incorporated both a 5 min warm-up and cool-down. The body of the sessions was performed at a rating of perceived exertion for leg discomfort of 5-8 on the Borg (CR-10) scale, which indicated that the exercise was being performed at a moderate (5-6) or high intensity (7-8) (Borg, 1998). Additionally, the participants were asked to perform these exercise sessions at a higher intensity at approximately every four

weeks if possible (Table 1). The circuit comprised functional exercises including wall press-ups, marching, step-ups, sit-to-stands, squats and basic resistance exercises. Compliance was measured by a roll call at the start of every exercise session to determine participation. Participants were contacted by either by phone, email, or in person each week for the first two weeks of the study, then fortnightly until 8 weeks at which time they were contacted every 4 weeks to ensure protocol familiarity, personal reassurance and motivation and as a check of their general wellbeing. This practice can assist in ensuring participant compliance (Lautenschlager *et al.*, 2008). An attendance rate of 40% of all of the available exercise sessions at the end of the 16 weeks was considered compliant (Rejeski *et al.*, 1997; Claxton *et al.*, 2001; Lautenschlager *et al.*, 2008).

Table 1: Composition of the exercise sessions, including session content, intensity and rating of perceived exertion.

Week/s	Day/s	Session	Intensity	Rating of perceived exertion (0-10)
1 – 2	Monday / Friday	30 min walking	Moderate	5
	Tuesday / Thursday	15 min walking	Moderate	5
		15 min circuit	Moderate-to-vigorous	6 – 7
3 – 5	Monday	35 min walking	Moderate	5 – 6
	Tuesday / Thursday	15 min walking, cycling, arm ergometry, rowing	Moderate	5 – 6
		15 min circuit	Vigorous	7 – 8
	Friday	15 min walking	Moderate	5 – 6
		3 x 6 min circuits		
6 – 8	Monday / Friday	15 min walking, cycling, arm ergometry, rowing	Moderate	6
		3 x 5 min circuits	Moderate	6
	Tuesday / Thursday	15 min walking, cycling, arm ergometry, rowing	Moderate	6
		15 min circuit	Vigorous	7 – 8
9 – 12	Monday / Friday	15 min walking, cycling, arm ergometry, rowing	Moderate	6
		3 x 5 min circuits	Moderate	6
	Tuesday / Thursday	15 min walking, cycling, arm ergometry, rowing	Moderate	6
		15 min circuit	Vigorous	7 – 8
13 – 14	Monday / Friday	5 min walking, cycling, arm ergometry, rowing	Moderate	6
		7 x 4 min circuits	Moderate-to-vigorous	7
	Tuesday / Thursday	10 min walking, cycling, arm ergometry, rowing	Moderate	6
		20 min circuit	Vigorous	8
15 – 16	Monday / Friday	5 min walking, cycling, arm ergometry, rowing	Moderate	6
		7 x 4 min circuits	Moderate-to-vigorous	7
	Tuesday / Thursday	5 min walking, cycling, arm ergometry, rowing	Moderate	6
		2 x 15 min circuits	Vigorous	8

Basal cerebral haemodynamics

Transcranial Doppler ultrasonography (TCD; DopplerBox X; Compumedics DWL, Singen, Germany) was used to measure basal cerebrovascular haemodynamics, including minimum, maximum and mean values for both CBF_V and cerebral pulsatility, as well as CVR in response to hypercapnia and cognitive stimuli (Edmonds Jr *et al.*, 2011; Barbour *et al.*, 2017; Evans *et al.*, 2017). Participants were seated and fitted with a headpiece which housed two 2-MHz TCD ultrasound probes that were fixed and aligned bilaterally to the left and right cranial temporal bone windows to insonate the middle cerebral arteries (MCA) at a depth of approximately 40-65 mm. Once a suitable blood flow signal was obtained, participants were asked to sit quietly while basal measurements were recorded for 30 s. If the MCA could not be insonated, the participant was excluded from the study.

Cerebrovascular responsiveness to hypercapnia

Participants were subsequently challenged with a hypercapnic stimulus for 3 min and monitored for another 1 min following removal. This process was performed in duplicate following a 5 min rest period (whilst participants breathed in room air) to ensure mean velocity returned to baseline values (Barbour *et al.*, 2017; Evans *et al.*, 2017). Participants breathed through a two-way non-rebreathing valve (model 2730, Hans Rudolph, Kansas City, MO, USA) whilst wearing a nose-clip. The inspiratory port of the two-way valve was connected to 1 m of wide bore tubing distal to a 100 L Douglas bag which contained carbogen gas (5% carbon dioxide and 95% oxygen; Carbogen 5; BOC, Toowoomba, Australia). Flow was measured from the expiratory port of the two-way valve using a pneumotachograph (MLT 300L; AD Instruments, Bella Vista, Australia) which was calibrated with a 3 L syringe prior to the commencement of each test. Volume was obtained by numerical integration of the flow signal. End-tidal partial pressures of carbon dioxide ($P_{ET}CO_2$) were sampled from the expiratory port of the two-way valve connected to a gas analyser (ADI ML206; AD Instruments, Bella Vista, Australia) that was calibrated across the physiological range with known gas concentrations (BOC, Toowoomba, Australia). Flow and $P_{ET}CO_2$ measurements were sampled at 200 Hz using a 4-channel

Powerlab analog-to-digital converter (AD Instruments, Bella Vista, Australia) interfaced with a computer and displayed in real time during testing. Data were stored for subsequent offline analysis using LabChart software (version 7.2, AD Instruments, Bella Vista, Australia).

Cognitive function and cerebrovascular responsiveness to cognitive stimuli

Cognitive tests included the Trail Making Task Parts A and B which assessed central executive function, Spatial Span Test (visuospatial short-term working memory) and a National Institute of Health (NIH) Toolbox, which is a battery of cognitive examinations (Strauss *et al.*, 2006; Evans *et al.*, 2017). The NIH Toolbox is comprised of the Dimensional Change Card Sort Test (cognitive flexibility and attention), Picture Vocabulary Test (language and crystallised cognition), List Sorting Working Memory Test (working memory), Oral Reading Recognition Test (language and crystallised cognition), Flanker Inhibitory Control and Attention Test (attention and inhibitory control), Picture Sequence Memory Test (episodic memory), Pattern Comparison Processing Speed Test (processing speed) (Slotkin *et al.*, 2012; Heaton *et al.*, 2014). An age adjusted total composite cognitive function score was also derived from the above (Heaton *et al.*, 2014). All tests excluding the Trail Making Task were delivered using an iPad (6^{th} generation, Apple Inc, Cupertino, CA, USA). The CVR to cognitive stimuli was assessed during each cognitive task and 30 s of baseline data was recorded before the start of each cognitive task.

Data capture and processing for cerebrovascular responsiveness

Beat-to-beat measurements of CBF_V were recorded from the MCA onto software (QL Reader; Compumedics DWL, Singen, Germany) sampling at 100 Hz and were stored for subsequent offline analysis. If a bilateral signal was not obtained, then analysis took place with only the side that was able to be obtained. These data were then normalised and analysed using Curve Expert Professional software (Hyams Development, Chattanooga, TE, USA) to determine peak CBF_V, resting CBF_V and

resting cerebral pulsatility index (CPI). Peak CBF_V was determined as the highest CBF_V during the 3 min period of hypercapnia or a cognitive task. CVR and CPI were calculated based on the equations [1] and [2] from previous work (Bakker *et al.*, 2004; Wong *et al.*, 2016b; Harris *et al.*, 2018)

$$[1] \quad \text{CPI} = \frac{\text{peak systolic CBFv} - \text{ end diastolic CBFv}}{\text{mean CBFv during a cardiac cycle}}$$

$$[2] \quad \text{CVR (\%)} = \frac{(\text{peak CBFv} - \text{resting CBFv})}{\text{resting CBFv}} \times 100 \div \text{resting CPI}$$

Anthropometrics and body composition

Participants were instructed to wear light clothing prior to testing and subsequently asked to remove their shoes for measurements. Body mass was measured to the nearest 100 g using an electronic scale (Tanita Ultimate Scale 2000; Tokyo, Japan) and waist and hip circumferences will be recorded to the nearest 1 cm using a standard tape measure as previously described (Welborn *et al.*, 2003). Height was recorded to the nearest 1 cm using a wall-mounted telescopic stadiometer (Seca220; Vogel & Halke, Hamburg, Germany). Height, body mass and waist and hip circumference measurements were measured in duplicate and the mean of the two measurements were analysed. BMI and a waist to hip ratio were calculated as previously described (Keys *et al.*, 1972; Welborn *et al.*, 2003). Dual-energy X-ray absorptiometry was used to obtain the following measures of whole body composition: lean mass, body fat percentage, bone mineral content and density (Luna Corp Prodigy Advance Model GE; Madison, WI, USA).

Cardiovascular function

Systolic and diastolic blood pressure, mean arterial pressure, heart rate and arterial elasticity were measured non-invasively using a HDI/Pulsewave™ CR-2000 Research Cardiovascular Profiling System (Hypertension Diagnostics, Eagan, MN, USA) (Prisant *et al.*, 2002). Participants rested in a seated position for 10 min prior

to measurements. Four consecutive readings were recorded approximately 5 min apart by an automated oscillometer, using an appropriately size blood pressure cuff over the left brachial artery, to assess blood pressure and a tonometer, placed over the right radial artery, to assess heart rate and estimate arterial elasticity, cardiac output and cardiac index by pulse wave analysis (Prisant *et al.*, 2002; Barbour *et al.*, 2017). The first reading was discarded and the mean of the three subsequent readings was used for analysis.

Biochemical analyses

Approximately 20 ml of venous blood was sampled using a suitable method (i.e. either evacuated tube system or winged-infusion set for difficult collections) from the veins of the antecubital fossa into a thrombin-based clot activator serum separator tubes (BD, Macquarie Park, NSW, Australia). Following collection, blood was left to stand for 30 min at 18-25°C prior to centrifugation at 1300 g and 18°C for 10 min, as outlined by the tube manufacturer and the testing laboratory (BD, 2019; QML, 2019). Following centrifugation, blood was separated as serum and analysed for the general chemistry profile and high-sensitivity C-reactive protein (hs-CRP) on a Siemens ADVIA® Labcell® (Siemens Healthcare, Bayswater, VIC, Australia), which utilises spectrophotometric (enzymes, metabolites, proteins, lipids), turbidimetric (hs-CRP) and potentiometric (electrolytes) techniques (Healthineers, 2019).

Exercise performance and handgrip strength

Exercise performance was assessed using a 6 minute walk test (6MWT) according to published guidelines (ATS, 2002). Handgrip strength was determined using hand dynamometry as previously described (Hillman *et al.*, 2005). Participants were permitted three attempts with both their dominant and non-dominant hands. The first reading for each hand was discarded and was used as a familiarisation and the second and third readings for each hand were averaged for each hand and were used for analysis. Both the 6MWT and handgrip strength were used to provide an estimate

of endurance exercise capacity and whole-body strength (ATS, 2002; Hillman *et al.*, 2005)

Statistical analysis

Statistical analyses were performed using SPSS for Windows (IBM, Chicago, USA). An initial power calculation was performed on the basis of previous research that has investigated the differences in CVR between participants who had undergone an intervention study (Wong *et al.*, 2016a; Wong *et al.*, 2016b; Barbour *et al.*, 2017; Evans *et al.*, 2017). It indicated that 32 participants would give 80% power to detect a significant ($p < 0.05$) 5% increase in the CVR to hypercapnia following exercise training. This was based on a 10% standard deviation observed in previous studies and a medium sized effect (Wong *et al.*, 2016a; Wong *et al.*, 2016b; Barbour *et al.*, 2017; Evans *et al.*, 2017). Recruitment was limited to 28 participants due to the impacts of COVID-19 and the restrictions placed on gathering, research and travel by the Queensland Government. Normality of data was assessed using a Shapiro-Wilk test. Comparisons between groups for anthropometric, body composition, cardiovascular, cognitive, exercise performance, strength and biochemical measures were determined using an independent t-test or a Mann-Whitney U-test for parametric and non-parametric data, respectively. A two-way analysis of variance (ANOVA) was used to determine the effects of 'treatment' (exercise vs. control) and 'intervention' (week 0 vs. week 16). A three-way ANOVA was used to determine the effects of 'treatment', 'intervention' and 'time' (baseline vs peak) for the CVR to hypercapnia and cognitive stimuli measures. Significant interaction effects were followed by planned pairwise comparisons between groups using the Bonferroni method. Pearson product-moment correlation coefficients were calculated to assess the relationship between the number of exercise sessions completed and the relative percentage change from week 0 to week 16 for the CVR to hypercapnia, total composite CVR to cognitive stimuli and total composite cognitive score in the exercise group (Schober *et al.*, 2018). The relative percentage change for each of these variables were determined by the following formula:

$$[3] \quad \text{relative percentage increase} = \frac{(\text{week 16 value} - \text{week 0 value})}{\text{week 0 value}} \times 100$$

Statistical significance was set at $P < 0.05$. Results are presented as means ± SEM.

Results

Participant characteristics

Figure 1 shows the CONSORT participant flow diagram. Twenty-seven participants were included in the final data and statistical analysis. Thirteen participants were in the control arm of the study. Fourteen participants completed the exercise intervention and compliance was good with 40 ± 3 (63 ± 5%) exercise sessions completed.

Baseline characteristics are shown in Table 2. No differences were observed between the groups except for the number of flights of stairs climbed daily which was higher in the control compared to the exercise group with a medium effect size ($d = 0.68$). Baseline general biochemistry profiles and hs-CRP are shown in Table 3. There were no differences between the groups. The participants were obese, had low-grade inflammation and met the International Diabetes Federation criteria of the metabolic syndrome (Alberti *et al.*, 2005).

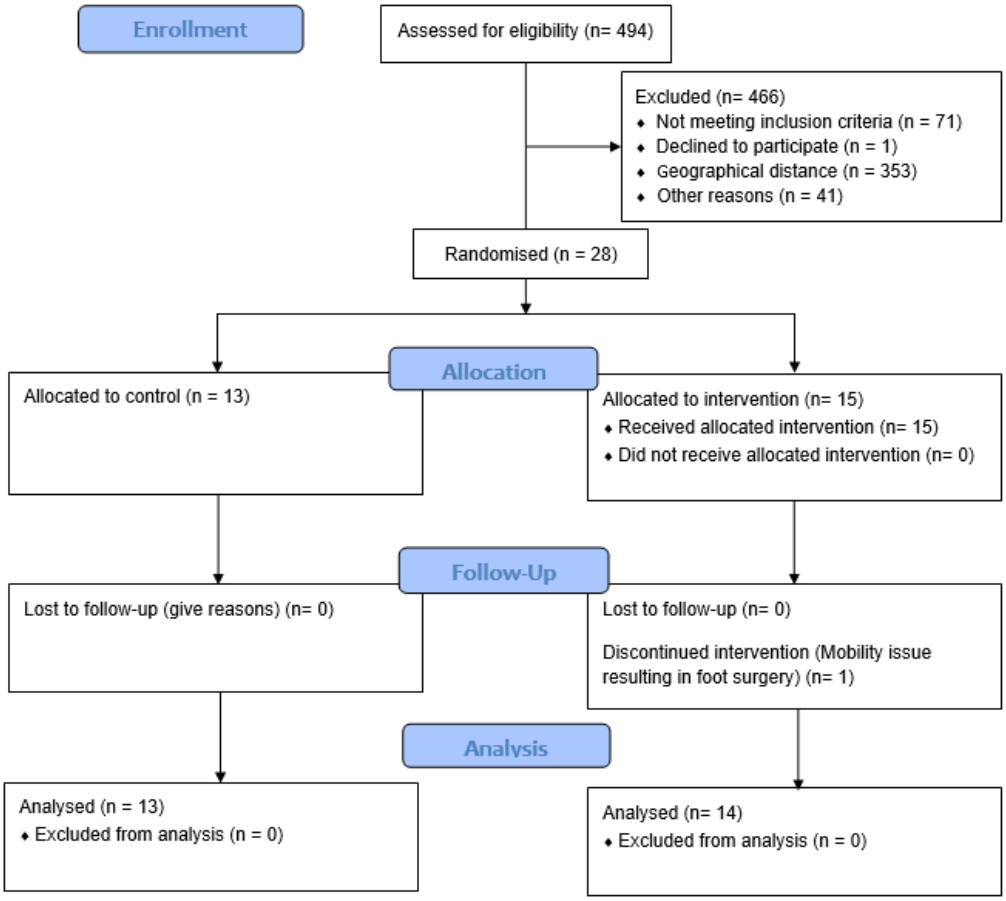

Figure 1: CONSORT Participant flow diagram.

Table 2: Baseline demographics, anthropometrics, nutritional intake and physical activity levels for the control and exercise groups. Values are means ± SEM.

Variable	Control (n=13)	Exercise (n=14)	P value
Demographics			
Age (years)	66 ± 2	67 ± 2	0.553
Sex (Male/Female)	2 / 11	4 / 10	0.618
Education (years)	16 ± 1	14 ± 1	0.440
Diagnosed hypertension (%)	31	36	0.781
Anthropometrics			
Body mass (kg)	93.5 ± 6.3	88.7 ± 2.9	0.928
Height (m)	1.64 ± 0.02	1.68 ± 0.02	0.208
Body mass index (kg/m^2)	34.6 ± 1.8	31.4 ± 0.5	0.339
Hip circumference (cm)	126 ± 4	117 ± 1	0.118
Waist circumference (cm)	114 ± 4	107 ±1	0.217
Hip-to-waist ratio	0.91 ± 0.02	0.91 ± 0.02	0.730
Nutritional intake			
Total energy intake (kcal)	2375 ± 213	2688 ± 299	0.393
Physical activity levels			
Energy expenditure (kcal/min)	70 ± 10	94 ± 20	0.560
Vigorous activity index	5 ± 2	1 ± 1	0.131
Leisurely walking index	5 ± 1	8 ± 3	0.527
Moving index	7 ± 1	8 ± 1	0.705
Standing index	5 ± 0	6 ± 1	0494
Sitting index	4 ± 0	4 ± 0	0.560
Flights of stairs climbed per day	2 ± 1	1 ± 1	**0.036**
Seasonal adjustment score	1 ± 0	1 ± 0	0.274

Table 3: Baseline biochemical analyses for the control and exercise groups. Values are means ± SEM.

Variable	Control (n=11)	Exercise (n=14)	P value
Glucose (mmol/L)	5.7 ± 0.4	5.6 ± 0.2	0.683
Urea (mmol/L)	6.1 ± 0.4	5.9 ± 0.3	0.610
Creatinine (mmol/L)	74 ± 6	67 ± 3	0.959
Estimated glomerular filtration rate (ml/min)	80 ± 4	84 ± 2	0.384
Total bilirubin (µmol/L)	9 ± 1	9 ± 1	0.574
Alkaline phosphatase (U/L)	92 ± 8	75 ± 7	0.123
Gamma-glutamyl transferase (U/L)	35 ± 7	29 ± 4	0.760
Alanine aminotransferase (U/L)	37 ± 6	30 ± 2	0.443
Aspartate aminotransferase (U/L)	35 ± 5	27 ± 1	0.384
Lactate dehydrogenase (U/L)	234 ± 21	202 ± 8	0.474
Total protein (g/L)	70 ± 1	69 ± 1	0.555
Albumin (g/L)	40 ± 1	42 ± 1	0.164
Globulins (g/L)	30 ± 1	27 ± 1	0.101
Total cholesterol (mmol/L)	5.3 ± 0.3	5.6 ± 0.3	0.330
Triglycerides (mmol/L)	1.4 ± 0.2	1.4 ± 0.1	0.931
High-density lipoprotein (mmol/L)	1.47 ± 0.07	1.45 ± 0.09	0.827
Low-density lipoprotein (mmol/L)	2.71 ± 0.26	3.18 ± 0.22	0.186
Total cholesterol-to-high-density lipoprotein ratio	3.7 ± 0.3	4.1 ± 0.1	0.292
High-sensitivity C-reactive protein (mg/L)	4.8 ± 0.9	3.0 ± 0.7	0.066

Body composition, grip strength, exercise performance, cardiovascular function

Body composition, grip strength, exercise performance and cardiovascular function measurements are shown in Table 4. The 6MWT distance at week 0 was higher in the exercise compared to the control group with a medium effect size (main effect of treatment, d = 0.74). Total lean mass (d = 0.18), 6MWT distance, and large arterial compliance (d =0.08) increased in both groups (main effect of intervention), while total body fat percentage (d =0.69), systolic blood pressure (d =0.19), mean arterial pressure (d =0.04) and total vascular impedance (d =0.01) decreased in both groups (main effect of intervention). There were no significant treatment x intervention interaction effects in any of the parameters, although the 6MWT distance (d =1.33) and total bone mineral content (d =0.31) were approaching significance.

Table 4: Body composition, grip strength, exercise performance and cardiovascular function at week 0 and week 16 for the control and exercise groups. Values are means ± SEM.

Variable	Control (n=13)		Exercise (n=14)		P value		
	Week 0	Week 16	Week 0	Week 16	Treatment	Intervention	Treatment x intervention
Body composition							
Total lean mass (kg)	45.6 ± 2.4	46.8 ± 2.7	48.2 ± 2.8	48.7 ± 2.7	0.551	**0.029**	0.299
Total body fat (%)	48.4 ± 1.9	47.1 ± 2.1	43.5 ± 1.5	42.7 ± 1.5	0.064	**<0.001**	0.353
Total bone mineral density (g/cm^2)	1.24 ± 0.04	1.24 ± 0.03	1.22 ± 0.04	1.22 ± 0.04	0.673	0.762	0.827
Total bone mineral content (g/cm)	2478 ± 127	2439 ± 132	2598 ± 149	2602 ± 151	0.484	0.113	0.052
Grip strength							
Dominant hand (kg)	27.0 ± 2.2	27 ± 2.1	28.7 ± 2.5	31.3 ± 2.8	0.332	0.364	0.324
Non-dominant hand (kg)	26.1 ± 1.7	25.8 ± 2.0	26.8 ± 2.3	30.1 ± 2.4	0.336	0.242	0.147
Exercise performance							
6-minute walk test distance (m)	461 ± 20	469 ± 25	511 ± 16	576 ± 18	**0.004**	**0.015**	0.058
Cardiovascular function							
Heart rate (beats/min)	76 ± 3	75 ± 3	72 ± 2	71 ± 3	0.213	0.719	0.810
Systolic blood pressure (mmHg)	144 ± 4	133 ± 4	139 ± 2	130 ± 3	0.347	**<0.001**	0.473
Diastolic blood pressure (mmHg)	78 ± 2	73 ± 3	76 ± 2	72 ± 1	0.401	0.055	0.714
Mean arterial pressure (mmHg)	104 ± 2	95 ± 3	99 ± 3	95 ± 2	0.336	**0.012**	0.183
Large arterial compliance (ml/mmHg x 10)	9.3 ± 0.9	11.5 ± 1.1	9.7 ± 0.9	11.8 ± 1.1	0.735	**0.007**	0.885
Small arterial compliance (ml/mmHg x 10)	3.9 ± 0.5	4.5 ± 0.6	4.5 ± 0.5	4.8 ± 0.9	0.501	0.291	0.532
Systemic vascular resistance ($dyne/sec/cm^{-s}$)	1663 ± 88	1534 ± 73	1630 ± 67	1543 ± 61	0.836	0.125	0.708
Total vascular impedance ($dyne/sec/cm^{-s}$)	202 ± 16	161 ± 13	178 ± 10	161 ± 12	0.431	**0.010**	0.218

Cerebrovascular responsiveness to hypercapnia

The CVR to hypercapnia and the cerebrovascular and respiratory parameters are shown in Figure 2 and Table 5. All variables measured increased during hypercapnia (main effect of time; *P < 0.001)*, except for CPI which decreased (main effect of time; *P < 0.001*) and breathing frequency, which did not change. The CVR to hypercapnia increased to a greater extent in the exercise than the control group (+40%; treatment x intervention interaction; *P = 0.021, d >0.82*). Although Week 0 CBF_V was lower in the exercise group than the control group, the increase in CBF_V during hypercapnia (treatment x intervention x time interaction) was greater following the intervention (+36%) in the exercise group (*d = 0.81)*. CPI decreased (main effect of intervention, *P = 0.001, d = 0.24*) in both the exercise and control groups following the intervention but there were no interaction effects. Maximum tidal volume and minute ventilation (treatment x intervention interaction) increased to a greater extent in the exercise compared to the control group following the intervention (*d >0.82* and *d = 0.28)*.

Cognitive function and cerebrovascular responsiveness to cognitive stimuli

Cognitive function and the CVR to cognitive stimuli are shown in Figure 2 and Table 6. There were no differences between the groups in any of the cognitive parameters at week 0. Following the intervention, the exercise group had higher overall cognitive function than the untrained group, which was demonstrated by a higher total cognitive composite score with a small effect size (3% vs. 10% improvement; treatment x intervention interaction; *P = 0.004, d = 0.49*). The exercise group also had increased working memory capacity compared to the control group with a large effect size following the intervention, demonstrated by the List Sorting Working Memory Test (*d > 0.82)*.

At week 0, there were no differences between the groups in any CVR measures except for the CVR to Part B of the Trail Making Task which was higher in the control than the exercise group with a small effect size (main effect of treatment, *d = 0.23*). Following the intervention, the exercise group had a higher total composite CVR to all cognitive stimuli (10% higher; treatment x intervention interaction; *P <*

0.001, d > 0.82) than the control group with a large effect size, as well as a higher CVR to all of the individual cognitive stimuli with a large effect size (*d > 0.82)*, excluding the Picture Vocabulary Test and the Flanker Inhibitory Control and Attention Test (treatment x intervention interaction).

Correlations between exercise sessions completed and cerebrovascular function and cognition

Figure 3 shows the correlations between the number of exercise sessions completed and the percentage increase from week 0 to week 16 for the CVR to hypercapnia, total composite CVR to cognitive stimuli and total composite cognitive score in the exercise group. There was a very strong positive correlation between the number of exercise sessions completed and the total composite CVR to cognitive stimuli. There were no significant correlations between the number of exercise sessions completed and either the CVR to hypercapnia or the total composite cognitive score.

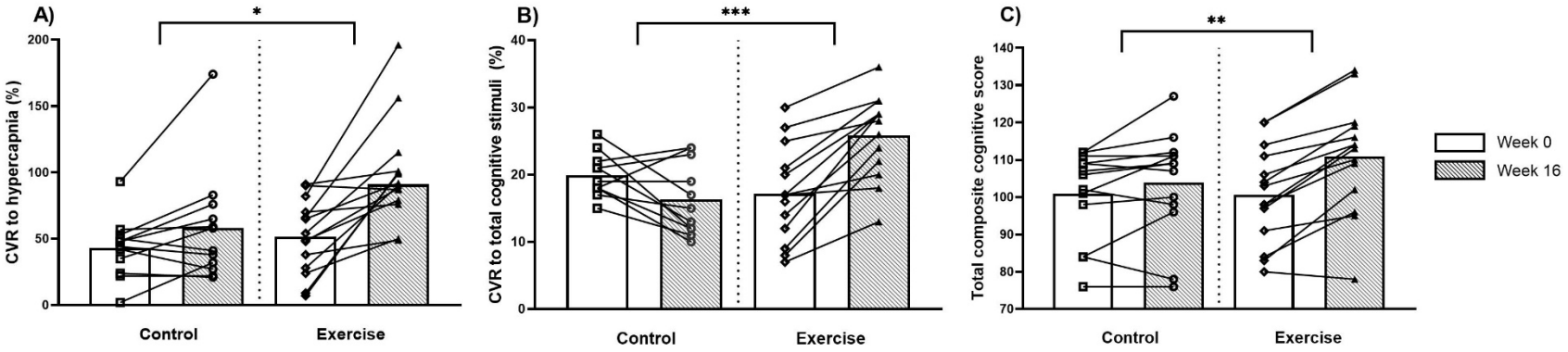

Figure 2: Cerebrovascular responsiveness (CVR) to hypercapnia (A), CVR to total composite of cognitive stimuli (B) and total composite cognitive score (C) at week 0 and week 16 for the control and exercise groups. Significant difference between groups * ($P < 0.05$), ** ($P < 0.005$), *** ($P < 0.001$).

Table 5a: Cerebrovascular and respiratory parameters at baseline and peak hypercapnia at week 0 and week 16 for the control and exercise groups. Values are means ± SEM.

Variable	Control (n = 13)				Exercise (n = 14)			
	Week 0		Week 16		Week 0		Week 16	
	Baseline	Peak	Baseline	Peak	Baseline	Peak	Baseline	Peak
Cerebrovascular variables								
CBF_V (cm/s)	37.4 ± 2.6	52.3 ± 4.3	41.6 ± 3.9	61.2 ± 5.3	31.0 ± 2.3	47.0 ± 3.6	33.5 ± 1.4	61.2 ± 2.3
CPI	1.22 ± 0.12	1.05 ± 0.14	1.00 ± 0.07	0.83 ± 0.05	1.20 ± 0.08	0.93 ± 0.05	0.95 ± 0.04	0.80 ± 0.03
Respiratory variables								
$P_{ET}CO_2$ (mmHg)	32.5 ± 1.6	37.1 ± 1.5	33.8 ± 1.5	38.6 ± 1.6	29.6 ± 1.0	35.9 ± 1.3	30.9 ± 1.1	37.2 ± 0.9
Tidal volume (L)	0.79 ± 0.09	1.13 ± 0.13	0.62 ± 0.08	0.93 ± 0.11	0.80 ± 0.08	0.98 ± 0.11	1.00 ± 0.07	1.34 ± 0.13
Breathing frequency (breaths/min)	16 ± 2	18 ± 3	16 ± 2	18 ± 3	15 ± 1	16 ± 2	13 ± 1	15 ± 2
Minute ventilation (L/min)	12.0 ± 1.2	16.8 ± 2.6	9.3 ± 1.2	14.8 ± 2.4	11.3 ± 1.4	14.6 ± 1.5	12.0 ± 1.3	17.0 ± 2.0
$CBF_V/P_{ET}CO_2$ (cm/s/mmHg)	1.24 ± 0.06	1.53 ± 0.09	1.24 ± 0.10	1.59 ± 0.12	1.10 ± 0.06	1.41 ± 0.09	1.10 ± 0.07	1.65 ± 0.06

Table 5b: Three-way analysis of variance results for cerebrovascular and respiratory parameters at baseline and peak hypercapnia at week 0 and week 16 for the control and exercise groups.

Variable	Treatment	Intervention	Treatment x intervention	Treatment x intervention x time
Cerebrovascular variables				
CBF_V (cm/s)	0.147	**<0.001**	0.116	**0.045**
CPI	0.971	**0.001**	0.319	0.350
Respiratory variables				
$P_{ET}CO_2$ (mmHg)	0.982	0.332	0.997	0.884
Tidal volume (L)	0.099	0.280	**0.002**	0.166
Breathing frequency (breaths/min)	0.406	0.434	0.200	0.812
Minute ventilation (L/min)	0.619	0.885	**0.035**	0.663
$CBF_V/P_{ET}CO_2$ (cm/s/mmHg)	0.232	0.263	0.853	0.384

Abbreviations for Table 5a and 5b = CBF_V, cerebral blood flow velocity; CPI, cerebral pulsatility index; $P_{ET}CO_2$, partial pressure of end tidal carbon dioxide.

Table 6: Cognitive function and cerebrovascular responsiveness to cognitive stimuli at week 0 and week16 for the control and exercise groups. Values are means ± SEM.

Variable	Control (n = 13)		Exercise (n = 14)		P value		
	Week 0	Week 16	Week 0	Week 16	Treatment	Intervention	Treatment x intervention
Cognitive function							
Dimensional change card sort*	7.46 ± 0.37	7.32 ± 0.52	7.78 ± 0.21	7.58 ± 0.33	0.708	0.313	0.939
Pattern comparison processing speed*	43 ± 3	47 ± 3	44 ± 3	53 ± 3	0.164	**0.006**	0.078
Picture vocabulary test*	6.16 ± 0.52	5.14 ± 0.61	6.06 ± 0.58	5.99 ± 0.60	0.492	0.215	0.118
Flanker inhibitory control and attention*	7.80 ± 0.14	8.09 ± 0.12	7.79 ± 0.11	8.16 ± 0.11	0.062	0.443	0.365
Picture sequence memory*	-0.67 ± 0.23	-0.90 ± 0.15	-0.36 ± 0.27	-0.62 ± 0.18	0.379	**0.005**	0.886
List sorting working memory*	16 ± 1	15 ± 1	16 ± 1	19 ± 1	0.352	**<0.001**	**<0.001**
Oral reading recognition*	4.61 ± 0.67	4.16 ± 0.6	5.10 ± 0.72	5.71 ± 0.69	0.921	**0.002**	0.080
Trail making task (Part A)							
Time (s)	36.3 ± 3.6	37.0 ± 3.7	36.5 ± 4.0	28.6 ± 3.3	0.410	0.173	0.152
Errors made	0.7 ± 0.3	0.6 ± 0.2	0.9 ± 0.3	0.1 ± 0.1	0.107	0.602	0.164
Trail making task (Part B)							
Time (s)	83.4 ± 13.6	77.9 ± 7.5	66.6 ± 6.6	67.2 ± 12.6	0.723	0.216	0.621
Errors made	2.4 ± 0.5	1.5 ± 0.6	2.5 ± 1.3	0.6 ± 0.2	0.052	0.550	0.687
Part B - Part A time difference	47.1 ± 10.8	40.9 ± 5.2	30.0 ± 4.6	38.5 ± 9.8	0.951	0.315	0.262
Spatial Span Test							
Time (s)	100.9 ± 5.7	97.4 ± 9.3	104.3 ± 10.6	105.3 ± 6.0	0.769	0.504	0.752
Total spans completed	5.6 ± 0.2	4.8 ± 0.3	5.2 ± 0.4	5.4 ± 0.2	0.215	0.697	0.129
Total composite cognitive score	101 ± 3	104 ± 4	101 ± 3	111 ± 4	0.508	**<0.001**	**0.004**
Cerebrovascular responsiveness (%)							
Dimensional change card sort test	16.9 ± 2.7	13.3 ± 1.8	12.1 ± 1.4	20.8 ± 1.7	0.329	0.289	**0.001**
Pattern comparison processing speed test	20.0 ± 2.0	18.0 ± 2.4	18.7 ± 3.1	24.5 ± 2.0	0.517	0.179	**0.048**
Picture vocabulary test	23.1 ± 2.1	20.0 ± 2.4	21.9 ± 3.6	27.2 ± 2.2	0.797	0.192	0.083
Flanker inhibitory control and attention test	13.1 ± 2.6	12.3 ± 1.6	14.0 ± 2.0	19.2 ± 1.6	0.342	**0.026**	0.080
Picture sequence memory test	21.9 ± 2.3	20.6 ± 2.4	17.5 ± 1.8	27.2 ± 3.2	0.238	0.529	**0.010**
List sorting working memory test	21.0 ± 1.8	17.8 ± 1.9	16.8 ± 1.7	28.1 ± 2.2	0.112	**<0.001**	**0.040**
Oral reading recognition test	19.9 ± 1.3	14.0 ± 2.1	10.4 ± 2.1	26.9 ± 2.8	0.067	0.572	**<0.001**
Trail making task (Part A)	24.0 ± 2.9	20.0 ± 2.5	16.6 ± 1.7	25.8 ± 2.0	0.405	0.441	**<0.001**
Trail making task (Part B)	17.4 ± 2.3	19.5 ± 2.8	16.9 ± 2.9	30.6 ± 1.7	**0.016**	0.153	**0.002**
Spatial Span Test	22.3 ± 1.4	16.1 ± 2.4	16.3 ± 1.9	25.8 ± 2.0	0.511	0.226	**<0.001**
Total composite CVR to cognitive stimuli	19.9 ± 1.0	16.4 ±	19.5 ± 2.8	25.9 ± 1.7	0.114	**0.026**	**< 0.001**

*Normalised, computed and standardised automatically by NIH Toolbox, based on validated measures (Slotkin *et al.*, 2012).

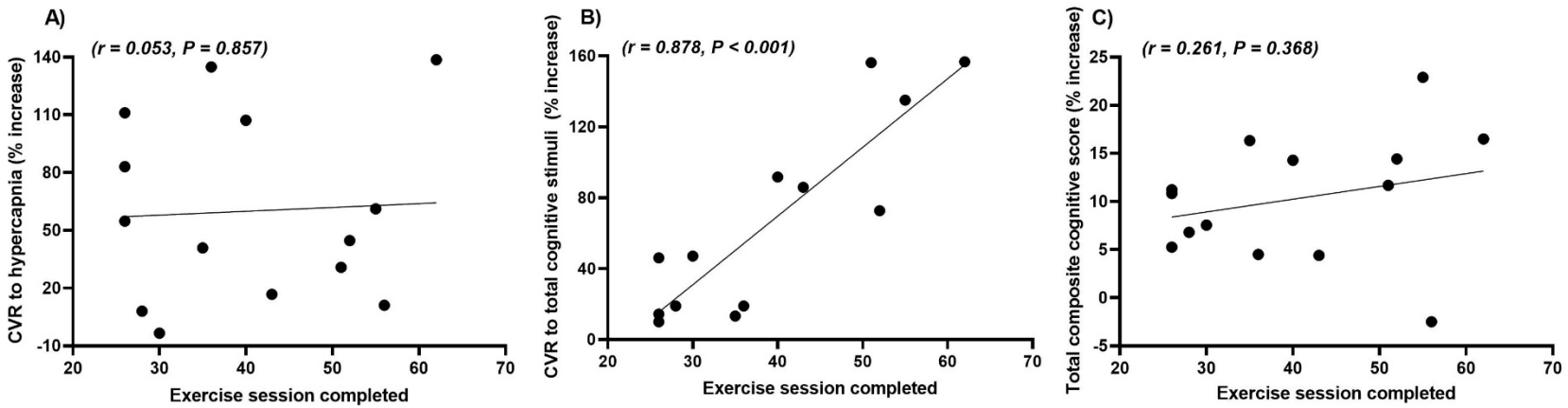

Figure 3: Correlations between the number of exercise sessions completed and the relative percentage change (% increase) in the cerebrovascular responsiveness (CVR) to hypercapnia (A), total composite CVR to cognitive stimuli (B) and total composite cognitive score (C) from week 0 to week 16 in the exercise group.

Discussion

Main findings

The aim of the study was to evaluate the effects of 16 weeks AT on cerebrovascular and cognitive function in sedentary, obese, older adults. We hypothesised that compared with control participants: 1) AT would improve both cognition and cerebrovascular function determined by the CVR to physiological and cognitive stimuli; and 2) the greater the dose of AT, the greater the improvements in cerebrovascular and cognitive function. The main findings were that AT increased the CVR to hypercapnia, CVR to cognitive stimuli and total composite cognitive score compared with the control group. A very strong relationship was observed between the number of exercise sessions completed and CVR to cognitive stimuli, but not for CVR to hypercapnia or total composite cognitive score. These results demonstrate that in sedentary, obese, older adults 16 weeks of AT can improve both improve both cognition and cerebrovascular function and there is a dose response relationship between the number of exercise sessions completed and CVR to cognitive stimuli.

Cerebrovascular responsiveness to hypercapnia

We observed an increase in the CVR to hypercapnia following AT in the exercise compared with the control group. This finding is similar to others who have also reported an increased CVR to hypercapnia in older, sedentary adults (Vicente-Campos *et al.*, 2012; Guadagni *et al.*, 2020) and stroke patients (Ivey *et al.*, 2011) following 6 months of moderate intensity AT. We also observed that the increase in CBF_V during hypercapnia was greater following the intervention in the exercise compared to the control group. Increased cerebral perfusion, whether measured directly or indirectly, following at least 12 weeks of AT is consistent with other studies that reported increases in either CBF or CBF_V in older adults who were previously sedentary (Vicente-Campos *et al.*, 2012; Chapman *et al.*, 2013; Maass *et al.*, 2014) and those with coronary artery disease who undertook 6 months of AT (Anazodo *et al.*, 2016). We found that CPI decreased in both the exercise and control groups following the intervention, but there were no differences between the groups.

A previous study reported no change in basal CPI in middle-aged to older sedentary adults who undertook a 12 week moderate intensity AT (Akazawa *et al.*, 2018). However, it was reported that these adults did have a decreased CPI following 30 min of acute exercise. The limitation of this study was that it was not a randomised control trial and only compared CPI changes between weeks 0 and 12. The decreased CPI reported following an acute bout of exercise may largely reflect post-exercise recovery, making it difficult to ascertain if an AT intervention can cause a sustained improvement of CPI in older adults (Akazawa *et al.*, 2018). The participants in that study differed from ours in that they were not obese and did not have cardiometabolic disease, thus suggesting that changes in CPI in those who are sedentary, obese and older may take longer than 12-16 weeks to elicit following an AT intervention. Further studies in this area are warranted to determine if AT can reduce arterial stiffness. In any case, our results collectively indicate that 16 weeks of AT can improve cerebrovascular function. The mechanisms for this improvement may be due to an increased ability of the microvasculature to respond to local chemical changes, modify regional blood flow in response to these changes and maintain cerebral autoregulation via improved endothelial function and its ability to synthesise nitric oxide (NO) in response to shear stress (Serrador *et al.*, 2000; Willie *et al.*, 2011; Duchemin *et al.*, 2012; Toth *et al.*, 2017). This may translate to improvements in the cerebrovasculature enabling it to respond to increased neuronal metabolism during times of increased cognitive demand.

Cognitive function and cerebrovascular responsiveness to cognitive stimuli

We observed that AT increased the total cognitive composite score and working memory capacity compared with the control group. We used the total composite score because this is a collective measurement that is more aligned with the demands of daily living. It is also an appropriate measure to use because TCD does not focus on a specific brain region mediating a particular cognitive function Rarely is only a single individual cognitive domain or subtype used in isolation and the domains are interdependent (Harvey, 2019). We noted that the values recorded at baseline, which were near 100, are considered as being average based on the normative and adjusted data described by the NIH Toolbox (Heaton *et al.*, 2014; Weintraub *et al.*, 2014).

However, we also observed an increase in individual cognitive domains, including working memory. This is consistent with previous studies that have reported an increase in individual cognitive domains following 12-24 weeks of AT in older adults who were sedentary (Lautenschlager *et al.*, 2008; Erickson *et al.*, 2011; Anderson-Hanley *et al.*, 2012; Chapman *et al.*, 2013; Guadagni *et al.*, 2020), suffered from mild cognitive impairment (Baker *et al.*, 2010), or had a diagnosis of a dementia (Hoffmann *et al.*, 2016; Sobol *et al.*, 2016). How AT improves cognitive function is not clear, with potential mechanisms being summarised in detail elsewhere (see Bliss *et al, 2021*). Briefly, those who have reported improvements in cognition have indicated that this may be associated with improved vascular function, cerebral perfusion and/or increased systemic brain-derived neurotrophic factor, which promotes synaptogenesis, neurogenesis and angiogenesis centrally (Lautenschlager *et al.*, 2008; Erickson *et al.*, 2011; Anderson-Hanley *et al.*, 2012; Chapman *et al.*, 2013; Guadagni *et al.*, 2020; Bliss *et al.*, 2021). Acute exercise increases cardiac output, which induces arterial shear stress, promoting endothelial NO synthase expression, which subsequently results in increased NO production (Toda, 2012; Rossman *et al.*, 2018). β-2 adrenoceptor activated endothelial vasodilatation, as occurs in skeletal muscle beds during aerobic exercise, may also induce increased NO production centrally. In any case, NO not only promotes vasodilatation and reduces arterial stiffness, but reduces oxidative stress and inflammation, as well as improving endothelial function and vascular health (Toda, 2012; Rossman *et al.*, 2018). Centrally, this results in improved cerebral perfusion where it also promotes the delivery of systemic molecules, such as BDNF, to the brain, where its effects can be exerted and further promote cognition (Vaynman *et al.*, 2004; Devika & Jaffar Ali, 2013; Sleiman *et al.*, 2016). Therefore, our findings and those from previous studies suggest that improvements in cognition following AT may be due to improved vascular health, which promotes improved cerebral perfusion and CVR during times of increased neuronal metabolism (i.e. improved NVC) (Guadagni *et al.*, 2020). This is supported by the increased cerebrovascular function we also observed.

We observed that following the intervention, the exercise group had a higher total composite CVR to cognitive stimuli than the control group, as well as a higher CVR to each of the individual cognitive stimuli, excluding the Picture Vocabulary Test and the Flanker Inhibitory Control and Attention Test. To our knowledge, we are the first to evaluate the effects of AT in sedentary, obese, older adults who are at risk of cognitive decline. Our findings support those of others who have measured the effects of an AT intervention on NVC and another study which measured differences in NVC between aerobic exercise trained and sedentary older adults. Ozturk et al. (Ozturk *et al.*, 2021) demonstrated that CVR to a working memory task improved following 6 months of AT in young adults with spinal-cord injuries and Fabiani *et al.* (2014) reported that older adults with greater aerobic fitness had higher NVC capacity. Both studies suggest that improvements in NVC are due to improvements in cardiovascular function, specifically endothelial function. Ozturk *et al.* (2021) suggested that those suffering from spinal cord injuries have reduced cognitive and endothelial function, which is partly demonstrated by increased arterial stiffness. In other words, a reduction in endothelial function may result from increased arterial stiffness, which reduces the capacity of the cerebrovasculature to supply oxygen and nutrient rich blood to the brain, thus resulting in reduced cognitive function. The authors also suggested that AT reduced arterial stiffness and improved endothelial function in this cohort, thus improving cognition. The characteristics of our participants with metabolic syndrome and those with spinal cord injury are very different. However, one central theme shared among those with spinal cord injuries and those with the metabolic syndrome is that they have reduced endothelial function and increased chronic low-grade systemic inflammation and, therefore, poor cardiometabolic status (Lteif *et al.*, 2005; Mohammadi *et al.*, 2015). Hence, it is clear that improved endothelial function is pivotal in improving cerebrovascular function and cognition. Further, the total composite CVR to cognitive stimuli decreased in the control group. Since this measurement describes NVC and is reflective of the relationship between the brain and its vasculature, this finding also indicates that reduced endothelial function promotes further decline in cerebrovascular and cognitive function and that improving endothelial health is pivotal to improving overall brain health (Duchemin *et al.*, 2012; Toth *et al.*, 2017).

Correlations between exercise sessions completed and cerebrovascular function and cognition

The exercise group completed 40 AT sessions on average over the 16 weeks. This equates to approximately 2.5 sessions per week or approximately 100 min of mixed intensity AT per week. This is less than that of the current physical activity guidelines described by both the Australian Department of Health and the American College of Sports Medicine (DOH, 2014; Piercy *et al.*, 2018). Only one other study has deviated from these guidelines and it was reported that 90 min of moderate intensity exercise per week for 12 weeks improved cerebral perfusion and cognition in older, apparently healthy adults (Maass *et al.*, 2014). We observed a very strong positive correlation between the number of exercise sessions completed and the total composite CVR to cognitive stimuli. This finding indicates that a dose-response relationship between these variables may exist and that NVC, a vital regulatory function in cerebrovascular function and neuronal metabolism, can be improved with less than 100 min of AT per week for 16 weeks. There were no significant correlations between the number of exercise sessions completed and the CVR to hypercapnia and total composite cognitive scores. This finding may suggest one of two things: Firstly, some exercise is better than none in improving cognition and CVR to hypercapnia, which reflects the autoregulatory function of the cerebrovasculature. Secondly, a dose-response relationship between these variables exists, but it was too low a dose to be determined in this study. In any case, further studies examining this relationship between the amount of exercise and improvements in overall brain health are warranted because it may be more attainable to promote and prescribe shorter bouts of exercise to improve exercise compliance and engagement in the community, particularly in older adults.

Methodological considerations

While we aimed to recruit an even number of men and women, it was not possible due to several confounding factors, such as geographical distance from the study location and potential participants not meeting the inclusion criteria. We acknowledge that the sex differences between the participants of this study may have cofounded our data, even though there were no significant differences between the

groups in distribution of men and women. Additionally, Figure 1 reflects the relatively low engagement of the target region (i.e. Ipswich) in health or at least health-related studies. This may have also contributed to the low uptake of the study by men. We noted that there were no significant treatment x intervention interaction effects in any of the data that was collected to define participant characteristics at baseline. This may have been influenced by the fact that the exercise group appeared marginally healthier than the control group at baseline, thus masking potential covariates that may lead to improvements in both cerebrovascular function and cognition. Additionally, the majority of exercise prescription was AT with a small component of resistance training. The resistance exercises were utilised and prescribed in a manner which predominantly focused on the recruitment of the aerobic energy system (i.e. aerobic-resistance training). In any case, we cannot exclude that resistance training may have influenced the results of this study. It must be acknowledged that another potential limitation to this study was that those in the control group may have participated in exercise sessions outside of the study or chose to make lifestyle changes, such as altering their nutritional intake. All included participants agreed at the start of the trial to continue with their current lifestyle and nutritional choices. In an attempt to encourage this, we informed all participants in the control group at Week 0 that once the study concluded that they would be provided with the entire exercise regime, including instructions on how to perform the exercises. We also made regular contact with the control group in an attempt to ensure compliance. Future studies may benefit from having a sham exercise group as a control or another arm added to the study, in which participants do not participate in exercise, rather they interact socially. The latter may be particularly important to control for given that there is evidence that socialisation and re-socialisation following isolation can improve cognitive performance and brain activity in animals (Rivera *et al.*, 2020) and older adults (Gallucci *et al.*, 2009). We did not use the gold-standard maximal oxygen uptake test to quantify aerobic exercise capacity in this study. Instead, a 6MWT was used, because it is a safe, inexpensive, tolerable and reliable measure of functional exercise capacity commonly utilised in older populations that may also increase compliance for future testing in this population (ATS, 2002; Maniscalco *et al.*, 2006; Ross *et al.*, 2010).

Conclusion

In conclusion, 16 weeks of AT increased the CVR to hypercapnia, CVR to cognitive stimuli and total composite cognitive score in sedentary, obese, older adults compared with the control group. A very strong relationship was observed between the number of exercise sessions completed and CVR to cognitive stimuli, but not for CVR to hypercapnia or total composite cognitive score. These results indicate that cognition and the responsiveness of the cerebrovasculature to physiological stimuli can be improved by as little as 100 minutes of exercise per week in previously sedentary, older, obese adults with metabolic syndrome. These individuals are at an increased risk of developing cognitive impairment and, potentially, a neurodegenerative disease such as dementia. Future studies should ascertain the minimum dose of AT needed to improve total cognitive capacity and CVR to hypercapnia in a cohort of older adults.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Author contributions

ESB, RHXW, PRCH and DEM conceptualised and designed the study protocol and experiments. ESB and DEM designed the training protocol for the study. ESB collected the data. ESB analysed the data. ESB and DEM performed statistical analysis, with all authors contributing to data interpretation. ESB, RHXW, PRCH and DEM contributed to revisions of intellectual content. All authors approved the final manuscript.

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CHAPTER 6: DISCUSSION AND SUMMARY

6.1 Discussion

My thesis aimed to investigate the effects of aerobic exercise training on cerebrovascular function and cognition in older adults. The following chapter will summarise the principal findings from each chapter, as well as the limitations and future directions of my research.

The aim of Chapter 3 was to evaluate the evidence regarding the benefits of exercise training on cerebrovascular function and cognition in ageing. This was achieved by undertaking a narrative review following a systematic search of the literature as outlined in the methods. In this study it was identified that the rate of dementia will treble in the next 30 years to over 150 million people globally, which is partially due to the fact that we are an ageing population (WHO 2018; ABS 2019; Nichols et al. 2019). Ageing is the greatest risk factor for the development of both cognitive and cerebrovascular decline, which also predisposes an individual to dementia (Nichols et al. 2019; Bliss et al. 2021). It is non-modifiable. This alone does not account for the projected increase and burden that dementia will place on the global healthcare systems and economy. Hence, it is important evaluate the current global health status and what may be contributing to the potential increase in dementia cases that are projected in the future.

Causal relationships have been identified between the development of dementia and chronic illnesses that are associated with modifiable risk factors that promote a reduction in cerebrovascular function and cognition (AIHW 2018a; Fayosse et al. 2020). These factors are largely associated with lifestyle choices or behavioural factors and are described in both Chapters 2 and 3 and are able to be quickly referenced in Table 2.2 of Chapter 2. The term cardiometabolic is appropriate to describe these risks factors, as they are essentially broken down into two categories, which are cardiovascular and metabolic risk factors. Behavioural risk factors and cardiometabolic risk factors are all interlinked because changes in one domain can influence another domain and ultimately influence or affect cardiometabolic health status (Fayosse et al. 2020). For example, choosing to lead a sedentary lifestyle

increases the risk of developing increased adiposity and reducing vascular health (Pikula et al. 2009; Toth et al. 2017; Chang, Flavahan & Flavahan 2018; Rossman et al. 2018; Bliss et al. 2021), as too does choosing to consume an energy-dense nutrient-poor diet (Bliss & Whiteside 2018).

The link between these risk factors is obviously complex. What they do have in common is that they promote endothelial dysfunction and chronic low-grade inflammation, which are probably also associated with and amplified by increased oxidative stress (Pikula et al. 2009; Toth et al. 2017; Chang, Flavahan & Flavahan 2018; Rossman et al. 2018; Bliss et al. 2021). Additionally, as highlighted in Chapter 3, ageing is strongly associated with increased oxidative stress, increased chronic low-grade inflammation and endothelial dysfunction. This essentially describes the senescent or ageing phenotype (Rossman et al. 2018). Therefore, any condition/s or behaviour/s that reduce cardiometabolic health can promote or exacerbate the senescent phenotype, thus increasing the risk of dementia development (Pikula et al. 2009; Toth et al. 2017; Chang, Flavahan & Flavahan 2018; Rossman et al. 2018; Fayosse et al. 2020; Bliss et al. 2021). The potential mechanisms that may describe this are highlighted in Chapter 3, specifically in Figures 1 and of 2 of Chapter 3.

It is important to note sections age-related cognitive decline and structural changes, ageing and cerebrovascular function and mechanistic evidence observed in animal studies of Chapter 3, as well as Figures 1 and 2, because they may provide information regarding potential future targets for treatments associated with slowing the progression of dementia and other neurodegenerative diseases. These targets may potentially improve the quality of life of those suffering from dementia or other neurodegenerative diseases. In other words, they may not be limited to how exercise can improve cerebrovascular function and cognition and potentially reduce the progression of neurodegenerative diseases, such as dementia. This highlights another potential knowledge gap in the development of age-related cognitive and cerebrovascular decline, as well as the cause of those changes that exceed the normal

rate of this decline. However, the focus of this thesis and this chapter is exercise as a potential method to improve cerebrovascular function and cognition in older adults.

As we age, exercise participation decreases, and many individuals do not meet the recommended physical activity guidelines (Taylor 2014; Bennie et al. 2016; AIHW 2018a; Piercy et al. 2018). This is concerning because, not only are we an ageing population, but because exercise maintains and/or improves our cardiorespiratory fitness, muscle endurance, mobility and cardiometabolic heath, while reducing the risk of chronic disease development, thus maintaining our quality of life and overall health and wellbeing (Paterson, Jones & Rice 2007; Taylor 2014; Lin et al. 2015; AIHW 2018a; Piercy et al. 2018; Seals, Nagy & Moreau 2019; Ashton et al. 2020). However, the evidence and impact around the effect of exercise on both cerebrovascular function and cognition and their decline, was not as well defined. There was limited literature that systematically compiled the findings of the effect of exercise on cerebrovascular function and cognition in older adults. This meant that it was difficult to ascertain the knowledge gaps in the area, what has been performed in the area and/or is it an area that is worth pursuing in order to improve or induce favourable changes in cerebrovascular function and cognition as we age. Collating the findings of these studies was important not only to highlight the work that has been done in the area, but also to start identifying how these two parameters are interrelated and may affect our quality of life. Essentially, the ability to maintain adequate vascular and cognitive functions are pivotal in contributing to our overall health and wellbeing and quality of life as we age and exercise, particularly aerobic exercise, is one of the most economic lifestyle options we can choose to participate in (AIHW 2012; Salthouse 2012; Chapman et al. 2013; Iadecola 2013; Brown, Hansnata & La 2017). My review highlighted this by indicating the following:

- Both cerebrovascular function and cognition can be improved by AT
- Resistance training (RT) can improve cognition
- Both cerebrovascular function and cognition can be improved by concurrent training (CT), particularly in those who have suffered from a condition resulting in reduced physiological function, such as a stroke.

However, my review did note the following shortcomings in the area:

- It is not known how little exercise is needed and/or what intensity of AT is required or preferable to elicit a positive response in cerebrovascular function or cognition (i.e. a dose-response relationship and intensity scale in middle-aged to older adults has not been determined)
- Little is known regarding the effect RT has on cerebrovascular function, which may be primarily due to the lack of studies performed exploring the effect of RT on both cognition and cerebrovascular function
- Very few studies have been conducted exploring the effect of CT on both cognition and cerebrovascular function
- The mechanisms associated with improvements in cognition and cerebrovascular function are poorly defined. How and why exercise may induce positive effects on cerebrovascular function and cognition has largely been attributed to the use of animal models
- There have been few studies, if any, that have correlated both cognition and cerebrovascular function, particularly when exercise is used as an intervention in older adults to improve both parameters.

Irrespective of these shortcomings, it is clear that exercise does have a positive impact on both cerebrovascular function and cognition and that more work was needed to be performed in the area.

Chapter 4 investigated the benefits of regular AT on cerebrovascular function and cognition in older adults. The primary reason behind this was that there is limited literature as to whether lifelong exercise training of any kind can maintain cerebrovascular function and cognition and potentially prevent dementia development. This was indicated and evident from Chapter 3. If there were benefits in performing lifelong exercise on brain health than it would provide a means to determine if participating in exercise later in life mirrors the benefits of lifelong exercise. It would also provide a means to determine if exercise reduces the deficit that may be caused by choosing a sedentary lifestyle and potentially having poor cardiometabolic status, which would increase the likelihood of dementia

development. The focus of this chapter and thesis was AT, mainly because of the ease in which it can be performed (e.g. walking and running) and the inexpensive nature of some AT compared with other modalities of exercise such as RT at a gymnasium (Burton et al. 2017). It is also important to note that in countries such as Australia, the rate of physical inactivity in older individuals is increasing. Currently over 69% of Australians who are 65 years or older are considered insufficiently active and only 15% of adults meet both the physical activity and muscle strengthening guidelines of ≥150 min/week of moderate-vigorous intensity aerobic exercise (AIHW 2020a). This data is not dissimilar to other studies which have noted that participation in RT is limited and that participation in AT is more common in older adults participating in physical activity (Bennie et al. 2016; Bennie et al. 2019; Bennie et al. 2020; Bennie & Tittlbach 2020; Bennie, De Cocker & Duncan 2021). RT is typically portrayed as only taking place within a gymnasium (Burton et al. 2017). This is important to note as this may be seen as a potential barrier to RT participation, because family and/or work obligations and responsibilities, cost, lack of gym facilities, confidence in usage of equipment and how to participate in RT, as well as accessibility are all barriers for participation in RT in older adults (Burton et al. 2017). Hence, given the data and the likelihood of RT participation, it was determined that AT would be the focus of the following chapters and of the thesis.

In Chapter 4 cerebrovascular function and cognition were compared between older adults who actively participate in regular AT (40 ± 4 years) and those who are sedentary. This study demonstrated differences between the two groups, whereby the trained group had higher cerebrovascular function and cognition than age and sex matched, untrained and sedentary older adults. This was evident as those who had participated in regular exercise over the course of 40 years had higher values of CVR to hypercapnia, CVR to cognitive stimuli (NVC) and total cognition than age and sex matched, untrained and sedentary older adults.

There were also two further aims in this study. One of these was to determine the association between cerebrovascular and cognitive function in these individuals. This

is because I noted in Chapter 3 that there are limited cross-sectional studies performed in this area that measured both cerebrovascular function and cognition simultaneously and that few studies, if any, had performed correlation analyses between cognition and cerebrovascular function. This study was also novel in that the data demonstrated a relationship between cerebrovascular and cognitive function in older adults exists. Specifically, it was observed that there were moderate correlations between CVR to hypercapnia and CVR to cognitive stimuli and the total composite cognitive score and that there was a strong positive correlation between the total composite CVR to cognitive stimuli and total composite cognitive score. Further, CVR to cognitive stimuli and total composite cognitive score were also strongly correlated with consistent exercise training (years). This suggests, potentially for the first time, that cerebrovascular function, specifically NVC, and total cognitive capacity are interrelated and that chronic exercise participation may modulate this response.

The final aim was to examine if cardiometabolic factors would account for the differences between the two groups. Here, I also suggested that there is an interaction between AT and cardiometabolic factors which may directly influence cerebrovascular and cognitive functions. The challenge with the final statement is whether AT is influencing cardiometabolic health which leads to improved cognition and cerebrovascular function, or whether cardiometabolic health influences AT capacity which leads to improved cognition and cerebrovascular function. The data collated suggests that AT may improve cerebrovascular function and cognition in the obese independent of any significant reduction in BMI or change in cardiometabolic health. This is because the differences between the groups were insignificant when adjusted for the covariates described in Chapter 4, thus suggesting the AT may mediate these changes in overall brain health. However, much like other areas of study, such as cardiovascular medicine, the effects of AT on the cardiovascular system and reduced disease burden are not completely due to AT alone (Mora et al. 2007; Nystoriak & Bhatnagar 2018). AT and the effect it has on major risk factors to cardiovascular diseases are thought to only account for approximately 60% of reductions in cardiovascular disease risk, while what accounts for the other 40% is

not clear or have not been readily measurable (Mora et al. 2007; Nystoriak & Bhatnagar 2018). This may also apply to brain health and the effect of long-term regular AT participation on cerebrovascular function and cognition – i.e. we know that AT is beneficial and we see changes in the major markers, as I have shown in Chapter 4, but there are still a myriad of other potential interactions that may mediate these changes. Essentially, I utilised the ANCOVA to examine the influence of these mediators (i.e. the cardiometabolic markers and educational status, as an important behavioural risk factor) on the resulting difference between the groups and demonstrated that AT status is not the only direct influence on cognitive and cerebrovascular, but rather there are many. In any case, the mainstay of this final aim was really to investigate whether exercise is a positive contributor to improving or maintaining overall brain health across the lifespan irrespective of other risk factors and whether these risk factors and AT are all interrelated when it comes to improving or maintaining overall brain health.

In summary, my hypothesis that cerebrovascular function and cognition in AT older adults would be higher than those who were untrained was supported by the data, despite the limitations that were outlined in the chapter. The study also demonstrated that AT may improve cardiometabolic risk factors that may be associated with an increased risk of developing a decline in cognition and cerebrovascular function, thus potentially predisposing an individual to the development of a neurodegenerative disease, such as dementia. It should also be noted that this was the first study that examined cognition and cerebrovascular responsiveness to both physiological and psychological stimuli in a single study in an older adult cohort who either participate in regular AT or are sedentary. It was also the first cross-sectional study that identified reduced cognitive and cerebrovascular function in older adults who fit the criteria for the metabolic syndrome.

What was evident from Chapter 4 is that those older adults recruited for the study who were sedentary were also obese. This is highlighted in Chapter 4 in detail as a limitation and the author here understands that obesity is a pathogenic condition. The

current obesity statistics and demographics of Australia and the region from which participants were recruited are described in detail in Chapter 2. Hence, it was not surprising to see that the sedentary older group of Chapter 4 displayed the characteristics described, when compared to the trained older adults, thus making this study reflective of the real-world rather than what is ideal in a research scenario, where all major baseline characteristics are completely matched. Additionally, it also highlights that these older adults in these regions are suitable targets for an interventional study that investigates the effect of AT on cerebrovascular function and cognition (i.e. Chapter 5).

Chapter 5 investigated the effects of 16 weeks AT performed for between two to four days per week on cerebrovascular and cognitive function in sedentary, obese, older adults. This was a randomised control trial and the intervention (i.e. AT) was supervised. As indicated above, Chapter 3 highlighted a current gap in the knowledge, namely it was not known how much AT or what intensity of AT is needed to elicit a positive response in cerebrovascular function or cognition. Hence, I also aimed to determine if a dose-response relationship exists between the amount of AT one participates in and changes in overall brain health. This led to the intervention design being composed of approximately 75 – 150 min of mixed intensity AT (i.e. moderate, moderate-vigorous, and vigorous intensity) per week. The Australian and American governments recommend that adults participate in at least 150 minutes of moderate intensity exercise per week (DOH 2014; Piercy et al. 2018). This is considered the minimum dosage required to reduce the risk for stroke, type 2 diabetes, obesity, certain cancers, sarcopenia, osteoporosis, osteoarthritis, respiratory disease, anxiety, depression and hypertension, atherosclerosis and other cardiovascular diseases (Greendale et al. 1995; Penninx et al. 2001; Brosse et al. 2002; Janssen, Heymsfield & Ross 2002; Thompson Paul et al. 2003; McDermott et al. 2006; Sigal et al. 2006; Nelson et al. 2007; Burtin & Hebestreit 2015; Piercy et al. 2018). Therefore, 150 min is at the lower end of the current physical activity guidelines described for adults, including older adults (i.e. the current minimum) and this is why this was chosen as the upper limit of supervised AT for this intervention. The lower limit was determined by simply reducing the 150 min by half (i.e. 4

sessions to 2 sessions collating to approximately 75 – 80 minutes per week). Additionally, given the high rates of physical inactivity in older adults residing in non-metropolitan areas of Australia, as defined in these guidelines, I wanted to ascertain if some exercise is better than none at all. While not the intention of this study, if there is benefit to simply moving and potentially improving brain health, then this is something that the public may be accepting of, thus resulting in increased AT participation and potential reductions in dementia burden. A previous systematic review noted that interventions that target sitting time and improving sedentary behaviour had favourable behavioural changes once individuals noted the potential benefits to altering this behaviour (Gardner et al. 2016). It is the author's opinion that this could apply in this area as well, particularly once more evidence is collated.

The first hypothesis of the study in Chapter 5 was that AT would improve both cognition and cerebrovascular function in this particular cohort. This hypothesis was supported by the data in that 16 weeks of AT, irrespective of duration, increased the CVR to hypercapnia, CVR to cognitive stimuli and total composite cognitive score in sedentary, obese, older adults compared with the control group. These findings are important because this population is at increased risk of developing dementia. It is also important, because these changes resulted without any changes to baseline characteristics when compared to the control group. In other words, AT improved cerebrovascular function and cognition in the obese independent of any significant reduction in BMI or other cardiometabolic risk factors. This may suggest that AT promotes favourable changes in overall brain health before changes are observed in systemic markers and that these may occur in the future / long term adaptations. In any case, it was suggested in this chapter that the changes observed in the AT group following the intervention were mostly associated with changes in improved endothelial function its ability to synthesise and release NO. This was demonstrated by the increase in CBF_V in the MCA during CVR to both physiological and cognitive stimuli, as the increased rate of CBF is reflective of the microvasculature downstream of the MCA to respond in dilate. This ability is largely attributed to NO resulting from improved endothelial function, of which TCD directly measures (Joris et al. 2018). As it has been highlighted in previous chapters of this thesis, increased

NO production promotes vasodilatation. This in turn improves the distribution of essential nutrients, oxygen, hormones and other molecules to the tissue that demands them (in this case the brain). Increased NO also increases the ability of the vasculature, particularly the microvasculature, to maintain its environment and respond to changes in its environment more readily when required, which in the case of the brain, is when neuronal metabolism increases and when carbon dioxide concentrations increase centrally. This improves the ability of the brain to acquire nutrient-rich blood and dispose of the metabolic waste it generates more effectively and efficiently than when there is decreased NO production and increased oxidative stress and inflammation in the local environment thus impeding endothelial function.

The second hypothesis for the study was that the greater the dose of AT, the greater the improvements in cerebrovascular and cognitive function. This hypothesis was partially supported because a very strong relationship was observed between the number of AT sessions completed and CVR to cognitive stimuli, but not for CVR to hypercapnia or total composite cognitive score. The lack of correlation between CVR to hypercapnia and the total composite cognitive score to the number of exercise sessions participated in was important. This is so, because it indicated that cognition and the responsiveness of the cerebrovasculature to physiological stimuli can be improved by as little as 100 minutes of AT per week in previously sedentary, older, obese adults with metabolic syndrome. However, it should be noted that we still do not know that minimum amount of AT required to elicit changes in an individual's total cognitive capacity and CVR to hypercapnia in this particular cohort of older adults. This study suggests that overall brain health can be improved in 100 minutes of AT per week.

This study is the first randomised control study using AT as an intervention that concurrently examined cognition and cerebrovascular responsiveness to both physiological and psychological stimuli, in a single study in this particular cohort. Additionally, it is potentially the first interventional study that identified improvements following an intervention in cognitive and cerebrovascular function in

older adults who fit the criteria for the metabolic syndrome. The principal message of this chapter is that a modest increase of AT can elicit overall improvements in brain health later in life despite being sedentary for a prolonged period of time. It could be said that it is never too late to start AT in order improve brain health.

6.2 Limitations

The major limitations for each chapter are outlined within them. However, it must be noted that recruitment and testing were terminated earlier than anticipated for both studies due to the impacts of COVID-19 and the restrictions placed on gathering, research and travel by the Queensland and Australian Governments. Retrospectively, Chapter 4 had approximately 56 participants enrolled to undertake testing. However, COVID-19 resulted in the cancellation of most of these appointments and testing. It was not possible to recruit these participants later during the pandemic. This significantly reduced the number of participants included in the study and it is unknown how this could or would have impacted these results. A similar effect was had on the study described in Chapter 5. My intention was to have another round of recruiting individuals into the randomised control trial. Another media release was performed, but unfortunately nearly all potential participants came from an area too far away from the USQ Ipswich campus to participate. COVID-19 would have cancelled any intervention that had started to take place and it would have been highly unlikely during the last year that a full intervention would have been able to take place until completion. Again, it is not known how this would or could have impacted the results of this thesis. However, I wish to acknowledge participant numbers, despite the power analyses performed, may be a potential significant limitation to the data collected for this thesis.

Another limitation to the study were that participants were not cognitively screened using standard tools such as the Addenbrooke's Cognitive Examination or the Montreal Cognitive Assessment Tool. This means that these studies may have participants recruited of different cognitive abilities and may have included those who were at greater risk of cognitive decline than others, thus skewing the data for

particular groups if a cognitively impaired participant was recruited into the study. This was not included in the study largely for ethical reasons and approvals, which did not permit for the inclusion of these tests due to potential distressing results for participants if they were found to below average or below the standard cut-off for further testing. However, the NIH Toolbox generated an age adjusted total composite cognitive function score was derived from the battery of tests that it is comprised of. The values generated by the NIH Toolbox identify or estimate cognitive capacity, so that if an individual was below average than this could be examined further and a decision made whether a participant could continue to participate in the study or not if they were at risk of severe cognitive decline. The results generated in this study indicated that none of the groups were below average cognitive capacity based on the interpretation data provided by the NIH Toolbox.

Finally, another major limitation in this thesis is that genetic predisposition to and epigenetic factors affecting both cognitive and cerebrovascular decline were not discussed. For example, apolipoprotein E ε4 carriers have been reported to be at greater risk of developing cognitive decline and reduced cerebrovascular function (Thambisett et al. 2010; Koizumi et al. 2018; Hays et al. 2020) . Further, studies suggest that those who are heterozygous have an increased risk of developing dementia, particularly Alzheimer's disease, by threefold, while homozygous individuals for the apolipoprotein E ε4 allele have up to a 12-fold increased risk (Thambisetty et al. 2010; Loy et al. 2014). While there are also other genes involved or that have been associated with an increased risk of cognitive decline, reduced cerebrovascular function and increased risk of developing dementia, there is limited, if any, evidence that carrying mutations or specific alleles of these genes will cause the development of reduced brain health and dementia (Ward et al. 2021). This statement excludes mutations in the three genes (i.e. Amyloid precursor protein, presenilin 1 and presenilin 2) involved in the development of young-onset Alzheimer's disease (i.e. familial Alzheimer's disease) which have all been shown to cause Alzheimer's disease (Loy et al. 2014; Ward et al. 2021). In any case, this may have implications in that those participants who were recruited to the study had lower cognitive capacity and cerebrovascular function compared to their peers due to

their genomic composition. However, it must be noted that individuals are noted routinely screened for specific mutations or alleles in general practice unless there is medical evidence to do so (Loy et al., 2014). Further, since these genes excluding the three involved in familial Alzheimer's disease, have not been shown to cause reduced brain health and dementia, then like most genes, epigenetic modification through environmental factors (e.g. exercise) and interaction with other genes, may have a significant impact on their regulation (Loy et al. 2014; Ward et al. 2021). Hence, genomic screening was not considered in this thesis for this reason, as well as the significant cost involved in screening individuals for specific alleles and mutations and simply. Future studies may wish to include screening for mutations or specific alleles such as the apolipoprotein E ε4 allele and determine the association between them, cognition, cerebrovascular function and the effect of exercise on brain health.

6.3 Future directions

It is clear from the studies conducted that AT is beneficial in both maintaining and improving cerebrovascular function and cognition in older adults who are at risk of developing a neurodegenerative condition, such as dementia. However, there are still a few questions that remained to be explored. The first of these is to explore whether RT has an effect on improving both cerebrovascular function and cognition in older adults. It is evident from Chapter 2, that there is very little known regarding the effect RT has on cerebrovascular function. There are few studies which have explored the effect of RT on cognition. Three studies have used RT as an intervention in older adults who were either sedentary or suffered from subjective memory complaints and reported that RT elicited positive improvements in cognitive performance (Cassilhas et al. 2007; Alexandre Leopold et al. 2008; Fiatarone Singh et al. 2014). Only one study has examined the effects of RT on cerebrovascular function and noted that cerebral perfusion was greater in older females who participated in RT compared with AT or flexibility training (Xu et al. 2014). However, no research has collectively measured the effect of RT on both cerebrovascular function and cognition. A design similar to the studies performed in this thesis could be utilised to determine whether RT improves or maintains

cerebrovascular function and cognition in older adults (i.e. both cross-sectional and randomised controlled trials). If the results were favourable in this instance, the next step would be to design a randomised controlled trial that combines both AT and RT as single intervention (i.e. multimodal exercise training) and determine the effect that this would have on both cerebrovascular function and cognition in older adults. How RT could improve both cerebrovascular function and cognition would also be of interest and novel. It is thought that RT may improve these parameters through the increased expression of neurogenic growth factors following, such as brain-derived neurotrophic factor, insulin-like growth factor 1 and vascular endothelial growth factor (Bliss et al. 2021). As summarised toward the end of Chapter 3, these have been associated with increased neuroplasticity, neurogenesis, neural repair, synaptogenesis and angiogenesis, as well as amyloid-β removal in animal studies (Bliss et al. 2021).

Chapter 5 also aimed to determine if a dose-response exists between the amount of exercise performed and improvements observed in cerebrovascular function and cognition. It was noted that there was a relationship between CVR to cognitive stimuli (a surrogate measure of NVC) and the extent of participation in exercise sessions. However, no significant correlations were observed between the number of exercise sessions completed and the CVR to hypercapnia and total composite cognitive scores. This could suggest one of two things, with one of those being that a dose-response relationship between these variables exists, but it was too low a dose to be determined. This is interesting because this means that it is still largely unknown how much AT is required to improve brain health. Based on the findings of this thesis and particularly the lack of correlation between exercise quantity and both CVR to hypercapnia and cognition, it would appear that health practitioners may be able to prescribe as little 100 minutes of moderate and moderate-to-vigorous intensity exercise in older adults suffering from metabolic syndrome in an attempt to prevent further decline in brain health. However, given that a dose-response relationship was seen with NVC and the amount of exercise performed, it could be recommended that up to 150 minutes of moderate and moderate-to-vigorous intensity exercise to ensure brain health improves or does not decline through older

age. It also indicates that more work is required to ascertain if a dose-response relationship exists. Future studies may wish to conduct even lower volumes of exercise to determine if one does exist or provide evidence that, potentially, cerebrovascular function and cognition can be improved with smaller doses of exercise. Future studies may require multiple arms, starting from a remedial amount of AT, whereby sitting time is replaced with AT in small bouts on multiple occasions or include restrictions on the number of sessions that can be attended by individuals weekly. For example, an exercise session may last for 30 min and participants can be allocated to different groups which either participate in 1, 2 or 3 sessions per week.

The findings from Chapter 5 may also indicate that some exercise is better than none in improving cognition and cerebrovascular function. Whether a dose-response relationship exists at lower levels of exercise may be important to note and have public health implications for older adults who are sedentary. It may also assist in improving care and quality of life for those that are institutionalised. Hence, further studies that aim to examine the relationship between the amount of exercise and improvements in overall brain health may be welcomed. This is because it may be more attainable to promote and prescribe shorter bouts of exercise to improve exercise compliance and engagement in the community, particularly in older adults. Additionally, the inverse needs to be considered. It has been reported that exercise, if performed chronically at high levels of exertion than the risk of infection, particularly upper respiratory tract infections, increases significantly (Nieman & Wentz 2019). We currently do not have enough evidence to determine if this is also the case with excessive exercise and cerebrovascular function and cognition. Large cross-sectional studies may provide initial insights into this question, as too would randomised controlled trials with exercise prescribed at higher doses. However, the predominant issue with the latter is participant compliance.

The participants recruited in both Chapters 4 and 5 were older adults who met the criteria of the metabolic syndrome, which is a constellation of risk factors with obesity being central to its development. This is the first time that the effect of

exercise on brain health has been reported in the literature in older adults meeting the criteria for metabolic syndrome. There are clear differences between these older adults and those who exercise and do not meet the criteria of metabolic syndrome as shown in Chapter 4. It was also shown that improvements in these adults following exercise in the older can improve these parameters. This is important because metabolic syndrome ultimately describes cardiometabolic disease and is largely a result of making inappropriate lifestyle choices (e.g. poor nutritional choices and being physically inactive). This thesis demonstrates that altering at least one aspect of lifestyle can have a significant impact on brain health in this cohort. Hence, future studies may explore the impact of exercise, particularly aerobic exercise, on brain health in older adults with metabolic syndrome. Finally, there has been no study to date which identifies whether those who fit the metabolic syndrome have reduced cognition and cerebrovascular function in comparison to a healthy population until now. Hence, future studies that explore the impact that metabolic syndrome has on brain health throughout the lifespan are warranted, particularly since the rate of obesity is increasing and that the rate of metabolic syndrome is undoubtedly underreported.

Finally, the results of this thesis raise an important question – is it too late to start exercising to improve cerebrovascular function and cognition? The results in Chapter 4 highlight that those who participated in regular AT across the lifespan had higher cerebrovascular and cognitive function than those who were sedentary. However, when sedentary older adults underwent 16 weeks of AT, improvements in their cognitive capacity and cerebrovascular function were evident. A recent study investigated the benefits of lifetime physical activity on cardiovascular-related and cancer-related mortality (Saint-Maurice et al. 2019). It was reported that those who performed exercise across the lifespan or commenced exercising during mid-life (40-61 years of age) had a lower risk of cardiovascular-related and cancer-related mortality than those who did not exercise or started and stopped participating in exercise. This result suggested it may not be too late to start exercising to reduce the risk of cardiovascular-related and cancer-related mortality. However, it is currently not known if exercising in later life can reduce the risk of cerebrovascular dysfunction and cognition decline and lower the risk of dementia-related mortality.

Future studies may wish to conduct a large-scale prospective cohort study in order to answer this novel question.

6.4 Summary

Chapters 2 and 3 identify ageing as the greatest factor in developing cerebrovascular and cognitive decline. However, it was highlighted that modifiable risks factors also reduce cardiometabolic health and exacerbate this age-related decline, thus predisposing an individual to a neurodegenerative disease, such as dementia. Chapter 3 summarised the current evidence associated with the benefit exercise training has on cerebrovascular function and cognition. Exercise training induces improves or maintains cerebrovascular and cognitive function in older adults. Chapter 4 specifically indicates that those older adults who participated in regular AT throughout the lifespan had higher cerebrovascular functional and total cognitive capacity than those who were sedentary, of the same age and sex, and met the criteria of the metabolic syndrome. Chapter 4 also determined that both cerebrovascular function and cognition are significantly lower in individuals with the metabolic syndrome than those who did not. This highlighted the important interaction between cardiometabolic health, training status and overall brain health. Finally, Chapter 5 demonstrated that cerebrovascular function and cognition could be improved in sedentary, obese, older adults who met the criteria for the metabolic syndrome following 16 weeks of AT performed for an average for 100 min per week. Hence, this thesis concludes that AT has a positive effect on overall brain health by improving both cerebrovascular function and cognition in older adults.

CHAPTER 7: REFERENCES

Note that the references presented here are for Chapters 2 and 6 only. The references used for Chapters 3, 4 and 5 are included in the references sections of the papers The references for these chapters follow the formatting guidelines requested by each of the journals in which they have been submitted to or accepted.

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