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Association Between Lifetime Physical Activity and Cognitive Functioning in Middle-aged and Older Community Dwelling Adults: Results from the Brain in Motion Study

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Association Between Lifetime Physical Activity and Cognitive Functioning in Middle-aged and Older Community Dwelling Adults: Results from the *Brain in Motion* Study

by

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A THESIS

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Abstract

Objective: Is total lifetime physical activity (PA) associated with better cognitive functioning with aging and does cerebrovascular function mediates this association?

Methods: 226 community dwelling middle-aged and older adults completed the Lifetime Total PA Questionnaire, underwent neuropsychological and cerebrovascular blood flow testing. Multiple robust linear regressions were used to model the associations between lifetime PA and global cognition. Mediation analysis was used to assess the effect of cerebrovascular measures on the association between lifetime PA and global cognition.

Results: Better cognitive performance was associated with higher lifetime PA ($p=0.045$), recreational PA ($p=0.018$), vigorous intensity PA ($p=0.004$), PA between the ages of 0-20 years ($p=0.028$), and the ages of 21-35 years ($p<0.0001$). Cerebrovascular measures partially mediated the relation between current fitness and cognition.

Conclusion: This study revealed significant associations between higher levels of lifetime PA and better cognitive function. Cerebrovascular function partially mediated the relation between current fitness and global cognition.

Preface

This thesis includes a manuscript presented in Chapter three. This manuscript has been accepted for publication in the Journal of International Neuropsychological Society special edition Physical Activity and Brain Plasticity. The first author on this manuscript was responsible for data analyses, interpreting the results and the writing of the manuscript, with support from the senior author and co-authors. All authors participated in the review of the manuscript.

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Dedication

I would like to dedicate this thesis to my late Father Glenn Bennett, Mother Sandy Jensen, loving supporter Kyle Garrett and the rest of my family who have supported me along the way, without you this would not have been possible and I am eternally grateful for every single one of you.

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List of Symbols, Abbreviations and Nomenclature

Symbol	Definition
↑	Increase
↓	Decrease
↔	No Change
>	Greater than
<	Less than
≥	Equal to or greater than
≤	Equal to or less than
±	Plus or Minus
~	Approximately
Δ	Change
^{15}O	Oxygen-15
ACA	Anterior Cerebral Artery
ACT	Auditory Consonant Trigrams
AD	Alzheimer's Disease
ADL	Activities of Daily Living
ANOVA	Analysis of Variance
AOR	Adjusted Odds Ratio
APOE	Apolipoprotein E
BDNF	Brain-derived Neurotropic Factor
BIM	Brain in Motion
BORG	Scale of Perceived Exertion
BMI	Body Mass Index
BP	Blood Pressure
CAIDE	Cardiovascular Risk Factors, Aging and Dementia
CANTAB	Cambridge Neuropsychological Test Automated Battery
CBF	Cerebral Blood Flow
CBFv	Cerebral Blood Flow Velocity
CBV	Cerebral Blood Volume
CERAD	Consortium to Establish a Registry for AD
CHREB	Conjoint Health Research Ethics Board
CI	Confidence Interval
CIND	Cognitive Impairment No Dementia
cIMT	Carotid Intima-Media Thickness
cfPWV	Carotid-femoral Pulse Wave Velocity
$CMRO_2$	Cerebral Metabolic Rate of Oxygen
CO_2	Carbon Dioxide
COX	Cyclooxygenase
CSHA	Canadian Study of Health and Aging
CVC	Cerebrovascular Conductance
CVCiso	Cerebrovascular Conductance during Isocapnia
CVCrest	Cerebrovascular Conductance at Rest

CVCi	Cerebrovascular Conductance Index
CVLT	California modified Verbal Learning Test
CVMR	Cerebral Vasomotor Reactivity
CVR	Cerebrovascular Reactivity/Resistance
CVR_{C02}	Cerebrovascular Resistance to Carbon Dioxide
CVRi	Cerebrovascular Resistance Index
D-KEFS	Delis-Kaplan Executive Function System
DHQI	Diet History Questionnaire I
DSM-III R	Diagnostic and Statistical Manual of Mental Disorders Third Edition Revised
Dx	Disease
EBMT	East Boston Memory Test
EDV	End Diastolic Volume
$ETCO_2$	End-Tidal CO_2
fMRI	Functional Magnetic Resonance Imaging
FINE	Finland, Italy, and the Netherlands Elderly
HAC	Health Aging Educational Control
HARMONY	Hypertension Analysis of Stress Reduction Using Mindfulness Meditation and Yoga
HDL	High-density Lipoprotein
HR	Heart Rate
HR	Hazard Ratio
HRR	Heart Rate Reserve
ICA	Internal Carotid Artery
IGF-1	Insulin-like Growth Factor 1
Kcal	Kilocalories
kPa	Kilo Pascal
LDL	Low Density Lipoprotein
LTPAQ	Lifetime Physical Activity Questionnaire
MA	Masters Athletes
MAP	Mean Arterial Pressure
MAPiso	Mean Arterial Pressure during Isocapnia
MAPrest	Mean Arterial Pressure at Rest
MCA	Middle Cerebral Artery
MCAv	Middle Cerebral Artery Velocity
MeSH	Medical Subject Heading
MET(s)	Metabolic Equivalent
mmHg	Millimeter of Mercury
MMSE	Mini-Mental State Exam
mMMSE	Modified Mini-Mental State Exam
MoCA	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
N	Sample Size
NAART	North American Adult Reading Test
NINCDS-ADRDA	National Institute of Neurological Disorders and Stroke – Alzheimer's Disease and Related Disorders Association

O_2	Oxygen
O_2Hb	Oxygen Saturation of Hemoglobin
OER	Oxygen Extraction Ratio
OR	Odds Ratio
p	p-value
PA	Physical Activity
$PaCO_2$	Partial Pressure of Arterial CO_2
PaO_2	Partial Pressure of Arterial O_2
PCA	Posterior Cerebral Artery
PET_{CO2}	Pressure of End Tidal CO_2
PET_{O2}	Pressure of End Tidal O_2
POMS	Profile of Mood State
PSV	Peak Systolic Velocity
Pt	Participant
r	Correlation rho
RCT	Randomized Control Trial
ROI	Region of Interest
RPE	Rating of Perceived Exertion
RR	Risk Ratio
SD	Standard Deviation
SE	Standard Error
SES	Socio-Economic Status
SQL	Structured Query Language
TCD	Transcranial Doppler
TICS	Telephone Interview for Cognitive Status
USMA	United States Masters Athletes-Sanctioned Events
VEGF	Vascular Endothelial Growth Factor
$\dot{V}O_2max$	Maximal oxygen uptake
$\bar{V}_P$	Peak velocity of blood moving through the MCA
WHICAP	Washington Heights-Inwood Columbia Aging Project
WHO	World Health Organization
WMS-R/LM-R	Logical Memory Subtest of the Wechsler Memory Scale-Revised

Chapter One: **INTRODUCTION**

1.1 Introduction

The natural aging process results in structural and functional changes to the cerebrovascular system, contributing to neurophysiological and psychological changes in old age (Davenport, Hogan, Eskes, Longman, & Poulin, 2012; Matteis, Troisi, Monaldo, Caltagirone, & Silvestrini, 1998). These changes include: a decline in cognitive functioning, reductions in cerebral blood flow (CBF) (Zimmerman et al., 2014) and cerebrovascular reactivity (Barnes, Taylor, Kluck, Johnson, & Joyner, 2013), which are associated with an increased risk of stroke (Gupta et al., 2012), Alzheimer Disease (AD) and related dementias (Amieva et al., 2005; Lautenschlager, Cox, & Cyarto, 2012), and premature mortality (Portegies, de Bruijn, Hofman, Koudstaal, & Ikram, 2014; Sabayan et al., 2013). With the rapidly ageing population, identifying modifiable lifestyle factors and effective prevention strategies for declining cognition and cerebrovascular health (i.e. CBF and cerebrovascular reactivity) has been an increasingly important area of research. One modifiable lifestyle factor of interest is physical activity (PA), defined as “any body movement that is produced by the contraction of skeletal muscles and the increase in energy expenditure”, and includes exercise and non-exercise activities (Caspersen, Powell, & Christenson, 1985). Physical activity has been associated with attenuated age-associated cognitive decline in older adults (Abbott et al., 2004; Buchman et al., 2012; Laurin, Verreault, Lindsay, MacPherson, & Rockwood, 2001b; Suvi Rovio et al., 2005; Scarmeas, Luchsinger, Schupf, & et al., 2009; Tarumi et al., 2013) as well as improved CBF and cerebrovascular reactivity (Ainslie et al., 2008; Bailey et al., 2013; Brown et al., 2010; Chapman et al., 2013; Tarumi et al., 2013).

Emerging research reveals that the incidence of cognitive decline (Yaffe et al., 2014) and changes in cerebrovascular functioning (Tarumi et al., 2013) start to occur in midlife rather than exclusively in old age (K. Yaffe, D. Barnes, M. Nevitt, L. Lui, & K. Covinsky, 2001a). Therefore, if changes in cognition and cerebrovascular functions are occurring earlier in life, it may be beneficial to assess the role of PA throughout lifetime, rather than exclusively in older age. To date, no study has examined the association between total lifetime PA and cognitive decline in an older adult population using a retrospective measurement of lifetime PA. Only one study has examined the association between self-reported recreational aerobic PA over lifetime (confirmed by a maximal aerobic fitness test) and CBF and cerebrovascular reactivity to hypercapnia demonstrating the importance of being physically active throughout life for improved CBF (Bailey et al., 2013).

Given the paucity of information regarding the effects of lifetime PA on cognitive and cerebrovascular outcomes in older adulthood, this study will address this knowledge gap by examining how the type, intensity and timing of PA done during life influences cognitive functioning in middle aged and older adults. More precise data defining the level of activity required for reduced cognitive decline with aging is necessary when creating PA public health recommendations. Moreover, this study is designed to assess if measures of cerebrovascular health mediate the relation between lifetime PA and cognitive functioning.

1.2 Statement of Aims and Hypotheses

This project aims to examine measures of lifetime PA in older adults and determine their relation to cognitive function.

General hypothesis: Higher levels of lifetime PA will be predictive of better cognitive abilities in this cohort of older adults.

Aim 1. To examine how the type, dose and timing of lifetime PA is related to an overall measure of global cognition and specific sub-domains of cognition including executive function, processing speed, figural memory and verbal memory.

Hypothesis 1. Being more physically active throughout life will result in a higher global cognition scores and higher scores in the cognitive sub-domain. Specifically, individuals who have been consistently physically active throughout their lifespan will perform better on cognitive tests done in later life.

Aim 2. To examine how the type, dose and timing of lifetime PA are related to cerebrovascular function (i.e. resting cerebral blood flood of the middle cerebral artery and cerebrovascular conductance responses to hypercapnia) by determining if cerebrovascular function mediates the relation between lifetime PA and cognitive functioning.

Hypothesis 2. Cerebrovascular functioning will mediate the relationship between lifetime PA and cognitive functioning. The benefits of increased lifetime PA should correlate with higher resting middle cerebral artery blood flow velocity and better cerebral hemodynamic responses (i.e., lower mean arterial blood pressure, higher cerebrovascular conductance) to euoxic hypercapnia. Additionally, higher resting CBF

velocity and increased cerebral hemodynamic responses should also be correlated with better performance on cognitive testing, fulfilling the assumptions of mediation analysis.

1.3 Review of Literature

1.3.1 Literature Search

The literature review was conducted using the online medical journal databases PubMed and MEDLINE. The search included keywords and medical subject heading (MeSH) terms (exploded) as follows: lifetime physical activity, physical activity, motor activity, exercise, cycling, swimming, gym, walk, treadmill, dance, yoga, tai chi, dementia, alzheimer, cognition, cognitive decline, cognitive deficit, cognitive aging, cerebrovascular blood flow, cerebrovascular reactivity, cerebrovascular circulation/physiology, aged, older adults, middle aged and included publications up until June 1, 2015. These searches were conducted using Boolean operating terms and no date, language, or geographical restrictions applied. The relevant literature and cited works have been reviewed and included where important.

1.3.2 Physical Activity and Cognitive Function in Older Adults

According to estimates made by World Health Organization (WHO), the incidence of dementia and AD is increasing with no foreseeable cure (Ballard et al., 2011; Kukull, 2006). This increase is attributable, in part, to the ageing population but may also be related to a decreases in healthy lifestyle behaviours that lead to an increased risk of these chronic and ultimately fatal diseases. In the older adult population adequate brain blood flow and cognitive functioning are predictive measures of dementia and AD (Naqvi, Liberman, Rosenberg, Alston, & Straus, 2013; Nation et al., 2013; Panza et al., 2005). Dementia is characterized as a clinical syndrome, caused by neurodegeneration (Prince et al., 2013) and is considered a loss of major brain function in more than two areas of cognition (Association, 2013). The main identifying characteristics of dementia include progressive cognitive impairment and inability for

independent living (Prince et al., 2013). Age-associated cognitive decline can be considered a precursor to the development of dementias, including AD (Amieva et al., 2005; Naqvi et al., 2013). There is minimal evidence for beneficial pharmaceutical interventions that can prevent or slow the progression of cognitive decline in the older adult population (Naqvi et al., 2013), thus emphasizing the need to focus on areas of lifestyle that can be improved. It has been found that inter-individual differences in genetic profiles account for ~30% of the natural ageing process while the other ~70% is attributed to individual lifestyle choices (Zhao, Tranovich, & Wright, 2014), emphasizing the importance of investigating and understanding preventive lifestyle factors such as PA.

Physical activity and exercise are essential components of an individual's physiological health and physical functioning (Kirk-Sanchez & McGough, 2014). Physical activity includes exercise and non-exercise activities, whereas exercise is "a subset of PA that is planned, structured, and repetitive and has a final or an intermediate objective of the improvement or maintenance" of one's health (Caspersen et al., 1985). With ageing there are deteriorations in physiological health, physical functioning, brain health and cognitive performance and PA is a modifiable lifestyle factor that has the potential to counteract some of these ageing processes (Kirk-Sanchez & McGough, 2014).

Physical activity is often categorized by the intensity at which the activity is performed using metabolic equivalents of the task (Voss, Carr, Clark, & Weng, 2014). These metabolic equivalents (METs) are based on pre-determined estimates of energy costs for a given activity based on physiological measures, therefore replacing the need to use invasive measurements (Voss et al., 2014); for example, one MET is equivalent to the amount of oxygen that is metabolized while at rest in a seated position, and is assumed to approximate 3.5 mL/kg/min of

oxygen consumption ($\dot{V}O_2$; normalized to body mass) (Jette, Sidney, & Blumchen, 1990). Previous studies assessing PA in older populations have assessed different aspects of PA and fitness using methods such as self-reported PA questionnaires of activity over the past week, month or year (capturing variations of the type, frequency, duration and intensity of activity), cardiopulmonary fitness testing (assessing maximal oxygen consumption ($\dot{V}O_2max$)), and active energy expenditure (Brown, Peiffer, & Martins, 2013). Despite possible limitations in the assessment of PA for an older population, such as inaccurate reporting on questionnaires and inability to perform $\dot{V}O_2max$ testing or reach their true $\dot{V}O_2max$, findings still suggest an inverse relation between PA or exercise done in old age and cognitive decline (Brown et al., 2010; Brown et al., 2013; Colcombe et al., 2004; Forbes, Thiessen, Blake, Forbes, & Forbes, 2013; Kramer et al., 1999; Prakash, Voss, Erickson, & Kramer, 2015).

Studies using questionnaires to measure and quantify PA have indicated that higher levels of self-reported PA are associated with a smaller risk of cognitive decline and dementia later in life, after controlling for confounding effects (de Bruijn et al., 2013; Kramer & Erickson, 2007). There is substantial evidence using self-reported measures of PA suggesting that as the duration of activity per week increases, the odds of declining cognitive functioning decrease in elderly populations (over the age of 55 years) (Abbott et al., 2004; Brown et al., 2013; S. Rovio et al., 2005; van Gelder et al., 2004; Weuve et al., 2004; K. Yaffe, D. Barnes, M. Nevitt, L. Y. Lui, & K. Covinsky, 2001b). For example, Yaffe et al. (2001a) used a measure of walking for exercise purposes as a determinant of recreational activity in females ≥ 65 years and found that women who walked more were least likely to develop cognitive decline. Suvi Rovio et al. (2005) demonstrated that self-reported leisure-time PA in midlife (age 44 to 57) is associated with a decreased risk of dementia and AD in late life. Data collected from The Rotterdam Study using

PA questionnaires to determine a combined measure of MET-hours per week spent in recreational and household activities in the previous two weeks, demonstrated increasing MET-hours per week was associated with a decreased risk of dementia (de Bruijn et al., 2013). Increased MET-hours per week of leisure time activity over the past year also resulted in an increase in mean cognitive scores (Weuve et al., 2004). Further, it has been suggested that individuals ≥ 65 years who exercise three or more times per week will maintain or improve their current level of cognitive function, or in some cases improve (Middleton, Mitnitski, Fallah, Kirkland, & Rockwood, 2008). Overall, the literature strongly suggests that increased levels or duration of PA improves cognitive performance in old age, decreases the risk for cognitive decline (Brown et al., 2013; Buchman et al., 2012; Laurin et al., 2001b; Middleton et al., 2008; van Gelder et al., 2004) and decreases the risk of developing dementia and AD in elderly populations (Abbott et al., 2004; Buchman et al., 2012; de Bruijn et al., 2013; Laurin et al., 2001b; Scarmeas, Luchsinger, Schupf, & et al., 2009).

A previous systematic review indicated that all levels of activity are protective against cognitive decline; however, these assessments generally focused on the volume and frequency of activity and less often differentiated low, moderate and vigorous intensity levels, hence a need exists for more studies assessing intensity of activity (Sofi et al., 2011). Recent research from the Finnish Twin Cohort study assessed the intensity of PA using a MET index based on structured questions on leisure and transportation PA, at two time points six years apart in individuals aged 24 to 60 years (Iso-Markku, Waller, Kujala, & Kaprio, 2015). This study discovered that individuals who engaged in more strenuous activity at both time points (considered to be persistently engaging in vigorous activity in midlife) had a decreased risk of mortality from dementia, support for which was provided by pair-wise analysis where active twins were

compared to their inactive counterpart (Iso-Markku et al., 2015). More studies involving an in-depth assessment of intensity levels of PA and the impact each level of intensity has on reducing the risk of cognitive decline is warranted.

The use of cardiopulmonary fitness testing has also provided strong evidence indicating lower $\dot{V}O_2$max is associated with lower levels of cognitive functioning (Brown et al., 2010; Colcombe et al., 2004; Kramer et al., 1999; Netz, Dwolatzky, Zinker, Argov, & Agmon, 2011; Prakash et al., 2015; Wendell et al., 2014). Evidence suggests that poorer performance on $\dot{V}O_2$max fitness testing at baseline is related to declines in cognitive functioning six years later (Barnes, Yaffe, Satariano, & Tager, 2003). Further, individuals with the lowest cardio-respiratory fitness had the poorest performance on all cognitive domains at baseline, and after a six year follow-up this group also had the greatest score decline for the cognitive testing. Finally, the longitudinal research of Wendell et al. (2014) proposes the importance of early interventions on improving cardiorespiratory fitness, to improve cognitive functioning later in life. Evidence using physiological measures of fitness is important for reinforcing the relationships that are observed using self-report measures of PA.

A recent (2014) systematic review and meta-analysis of longitudinal studies examining the effects of PA in preventing cognitive decline and dementia included twenty-one cohorts on PA and cognitive decline, and twenty-six cohorts on PA and dementia (Blondell, Hammersley-Mather, & Veerman, 2014). The main findings were that participants with higher levels of PA, compared to those with lower levels of PA, are at a reduced risk of cognitive decline, RR=0.65, 95%CI= 0.55-0.76 and of dementia, RR=0.86, 95%CI=0.76-0.97 (Blondell et al., 2014). Another recent (2014) systematic review looking at PA and cognitive function in individuals over 60 years of age found that almost all studies included (26/27 studies), reported a significant relation

between PA later in life and cognitive function (Carvalho, Rea, Parimon, & Cusack, 2014). This review looked at multiple measures of PA including self-report questionnaires, accelerometers/actigraphs, physical functioning tests, and cardiovascular fitness assessments. The benefits of PA that were identified include both maintaining and improving current cognitive functioning as well as preventing cognitive decline or delaying the transition to AD or dementia (Carvalho et al., 2014).

A number of studies have assessed PA in midlife (midlife considered 40-60 years old) with a follow-up assessment of cognition or dementia in later life; these studies have revealed an association between activity done in midlife and reduced incidence of dementia (Andel et al., 2008; Chang et al., 2010; Kareholt, Lennartsson, Gatz, & Parker, 2011; S. Rovio et al., 2005; Sun et al., 2010; Tolppanen et al., 2014). In contrast, research by Middleton, Barnes, Lui, and Yaffe (2010) assessing self-reported PA in females during teenage years, age 30, age 50 and later life, found the strongest relationship between PA during teenage years and a decreased chance of cognitive impairment in later life. This contrasting evidence suggests that perhaps the benefits of early life PA are also important, if these assessments are obtained. Therefore more studies are needed that use reliable methods to obtain measures of PA in early life, prior to a midlife assessment.

Previous studies have explored the relation between PA or exercise and brain health differences between sexes, with increasing evidence suggesting males and females have different physiological responses to PA (Brown et al., 2013; Colcombe & Kramer, 2003; Ho, Woo, Sham, Chan, & Yu, 2001; Laurin, Verreault, Lindsay, MacPherson, & Rockwood, 2001a). For example, physiological responses associated with exercise, such as enhanced oxygen delivery to the brain needed to maintain cerebrovascular integrity appear to be sex-dependent, and these differences

may be relevant for the cognitive response to PA (Schuit, Feskens, Launer, & Kromhout, 2001). From a variety of mixed sex studies, it has been found that exercise positively impacts both sexes; however, the effects of increased exercise on cognitive functioning seem to be more pronounced in women (Ho et al., 2001; Laurin et al., 2001a), specifically in post-menopausal women (Matteis et al., 1998). Proposed reasons for these sex differences include demographics, variation in cognitive strengths for men and women as a result of differences in sex hormones (Kimura, 2002; Kimura & Hampson, 1994; Kramer & Erickson, 2007) and subsequently the different changes of sex hormones in older age (Brown et al., 2013; Matteis et al., 1998). It has been suggested that sex hormones (testosterone and estrogen) have neuro-protective properties (Brown et al., 2013). As females experience a significant drop in sex hormones during menopause relative to men (who experience a slower decline in andropause (Brown et al., 2013), it has been hypothesized that women may start exercise programs with lower levels of sex hormones and therefore may see more benefit; however the exact mechanism remains unknown (Brown et al., 2013).

To conclude, remaining physically active appears to result in many favourable physiological adaptations. In addition to the effects of PA on cognitive ability, of special interest is the alteration in cerebrovascular functioning, including CBF and cerebrovascular reactivity as these changes may mediate the relation between PA and cognition in older adults (Brown et al., 2010) with evidence supporting mediation of the relationship between PA and cognitive inhibitory control through CBF regulation in healthy young adults (Guiney, Lucas, Cotter, & Machado, 2015).

1.3.3 Physical Activity and Cerebrovascular Functioning in Older Adults

Cerebrovascular health and functioning is determined by a number of measures, including CBF and cerebrovascular reactivity. Reduced cerebrovascular regulation has been proposed as a mechanism contributing to cognitive and cerebrovascular dysfunction (Davenport et al., 2012) and established as a precursor associated with AD and dementia (Nation et al., 2013). To study cerebrovascular functioning, physiological measures of cerebrovascular reactivity to hypercapnia are often used (Oudegeest-Sander et al., 2014). Specifically, changes in partial pressure of arterial CO_2 ($PaCO_2$) induce a change in CBF and the index of the change in CBF to the change in $PaCO_2$ is described as cerebrovascular reactivity. Studying cerebrovascular reactivity may provide crucial insights into vascular hemodynamic properties and vascular endothelial functioning in the brain that maintain cardiovascular homeostasis by contributing to vasoconstriction and vasodilation (Oudegeest-Sander et al., 2014).

A decrease in resting CBF has been identified with increasing age (Lipsitz, Mukai, Hamner, Gagnon, & Babikian, 2000; Oudegeest-Sander et al., 2014; Zhu et al., 2013). It has been hypothesized that this decrease is attributed to a decline in cerebral metabolic rate or, alternatively, to increasing cerebrovascular abnormalities (Leenders et al., 1990). A normal ageing process has an estimated decrease of CBF by 25-30% between the ages of 20 and 80 (Ainslie et al., 2008; Demirkaya, Uluc, Bek, & Vural, 2008) or a decrease of approximately 5% every 10 years (Grolimund & Seiler, 1988).Cerebrovascular reactivity to hypercapnia has been found to decline significantly up to the age of 90 years old (Bakker et al., 2004), with recent findings linking low cerebrovascular reactivity to hypercapnia with a higher risk of death (Portegies et al., 2014). A cross-sectional study indicated that older adults (>60 years) had a significantly lower cerebrovascular reactivity to hypercapnia as compared with younger adults

(<30 years old) (Bailey et al., 2013). Research comparing CBF between young (<35 years) and old (>55 years) individuals provided evidence that CBF was higher in the younger age group (Ainslie et al., 2008; Bailey et al., 2013; Barnes et al., 2013; Zhu et al., 2013). When comparing young and old participants with trained and untrained groups for each age category, CBF was still higher in the young age category regardless of training status (Bailey et al., 2013).

With strong evidence suggesting that CBF and cognitive functioning decrease with advancing age, various studies have focused on the extent to which changes in CBF explain, at least in part, the declines in cognition (Brown et al., 2010; Chapman et al., 2013; Tarumi et al., 2013). Cross-sectional studies of PA and CBF have found that trained individuals (habitual aerobic-endurance exercisers) have increased CBF compared to their inactive (no regular PA) counterparts, providing evidence that habitual PA may improve cerebral hemodynamics in the elderly population (Ainslie et al., 2008; Bailey et al., 2013). Further, assessing fitness levels using a measurement of $\dot{V}O_2$max found fitness levels positively correlated with cerebrovascular conductance (Bailey et al., 2013; Brown et al., 2010). Research from a randomized controlled trial (RCT) revealed an increased resting CBF following 12-weeks of aerobic training (i.e., three 60-min sessions per week at 50-75% of maximal heart rate) (Chapman et al., 2013; Murrell et al., 2013). Another RCT concluded that after four months of aerobic training (150 min/week), elderly healthy adults (70-85 years old) had an increase in hippocampal blood flow (Burdette et al., 2010). In contrast, when studying elderly master's athlete participants (endurance training greater than 15 years and still active running/swimming/cycling 20-50 miles/week and participating in races) there was no difference in CBF velocity compared to sedentary elderly indicating lifelong PA has no effect (Aengevaeren, Claassen, Levine, & Zhang, 2013; Thomas et al., 2013).

Literature assessing relations between fitness or current levels of PA, cognition and cerebrovascular function in an older population found improved cardiovascular fitness was associated with both improved cognition and cerebrovascular health (Brown et al., 2010; Chapman et al., 2013; Tarumi et al., 2013), with more evidence needed to pinpoint cerebrovascular regulation as a mediating factor of this relation. More recently in healthy young adults, mediation analyses was used to assess if CBF regulation mediates the relation between exercise and cognition (Guiney et al., 2015). It was found that higher fitness levels, correlating to higher levels of past week activity, were associated with cognitive control (inhibition and switching) and that these relations were mediated by cerebrovascular regulation (Guiney et al., 2015). This study provides promising evidence that cerebrovascular health indices mediate the association of interest; however more research is needed to pinpoint these mechanisms in an older population.

A number of studies have focused on the association between PA (versus physiological measures of fitness) and cerebrovascular reactivity to hypercapnia. It is suggested that an increased age-related cerebrovascular resistance index (CVR; mean arterial pressure divided by middle cerebral artery velocity: MAP/MCAv) was greater in untrained versus trained older participants (Ainslie et al., 2008). This increase in CVR (i.e., "resistance" to blood flow) has a negative impact on blood perfusion to the brain, indicating that greater PA levels (likely leading to higher $\dot{V}O_2$max) may help improve vessel health and decrease vessel resistance. Additional evidence indicates lower carotid artery stiffness for endurance-trained middle aged adults (52±1 year) compared to their inactive counterparts (less than one hour of self-reported exercise per week for the last year) (Tarumi et al., 2013). Carotid artery stiffness is a hallmark of vascular ageing and is associated with lower subcortical perfusion and an increased risk of cognitive

dysfunction, indicating that endurance training for middle aged adults helps prevent cerebrovascular stiffness and may be beneficial for maintaining cognitive function (Tarumi et al., 2013). Further, being continuously physically active throughout adult lifespan (self-reported ≥150 minutes of moderate to vigorous intensity recreational aerobic activity per week) is associated with an increased cerebrovascular response to CO_2 and a decrease in the brain's hemodynamic age (approximately 11 to 18 years reduction in hemodynamic age as estimated by changes in cm/sec/year of vessel flow), thus highlighting the potential for augmented PA to improve cerebral hemodynamics (Bailey et al., 2013). There is additional evidence supporting these findings, specifically, cerebrovascular reactivity to hypercapnia at rest was correlated with maximal aerobic capacity in an older adult age groups (Barnes et al., 2013; Brown et al., 2010). These findings suggest that in older adults, higher levels of PA or fitness may have a beneficial effect on cerebrovascular functioning and cerebral vasodilator responses (Barnes et al., 2013; Brown et al., 2010). Further, after a 12-week aerobic based training program there was an increase in cerebrovascular reactivity to hypercapnia at rest and during sub-maximal exercise (70% of heart rate range), again providing evidence of the beneficial effect training has on cerebrovascular health (Murrell et al., 2013). Contrasting evidence has arisen when studying elderly master's athletes compared to sedentary adults there is no difference between cerebrovascular reactivity to CO_2 (Thomas et al., 2013).

Overall, these findings provide strong evidence suggesting that PA and increased levels of physical fitness are related to an increase in cerebrovascular reactivity to hypercapnia, indicating that PA likely has profound cerebrovascular health benefits in older age.

1.4 Chapter One Tables

Table 1. Literature review summary table: physical activity/exercise and cognition.

First author (year)	Study population	Design & Duration	Physical Activity Measure	Outcome measure	Results	Confounders	Comments
Abbott, R.D., et al. 2004	n=2257 males, 71-93 years old.	Prospective Cohort study, 3 year follow up.	Distance walked per day divided into <0.25 miles/day, 0.25-1.0 miles/day, >1to 2 miles/day, & >2 miles/day.	Overall dementia, Alzheimer disease & vascular dementia.	Men who walked the least (<0.25miles/day) had a 1.8 fold excess of total dementia compared to those that walked >2 miles/day. Excess dementia (1.71 HR) for those walking 0.25-1 miles/day vs. those who walked the most (>2 miles/day).	Age, presence of *APOE* ε4 allele, baseline cognitive screening score, ↓in PA since mid-adulthood, physical performance score, years of education, BMI, childhood years spent living in Japan, status as skilled professional, hypertension, diabetes, prevalent coronary heart disease, total & HDL cholesterol.	
Andel, R., et al. 2008	n=3134 males & females; n=2870 controls & n=264 dementia cases, n=176 AD cases. 61% females. 48.1±4.9 years at baseline & 79.5±5.0 years at the cognitive follow up screening.	Prospective Case-Control study, 31 year follow-up. Cohort: The Swedish Twin Registry via the HARMONY study.	Assessed using a questionnaire asking: "How much exercise have you had from age 25 to 50?" Exercise was measured on a 4 point scale: 0: hardly any exercise; 1: light exercise such as walking or light gardening; 2: regular exercise involving sports; 3: hard physical training.	Follow-up involved telephone screening of the twin, followed by an in person clinical evaluation for dementia for those who screened positive for cognitive impairment, as well as their co-twin.	Light exercise & regular exercise was associated with ↓ odds of dementia compared to hardly any exercise. OR=0.34 (95%CI=0.16-0.72 for regular exercise). Findings were similar for AD alone. Co-twin analyses showed ↑ levels of exercise & ↓ odds of dementia approached significance (OR=0.50, 95%CI=0.23-1.06) p=0.072).	Age (continuous), sex, education (basic/ more than basic). Baseline values of: portion of fruits & vegetables in diet (small or no part/medium or great part). BMI (<25 BMI/ ≥25 BMI), alcohol drinking (no drinks per week/one or more drinks per week), current smoking status (yes/no) & angina pectoris (yes/no).	Analyses controlled for age, sex, education, diet, smoking, drinking alcohol, BMI, & angina.
Barnes, D.E., et al. 2003	n=2092 males & females, ≥55 years old.	Prospective Cohort study, 6 year follow up.	VO_2 peak treadmill test (33% of females & 55% of males achieved near maximal exercise). Performance on VO_2 test was divided into tertiles.	mMMSE examination at baseline & 6 year follow up. At 6 year follow up a subset of participants received a detailed cognitive battery including the full MMSE & measures of attention/executive function, verbal memory & verbal fluency.	Baseline peak VO_2 was positively associated with preservation of mMMSE scores & all cognitive tests performed over the 6 year follow up.	Sex, age, years of education, income, hypertension, thyroid disorder, self-rated health, & smoking.	Unclear which confounders were included in analyses.

First author (year)	Study population	Design & Duration	Physical Activity Measure	Outcome measure	Results	Confounders	Comments
Buchman, A.S, et al. 2012	n=716 males & females, 81.6±7.12 years, 76% female.	Prospective Cohort study, ~4 year follow up.	Total daily PA: actigraph worn on non-dominant wrist for 10 days. Late-life PA: Questionnaire adapted from the 1985 National Health Interview Survey; hours/week spent in 5 activities, walking for exercise, gardening or yard work, calisthenics or general exercise, bicycle riding & swimming.	Cognitive function was assessed using a battery of 19 tests used to create a global cognition measure. Clinicians diagnosed AD using National Institute of Neurological & Communicative Disorders & Stroke-Alzheimer's Disease & Related Disorders Association criteria.	Adjusting for age, sex & education total daily PA was associated with incident AD (HR=0.477, CI=0.273-0.832). The level of total daily PA was associated with the rate of global cognitive decline (estimate 0.033, SE=0.012, p=0.007).	Age, sex, education, self-report PA, social & cognitive activities, current level of motor function, depressive symptoms, chronic health conditions, *APOE* ε4 genotype.	
Chang, M., et al. 2010	n=4,945 males & females; mean age at midlife was 51 years & at follow up 76 years.	Prospective Cohort study, 26 year follow up.	Midlife PA: Asked two questions relating to PA, 1) Have they ever regularly participated in sports or exercised at any time during their adult life, if answered Yes 2) How many hours/week they exercised during the summer & winter months. Given three categories to answer 1: none; 2: ≤ 5 hours; 3: > 5 hours. Hours/week calculated from total sum of hours in winter & summer & classified as a) reported no PA; b) ≤ 5 hours of PA/week; c) > 5 hours/week.	Battery of cognitive tests for domains of processing speed (digit symbol substitution test, figure comparison & a modified Stroop test part I word reading & part II color naming), memory (modified version of the California modified Verbal Learning Test, immediate delayed recall) & executive function (Digits Backwards, a shortened version of the CANTAB Spatial Working Memory test & the Stroop Test part III, word-color interference). Dementia diagnosis made by a geriatrician, neurologist, neuropsychologist, & neuro-radiologist.	Excluding pt with dementia compared to the no PA group both PA groups had significantly ↑ speed of processing (p trend < .0001), better memory (p trend < .0001), & executive function (p trend < .0001), after controlling for demographic factors. The ≤ 5 hour PA group was less likely to have dementia in late like (OR=0.60, 95%CI=0.40-0.88).	Measures from midlife: blood pressure, BMI, serum cholesterol, self-reported smoking status (never smoker/ever smoker) & resting heart rate. Measures from late life: depressive symptoms, education (elementary school, high school, undergraduate & more than undergraduate education), *APOE* ε4 genotype.	

First author (year)	Study population	Design & Duration	Physical Activity Measure	Outcome measure	Results	Confounders	Comments
Colcombe, S.J., et al. 2004	Study 1: n=41 males & females, High fit pt 66.2±8.2Years, Low fit pt 67.9±7.8 Years. Study 2: n=29, 65.6±5.7Years, 11 males & 18 females.	Study 1: Cross sectional Study design. Study 2: Randomized clinical trial.	Study 1: Rockport 1-mile walk test. Subsample performed a VO_2 peak treadmill test Study 2: Randomly assigned aerobic group or toning group. VO_2 peak treadmill test pre and post intervention.	Study 1: Performed flanker task while scanned with fMRI Study 2: Same as study 1	Study 1: Older adults with ↑ cardiovascular fitness had significantly ↑ activation in several cortical regions associated with effective attention control. Study 2: After 6 month intervention pt in aerobic group had significantly ↑task related control in areas of attention control, extending the findings from study 1.	N/A	
de Bruijn, R.F., et al. 2013	n=4406 males & females, 72.7±7.2 Years, 59% female.	Prospective Cohort study, 4 & 8 year follow up. Cohort: The Rotterdam Study.	PA assessed using an adapted version of the *Zutphen Physical Activity Questionnaire* to obtain Measures of MET-hours/week of PA based on recreational & household activities in the past two weeks.	Assessed dementia using 3-step protocol: MMSE & Geriatric Mental Schedule, if tested positive underwent examination with the Cambridge Examination for Mental Disorders in the Elderly. If suspected of having dementia underwent further neuropsychological testing. Used neuro-imaging for help on diagnosing. Final decision made by a consensus panel using the standard criteria (DSM-III R for dementia & the NINCDS-ADRDA for AD).	During 38,631 person years 583 participants developed dementia. Borderline significant association between ↑PA & low risk of dementia (HR=0.95, 95%CI=0.87-1.04). This association remains when confined to 4 year follow up (HR= 0.82, 95%CI=0.71-0.95), but not at 8 year follow up.	Age, sex, smoking, *APOE ε4* genotype, blood pressure, hypertensive status, BMI, Diabetes, serum glucose, total cholesterol, HDL, MMSE at baseline.	

First author (year)	Study population	Design & Duration	Physical Activity Measure	Outcome measure	Results	Confounders	Comments
Iso-Markku, P., et al. 2015	n=21,791 males & females aged 24-60 years old at enrolment.	Prospective Cohort study, 29 year follow-up. Cohort: the older Finnish Twin Cohort.	PA was assessed twice, 6 years apart. Questionnaires asked about PA during leisure time & transportation. PA was assessed for intensity level: 1) walking; 2) alternately walking & jogging; 3) jogging (light running); 4) running. Vigorous intensity activity was considered 2, 3 or 4. Created 3 subgroups: 1) no vigorous PA at both time points 2) vigorous PA at both time points 3) people who switched from vigorous to non-vigorous or vice versa.	Dementia mortality assessment: data on emigration & exact dates of death were obtained from the Causes of Death Register available from Statistics Finland. Dementia death was defined according to the appropriate versions of the International Classification of Diseases.	353 subjects died of dementia. Age-sex adjusted HR=0.65 (95% CI= 0.43-0.98) for subjects taking part in vigorous PA at both time periods compared to those who were inactive at both time points. The corresponding HR for within-pair comparisons of the less active twin versus the more active co-twin was 0.48 (95%CI=0.17-1.32). Results for the analyses of the volume of PA were inconclusive.	Age, sex, length of education, heavy use of alcohol, BMI, smoking, hypertension.	No change observed after adjusting for confounding factors.
Kareholt, I., et al. 2011	n=1643 aged 46-75 years, mean age of 57.4 years at baseline.	Prospective Cohort Study, mean 22.8 year follow up.	Asked questions about doing sports, gardening, & dancing. These questions had three response categories scores '0' for no, '1' for yes, sometimes, '2' for yes, often.	Cognition was based on items from the MMSE: Registration & repeating three objects, orientation, delayed recall of three objects, attention/concentration.	PA was significantly associated with cognition only among women ($p<0.001$).	Age, age-squared, sex, follow-up-time, mobility problems, symptoms of mental distress, employment status, education, adult & childhood SES, mental, socio-cultural, social, organizational activities.	These analyses focused a large portion on non-physical leisure time activities.
Kramer A.F., et al. 1999	n=124, aged 60-75.	Intervention Study, 6-month exercise intervention with participants randomly assigned to aerobic or anaerobic group.	Aerobic group exercise consisted of walking and anaerobic group exercise consisted on stretching and toning. Cardiorespiratory fitness tests were performed pre and post intervention to measure the rate of oxygen consumption.	Cognitive tasks including: task switching, response compatibility and stopping.	For task conditions depending on executive control processes (including task-switching) the walking group had statistically significant improvements compared to the toning group.	N/A	Short report, therefore no demographic information presented and no indication of the type of VO_2 max test performed.

First author (year)	Study population	Design & Duration	Physical Activity Measure	Outcome measure	Results	Confounders	Comments
Laurin, D., et al. 2001	n=4615 males & females; n=3894 controls, n=436 pt with CIND (Cog. Impairment no Dementia), n=285 pt with dementia. All pt ≥65 years old	Case-control study, sample: CSHA prospective cohort.	2 questions pertaining to frequency (≥3x/week, weekly or <weekly) & intensity (more vigorous, equal to, or less vigorous than walking). Categorized as high: exercise 3 or more times but at intensity equal to walking; low: all other combinations of frequency & intensity. No PA was the reference category.	mMMSE to screen for dementia; Sub-sample was assessed using a neuropsychological test battery to ensure proper identification of: no cognitive impairment, CIND, & AD.	Compared to no exercise, low, mod. & high levels of PA were associated with a ↓ risk of cognitive impairment, AD & dementia of any type. ↑protection with ↑ PA. High level of PA was associated with a ↓ risk of cognitive impairment (OR=0.58, 95%CI=0.40-0.98, AD (OR=0.50, 95%CI=0.28-0.90), & dementia of any type (OR=0.63, 95%CI=0.40-0.98).	Age, sex, education (included in all models), family history of dementia, regular smoking, regular alcohol consumption, use of non-steroidal anti-inflammatory drugs, a summation score for the 7 items of instrumental activities of daily living, self-rated health, reported chronic diseases.	
Middleton, L.E., et al. 2008	n= 7595; High exercisers: n=3264 74.4±6.6 years, 53.4% females. Low exercisers: n= 4331, 77.4±7.7 years, 64.4% females.	Prospective Cohort Study, 5 year follow up. Secondary analysis.	Pt classified as 'high exercise' (≥ 3x/week doing activities at least as intense as walking) or 'low/no exercise' (all other exercisers & non-exercisers) based on self-reported questionnaires.	Cognitive change as measured by the mMMSE with transition from high cognition to low cognition indicated by groupings of 3 errors on the 30 point extension of the mMMSE. Death.	High exercisers had less cognitive decline from baseline over 5 years than did the low/no exercisers ($p<0.0001$). High exercisers also had a higher chance of cognitive improvement/stability (89.7% vs. 84.2% in low exercisers) $p<0.0001$.	Age, education.	
Middleton, LE., et al. 2010	n=9344 women 71.6±5.2years.	Cross-sectional study.	Self-reported PA in teenage, age 30, age 50, and current (later life) yearly frequencies of low, moderate or high-intensity PA using the modified *Paffenbarger* questionnaire.	26-point mMMSE.	Women who reported being PA had a ↓ prevalence of cognitive impairment in later life than women who were inactive at each time (teenage: AOR=0.65, 95%CI=0.53-0.80, age 30: AOR=0.80, 95%CI=0.67-0.96, age 50: AOR=0.71, 95%CI=0.59-0.85, old age: AOR=0.74, 95%CI=0.61-0.91). Analyzing four groups together, teenage PA was associated with a ↓ odds of late life cognitive impairment (OR=0.73, 95%CI=0.58-0.92)	Teenage analyses: age, education, marital status, diabetes mellitus, depressive symptoms, smoking, BMI. Age 30 analyses: education, diabetes mellitus, depressive symptoms, smoking, BMI. Age 50 analyses: age, education, marital status, diabetes mellitus, depressive symptoms, smoking, BMI. Old age analyses: age, education, marital status, diabetes mellitus, hypertension, depressive symptoms, BMI.	

First author (year)	Study population	Design & Duration	Physical Activity Measure	Outcome measure	Results	Confounders	Comments
Netz, Y. et al. 2011	n=38, 26 women & 12 men, 77.54±5.28 years; Low fitness: n=20, 15 Women, 5 men; 77.77±4.35years. Moderate fitness: n=18, 11 women, 7 Men; 77.29±6.3 years.	Cross-sectional study.	PA assessment using *The Habitual Physical Activity Questionnaire.* Aerobic fitness (VO_2 peak): divided into Moderate VO_2 group (>18.5 ml*kg-1*min-1) & Low VO_2 group (<18.5 ml*kg-1*min-1) based on median fitness score.	Mind streams computerized battery including: Go-Nogo Response Inhibition, Verbal Memory, Stroop Interference, Nonverbal Memory, Catch Game & Visual Spatial Imagery producing four summary scores for the following cognitive domains: Memory, Attention, Visual-spatial, Executive Function, & a Global Cognitive Score.	Moderate VO_2 group had significantly better scores (absolute values) compared to low VO_2 group for Attention (p=0.036) & Global Cognition Score (p=0.04), while there was a non-significant trend for all other domains.	None indicated	
Rovio, S., et al. 2005	n=1251; n=515 active, 50.8±6.1 years, n=228 male & n=287 female. n=736 sedentary, 49.5±5.8 years, n=265 male & n=471 female.	Prospective Cohort study, 21 year mean follow up. Cohort: survivors from the CAIDE study.	Leisure time PA assessed using a questionnaire asking: "How often do you participate in leisure time PA that lasts at least 20-30 min & causes breathlessness & sweating?"	Mean follow up of 21 years to obtain diagnosis of dementia & AD.	Leisure –time PA at midlife at least 2x/week was associated with a reduced risk of dementia & AD (OR=0.48, 95%CI=0.17-0.85).	Age, sex, education, follow-up time, locomotor disorders, *APOE* ε4 genotype, vascular disorders, smoking, & alcohol drinking.	The main findings remained after adjusting for all confounders & were more pronounced in *APOE* ε4+ carriers.
Scarmeas, N., et al. 2009	n=1880	Prospective Cohort study. Cohort: two cohorts recruited through the Washington Heights-Inwood Columbia Aging Project (WHICAP).	*Godwin leisure time exercise questionnaire* for the previous 2-week period asking questions about frequency, duration & intensity of PA. This allowed constructing a summary PA score using the formula: # of min. x # of times x coefficient (9 for vigorous, 5 for moderate, & 3 for light activity. Corresponding to the Metabolic equivalent). They trichotomized into No, Some & Much PA.	Time to incident AD. AD was classified based on medical & neurological history, in-person interview including neuropsychological battery for tests of memory, orientation, abstract reasoning, language, & visual-spatial abilities, grouping into four cognitive factors (memory, language processing speed & visual-spatial ability). Used the criteria from the Diagnostic & Statistical Manual of Mental Disorders for diagnosis.	Higher PA was independently associated with ↓ AD risk. Compared to no PA, the HR for some PA was 0.75 (95%CI=0.54-1.04), the HR for much PA was 0.67 (95%CI=0.47-0.95), p=0.03.	Cohort, age, sex, ethnicity, education, *APOE* ε4 genotype, caloric intake, BMI, smoking status, depression, leisure activities, a comorbidity index, & baseline Clinical Dementia Rating score.	This study also looked at diet.

First author (year)	Study population	Design & Duration	Physical Activity Measure	Outcome measure	Results	Confounders	Comments
Sun, et al., Q., 2010	n=13535 females mean age of 60 at baseline.	Prospective Cohort study. Cohort: Nurses' Health Study.	Baseline assessment: asked the average time/week in the past year spent doing 10 different leisure-time PA's. Also inquired about flights of stairs walked per day & the pace of walking (if a walker). Calculated MET-hour/week & grouped participants into quintiles of METs. Also assessed METs for walking only.	Telephone administered interview for cognitive status (TICS) modeled on the MMSE. Scores ranged from 0 to 41, with a score lower than 31 indicating cognitive impairment. Also looked at the outcome of mortality (not due to dementia). Death.	↑PA levels (MET-hours/week) at midlife (age 60) were significantly associated with better odds of successful survival. Lowest quintile OR=0.98 95% CI=0.80-1.20, second quintile OR=1.37 95%CI=1.13-1.65, third quintile OR=1.34 95%CI=1.11-1.61, fourth quintile OR=1.99 95%CI=1.66-2.38. ↑energy expenditure from walking associated with increased odds of survival.	Baseline variables: age, education (registered nurse, bachelor's degree, master's degree or doctorate), marital status, if married husbands education, postmenopausal hormone use, smoking status, family history of heart disease, diabetes, or cancer, dietary polyunsaturated to saturated fat ration, intakes of trans fat, alcohol, & cereal fibre, & intakes of fruits & vegetables & red meat.	Cognition was not the main outcome of this study, they measured it as part of their overall measure of successful aging. Mortality was the main outcome.
Tolppanen, A.M., et al. 2014	n=3559 males & females, 50.6±6.0 years at baseline (considered midlife) & 78.6±3.7 years at follow up.	Prospective cohort study, 28 year follow up. Cohort: the CAIDE study.	Assessed leisure time PA asking: "How often do you participate in leisure time PA that lasts at least 20-30 min & causes breathlessness & sweating?" Response options 1) daily; 2) 2-3x/week; 3) 1x/week; 4) 2-3x/month; 5) a few times a year; 6) never due to illness or injury. These were condensed into three categories 1) high (Reponses 1 & 2); 2) moderate (responses 3 & 4); 3) low (responses 5 & 6).	Cognitive assessment: Three phases: Screening, clinical phase, & differential diagnosis phase. Full assessment at follow-up if scored ≤24 on MMSE at screening phase, or if there was a decrease ≥3 points on MMSE at follow up, or <70% delayed recall in the CERAD word list. Clinical phase included: neurological, cardiovascular & neuropsychological exams. Primary diagnosis made by physician, neuropsychologist & senior neurologist. Additionally, used Dementia Diagnosis registers.	Moderate (HR=1.46 95%CI=1.08-1.99) & low levels (HR=1.39 95%CI=0.99-1.95) of midlife leisure time PA associated with higher risk of dementia compared to the highest PA category. Maintaining high PA (HR=0.16 95%CI=0.06-0.41) or ↑PA (HR=0.19 95%CI=0.09-0.41) after midlife associated with lower dementia risk. Similar results observed for AD.	Age, sex, years of education, marital status, physically demanding occupation, midlife BMI, *APOE ε4* genotype, cardiorespiratory & musculoskeletal diseases. Identified sex, BMI & *APOE ε4* genotype as being assessed as effect modifiers.	Benefits were more pronounced for men, overweight individuals and non-*APOE ε4* carriers.

First author (year)	Study population	Design & Duration	Physical Activity Measure	Outcome measure	Results	Confounders	Comments
van Gelder, B.M., et al. 2004	n=295; n=46 Finnish men 73.6±3.6 years; n=118 Dutch men 74.2±3.6 years; n=131 Italian men 76.0±3.2 years.	Prospective Cohort study. Cohort: Healthy survivors from The FINE Study.	PA was assessed each survey round using a validated self-administered questionnaire that asked questions on the frequency duration & pace of walking & bicycling during the previous week, amount of time spent on hobbies & gardening & the amount of time spent monthly on odd jobs & sport. Computed intensity & duration measures to use for analysis.	The MMSE was used to assess cognitive function.	The rates of cognitive decline did not differ among men with high or low duration of activity at baseline. A decrease in activity duration of >60 min/day over 10 years resulted in a decline of 1.7 points ($p<0.0001$) on the MMSE. Men with the lowest intensity quartile at baseline had a 1.8 ($p=0.07$) to 3.5 ($p=0.004$) times stronger 10-year cognitive decline than those in the other quartiles.	Age, education, country, alcohol consumption, smoking status, mental activities, & alternately PA intensity or duration, ADL, depression, BMI, use of antihypertensive drugs, HDL, total cholesterol, blood pressure, & baseline cognitive function.	
Weuve, J., et al. 2004	n=16466 females aged 70 to 81 years, 74±2.3years.	Prospective Cohort study, 2 year follow up. Cohort: the Nurses' Health Study.	Telephone questionnaire obtaining detailed information on leisure-time PA. Estimates on average amount of time/week during the past year spent doing various activities, walking paces & number of flights of stairs climbed daily were obtained. Each activity was assigned a MET value, & the energy expenditure in MET-hours/week was obtained. Separated into 5 quintiles of average energy expended in MET-hours/week: 1) <5.2; 2) 5.2-10.0; 3)10.1-16.2; 4)16.3-26.0; 5)>26.0.	Telephone Interview for Cognitive Status (TICS) (modeled after the Mini-Mental State Examination); East Boston Memory Test (EBMT) for immediate & delayed recall; Digital Span Backwards test for working memory & attention; an overall global score that was created by averaging the z-scores from all tests.	Statistically significant trend of ↑ mean scores on all cognitive measures with ↑ levels of long-term PA ($p<0.001$ for all 5 tests). For the global score females in the highest quintile (>26.0 MET-hour/week) had 20% lower odds of cognitive impairment at baseline then women in the lowest quintile (<5.2 MET-hour/week) (OR=0.80 95%CI= 0.67-0.95).	Included in final model: Age at cognitive assessment, education, husbands' education, alcohol consumption, aspirin use, ibuprofen use, Vitamin E supplementation, antidepressant use, poor mental health, history of osteoarthritis, history of emphysema or chronic bronchitis, low vitality on energy fatigue scale, problems with balance, moderate to severe body pain, & health limitations in walking a block. Not Included: postmenopausal hormone therapy, *APOE* ε4 genotype.	Analyses were also performed using walking quintiles to ensure different analyses showed the same relationships with cognition.

First author (year)	Study population	Design & Duration	Physical Activity Measure	Outcome measure	Results	Confounders	Comments
Wendell, C.R., et al. 2014	Full sample: n=1400 aged 19-94 years, 54.3±16.2years, 50.5% male. Longitudinal sample: n= 615, 56.1±14.6years, 51.5% male.	Prospective Cohort study, up to 18 Years follow-up.	Cardiorespiratory fitness estimates, or VO_2peak/Max.	Neuropsychological assessment: Global cognitive status, attention & concentration, verbal learning & memory including immediate free recall, learning slope, short & long delay free recall, visual memory, perceptuomotor speed, visuomotor scanning, mental flexibility, executive function, confrontation naming, language ability, mental spatial rotation.	Significant interactions of VO_2max & age (indicating change over time) for Retention test ($p<0.0001$), memory & concentration test ($p=0.014$), immediate free recall ($p=0.001$), learning slope ($p=0.009$), short delay free recall ($p=0.023$), long delay free recall ($p=0.006$). Using conservative Bonferroni corrections a significant interaction remained for retention ($p=0.0005$) & immediate free recall ($p=0.0025$).	Age, education, sex, race, use of antihypertensive medications, blood pressure, hypertensive status, BMI, cardiovascular dx, inflammatory dx, self-reported depressive symptomatology.	All analyses were performed with raw cognitive scores therefore regression coefficients were not directly comparable across all measures.
Yaffe, K., et al. 2001	n=5925, ≥65 years old.	Prospective Cohort study, 6-8 year follow up.	At baseline asked how many city blocks (1block ~ 160m) walked each day for exercise & how many flights of stairs were climbed each day. Also assessed PA using the *Paffenbarger Scale* where interviewers ask subjects to report the frequency & duration per week during the past year of 33 different PA. Total PA (kilocalories expended/week) was calculated by adding the kcals for each activity, blocks walked & flights of stairs climbed. Both blocks walked & kcals were divided into quartiles.	MMSE (brief global cognitive function test with concentration, language, & memory components designed to screen for cognitive impairment).	Females in the highest quartile were less likely than women in the lowest quartile to develop cognitive decline during the 6-8 year follow up. For blocks walked OR=0.66 95%CI=0.54-0.82 & for total kilocalories OR=0.74 95%CI=0.560-0.90. Associations remained after adjustment for covariates.	Baseline age, education level, health status, functional limitation, depression score, stroke, diabetes, hypertension, myocardial infarction, smoking & estragon use.	

Table 2. Literature review summary table: physical activity/exercise, cerebrovascular function and cognition.

First author (year)	Study population	Design & Duration	Physical Activity/Exercise/Fitness Measure	Intervention	Outcome measure	Results	Confounders	Comments
Brown, A.D., et al. 2010	n=42 females, 65.1±8.4years; dichotomized for analysis: n=21 young (58.3±4.2 years) & n=21 old (72±5.3 years), or n=28 fit & n=13 sedentary (one women did not qualify for the sedentary group).	Cross sectional study.	PA assessment: Completion of a lifestyle questionnaire adapted from the *Past Year Total Physical Activity Questionnaire.* Fitness: VO_2max test on a modified recumbent cycle ergometer.	N/A: single time point	Neurocognitive assessment: neuropsychological test battery assessing seven domains: verbal knowledge, spatial reasoning, memory, processing speed, complex attention, executive function & verbal fluency. CBF: using TCD to measure flow velocity in the right MCA, MAP & CVC (in response to isocapnia (raised to +1 Torr, +5 Torr, & +8 Torr above natural resting levels), & sub-maximal exercise as determined by previous VO_2max test.	Cognitive function - correlated with age (r= -0.39, p=0.012) & + correlated with VO_2max (r=0.41, p=0.008). Cognitive function was higher in the active vs. sedentary group (p=0.007) (controlled for education & age). MAPiso & CVCiso were predictors of overall cognitive function (r=0.657, p=0.001; r=0.594, p=0.004 respectively). ↓MAP in active vs. sedentary women during rest, sub-maximal exercise & hypercapnia (+8 torr CO_2.) CVC ↑ in active vs. sedentary group during iso & hypercapnia (+8 torr CO_2). MAPrest was - correlated with VO_2max (r= -0.414, p=0.028). CVCrest + correlated with VO_2max (r=0.50, p=0.006). ↑ CVC in the fit group than sed. group at baseline, sub-maximal exercise, & recovery. ↑ CVC in fit group vs. sedentary.	Age, education, % body fat, BP, ovarian hormones, VO_2max.	
Chapman, S.B, et al. 2013	n=37 cognitively normal adults 64±3.9 years; two groups: n=18 physical training (64years±4.3years)(5 male/13 female) & n=19 waitlist controls (64years±3.6years) (5 males/14 females).	RCT, 12 weeks.	VO_2max at baseline, mid & end of PA training.	3x 60-mins supervised sessions of aerobic training per week (goal of 150 min/week). Cycling or treadmill workouts (warm-up, reaching 50-75% of predicted VO_2max from fitness testing, cool down).	Neurocognitive measures: executive function, memory, & complex attention. CBF: measured by MRI; whole brain blood flow values were calculated by averaging all the voxels in the CBF map. Physiological parameters: weight, HR, VO_2max, RPE (BORG Scale 6-20).	↑ VO_2max at mid-exercise program for training group relative to controls (p=0.02). ↑RPE between beginning & end of exercise in the training compared to the control group (p=0.01). ↑ Memory in training group compared to controls over training sessions. Cognitive function in exercise group. ↔ in the CBF of the hippocampus between training & controls over the 3 time points. ↑ CBF in anterior cingulate gyrus in training group compared to control (p<0.05).	N/A	HR measured using 50-75% of maximum, not HRR. 90 % training compliance required for inclusion in analysis.

First author (year)	Study population	Design & Duration	Physical Activity/Exercise/Fitness Measure	Intervention	Outcome measure	Results	Confounders	Comments
Guiney, H., et al. 2015	n=55 healthy young adults, 24 males & 31 females, 21.8±2.5years.	Cross sectional study.	PA assessed using the self-report *New Zealand Physical Activity Questionnaire*-Short Form for an index of weekly PA. A graded submaximal aerobic fitness test on a cycle ergometer to obtain VO_2max.	N/A: single time point	Cognitive testing: pro (reaction time & accuracy), anti (inhibitory control) & pro/anti (switching performance, visuomotor & inhibitory control). CBF: using TCD to measure flow velocity in the right MCA (in response to isocapnia (raised to baseline, steady-state hypercapnia (5% CO_2) a hypocapnia (volitional hyperventilation).	More frequent PA predicted better cognitive inhibitory control (p=0.005), & VO_2max predicted better cognitive inhibitory control (p=0.046). More frequent PA predicts better CBF (hypercapnic reactivity p=0.047, hypocapnic reactivity p=0.022). VO_2max predicted better CBF (hypercapnic reactivity p=0.049, hypocapnic reactivity p=0.054). CBF predicted better cognitive inhibitory control (hypercapnic reactivity p=0.005, hypocapnic reactivity p=0.011). Both hypocapnic reactivity (p=0.021) & hypercapnic reactivity (p=0.021) mediated the relationship between PA & cognitive inhibitory control.	None identified.	All models had small variance, nothing greater than 18%.
Tarumi, T., et al. 2013	n=58; n=26 sedentary, 10 males &16 females, 54±1years, n=32 endurance-trained, 11males & 21 females, 52±1years.	Cross sectional study.	Modified PA questionnaire classified pt as endurance trained: moderate to vigorous aerobic exercise 7.5±0.6hr/week, sedentary: exercising less than once per week for the past year. VO_2max test verified level of fitness.	N/A: single time point	Neuropsychological Assessment: For global cognitive function the MMSE & Wechsler Test for Adult Reading. Memory: California Verbal Learning Test II immediate recall & delayed recall. Attention-executive function: Trail Making B time to completion, Controlled Oral Word Association Test & Weschler Adult Intelligence Scale III Digit Span Subtest. CBF: measured using MRI, VO_2max, central arterial stiffness: measured by carotid-femoral pulse wave velocity (cfPWV),	↓BMI, %body fat in trained group compared to sedentary group (all p<0.05). Sleep indices & dietary habits were not significantly different between groups (all p>0.05). ↑ total, memory, & attention-executive function in trained compared to sedentary (all p<0.05) - total & attention-executive function differences disappeared after controlling for carotid distensibility, & memory differences disappeared when controlling for BMI (all p=0.05). ↓ cfPWV in trained compared to sedentary (p=0.02). ↑ VO_2max in trained group compared to sedentary group. ↓ Common carotid arterial stiffness in trained compared to sedentary. Cardiopulmonary fitness correlated with cognitive function (r=0.40, p<0.01), memory (r=0.3p<0.018), & attention-executive function (r=0.28, p=0.03). VO_2max pos. correlated with total composite (r=0.39, p<0.01), & memory (r=0.40, p<0.01) after controlling for age, sex, & education.	Age, sex, education level, sleep quality, diet, anthropometry, carotid distensibility.	

Table 3. Literature review summary table: cerebrovascular function and cognition.

First author (year)	Study population	Design & Duration	Physical Activity Measure	Intervention	Outcome measure	Results	Confounders	Comments
Ainslie, P.N., et al. 2008	n=307 healthy males 18-79 years old; n=153 sedentary, n=154 endurance trained.	Cross Sectional study.	Pt recruited based on PA status from past 2 years. Sedentary: no regular PA. Endurance exercise trained: vigorous aerobic-endurance exercise more than 4x/ week & competing in local road or cycling races.	N/A	CBF: using TCD to measure flow velocity in the right or left MCA. CVRi=MAP/MCAv.	↑ CBF in trained compared to sedentary. ↑ CVRi & ↓CBF with age. ↑ CVR rate of decline was greater in sedentary compared to trained individuals.	Age, BMI, Maximal Oxygen consumption (aerobic fitness), training status, MAP.	
Aengevaeren, V.L., et al. 2012	n=23; n=12 masters athletes (MA) 73s±6years, n=11 sedentary adults 71±6years.	Cross Sectional study.	MA status defined as endurance training greater than 15 years & still active running/swimming/cycling 20-50 miles/week & participating in races; sedentary adults had done <30 min of PA 3x/week for the last 2 years.	N/A	Blood pressure, heart rate, cardiac baroflex function, dynamic cerebral auto regulation & CBF velocity at rest & during sit & repeated sit stand manoeuvres using TCD to measure flow velocity in the right MCA.	Cardiac baroflex gain more than doubled in MA compared to sedentary adults (p=0.018); ↔ in dynamic cerebral auto regulation between the two groups (p=0.792	N/A	
Bailey, D.M., et al. 2013	n=81 males; Four groups: n= 19 young sedentary, n=20 young trained (young: <30years); n=19 old sedentary, n=23 old trained (old: >60years).	Cross Sectional study.	Sedentary & Trained status defined according to self-report Lifetime PA levels (questionnaire). Trained: ≥150 minutes of moderate to vigorous intensity recreational aerobic activity/week sustained during adult lifespan. Sedentary: no formal recreational activity outside of everyday living.	N/A	CBF: using TCD to measure flow velocity in the right or left MCA, CVCi=MCAv/MAP, CVRi=MAP/MCAv, CVR_{co2} (response to 3 min breathing 5% CO_2), MAP, VO_2max.	Older adults: ↓ CBF, CVC, CVR_{CO2} & VO_2max. ↑ BMI & CVRi. MAP remained unchanged. Positive linear relationships between VO_2max & both CBF, CVR_{CO2} (pooled sedentary & active) in both young & old. VO2max-CBF relationship in young sedentary/trained r=0.58, old sedentary/trained r=0.59. VO_2max-CVR_{CO2} in young sedentary/trained r=0.67, old sedentary/trained r=0.77, all relationship p<0.05. Difference between trained & sedentary MCAv & CVR_{co2} equated to ~11-18 year reduction in the brain's hemodynamic age. ↔ decline CBF & CVR_{CO2} with age in trained & sedentary.	N/A	1 min on/off CO_2 for CVR measurement.

First author (year)	Study population	Design & Duration	Physical Activity Measure	Intervention	Outcome measure	Results	Confounders	Comments
Bakker, S.L., et al. 2004	n=1720, 70.7±6.4years, 54% males & 46% females.	Cross Sectional study.	N/A	N/A	CBF: using TCD to measure mean velocity, peak systolic velocity & end-diastolic velocities for both sides of MCA. CVR to 5% CO_2 for 2 min.	↓ in all CBF velocity measures with ↑age. ↓ CVR to CO_2 per year (-0.6%kPa/year 95%CI: -0.8 to -0.4). End-diastolic, peak systolic & mean CBF velocities ↓ in men compared to women.	Age, sex, BMI, Intima-media thickness, number of plaques.	36 people had a stroke prior to the TCD exam & there CBF velocities were similar to people without previous stroke.
Barnes, J.N., et al. 2013	n=29 healthy sedentary adults; n=16 young 18-34years old (8 males & 8 females), n=13 old 55-77years old (7 males & 6 females).	Cross sectional study.	One time VO_2max test using cycle ergometer.	Indomethacin (a COX inhibitor) treatment vs. placebo while performing hypercapnia trial.	CBF: using TCD to measure flow velocity in the right MCA. CVR_{CO2} from a stepped hypercapnia trial (2%, 4%, 6% CO_2 added for 3 minutes each), CVCi: calculated from the slope of the relationship between CVCi (MCAv/MAP) & ET_{CO2}, VO_2max.	↑ CBF reactivity & VO_2max in young compared to old in young vs. old. MCAv & CVCi reactivity to hypercapnia ↓ in old vs. young. After Indomethacin treatment ↓ MCAv, CVCi, MCAv reactivity & CVCi reactivity for both young & old. In older adults VO_2max + associated with Δ MCAv reactivity ($r=0.59$; $p<0.05$). Correlation between CVR_{CO2} & VO_2max in older healthy adults ($r=0.64$, $p=0.02$) with no association found in young.	N/A	Examined indomethacin treatment effect on cerebral vasodilation.
Burdette, J.H., et al. 2010	n=11; n=6 older adults, 77.6±5.0years exercise training (3 males & 3 females), n=5 older adults, 74±2.5years, educational control (5 males only).	RCT; 4 months: 2 center & 2 home based sessions per week.	No pre & post PA measure.	Target 150 min/week of aerobic training with RPE of 12-14. HAC combined health classes with light stretching.	CBF: measured using MRI (performed a ROI analysis of the hippocampus) & resting fMRI. Assessed whole brain functional connectivity using graph theory methods.	↑ Hippocampal CBF in exercise trained group compared to healthy aging educational group ($p<0.0002$).	N/A	Regulated exercise intensity with RPE rather than HR. HAC sessions not the same amount as training sessions. MRI scans took part up to 1-month after exercise program, but continued to exercise even after the program until they were scanned.

First author (year)	Study population	Design & Duration	Physical Activity Measure	Intervention	Outcome measure	Results	Confounders	Comments
Demirkaya, S., et al. 2008	n=63 healthy subjects 5-69 years old, n=30 males (32.3±18.5years, n=33 females (31.9±17.1years.	Cross Sectional study.	N/A	N/A	CBF: mean velocity, peak systolic velocity, & end diastolic velocities were determined for middle, anterior & posterior cerebral arteries using TCD.	↓ in CBFv with ↑ age, pronounced in subjects over 40 years ($p<0.05$). Mean velocity, PSV & EDV highest in 5-10yr olds & lowest in >60yr olds ($p<0.05$).	N/A	No exercise intervention.
Grolimund, P. & Seiler R.W. 1988	n=535, 54.9±16years.	Cross Sectional study.	N/A	N/A	CBF: measured velocities of the middle, anterior & posterior cerebral arteries using TCD.	↓ in the force velocity of all 4 arteries with ↑ age ($p<0.001$). ↓ 5.1%/10 year for MCA, 5.6%/10yr for ACA, 3.7%/10yr for PCA & 4%/10yr for ICA	N/A	Estimates/year based on a theoretical value of the intercept of the regression line (zero age) as 100% blood flow velocity ↓.
Leenders, K.L., et al. 1990	n=34, 22-82 years old, 45.1±15.2years.	Cross Sectional study.	N/A	N/A	CBF, OER, $CMRO_2$, CBV: measured using ^{15}O stead-state inhalation method & positron emission tomography.	Between subject CBF correlated + with $CMRO_2$. OER was not dependent on $CMRO_2$, but highly - correlated with CBF. CBV + correlated with CBF. Within subjects, coupling between $CMRO_2$ & CBF & between CBF & CBV, while OER was independent of CBF & $CMRO_2$. In pure grey & white matter regions $CMRO_2$, CBF & CBV ↓ with age 0.5% per year.	N/A	No exercise intervention.

First author (year)	Study population	Design & Duration	Physical Activity Measure	Intervention	Outcome measure	Results	Confounders	Comments
Murrell, C.J., et al. 2013	n=20 sedentary adults; n=10 young (23±5years), n=10 older (63±5years).	Non-randomized trial: pre/post- 12 week aerobic exercise intervention (young vs. old)	Measured VO_2max pre & post exercise intervention.	Aerobic-based exercises, monitored with recordable HR monitors & PA log (mode, duration & intensity recorded). Supervised exercise, 5 circuits gym-based & 9-walking/jogging group based. Weeks 1-4 3 sessions/week to 4 sessions/week (weeks 9-14) Intensity determined by initial VO_2max: 50-60% HRR (weeks 1-4) to 65-80% HRR (weeks 9-12); duration ranged from 20-30 min (weeks 1-4) to 40-50 min (weeks 9-12).	VO_2max on cycle ergometer, CVR: using TCD to measure flow velocity in the MCA. CVR measured during hypercapnia (5% CO_2 for 3 mins) then hypocapnia (hyperventilated for 3 mins). CVR during hypercapnia during steady-state sub-maximal exercise at 30 & 70% HRR.	↑MCAv during sub-maximal cycling exercises in both young & old ($p<0.01$), ↑ Mean PET_{CO2} with exercise in both young & old, with greater absolute ↑ in young ($p<0.01$). ↑ in hypercapnic CVR during exercise independent of age. Effects of training: ↑ in VO_2max by 6% after training program ($p<0.05$), ↓ PET_{CO2} post training ($p<0.05$), ↑ MCAv following training ($p=0.02$), ↓ in resting HR in young post training ($p<0.05$), ↑ in hypercapnic CVR in both young & old ($p=0.01$), ↔ hypocapnic reactivity or ventilatory sensitivity to hypercapnia following training, training had no effect on MCAv during exercise for young or old ($p>0.05$).	Age, sex, & within-subject factors: training & exercise.	Had to correct for PET_{CO2} to show differences in reactivity.
Oudegeest-Sander, M.H., et al. 2013	n=58; 3 groups: n=20 young 9 males & 11 females (24±2years), n=20 elderly 13 males & 7 females (66±1years), n=18 older elderly 15 males & 3 females (78±3years).	Cross Sectional study.	Sit-stand manoeuvre (10 sec sit & 10 sec stand) for 5 minutes. Single squat stand manoeuvre (standing for 1 min & squatting for 1 min).	N/A	HR, BP, CBFv: measured using TCD to measure flow velocity in the MCA, MAP, CVRi to CO_2 (hyperventilation to induce hypocapnia), Oxygenation of frontal cortex: O_2Hb (measured changes in the concentration of oxygenated & deoxygenated hemoglobin).	↑ mean CBFv in young compared to both elderly & older elderly ($p<0.01$) & ↓ CVRi compared to older elderly group ($p<0.01$). ↑ CBFv in young compared to both elderly groups ($p<0.001$) & ↓CVRi in young compared to the older elderly group ($p=0.008$) during the repeated sit-to-stand test. ↓ CBFv & ↑ CVRi with increasing age during both squat & standing positions ($p<0.01$).	N/A	

First author (year)	Study population	Design & Duration	Physical Activity Measure	Intervention	Outcome measure	Results	Confounders	Comments
Portegies, M.L., et al. 2014	n=4797, n=1695 eligible 910 males & 785 females, 70.7±6.3years.	Prospective Cohort study.	N/A	N/A	CBF: using TCD to measure flow velocity in the MCA, BP. Mortality & stroke.	Hazard Ratio per SD: ↓ in vasomotor reactivity was 1.10 (95%CI: 0.99-1.21) for all-cause mortality & 1.09 (95%CI: 0.94-1.26) for cardiovascular mortality, & 1.10 (95%CI: 0.99-1.21) for non-cardiovascular mortality. Persons with a lower cerebral vasomotor reactivity have an increased risk of mortality, & these associations are independent from cardiovascular risk factors & incident stroke.	Age, sex, BP, current smoker, former smoker, use of BP-lowering medications, systolic BP, diastolic BP, diabetes mellitus, total cholesterol, HDL-cholesterol, use of statins, history of vascular disease & cIMT.	Epidemiological analysis using person-years & investigating time-to-event data. Confidence intervals are close to the null value of 1.0.
Thomas, B.P., et al. 2013	n=10 MA 7 males & 3 females, (74.5±5.8years), n=10 sedentary old 8 males & 2 females (75.34±5.6years), n=9 sedentary young 5 males, 4 females (27±3.6years).	Cross Sectional study.	Maximal oxygen uptake (VO_2 max) on treadmill.	N/A	CBF & CVR to changes in CO_2 (hypercapnia) measured using a 3T MRI scanner.	↑ fitness for MA compared to SE. ↔ in CBF between MA & SE. ↓ in CVR in MA compared to SE.	N/A	Used MRI instead of TCD techniques.
Zhu, Y.S., et al. 2013	n=33; n=12 healthy sedentary young 7 males & 5 females (27±4years); n=10 healthy sedentary old 7 males & 3 females (72y±4years); n=11 MA 9 male & /2 females (72±6years).	Cross Sectional study.	No measure. Screened PA groups based on history, Sedentary: excluded if ≥30 minutes of exercise 3x/week MA's: recruited from race records of the US MA sanction events; those recruited were runners with a weekly running mileage of 20-50 miles for more than 15 years & were still engaged in exercise & training at the time of the study.	N/A	CBF: using TCD to measure flow velocity in the MCA, CVC, BP, HR, CVR_{CO2} (voluntary hyperventilation).	MA's had ↓resting HR compared to young & old sedentary ($p<0.05$). Systolic, diastolic, mean & pulse CBFv & CVCi ↓ in MA's & sedentary old compared to sedentary young. ↑CVR_{CO2} (%), CVMR (%) in sedentary old & MA compared to sedentary young, ↓ CBF older adults (both sedentary & MA's) compared to younger adults during hypercapnia, & CBF lowest in MA.	Sex	Suggested that conducting hypocapnic test & hypercapnic test together is not good, however still proceeded to conduct one after the other. Hypercapnic test was rebreathing from a bag. No VO_2 data.

Chapter Two: **RESEARCH METHOD**

2.1 Ethics and approvals

The protocols for the *Brain in Motion* (BIM) study have been approved by the University of Calgary Research Ethics board 'Conjoint Health Research Ethics Board (CHREB) at the University of Calgary; Ethics Protocol ID # 22502'. The research conducted for this project was added to the CHREB ethics protocol on September 4th 2014. All participants provided written informed consent prior to enrolment in the study.

2.2 Study Design

The BIM study is an on-going intervention cohort study consisting of multiple testing phases examining the effects of a 6-month aerobic exercise intervention on cerebrovascular regulation and cognitive function in middle aged and older adults (Tyndall et al., 2013). The data for these analyses were taken from the baseline assessments of the BIM study participants; therefore a cross-sectional study design was used. At baseline (BIM study P1A) the data from the *Lifetime Physical Activity Questionnaire* (LTPAQ) interview, cognitive assessment and cerebrovascular blood flow test were collected at three separate visits assessed at the same point in time.

2.3 Study Population and Sample Size

Participants (n=266) were considered healthy, community dwelling, currently inactive, middle-aged and older adults. They were recruited through the use of media, posters and advertisements in local newspapers, communities, and through the University of Calgary. A two-stage screening process was used to ensure volunteers met all eligibility criteria. The initial

telephone-based interview assessed the following eligibility criteria: English-speaking males or females ≥55 years old, considered inactive (< 30 minutes of moderate exercise four days per week or 20 continuous minutes of vigorous exercise two days per week), able to walk independently outside and up and down at least 20 stairs, a body mass index (BMI) less than 35 kg/m^2 (to avoid co-morbidities associated with extreme obesity), no history of clinically active cardiovascular disease or obstructive airway disease, non-smoker for the past 12 months, no major trauma or surgery in the last six months, no debilitating neurological disorders, physician clearance and written informed consent. The secondary screening stage entailed an on-site medical examination including the completion of the Montreal Cognitive Assessment (MoCA) with a score ≥24 to be classified as free from cognitive impairment (Nasreddine, Phillips, & Chertkow, 2012), medical interview to attain history of cardiovascular, respiratory, hepatic, endocrine, neurological, and musculoskeletal health, information on allergies and past substance abuse and a physical assessment performed by a study physician to determine abilities for the safe execution of exercise. All eligibility criteria helped to ensure subjects entering the study were healthy with no underlying medical conditions that would hinder their performance on the tests required to complete the study. Figure 1 provides a detailed flow of participants. Participants who completed the LTPAQ, the neuropsychological assessment, and the CBF test (n=226) at baseline were included in this study. With a sample size of 226 we had 100% power to detect a 0.40 change in global cognition z-score at α=0.05.

2.4 Data Collection

2.4.1 Lifetime Physical Activity Questionnaire Interview

Lifetime total PA was assessed using the interviewer-administered LTPAQ, a PA questionnaire with demonstrated reliability (Friedenreich, Courneya, & Bryant, 1998). Previously, a reliability study was conducted wherein 115 women were interviewed twice 6 to 8 weeks apart by interviewers. The test-retest correlation for total lifetime PA was 0.74, occupational lifetime PA was 0.87, household PA was 0.77 and recreational PA was 0.72 indicating high reliability. This questionnaire measures all types of PA, occupational, transportation, household and recreational physical activities from childhood to time of interview, reporting the frequency, duration and intensity of PA (Appendix A). Prior to the interview, participants received two recall calendars as memory aids to complete. One calendar allowed participants to recall history of educational and occupational activities, while the other helped to remember the timing of major life events. Participants were asked to bring these recall calendars to their appointment where the LTPAQ interview was conducted. An interviewer trained in cognitive interviewing techniques used the calendars to help facilitate recall of PA history. Specifically, the cognitive interview techniques were used to ensure proper question comprehension, information retrieval, judgment and estimation, and the participants response formulation for the most accurate account of their PA history (Friedenreich et al., 1998).

Data for occupational activities included the description of the activity, age started, age stopped, and number of months per year, number of days per week, amount of time per day, and self-perceived intensity of the activity for both sedentary and non-sedentary activities. Next, the participant was asked if they had used an active form of transportation to get to or from that job. For transportation PA the mode of activity was recorded (walking, biking, running, or

rollerblading to their workplace; multiple modes of transportation were accepted) and the number of months per year, days per week, hours per day and the self-perceived intensity of the transportation PA. For household activity, the recorded information included a description of the activity, age started, age stopped, number of months per year, number of days per week, hours per day, and hours spent in intensity categories 2, 3 or 4. Interviewers explained the differences between the intensity categories for home activities, home repair and lawn and garden activities to ensure accurate reporting. The final section asked for the lifetime record of exercise and sports activities, defined as recreational PA, and asked for the description of the exercise or sport, the age started, age stopped, frequency of the activity (combination of days/week/month/year), time per activity and the self-perceived intensity of the activity. All documents used to explain self-perceived intensity levels to participants can be found in Appendix B. Upon completion of the interview, all LTPAQs underwent quality control by an experienced interviewer to ensure that all coding and quantities were correctly done. Each questionnaire was entered into Blaise ©, a computer assisted interview system. These data were then exported into a Structured Query Language (SQL) database and converted into a STATA © dataset.

Lifetime total PA was the main exposure for this study. Intensities were assessed in two ways: 1) by self-report as sedentary (only for occupational activity described as activities sitting down), light, moderate, and vigorous activity (detailed description of self-reported intensity levels for each type of activity are found in Appendix B) and 2) as assigned by the study staff (a combination of self-report and activity description). For the latter approach, a MET value for each reported activity was assigned based on the *Compendium of Physical Activities* (Ainsworth et al., 2011). A MET is defined as the ratio of the associated metabolic rate for an activity compared to the resting metabolic rate. For example, one MET is equivalent to the amount of

oxygen that is metabolized while at rest in a seated position, and is approximately 3.5 mL/kg/min of oxygen consumption ($\dot{V}O_2$; normalized to body mass) (Jette et al., 1990). The main exposure variable for these analyses was the average MET-hours/week/year of lifetime PA estimated as the sum of occupational, transportation, household and recreational activity done from childhood to time of LTPAQ interview. Additional analyses by type of activity, dose and a subset of time period in life (ages <20, 21-35, 36-50, 51-65 years) were conducted. Past year PA measures were also abstracted from the LTPAQ to perform *post-hoc* analyses.

2.4.2 Neuropsychological Assessment

Data on cognitive functioning was obtained through a 2.5-hour neuropsychological test battery administered by trained study staff. The test battery was composed of eleven tests assessing seven cognitive domains. These domains include verbal memory, figural memory, processing speed, executive functioning, complex attention, verbal knowledge, and spatial reasoning. Descriptions of the neuropsychological tests corresponding to these domains of cognitive activity are listed in Table 4. The test battery is consistent with, but considered harder than the National Institute of Neurological Disorders and Stroke–Canadian Stroke Network Vascular Cognitive Impairment Harmonization Standards (Hachinski et al., 2006). Each of the seven cognitive domains received a corresponding score that was calculated by taking the average z-score of all tests/component scores within each domain, and the global cognition score is the sum of the seven equally weighted domain scores. The primary analyses used the global cognition z-score as the main outcome and secondary analyses focused on executive functioning, processing speed, and memory since these domains have previously been shown to correlate with PA and exercise (Chang et al., 2010; Eskes et al., 2010). The North American Adult Reading

Test (NAART) was completed during the neuropsychological assessment to obtain a measure of verbal intellectual ability (Blair & Spreen, 1989). NAART is sensitive to education (both formal and informal) and insensitive to mild forms of cognitive impairment, making it a better covariate than formal education when assessing cognitive abilities in older adults (Uttl, 2002).

2.4.3 Assessment of Indices of Cerebrovascular Blood Flow

To obtain measures of cerebrovascular health and functioning participants underwent a two-hour assessment administered by trained staff. Two hours prior to testing, participants refrained from eating or drinking anything other than water and refrained from engaging in exercise the day of testing. Blood flow velocity of the middle cerebral artery (MCAv) was measured non-invasively using a 2-MHz pulsed transcranial Doppler ultrasound system (TCD; Toc Neurovision™, Multigon Industries, Inc., Yonkers, NY), search techniques described elsewhere (Aaslid, Markwalder, & Nornes, 1982; Poulin, Liang, & Robbins, 1996; Poulin & Robbins, 1996). Maximum peak MCAv, heart rate (HR), blood pressure (beat-by-beat using finger pulse photoplethysmography, Finometer, Finapres Medical Systems, Amsterdam, The Netherlands; corroborated with three resting brachial measurements), and arterial O_2 saturation (finger pulse oximetry; 3900p, Datex-Ohmeda, Madison, WI, USA) were measured continuously throughout the protocol, as previously described (Brown et al., 2010). Dedicated software (Chamber, University Laboratory of Physiology, Oxford, UK) recorded end-tidal P_{CO2} and P_{O2} during 10 minutes of seated rest; MCAv, HR, and arterial blood pressures and O_2 saturation were also continuously monitored during this period. Each participant had their nose occluded and breathed room air through a mouthpiece. A fine capillary line inserted in a port immediately distal to the mouthpiece and connected to a mass spectrometer (AMIS 2000, Innovision, Odense,

Denmark) measured the concentration of O_2 and CO_2 continuously at the mouth, and specialized software allowed the determination of breath-by-breath values for end tidal CO_2 (PET_{CO2}) and O_2 (PET_{O2}). These end-tidal responses were averaged over the 10 minutes of rest and were used to determine the desired PET_{CO2} and PET_{O2} to assess the cerebrovascular response to the euoxic hypercapnia testing. Accurate control of desired PET_{CO2} and PET_{O2} values were continuously achieved using customized software (BreatheM v2.40, University Laboratory of Physiology, Oxford, UK), dynamic end-tidal forcing technique (Poulin et al., 1996; Poulin, Liang, & Robbins, 1998), and experimental protocols (Brown et al., 2010, Tyndall et al., 2013), as previously described. The euoxic hypercapnia test lasted 12 minutes and included two 3-minute step increases in PET_{CO2}. Participants breathed only room air for the first minute, followed by a 5-minute period during which PET_{CO2} was held constant at +1.0 mmHg above each participant's resting PET_{CO2} value. Again, using a step change, PET_{CO2} was increased to +5.0 mmHg above normal resting values for three minutes and further increased to +8.0 mmHg above resting values for an additional 3-minute period. The physiological responses (see next paragraph) were calculated as the mean response over the final 30 seconds of each stage (i.e., +1.0, +5.0 and +8.0 mmHg) during the hypercapnic challenge.

This protocol produced four measures of cerebrovascular function for analysis including peak velocity of blood moving through the MCA ($\bar{V}_P$), cerebrovascular conductance (CVC) which is the change in $\bar{V}_P$ divided by the change in mean arterial blood pressure obtained at +1 mmHg PET_{CO2}, and $\bar{V}_P$ and CVC reactivity during the hypercapnic challenge. Specifically $\bar{V}_P$ reactivity was calculated as the change in $\bar{V}_P$ divided by the change in PET_{CO2} from +1 to +8 mmHg while CVC reactivity is the change in CVC divided by the change in PET_{CO2} from +1 to +8 mmHg.

2.4.4 Demographic Information and Confounding Variables

In addition to baseline testing, information on participant's socio-demographic, health and lifestyle, maximal aerobic capacity ($\dot{V}O_2$max), anthropometric, and blood work were obtained. Health and lifestyle information was collected through self-reported questionnaires and included mood assessed using the Profile of Mood State questionnaire (Nyenhuis, Yamamoto, Luchetta, Terrien, & Parmentier, 1999), alcohol consumption and dietary intake assessed with the Canadian Diet History Questionnaire I (DHQI) (Csizmadi et al., 2007), hypertensive status (based on resting blood pressure measures and medications reported) and smoking history. To assess maximal aerobic capacity a $\dot{V}O_2$max test was performed using a motorized treadmill following the Bruce protocol (Paterson, Cunningham, Koval, & St Croix, 1999) described elsewhere (Tyndall et al., 2013). Anthropometric measures were taken by trained staff and included height, weight, BMI, percent body fat (obtained from bioelectrical impedance analysis), waist circumference and waist to hip ratio. To collect participants blood lipid profile, a 12-hour fasted venous blood draw was performed to provide measures of cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), total high density lipoprotein (total HDL), triglycerides and fasting glucose (all mmol/L). For participants who provided additional genetic consent, a blood sample was taken for genetic testing that includes *APOE* ε4 genotyping.

2.5 Data Analyses

2.5.1 Preliminary Descriptive Analysis

Descriptive statistics were prepared to characterize the study sample and examine sex differences (Table 5). Spearman's correlations were used to assess the relationship between all continuous predictor variables to determine the presence of collinearity. If two variables were

highly correlated (>0.6), it was decided which variable would be used for analysis. For the categorical variables Analysis of Variance (ANOVA) and chi-square tests were used to identify between-group difference. If these tests were significant ($p<0.05$), this indicated the variables were highly associated and only one would be used for analysis.

The distribution of the primary (cognitive functioning) and secondary (cerebrovascular regulation) outcome variables were tested for normality using the Wilk-Shapiro test (Shapiro & Wilk, 1965). These variables were not normally distributed based on the p-value from the Wilk Shapiro test (global cognitive function $p= 0.00002$, all CBF measures $p<0.05$). Log transformations were best suited for these data, however the Wilk Shapiro test indicated the transformation did not resolve the normality issues.

2.5.2 Regression mediation analysis

Linear regression modeling was proposed because of the continuous nature of the lifetime PA variables and global cognition scores and indices of cerebrovascular function, however since these variables were not normally distributed as is required for linear regression, robust linear regression was used. Initially, a backwards-stepwise method for robust regression was used. Continuous variables considered as confounders were age, NAART, years of education, mood, $\dot{V}O_2$max, blood pressure, BMI, percent body fat, waist circumference, waist to hip ratio, cholesterol, HDL, LDL, total HDL, triglycerides, fasting glucose, alcohol consumption and calories consumed per day (kcal). The categorical variables considered were sex, marital status, income, retirement status, education classification, hypertensive status, hypercholesterolemia, smoking status and *APOE* ε4 genotype (ensuring highly correlated variables were not in the model concurrently). Confounders were included in the final model if

the change in the β coefficient was greater than 15%; if this change was less than 15% the confounder was not included since it did not confound the relationship of interest. Confounders were forced into the model if they were considered a key biologic variable of importance (age, sex, NAART, *APOE* ε4 genotype, BMI and blood pressure (Brown et al., 2010; Kivipelto et al., 2008; van Gelder et al., 2004; Wendell et al., 2014) regardless of the percent change that was observed and only if they improved the variance explained by the model. The final covariates, age, sex, NAART, $\dot{V}O_2$max, BMI, and interactions between age, sex, and predictor (age-sex, age-predictor, sex-predictor and age-sex-predictor) were chosen using both stepwise regression and assessment of the coefficient of determination (model R^2).

To characterize the relation between lifetime PA and cognitive functioning while properly addressing the potential mediating effects of cerebrovascular regulation, a series of robust linear regression models was used to perform mediation analysis (Baron & Kenny, 1986). Figure 2 depicts the relationships that were modeled. The overall analytical framework was broken down into a four-model approach as outlined in Table 6. In this approach, robust linear regression analysis was performed for each of the relations being tested, and the same covariates included as predictors in the regression between lifetime PA and global cognition (model 1) were adjusted for in each subsequent model to ensure congruency. The coefficients from each model were used to determine if the proposed relation being tested by each linear model is significant. This statistical method individually examined each proposed objective, while also determining if mediation of the overall relationship is present.

Models one through three (identified in Table 6) examined if the relation between the proposed variables was significant (Baron & Kenny, 1986). If the regression coefficients for the first three models was not significant then it was concluded that cerebrovascular regulation did

not mediate the relation between lifetime PA and cognitive functioning, however if all the regression coefficients from models one through three were significant the robust linear regression for model four could be performed. Model four was used to determine if there was partial or full mediation. Partial mediation occurred when both lifetime PA and cerebrovascular regulation predicted cognitive functioning, while full mediation was when lifetime PA was no longer significant when cerebrovascular regulation was controlled for (Baron & Kenny, 1986). The indirect effect was when lifetime PA affected cognitive functioning through both direct and indirect pathways. Upon completing all four models the indirect effect could be calculated and tested for significance. To test the indirect effect two linear regressions (Table 7) were used (Sobel, 1982).

The regression coefficient for the indirect effect represents the change in cognitive functioning for every unit change in lifetime PA that is mediated by cerebrovascular regulation. In order to estimate the indirect coefficient the coefficients from models five and six would be multiplied: $\beta_{indirect} = (\beta_2)(\beta)$ (Sobel, 1982). This results in a product from the partial regression effect for cerebrovascular regulation predicting cognitive functioning, β_2 and the simple coefficient for lifetime PA predicting cerebrovascular regulation, β. To test the significance of the indirect effect (mediating effects), $\beta_{indirect}$, both bootstrapping for standard errors (Shrout & Bolger, 2002) and the Sobel test will be performed (Sobel, 1982) (i.e. testing if lifetime PA has a significant indirect link with cognitive functioning via cerebrovascular regulation). Both methods are used to ensure the same results and confirm the findings. All statistical analyses are conducted in STATA© version 13.0 (StataCorp, 2013).

2.6 Chapter Two Figures and Tables

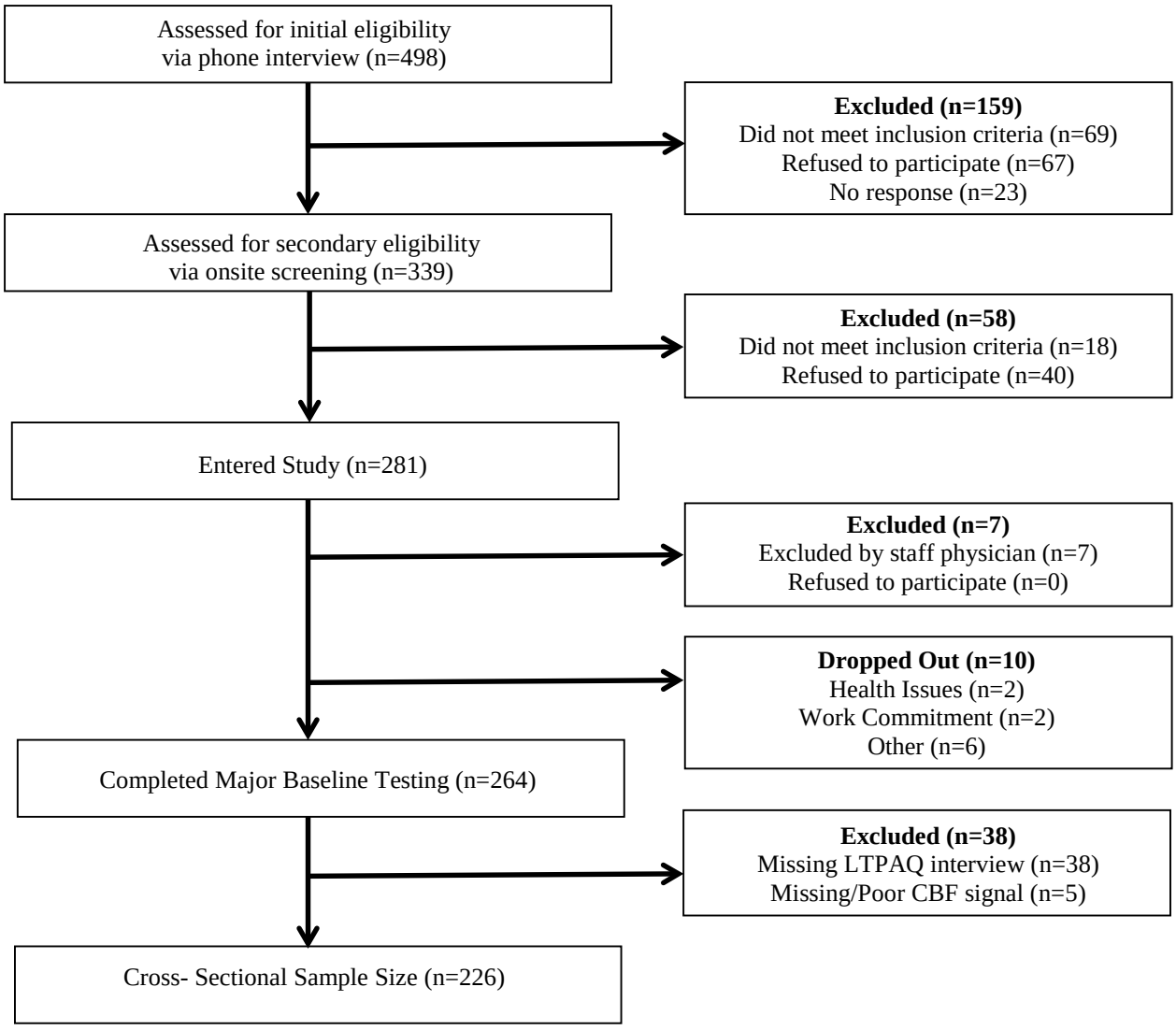


Figure 1. Participant flow for the *Brain in Motion* Study, Calgary, Alberta, Canada.

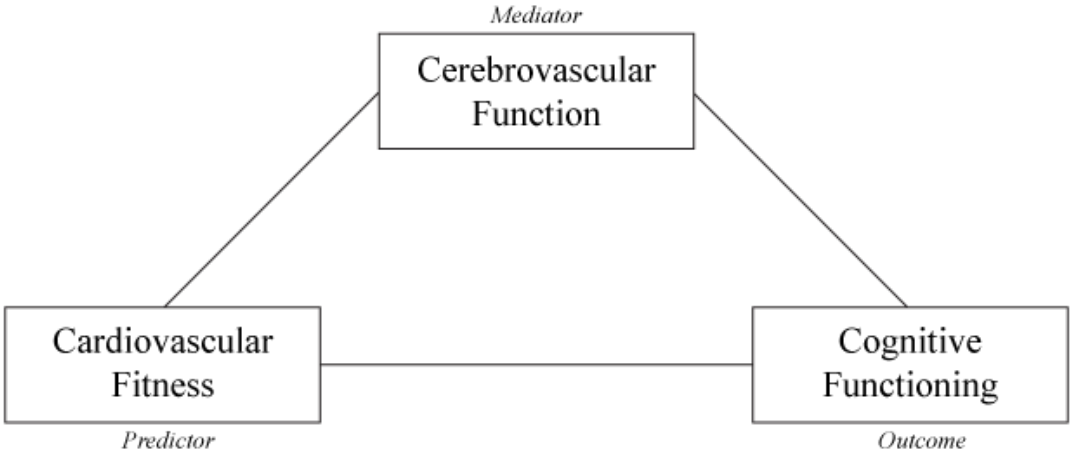


Figure 2. Mediation analysis analytical framework

Table 4. Seven cognitive domains with corresponding neuropsychological tests administered during the neuropsychological assessment for the *Brain in Motion* Study, Calgary, Alberta, Canada.

Cognitive Domain	Neuropsychological Test
Verbal Memory	Buschke Selective Reminding Test Delayed Recall
	Buschke Selective Reminding Test Immediate Recall
Figural Memory	Medical College of Georgia Complex Figures Test Delayed
	Medical College of Georgia Complex Figures Test Immediate
Processing Speed	D-KEFS Color Word Interference Color time
	D-KEFS Color Word Interference Word time
	Symbol-Digit Modalities Test Oral score
	Symbol-Digit Modalities Test Written score
Executive Function	D-KEFS Color Word Interference Switch time
	D-KEFS Color Word Interference Inhibit time
	D-KEFS Verbal Fluency Category Switching
	D-KEFS Verbal Fluency Test Target Words Correctly Produced
	D-KEFS Card sorting Recognition Description score
	D-KEFS Card sorting Free Sort Description score
	D-KEFS Card Sorting Free Sort: Number of Correct Sorts
Complex Attention	ACT Perseverations
	ACT Total Correct
Verbal Knowledge	D-KEFS Verbal Fluency Test: Category Fluency Score
Spatial Reasoning	Medical College of Georgia Complex Figures Test: Copy

Abbreviations: D-KEFS = Delis-Kaplan Executive Function System; ACT= Auditory Consonant Trigrams

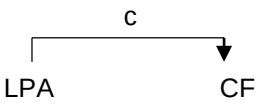
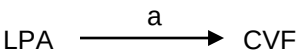
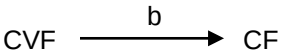
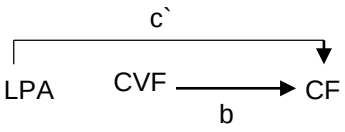
Table 5. Baseline characteristics for male and female participants (n=226) in the *Brain in Motion* Study, Calgary, Alberta.

Variable	Male		Female		Total		P value
	N		N		N		
Demographics							
Age (years): M (SD)	108	67.0(6.9)	118	66.1(6.0)	226	66.5(6.4)	.330
Marital Status (%)	108		118		226		
Married/Common Law	97	89.8%	86	72.9%	183	81.0%	.005
Widowed/Divorced	9	8.3%	27	22.9%	36	15.9%	
Single	2	1.9%	5	4.2%	7	3.1%	
Income (%)	108		115		223		
$20,000 to $59,999	5	4.6%	16	13.9%	21	9.4%	.074
$60,000 to $99,999	24	22.2%	31	27.0%	55	24.7%	
$100,000 to $139,999	37	34.3%	29	25.2%	66	29.6%	
$140,000 to $179,999	23	21.3%	17	14.8%	40	17.9%	
$180,000 to $200,000+	19	17.6%	22	19.1%	41	18.4%	
Retirement Status (%)	108		118		226		
Yes	52	39.8%	74	62.7%	126	55.8%	.084
Semi	13	12.0%	9	7.6%	22	9.7%	
No	43	39.8%	35	29.7%	78	34.7%	
Education Level (%)	108		118		226		
Less than a Bachelors Degree	37	34.3%	57	48.3%	94	41.6%	.032
Bachelors degree or greater	71	65.7%	61	51.7%	132	58.4%	
Education(years): M (SD)	108	16.3(2.8)	118	15.7(2.2)	226	16.0(2.5)	.080
NAART: M (SD)	107	110(6.9)	116	111.2(6.0)	223	110.6(6.4)	.160
Health Status							
$\dot{V}O_2$max fitness (ml/kg/min): M (SD)	108	28.9(5.0)	118	23.6(4.4)	226	26.2(5.4)	<.001
Blood Pressure (mm Hg)							
Systolic: M (SD)	108	126.24(14.44)	118	123.98(16.90)	225	125.06(15.78)	.280
Diastolic: M (SD)	108	75.12(7.31)	118	70.04(9.08)	225	72.45(8.65)	<.001
Hypertensive (% yes)	62	57.4%	118	50.9%	226	54.0%	.360
Weight (kg): M (SD)	108	87.0(11.3)	118	70.2(11.9)	226	78.3(14.3)	<.001
BMI (kg/m^2): M (SD)	108	28.0(3.4)	118	26.6(4.1)	226	27.3(3.9)	.005
Percent Body Fat: M(SD)	105	26.9(5.2)	118	37.1(5.1)	223	32.3(7.2)	<.001
Waist Circumference (cm): M (SD)	105	101.7(9.7)	118	91.9(11.7)	223	96.5(11.8)	<.001
Waist to Hip Ratio: M (SD)	105	0.99(0.05)	118	0.90(0.07)	223	0.94(0.076)	<.001

Variable	Male		Female		Total		P value
	N		N		N		
Blood Lipid Profile *(all mmol/L: M (SD))*							
Cholesterol	108	5.18(0.94)	118	5.40(0.92)	226	5.30(0.94)	.080
HDL	108	1.38(0.36)	118	1.80(0.55)	226	1.60(0.51)	<.001
LDL	108	2.98(0.81)	118	3.21(0.81)	226	3.10(0.82)	0.03
Total HDL	108	3.83(1.13)	118	3.33(1.06)	226	3.57(1.12)	<.001
Triglycerides	108	1.46(0.68)	118	1.20(0.47)	226	1.32(0.59)	.001
Fasting Glucose	108	5.63(0.73)	117	5.32(0.72)	226	5.47(0.74)	.001
Genetic Characteristics	104		113		217		
APOE ε4 - (%)	70	69.3%	87	78.4%	157	74.1%	.130
APOE ε4 + (%)	31	30.7%	24	21.6%	55	25.9%	
Lifestyle							
Alcohol consumption (g/day): M (SD)	87	13.4(16.4)	98	9.4±15.0	185	11.3(15.7)	.090
Calories consumed per day: M (SD)	87	1803.2(668.9)	98	1423.8(496.9)	185	1602.2(612.6)	<.001
Smoking status (% Ever smoked)	108	53.70%	118	39.83%	226	46.46%	.040
Indices of Cerebrovascular Blood Flow (*M (SD)*)							
$\bar{V}$P	106	49.1(11.4)	116	56.9(12.4)	222	53.1(12.5)	<.001
CVC	106	0.5(0.1)	116	0.7(0.2)	222	0.6(0.2)	<.001
$\bar{V}$P reactivity	106	2.1(0.9)	116	2.3(1.0)	222	2.2(0.9)	0.200
CVC reactivity	106	0.01(0.007)	116	0.01(0.01)	222	0.01(0.009)	0.210

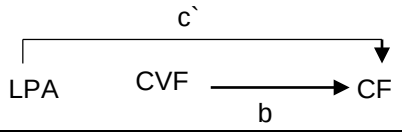
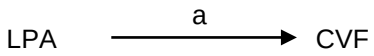
Abbreviations: NAART = North American Adult Reading Test; $\dot{V}O_2$max = Maximal oxygen uptake; BMI = Body mass index; HDL = High density lipoprotein cholesterol; LDL = Low density lipoprotein cholesterol; *APOE* ε4 = Apolipoprotein ε4 genotype; $\bar{V}$P = blood flow velocity at +1 mmHg; CVC = cerebrovascular conductance at +1 mmHg; $\bar{V}$P reactivity= blood flow reactivity to a hypercapnic challenge from +1 mmHg to +8 mmHg; CVC reactivity= cerebrovascular conductance reactivity to a hypercapnic challenge from +1 mmHg to +8 mmHg.

Table 6. Models used in the steps to perform mediation analysis for the association between lifetime physical activity, cognitive function and cerebrovascular function.

	Analysis	Visual
Model 1	Robust regression analysis with lifetime PA predicting cognitive functioning to test for path c alone. C $=\beta_0 + \beta_1 P + \varepsilon$	
Model 2	Robust regression analysis with lifetime PA predicting cerebrovascular regulation to test for path a alone. B $=\beta_0 + \beta_1 P + \varepsilon$	
Model 3	Robust regression analysis with cerebrovascular regulation predicting cognitive functioning to test the significance of path b alone. C $=\beta_0 + \beta_1 B + \varepsilon$	
Model 4	Multiple regression analysis with lifetime PA and cerebrovascular regulation predicting cognitive functioning, testing the combined effect. C $=\beta_0 + \beta_1 P + \beta_2 B + \varepsilon$	

*Legend: LPA & P: lifetime PA; CF and C: cognitive functioning; CVF and B: cerebrovascular function. Models are shown in a simplified presentation omitting potential effect modifiers and confounders. Based on findings from previous research, the same significant confounders, such as age, sex, education, *APOE* ε4 genotype, BMI and blood pressure will be adjusted for in each model (Brown et al., 2010; Kivipelto et al., 2008; van Gelder et al., 2004; Wendell et al., 2014).

Table 7. Models for examining the overall effect of lifetime physical activity on cognitive function and the effect of lifetime physical activity on cerebrovascular function to determine the indirect relationship mediated by cerebrovascular function.

	Analysis	Visual
Model 5	C =$\beta_0 + \beta_1 P + \beta_2 B + \varepsilon$	
Model 6	B =$\beta_0 + \beta P + \varepsilon$	

*Legend: LPA & P: lifetime PA; CF and C: cognitive functioning; CVF and B: cerebrovascular function. a: direct effect, b and c`: indirect effects. Models are shown in a simplified presentation omitting potential effect modifiers and confounders.

Chapter Three: **Association Between Lifetime Physical Activity and Cognitive Functioning in Older Community Dwelling Adults: Results from the *Brain in Motion* Study**

The contents of this chapter have been accepted for publication as a manuscript in the Journal of the International Neuropsychological Society special issue 'Physical Activity and Brain Plasticity'. Please see Appendix D.

Furthermore, this work has been accepted as a Poster Presentation at the following conferences:

Gill S., Friedenreich C., Sajobi T., Longman R.S., Drogos L., Davenport M., Tyndall A., Eskes A., Hogan D., Hill M Parboosingh J., Wilson B. and M.J.Poulin. *Association between lifetime physical activity and cognitive functioning in older community dwelling adults.* Abstract accepted for Poster presentation at the Society for Neuroscience 45th Annual meeting: Neuroscience 2015 on October 21st, 2015 in Chicago USA. Abstract Control Number: 10067.

Gill S., Friedenreich C., Sajobi T., Longman R.S., Drogos L., Davenport M., Tyndall A., Eskes A., Hogan D., Hill M Parboosingh J., Wilson B. and M.J. Poulin. *Association between lifetime physical activity and cognitive functioning in older community dwelling adults.* Abstract accepted for Poster presentation at the Canadian Association on Gerontology 44th Annual Scientific and Educational Meeting 2015 on October 24th, 2015 in Calgary Canada.

3.1 Abstract

OBJECTIVE

To determine if total lifetime physical activity (PA) is associated with better cognitive functioning with aging and if cerebrovascular function mediates this association.

METHODS

A sample of 226 (52.2% female) community dwelling middle-aged and older adults (66.5±6.4 years) in the *Brain in Motion* Study, completed the Lifetime Total Physical Activity Questionnaire and underwent neuropsychological and cerebrovascular blood flow testing. Multiple robust linear regressions were used to model the associations between lifetime PA and global cognition after adjusting for age, sex, North American Adult Reading Test results (i.e., an estimate of premorbid intellectual ability), maximal aerobic capacity, body mass index and interactions between age, sex, and lifetime PA. Mediation analysis assessed the effect of cerebrovascular measures on the association between lifetime PA and global cognition. *Post-hoc* analyses assessed past year PA and current fitness levels relation to global cognition and cerebrovascular measures.

RESULTS

Better global cognitive performance was associated with higher lifetime PA ($p=0.045$), recreational PA ($p=0.021$), vigorous intensity PA ($p=0.004$), PA between the ages of 0 and 20 years ($p=0.036$), and between the ages of 21 and 35 years ($p<0.0001$). Cerebrovascular measures did not mediate the association between PA and global cognition scores ($p>0.5$), but partially mediated the relation between current fitness and global cognition.

CONCLUSION

This study revealed significant associations between higher levels of PA (i.e., total lifetime, recreational, vigorous PA and past year) and better cognitive function in later life. Current fitness levels relation to cognitive function may be partially mediated through current cerebrovascular function.

MeSH Terms: Humans, Aging, Exercise, Prevention, Cerebrovascular Function, Questionnaires

Abbreviations: CBF- Cerebral Blood Flow, CVC- Cerebrovascular Conductance at +1 mmHg, LTPAQ-Lifetime Physical Activity Questionnaire**,** MCAv- Middle Cerebral Artery Velocity, MET- metabolic equivalents, NAART-North American Adult Reading Test, PA- Physical Activity, $\dot{V}O_2$ max- maximal aerobic capacity, $\bar{V}_P$ - blood flow velocity at +1 mmHg.

3.2 Introduction

Normal aging may result in structural and functional modifications to the brain, such as a reduction in brain volume (Good et al., 2001; Peelle, Cusack, & Henson, 2012), decline in resting cerebral blood flow (CBF) (Brown et al., 2010; Zimmerman et al., 2014), and cerebrovascular reactivity (Barnes, Taylor, Kluck, Johnson, & Joyner, 2013; Brown et al., 2010). These changes in cerebrovascular health and cell integrity have been associated with an increased risk of stroke (Gupta et al., 2012), premature mortality (Portegies, de Bruijn, Hofman, Koudstaal, & Ikram, 2014; Sabayan et al., 2013), Alzheimer's disease and related dementias (Amieva et al., 2005; Lautenschlager, Cox, & Cyarto, 2012) and declining cognitive function (Davenport, Hogan, Eskes, Longman, & Poulin, 2012; Matteis, Troisi, Monaldo, Caltagirone, & Silvestrini, 1998). Physical activity (PA) has been identified as one of the most promising modifiable lifestyle factors for improving cerebrovascular health (Ainslie et al., 2008; Bailey et al., 2013; Brown et al., 2010; Chapman et al., 2013; Prakash, Voss, Erickson, & Kramer, 2015; Tarumi et al., 2013) and preventing age-associated cognitive decline (Abbott et al., 2004; Buchman et al., 2012; Laurin, Verreault, Lindsay, MacPherson, & Rockwood, 2001b; Rovio et al., 2005; Scarmeas, Luchsinger, Schupf, Brickman, et al., 2009; Tarumi et al., 2013). Furthermore, the benefits of PA include increased cerebrovascular function (Ainslie et al., 2008; Bailey et al., 2013; Brown et al., 2010; Burdette et al., 2010; Chapman et al., 2013; Davenport et al., 2012), decreased risk of cerebrovascular and cardiovascular diseases (Qiu & Fratiglioni, 2015) and a decreased risk of Alzheimer's disease and related dementias (de Bruijn et al., 2013; Nation et al., 2013; Rovio et al., 2005).

Previous research indicates that older adults who engage in more physically active recreational activities or have higher cardiovascular fitness are at lower risk for cognitive decline

compared to inactive older adults (Blondell, Hammersley-Mather, & Veerman, 2014; Colcombe et al., 2004; Forbes, Thiessen, Blake, Forbes, & Forbes, 2013; Kramer et al., 1999; Prakash et al., 2015; Prakash et al., 2011). Attention has been focused on the effects of current leisure time or recreational PA on cognitive function, demonstrating the potential importance of remaining active in older age (Rovio et al., 2005; Weuve et al., 2004; Yaffe, Barnes, Nevitt, Lui, & Covinsky, 2001). For example, in females ≥ 65 years, walking more than three times per week was associated with a decreased risk of cognitive decline (Yaffe et al., 2001). Rovio et al. (2005) demonstrated that leisure-time PA in midlife (age 44 -57) is associated with a decreased risk of dementia in late life, while Verghese et al. (2003) showed increased participation in leisure activities for individual's ≥75 years old reduced the risk of developing dementia and Alzheimer's disease.

Physical activity can be measured using metabolic equivalents (MET). A MET is defined as the ratio of the associated metabolic rate for an activity compared to the resting metabolic rate. One MET is equivalent to the amount of oxygen that is metabolized while at rest in a seated position, and is approximately 3.5 mL/kg/min of oxygen consumption ($\dot{V}O_2$; normalized to body mass) (Jette, Sidney, & Blumchen, 1990). With increasing intensity of PA, the MET value increases; for example a 3 MET activity is achieved by walking at 2.5 miles per hour on a flat firm surface, while cross country hiking is rated as a 6 MET activity (Ainsworth et al., 2011). It has been demonstrated that increasing MET-hours/week spent in recreational and household activities over the past two weeks is associated with a lower risk of dementia (de Bruijn et al., 2013), and increasing MET-hours/week of leisure time PA over the past year resulted in increased mean cognitive scores (Weuve et al., 2004).

Cerebrovascular health and function can be measured using indices of resting CBF and

cerebrovascular reactivity. Cerebrovascular reactivity is the magnitude of change in CBF for a given stimulus (e.g., increased partial pressure of CO_2 (PCO_2)), with enhanced vascular reactivity thought to represent better cerebrovascular function and health (Brown et al., 2010; Davenport et al., 2012). Previous research provides evidence suggesting that increased levels of PA or cardiovascular fitness are associated with improved cerebrovascular functioning (Ainslie et al., 2008; Bailey et al., 2013; Burdette et al., 2010), with additional studies indicating that cerebrovascular functioning is also associated with improved neurocognitive function within the same sample (Brown et al., 2010; Chapman et al., 2013; Tarumi et al., 2013). Reduced cerebrovascular functioning has been proposed as a mechanism underlying cognitive and cerebrovascular dysfunction (Davenport et al., 2012). Recently it has been shown that indices of cerebrovascular function mediate the relation between PA and cognition in healthy young adults providing support for the hypothesis that cerebrovascular health is a plausible pathway linking frequent PA and improved cognitive status (Guiney, Lucas, Cotter, & Machado, 2015). Specifically, more frequent PA was associated with enhanced cognitive control and this relationship was mediated by cerebrovascular reactivity to PCO_2, as per statistical mediation analysis (Guiney et al., 2015). Together these studies suggest that cardiovascular and cerebrovascular health may contribute to better cognitive functioning.

Dysfunction in both cognitive performance (Andel et al., 2008; Rovio et al., 2005; Yaffe et al., 2001) and cerebrovascular functioning (Tarumi et al., 2013) can begin in midlife (i.e. ~40-60 years old) rather than exclusively in old age (Kareholt, Lennartsson, Gatz, & Parker, 2011). Previous research has highlighted the need for additional investigations addressing the influence of PA on cognitive abilities throughout the lifespan to complement current work that focuses attention on periods more proximate to the onset of disease. Our study addresses this knowledge

gap regarding the effects of lifetime total PA on cognitive and cerebrovascular outcomes in mid to later life while examining potential sex differences in these outcomes. Sex differences were considered as there is evidence suggesting that males and females have different physiological responses to PA (Brown, Peiffer, & Martins, 2013; Colcombe & Kramer, 2003; Ho, Woo, Sham, Chan, & Yu, 2001; Laurin, Verreault, Lindsay, MacPherson, & Rockwood, 2001a). A variety of mixed sex studies have found that exercise positively impacts both sexes; however, the effects of increased exercise on cognitive functioning seem to be more pronounced in women (Brown et al., 2013; Ho et al., 2001; Laurin et al., 2001a). Additionally, when studying cognition in a mixed-sex study it is important to account for sex differences (Kimura, 2002; Kimura & Hampson, 1994).

This study tests the mediating effect of current cerebrovascular health on the relation between measures of lifetime PA and current cognitive functioning. We hypothesized that increased lifelong PA is associated with better global cognition and cerebrovascular function is associated with current cognitive performance, completing the proposed mediation relationship.

3.3 Methods

3.3.1 Research Participants

The study population comprised participants in an ongoing intervention-cohort study on the effects of a six-month aerobic exercise intervention on cerebrovascular regulation and cognitive function in middle-aged and older adults. The *Brain in Motion* study methods and protocol for the eligibility screening process has been previously described (Tyndall et al., 2013). Participants (n=264) are healthy, community dwelling, currently inactive, middle-aged and older adults and were recruited through the use of media, posters and advertisements in local newspapers, communities, and through the University of Calgary. Eligibility criteria included: English speaking males or females ≥55 years old, considered currently inactive (< 30 minutes of moderate exercise four days/week or 20 continuous minutes of vigorous exercise two days/week), able to walk independently outside and up and down at least 20 stairs, a body mass index (BMI) less than 35 kg/m^2 (to avoid co-morbidities associated with obesity), no history of clinically active cardiovascular disease or obstructive airway disease, non-smoker for the past 12 months, no major trauma or surgery in the last six months, no debilitating neurological disorders, physician clearance, and written informed consent. A detailed flow of participants is provided in Figure 3. The sample consists of participants who completed the *Lifetime Total Physical Activity Questionnaire* (LTPAQ) in addition to the neuropsychological assessment, and the cerebrovascular blood flow test (n=226) at baseline. The University of Calgary Conjoint Health Research Ethics Board approved all study procedures.

3.3.2 Assessment of Lifetime Physical Activity

Lifetime total PA was assessed using the interviewer-administered LTPAQ, a tool with demonstrated reliability (Friedenreich, Courneya, & Bryant, 1998). This questionnaire assesses occupational, transportation, household and recreational physical activities from childhood to time of interview. Additionally, the frequency, duration and intensity of PA are also reported. Prior to the interview, participants received two recall calendars as memory aids to complete. An interviewer trained in cognitive interviewing techniques used the calendars to help facilitate recall of PA history.

Lifetime total PA was the main variable of interest for this study. Intensities were assessed in two ways: 1) by self-report as sedentary (only for occupational activity described as activities sitting down), light (activities done mainly standing that do not increase heart rate and cause no sweating), moderate (activities that cause heart rate to increase slightly and cause light sweating) and vigorous activity (activities that cause heart rate to increase substantially and cause heavy sweating) and 2) as assigned by the study staff. For the latter approach, a MET value for each reported activity was assigned based on the *Compendium of Physical Activities* (Ainsworth et al., 2011). The main predictor for these analyses was the average MET-hours per week per year of life (MET-hour/week/year) of lifetime PA estimated as the sum of occupational, transportation, household and recreational activity done from childhood to time of LTPAQ. For this study, additional analyses by type of activity, intensity of activity (0-3 METs: low, 3-6 METs: moderate and >6 METs: Vigorous) and activity during different age period in life (ages <20, 21-35, 36-50, 51-65 years) were conducted.

3.3.3 Neuropsychological Assessment

This assessment consisted of a two and a half hour neuropsychological test battery administered by trained staff. The test battery was composed of eleven tests assessing seven cognitive domains including verbal memory, figural memory, processing speed, executive functioning, complex attention, verbal knowledge, and spatial reasoning. The list of neuropsychological tests corresponding to these domains of cognitive activity are displayed in Table 14 (Supplemental Material), and a detailed description has been previously published (Tyndall et al., 2013). Seven cognitive domain scores were calculated by taking the average z-score of all tests within each domain. The global cognition score is the sum of seven equally weighted domain z-scores, used as the cognitive outcome for all analyses. At the time of the cognitive assessment participants also completed the North American Adult Reading Test (NAART) as a measure of premorbid verbal intellectual ability (Blair & Spreen, 1989). The NAART is sensitive to education (both formal and informal) and insensitive to mild forms of cognitive impairment, making it a better covariate than formal education when assessing cognitive abilities (Uttl, 2002).

3.3.4 Assessment of Indices of Cerebrovascular Blood Flow

Participants underwent a two-hour assessment administered by trained staff. Two hours prior to testing, participants fasted and refrained from exercising. Blood flow velocity of the middle cerebral artery (MCAv) was measured using a 2-MHz pulsed transcranial Doppler ultrasound system recording measurements at an optimal placement slightly above and in front of the right ear (Aaslid, Markwalder, & Nornes, 1982; Poulin, Liang, & Robbins, 1996; Poulin & Robbins, 1996). Peak MCAv, heart rate, beat-by-beat blood pressure measurements and arterial

O_2 saturation were measured continuously throughout the protocol. Dedicated software recorded the exhaled CO_2 and O_2 at the end of each breath (referred to as end-tidal P_{CO2} and P_{O2}) during 10 minutes of seated rest. Each participant had his/her nose occluded with a nose clip and breathed room air through a mouthpiece. A fine capillary line inserted in a port immediately distal to the mouthpiece and connected to a mass spectrometer measured the concentration of CO_2 and O_2 continuously at the mouth, and breath-by-breath values for end tidal CO_2 (PET_{CO2}) and O_2 (PET_{O2}) were determined. These end-tidal values were averaged over the 10 minutes of rest and were used to determine the desired PET_{CO2} and PET_{O2} to assess the cerebrovascular response to the changes in the pressure of CO_2, also referred to as euoxic hypercapnia testing. The euoxic hypercapnia test lasted 12 minutes and included two 3-minute step increases in PET_{CO2} as previously described (Brown et al., 2010; Tyndall et al., 2013). Physiological responses were calculated as the mean responses over the final 30 seconds of each stage during the hypercapnic challenges. A more technical description of the testing protocol can be found in the supplemental material.

This protocol yielded four measures of cerebrovascular function for analysis including peak velocity of blood moving through the MCA ($\bar{V}_P$), cerebrovascular conductance (CVC*; MCAv/Mean Arterial Pressure*), $\bar{V}_P$ and CVC reactivity during the hypercapnic challenge. Specifically $\bar{V}_P$ reactivity was calculated as the change in $\bar{V}_P$ divided by the change in PET_{CO2} from +1 to +8 mmHg while CVC reactivity is the change in CVC divided by the change in PET_{CO2} from +1 to +8 mmHg. These measures are widely used in the cerebrovascular literature employing transcranial Doppler ultrasound techniques (Aengevaeren, Claassen, Levine, & Zhang, 2013; Ainslie et al., 2008; Bailey et al., 2013; Barnes et al., 2013; Brown et al., 2010; Demirkaya, Uluc, Bek, & Vural, 2008; Murrell et al., 2013; Zhu et al., 2013).

3.3.5 Additional Measures

At baseline socio-demographic, health and lifestyle, maximal aerobic capacity ($\dot{V}O_2$ max) and anthropometric were obtained (Table 8). Health and lifestyle information was obtained through self-reported questionnaires and included mood, alcohol consumption and dietary intake assessed with the Canadian Diet History Questionnaire I (DHQI) (Csizmadi et al., 2007), hypertensive status (based on resting blood pressure measures and medications reported) and smoking history. Maximal aerobic capacity was obtained using a motorized treadmill following the Bruce protocol (Paterson, Cunningham, Koval, & St Croix, 1999) described elsewhere (Tyndall et al., 2013). Anthropometric measures were taken by trained staff and included height, weight, BMI, percent body fat (obtained from bioelectrical impedance analysis) and waist circumference. For participants who provided additional genetic consent, a blood sample was taken for genetic testing that included *APOE* ε4 genotyping.

3.3.6 Statistical Analyses

Descriptive statistics were prepared to characterize the study population and to examine differences between sexes. Continuous variables were summarized using means and standard deviations, while frequency distributions were used for categorical variables. Chi square tests were used to identify between-group differences for categorical variables and a Spearman's correlation was used to assess potential collinearity among predictor variables. The global cognition and sub-domain z-scores were calculated from raw data. Both cognitive and cerebrovascular outcome measures were assessed for normality using the Shapiro-Wilk test (Shapiro & Wilk, 1965). Continuous variables considered as confounders were age, NAART,

mood, $\dot{V}O_2$ max, blood pressure, BMI, percent body fat, waist circumference, waist to hip ratio, cholesterol, HDL, LDL, total HDL, triglycerides, fasting glucose, alcohol consumption and calories consumed/day. While the categorical variables considered were sex, marital status, income, retirement status, education, hypertensive status, hypercholesterolemia, smoking status and *APOE* ε4 genotype. Multiple robust linear regression analyses were used with all final lifetime PA models using lifetime PA predictors adjusting for age, sex, NAART, $\dot{V}O_2$ max, BMI and interaction terms (age-sex, age-predictor, sex-predictor, age-sex-predictor). Final covariates were chosen using both stepwise regression and assessment of the coefficient of determination (model R^2). All other variables were disregarded, since they did not improve the fit of the model. In subsequent analyses looking at the type, intensity and life period of PA, each respective grouping of activity was also controlled for (e.g. model for recreational PA adjusts for occupational and household activity). To characterize the relation between lifetime PA and cognitive functioning, while properly addressing the potential mediating effects of cerebrovascular indices (CVC, $\bar{V}_P$, CVC reactivity and $\bar{V}_P$ reactivity), mediation analysis was used (Baron & Kenny, 1986). To test the hypothesis that cerebrovascular function mediates the lifetime PA-cognitive functioning relation, the results of robust linear regression were assessed to determine if statistical significance (α=0.05) was achieved. The following inter-relations required for mediation were assessed: the predictor lifetime PA had to be significantly associated with both the outcome cognitive functioning and the mediator cerebrovascular regulation, and cerebrovascular regulation had to be significantly associated with cognitive functioning. If these relations were statistically significant, the Sobel's test was used to determine the significance of the indirect mediating effects, or the amount of mediation present

(Baron & Kenny, 1986). Figure 2 represents the analytical framework for mediation analysis highlighting relevant regression coefficients.

Two *post-hoc* mediation analyses were performed assessing the relation between past year PA and current fitness on cognitive performance, assessing the mediating effect of cerebrovascular function in order to determine if current PA levels or fitness are more important for cerebrovascular health and cognitive function than lifetime exposure. All predictors were evaluated for statistical significance at α=0.05. To assess the fit of each model, R^2 was used to measure the proportion of variance in the dependent variable that is explained by the robust linear model. To adjust for multiple regression comparisons a Bonferroni correction was calculated for the analyses performed for type, intensity and timing of PA if the main relation of interest was significant (Figure 5). No corrections were calculated for the between group differences in Tables 8, 9 and 10 as these were for descriptive purposes. All statistical analyses were performed in STATA 13.1 (StataCorp, 2013).

3.4 Results

3.4.1 Demographics

Participants had a mean age of 66.5±6.4 years (n=226; 118 females) on study entry, were well educated with a moderate to high socioeconomic status and 55.8% were retired (Table 8). Table 8 provides information on demographic, health, genetic, lifestyle and cerebrovascular measures. The distributions of the *APOE* ε4 allele are similar to those found in the general population; 25.9% of participants were *APOE* ε4+ while 74.1% were *APOE* ε4- (McKay et al., 2011). Descriptive statistics for lifetime PA are presented in Table 9. As expected, the neuropsychological raw test scores had few absolute sex differences (Kimura & Hampson,

1994), however the female advantages on verbal tests are consistent with known sex effects on memory and verbal fluency (Bleecker, Bolla-Wilson, Agnew, & Meyers, 1988; Kramer, Delis, & Daniel, 1988; Weiss, Kemmler, Deisenhammer, Fleischhacker, & Delazer, 2003). See Table 14 (Supplemental Material).

3.4.2 Lifetime PA and Current Cognitive Function

Cognitive and cerebrovascular outcomes were not normally distributed. Since no transformations resolved the issue with non-normal distributions, robust linear regression was used. Three participants had missing NAART scores since English was a second language and were excluded from all analyses. Results presented are for the remaining 223 participants (n=116 female). All analyses using measures of lifetime PA controlled for age, sex, NAART, $\dot{V}O_2$ max and interaction terms age-sex, age-lifetime PA, sex-lifetime PA, age-sex-lifetime PA. The adjusted model for the relation between lifetime PA and cognitive functioning is significant ($p=0.045$). With every unit increase in MET-hour/week/year of lifetime total PA there was a 0.40 increase in global cognition z-score (Table 10).

Figure 6 describes the significant three-way interaction between age, sex and lifetime PA, using age categories to depict the interaction. This statistically significant interaction indicates that the relation between lifetime PA and global cognition differs by sex and age, for males the amount of lifetime PA decreases with increasing age with the opposite relation observed in females. Figure 7 describes how cognitive performance changes with increasing lifetime PA using age categories (≤ 65 and >65) for males and females. There was a significant difference between global cognition scores between males and females at all lifetime PA levels ($p<0.05$), and males have increasing cognition score as levels of lifetime PA increase ($p<0.0001$) (Figure

7). Lifetime PA was not associated with any measures of cerebrovascular health and cerebrovascular measures were not associated with cognition scores (data not shown).

3.4.3 Relative Components of Lifetime PA and Current Cognitive Function

The relation between lifetime PA and global cognition was significant at $\alpha=0.05$, therefore subsequent analyses were performed assessing type, intensity and timing of PA (Figure 5). The results presented for the type, intensity and timing of PA adjust for the same covariates and interaction terms as the main relation between total lifetime PA and cognition. There were statistically significant relations between lifetime recreational PA, vigorous intensity PA and PA done between childhood to age 20 and age 21 to age 35. Specifically, for every unit increase in MET-hours/week/year of lifetime recreational PA there was a 1.18 increase in global cognition z-score ($p=0.021$). For vigorous intensity PA over lifetime there was a 9.85 increase in global cognition z-score for every hour/week of activity ($p=0.004$). For every unit increase in MET-hours/week/year of PA from early childhood to age 20 there was a 0.47 increase ($p=0.036$), and for activity between the ages of 21 and 35 years old there was a 0.36 increase in global cognition z-score ($p<0.0001$). Table 11 summarizes the results for the associations between type, dose and timing of lifetime PA and their associations with cerebrovascular indices, if significant. The three-way interaction between age, sex and predictor was used in these analyses; however the interaction effect is not shown. These analyses were repeated controlling for all other types of activity, all other intensities, and all other life periods in the same multivariate model (Table 12). These relations remained significant indicating the unique variance of these findings. Physical activity done from age 21 to 35 switched from significant to trending towards significance ($p=0.053$) when controlling for all age periods, however when just controlling for past year PA it

remained significant (Table 12). The second level of analyses (type, intensity and timing) were assessed at both α=0.05 and α=0.005 based on a Bonferroni correction (Table 11 and 12).

3.4.4 Current measures and Current Cognitive Function

In addition to long-term effects of PA, we also examined relatively acute effects of fitness and past year PA. All *post-hoc* analyses were adjusted for sex, NAART, waist circumference, blood pressure, smoking status and alcohol consumption, and revealed a statistically significant relation between past year PA and global cognition (p=0.019) (Table 13), with no mediating effects of cerebrovascular indices (data not shown). Past year PA was associated with current $\dot{V}O_2$ max (p<0.0001). In contrast, relations were observed between current fitness ($\dot{V}O_2$ max), global cognition and cerebrovascular health using mediation analysis (Figure 4b). For every one unit increase (ml/kg/min) in $\dot{V}O_2$ max there was a 0.57 increase in global cognition z-score (p<0.001) (Table 13); for every one unit increase in $\dot{V}O_2$ max there was a 0.60 unit increase in CVC (p=0.004) and a 0.0081 unit increase in $\bar{V}P$ (p=0.001) (Table 15 Supplemental Material). Finally, with every one unit increase in CVC there was a 13.31 increase in global cognition z-score (p=0.005) while for $\bar{V}P$ there was a 0.14 increase in global cognition z-score (p=0.014) (Table 16 Supplemental Material). The first three pathways of mediation were statistically significant and therefore the estimated indirect effect of CVC was calculated and accounted for about 13.3% of the total effect of $\dot{V}O_2$ max on cognition, while $\bar{V}P$ accounted for 8.4%. However, the Sobel test revealed that the indirect effect of CVC and $\bar{V}P$ on the relation between $\dot{V}O_2$ max and cognition was not statistically significant (p=0.089 and p=0.17 respectively).

3.5 Discussion

The primary finding for this study demonstrated that greater total lifetime PA is associated with better global cognitive performance. The impact of lifetime PA on global cognitive performance differed for males and females as a result of an interaction between age, sex and lifetime PA. In our sample, males followed the expected trajectory of increased global cognitive performance with increased levels of lifetime PA whereas females did not (Figure 7). Many studies have reported no difference between males and females when assessing the relation between PA and cognition (Chang et al., 2010; Middleton, Mitnitski, Fallah, Kirkland, & Rockwood, 2008; Wendell et al., 2014). Furthermore, evidence from all male studies suggest a positive associations between increasing PA levels and decreased risk of cognitive impairment, Alzheimer's disease and related dementias (Abbott et al., 2004; van Gelder et al., 2004). Our findings are contrary to the hypothesis that the effects of PA on cognitive functioning may be more prominent in women (Brown et al., 2013; Colcombe & Kramer, 2003; Ho et al., 2001; Laurin et al., 2001a) It has been proposed that women should show greater cognitive change in response to exercise as compared to men is the variation in cognitive strengths between men and women as a result of different sex hormones and the organizational effects of these hormones (Kimura, 2002; Kimura & Hampson, 1994; Kramer & Erickson, 2007). Declines in circulating sex steroid hormones associated with aging have been implicated as underlying age-related changes in brain health that differ for males and females. Specifically, there is evidence of altered CBF (Matteis et al., 1998), volume of the frontal and temporal lobes of the brain (Cowell et al., 1994) and increases in an indicator of cortical atrophy, increased peripheral and ventricular and peripheral cerebrospinal fluid volume (Coffey et al., 1998) in older men, compared to women.

Our finding that increased PA during lifetime is associated with greater cognitive functioning in middle-aged and older adults accords with findings from a recent systematic review and meta-analysis by Blondell et al. (2014). Previous literature indicates that increasing levels of PA in later life improved cognitive performance, decreased the risk for cognitive decline after the age of 55 years (Brown et al., 2013; Buchman et al., 2012; Laurin et al., 2001b; Middleton et al., 2008; van Gelder et al., 2004) and decreased the risk of developing dementia and Alzheimer's disease (Abbott et al., 2004; Buchman et al., 2012; de Bruijn et al., 2013; Laurin et al., 2001b; Scarmeas, Luchsinger, Schupf, & et al., 2009). To date, no study has sought to combine information on the duration, frequency and intensity of all types of activity to create one comprehensive measure describing the average volume of PA completed across the lifetime. Therefore, using the measure of average MET-hours/week/year of PA provides novel insight into the positive effects that higher levels of PA throughout life will have on cognitive abilities in older age.

Timing and intensity of activity were also deemed to be important in the relation between PA and cognitive performance. When assessing the association between lifetime engagement in low, moderate or vigorous PA and cognitive functioning, only vigorous intensity activity was associated with better global cognitive performance. The average hours/week/year of vigorous intensity PA over lifetime had the greatest impact on global cognition z-scores, indicating vigorous intensity activity may be the most important for maintaining cognitive functioning into old age. Our findings align with the results of the Finnish Twin Cohort study (Iso-Markku, Waller, Kujala, & Kaprio, 2015) showing that participants who persistently engaged in vigorous activity in midlife had a decreased risk of mortality from dementia (Iso-Markku et al., 2015). Our findings also provide evidence that vigorous intensity activity above low or moderate intensity

will help reduce cognitive deficit and potentially other devastating effects of dementia. Further, lifetime recreational (including transportation) activity was independently associated with greater cognitive functioning. This finding aligns with previous investigations suggesting that current engagement in leisure time or recreational activities is associated with better cognitive function into older age (Rovio et al., 2005; Weuve et al., 2004; Yaffe et al., 2001). This finding promotes the etiologic role of sustained, planned PA throughout life for delaying or preventing age-related cognitive decline.

Physical activity in early childhood to midlife (age 0-35) had a substantial impact on better global cognitive performance at an older age. A number of studies have assessed PA in midlife (i.e. 40-60 years) and have reported an association between greater midlife activity and a reduced incidence of dementia (Andel et al., 2008; Chang et al., 2010; Kareholt et al., 2011; Rovio et al., 2005; Sun et al., 2010; Tolppanen et al., 2014). These results are contradictory with our findings of PA in early life being associated with improved cognitive performance in middle and older age. Relations may not have been observed in midlife as a result of our sample being sedentary prior to enrolment (age 50-65 or midlife for many participants). It is likely that many individuals in our sample have been more sedentary in years leading up to the assessment than in early life. However, our findings closely align with Middleton (2010) who assessed self-reported PA at multiple points in time, and found that the strongest relationship was between the level of PA during adolescence and cognitive status during later life. Therefore, more research is warranted to determine the life periods in which PA levels contribute to better cognitive abilities.

Although lifetime PA contributes to better cognitive performance in middle and older age, no associations were observed with measures of cerebrovascular function. Based on previous research, we hypothesized that measures of acute fitness or high levels of current PA

may have more impact on cerebrovascular health. *Post-hoc* analyses were performed assessing past year PA and current fitness; revealing $\dot{V}O_2$ max measured at baseline (i.e. in later life) was more predictive of cerebrovascular health than lifetime or past year measures of PA. Similarly, Bailey et al. (2013) reported that adults who were more active doing recreational activities over lifetime (confirmed with $\dot{V}O_2$ max) had better cerebrovascular function. Previous literature has linked current fitness levels to enhanced cerebrovascular function (Ainslie et al., 2008; Barnes et al., 2013; Burdette et al., 2010) and improved cognition (Colcombe et al., 2004; Forbes et al., 2013; Kramer et al., 1999; Prakash et al., 2015; Prakash et al., 2011). Therefore, by determining that measures of cerebrovascular health ($\bar{V}P$ and CVC) partially mediate the relation between $\dot{V}O_2$ max and global cognitive performance provides evidence that cerebrovascular health may play a part in the relation between current fitness and cognition.

A major strength of this study was the comprehensive, reliable measure of lifetime total PA (Friedenreich et al., 1998), which captured types, intensities and time periods in life when PA could be most beneficial for reducing cognitive decline associated with aging. Additionally, we were not limited in our analyses to fully explore the association between PA, cerebrovascular measures and cognition. An additional strength was the unique testing protocols, such as the extensive neuropsychological test battery for cognitive abilities and the CBF test for cerebrovascular measurements (Brown et al., 2010; Tyndall et al., 2013). Finally, the quality and extent of participant information collected permitted a full assessment of covariates in the analysis.

Lifetime PA and other factors (i.e., age, sex, NAART, $\dot{V}O_2$ max, BMI, age-sex, age-lifetime PA, sex-lifetime PA and age-sex-lifetime PA interactions) explain between 34.0% and 36.1% of the variance in global cognition. A better model fit could be potentially obtained by

considering factors such as current social activities, history of depression, or family history. Additionally, it is possible that other factors may have mediated the relation between lifetime PA and cognitive functioning. In the future when assessing lifetime measures of PA it would be beneficial to explore biological and environmental factors as mediators that may have an impact over one's lifetime such as history of socio-economic status (impacting opportunities over one's lifetime) or intellectual ability in the individual's youth (impacting decisions to participate in PA).

We did not collect information on hormone levels at baseline and therefore we are limited in our ability to fully explore the reason for observed sex differences between males and females. Further our findings have limited generalizability to all older adults given that it is based on a highly educated, mostly Caucasian volunteer sample. There is the possibility of misclassification of lifetime PA since participants may not have been able to recall their activities accurately. However, given that questionnaire has high reproducibility (Friedenreich et al., 1998), we anticipate the effect of this measurement error to be minimal and any misclassification to be non-differential with the effect of reducing our ability to show a relation between PA and cognition suggesting that these results are conservative estimates of the true effect. Additionally, the questionnaire has not been tested for validity. An ideal but unrealistic validation study would require historical PA data on a cohort of study participants assessed repeatedly over their lifetimes to capture the same data as are assessed in the LTPAQ used here. It is possible that PA from earlier in life is not accurately captured.

We used the Bonferroni correction for multiple regression comparisons to reduce the risk of type I error. Using this correction resulted in loss of significance for some findings. Although we reduced type I error with a conservative α level, these corrections reduce statistical power and

increase the risk of type II error and therefore the corrected α level should be interpreted with caution (Rothman, 1990). Finally, a cross-sectional study design cannot assess causality. Recent research by Belsky et al. (2015) demonstrate that children with higher levels of cognitive ability choose healthier lifestyles, and also had improved cognitive functioning later in life. These findings suggest that causality cannot be concluded. However, there has also been evidence suggesting cognitive abilities are not consistent over one's lifespan and speculate that both innate abilities and lifestyle must be considered together rather than looking at them as separate entities for determining cognitive changes with aging (Deary, Whiteman, Starr, Whalley, & Fox, 2004). A prospective longitudinal study with multiple data collection and testing periods would be required to address this question more fully.

This study adds to previous evidence that PA protects against poor cognitive functioning in older age while providing new insight into the importance of lifetime PA and the potential mediating effects of cerebrovascular health. We found that total lifetime PA, specifically participation in recreational activities, hours spent in vigorous intensity activity over lifetime, and PA done in early childhood to midlife, is associated with improved global cognitive performance in older age. Although cerebrovascular health did not mediated the association between lifetime or past year PA and global cognition, it appeared to partially mediate the association between current fitness levels and global cognition in middle-aged and older adults. Thus, higher levels of PA throughout life and in the past year of life are associated with better cognitive functioning in older age, while current fitness levels may be more important for improved cerebrovascular health in addition to cognitive functioning. This difference emphasizes the finding that cerebrovascular health may be more closely linked to physiological measures of fitness than subjective measures of activity.

3.6 Acknowledgments

The authors thank all collaborators, staff and participants of the *Brain in Motion* project, and staff from the department of Cancer Epidemiology and Prevention Research at Alberta Health Services for assistance with data management and analysis. The authors report no conflicts of interest.

3.7 Chapter Three Figures and Tables

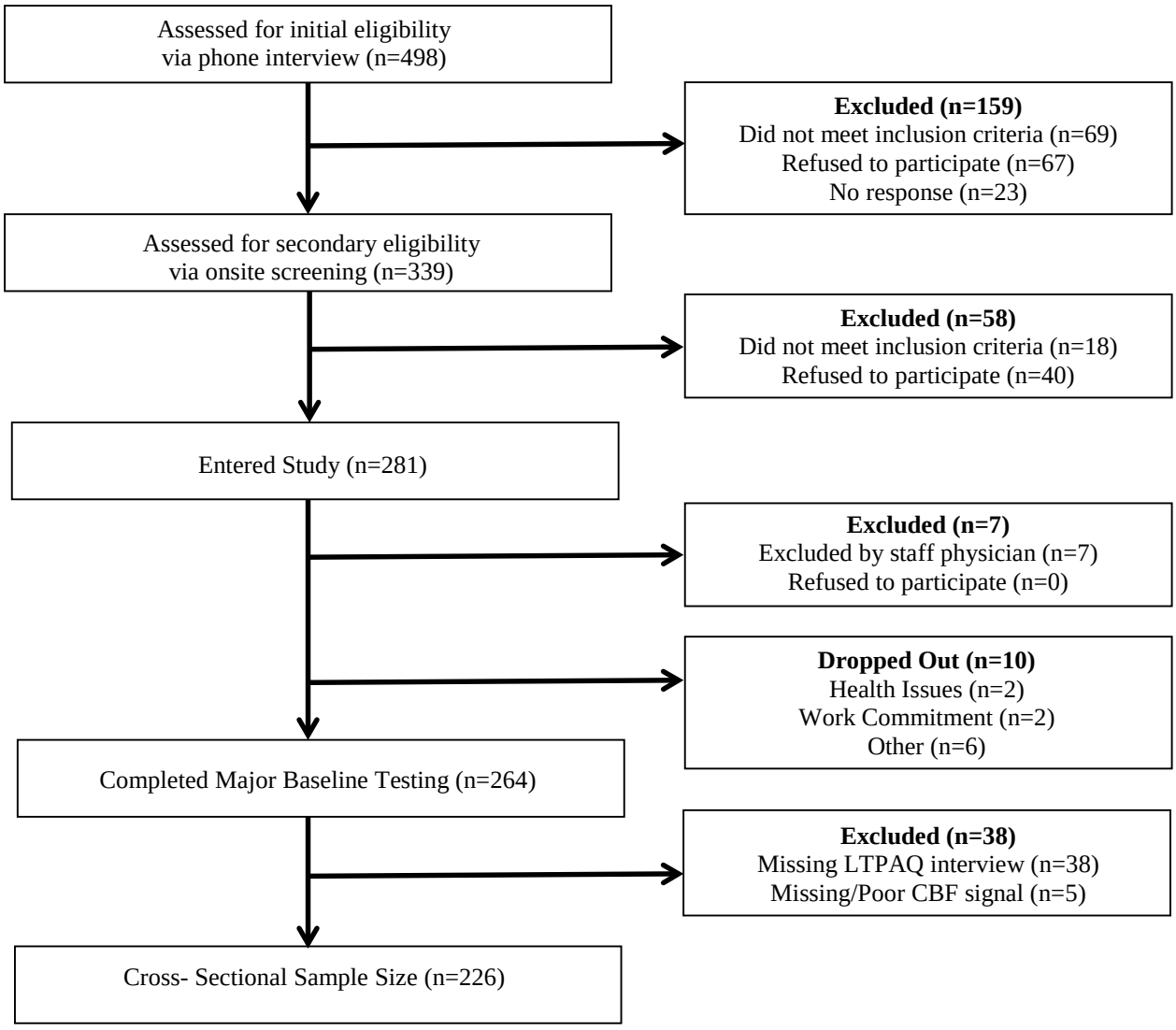
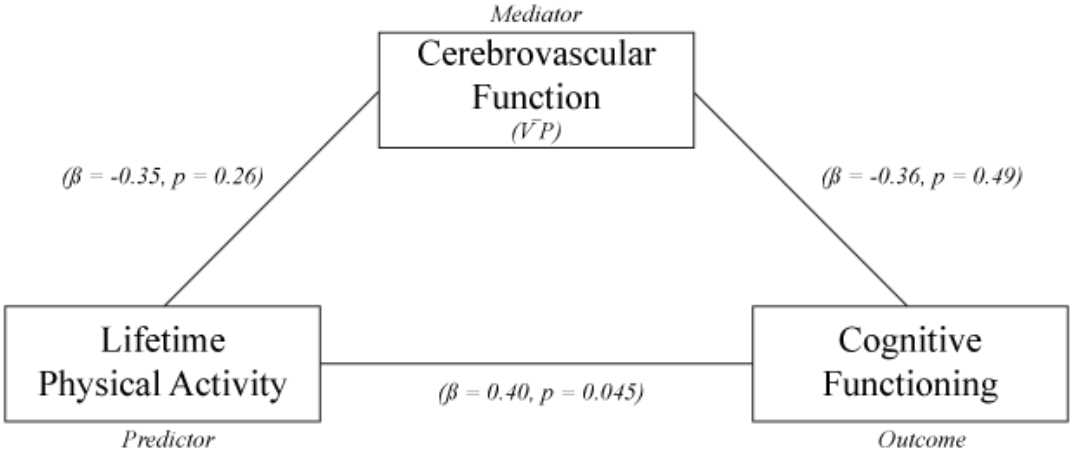


Figure 3. Participant flow for the *Brain in Motion* Study, Calgary, Alberta, Canada.

A) Lifetime Physical Activity



B) Cardiovascular Fitness

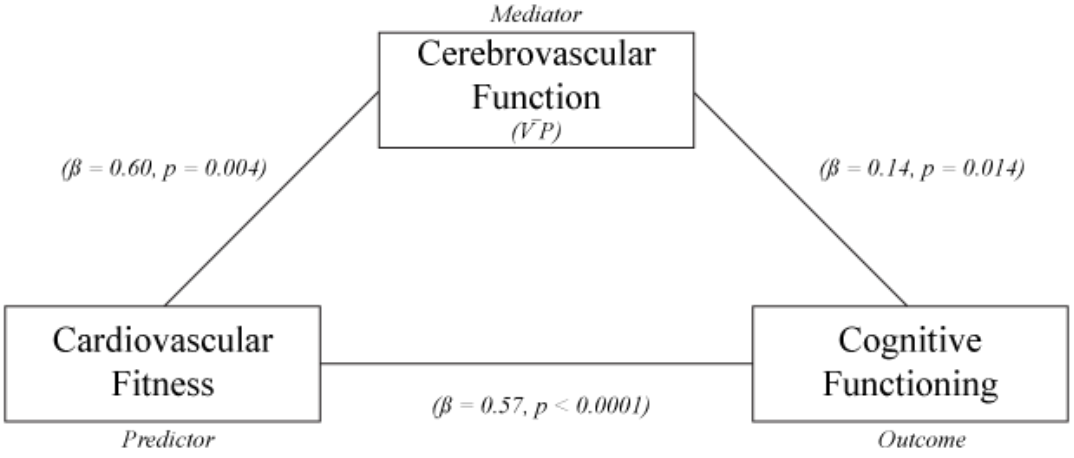


Figure 4. Analytical framework for mediation analysis.

Note: $\bar{V}$P was used as a representative measure of cerebrovascular function in this model.

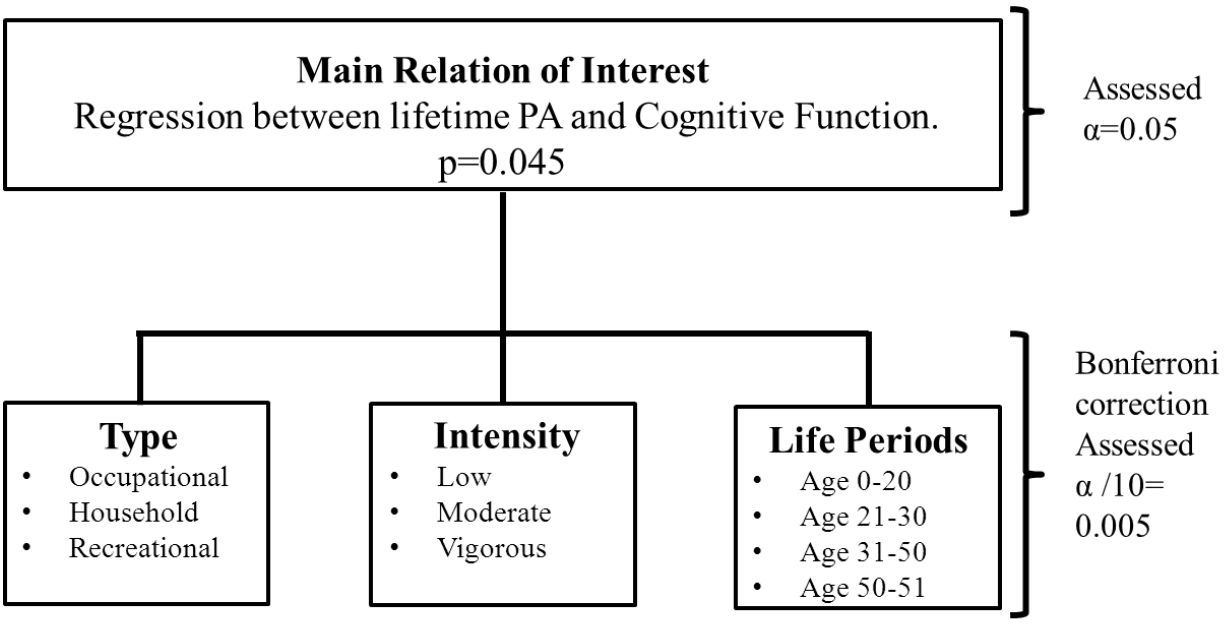


Figure 5. Structure for determining multiple regression adjustments.

The main relationship had to be significant at 0.05 to proceed with any other analyses.

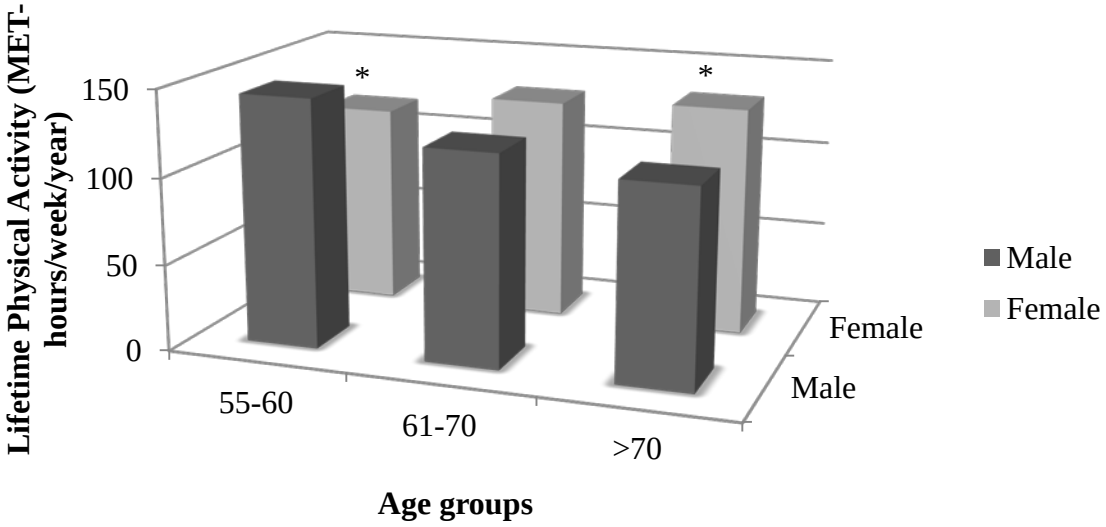
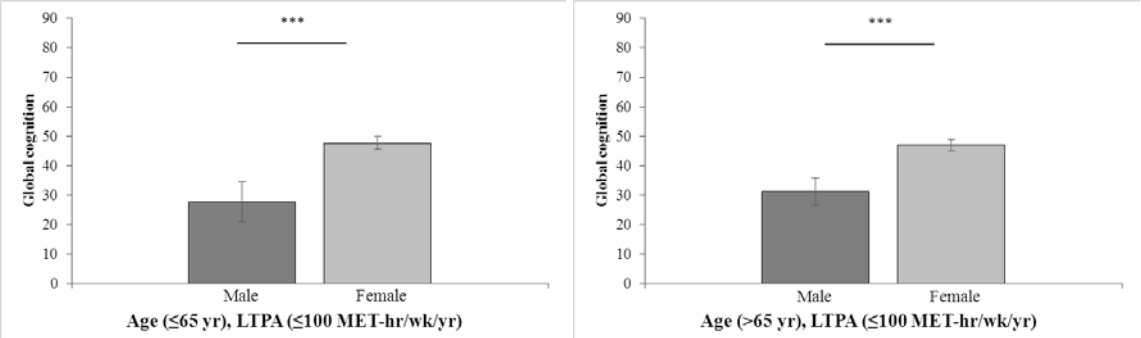


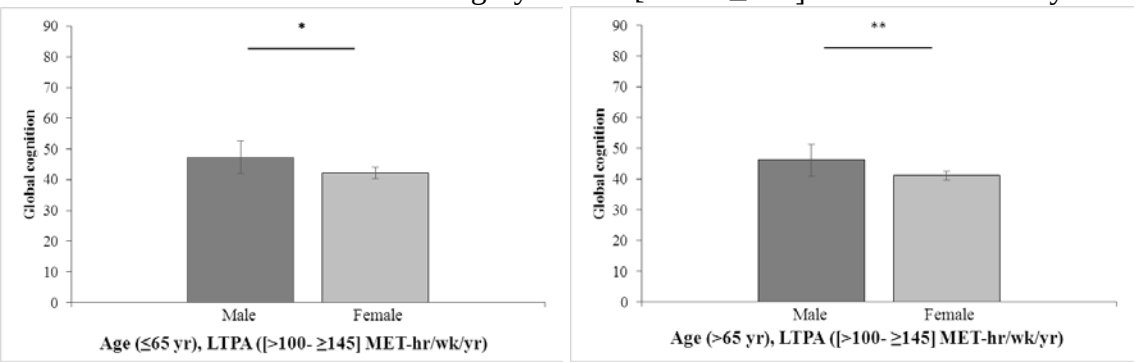
Figure 6. Interaction between age, sex and lifetime physical activity.

*p-value <0.05
Note: age group trichotomized to display interaction, continuous variable used in all analyses.

Lowest Lifetime PA Category: LTPA ≤100 MET-hours/week/year



Middle Lifetime PA Category: LTPA [>100- ≥145] MET-hours/week/year



Highest Lifetime PA Category: LTPA ≥145 MET-hours/week/year

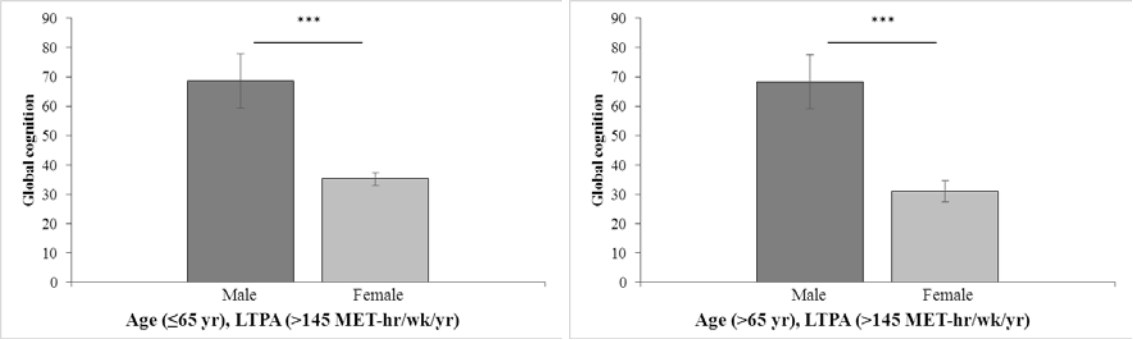


Figure 7. Relation between lifetime PA and global cognitive performance.

Created using regression coefficients from Table 10.
***p-value<0.0001
**p-value<0.001
*p-value<0.005

Table 8. Baseline characteristics for male and female participants (n=226) in the *Brain in Motion* Study, Calgary, Alberta.

Variable	Male		Female		T or χ^2 statistics	P value[¥]
	N		N			
Demographics						
Age (years): M(SD)	108	67.0(6.9)	118	66.1(6.0)	0.98	.33
Retirement Status (%)	108		118			
Yes	52	39.8%	74	62.7%	5.0	.084
Semi	13	12.0%	9	7.6%		
No	43	39.8%	35	29.7%		
Education (years): M(SD)	108	16.3(2.8)	118	15.7(2.2)	1.8	.08
NAART Estimated IQ: M(SD)	107	110(6.9)	116	111.2(6.0)	-1.4	.16
Health Status						
$\dot{V}O_2$ max fitness (ml/kg/min): M(SD)	108	28.9(5.0)	118	23.6(4.4)	8.4	<.0001
Blood Pressure (mm Hg)						
Systolic: M(SD)	108	126.24(14.44)	118	123.98(16.90)	1.1	.28
Diastolic: M(SD)	108	75.12(7.31)	118	70.04(9.08)	4.6	<.0001
Weight (kg): M(SD)	108	87.0(11.3)	118	70.2(11.9)	10.9	<.0001
BMI (kg/m^2): M(SD)	108	28.0(3.4)	118	26.6(4.1)	2.8	.005
Waist Circumference (cm): M(SD)	105	101.7(9.7)	118	91.9(11.7)	6.8	<.0001
Genetic Characteristics	104		113			
APOE ε4- (%)	70	69.3%	87	78.4%	2.3	.13
APOE ε4+ (%)	31	30.7%	24	21.6%		
Lifestyle						
Alcohol consumption (g/day): M(SD)	87	13.4(16.4)	98	9.4(15.0)	1.7	.09
Calories consumed per day: M (SD)	87	1803(669)	98	1424(497)	4.4	<.001
Smoking status (% Ever smoked)	108	53.70%	118	39.83%	4.4	.04
Indices of Cerebrovascular Blood Flow (*M(SD)*)						
$\bar{V}P$	106	49.1(11.4)	116	56.9(12.4)	-4.9	<.0001
CVC	106	0.5(0.1)	116	0.7(0.2)	-6.0	<.0001
$\bar{V}P$ reactivity	106	2.1(0.9)	116	2.3(1.0)	-1.3	0.20
CVC reactivity	106	0.01(0.007)	116	0.01(0.01)	-1.3	0.21

Abbreviations: NAART = North American Adult Reading Test; $\dot{V}O_2$ max = Maximal oxygen uptake; BMI = Body mass index; *APOE* ε4 = Apolipoprotein ε4 genotype; $\bar{V}P$ = blood flow velocity at +1 mmHg; CVC = cerebrovascular conductance at +1 mmHg; $\bar{V}P$ reactivity= cerebral blood flow reactivity to a hypercapnic challenge from +1 mmHg to +8 mmHg; CVC reactivity= cerebrovascular conductance reactivity to a hypercapnic challenge from +1 mmHg to +8 mmHg.
[¥]P-values are comparing differences between males and females.
T-statistics for continuous data and Chi^2-statistics for categorical data.

Table 9. Average lifetime physical activity measures for male and female participants (n=226) in the *Brain in Motion* Study, Calgary, Alberta.

Variable	Male (n=108) M (SD)	Female (n=118) M (SD)	T-statistic	p-value[¥]
Lifetime total physical activity (MET-hr/wk/yr)	122.2(37.1)	127.3(39.2)	-1.0	.320
Past year physical activity (MET-hr/wk)	129.8(95.1)	131.8(88.3)	-0.16	0.870
Lifetime physical activity by type (MET-hr/wk/yr)				
Non-sedentary Occupational physical activity	45.4(34.2)	30.9(26.7)	3.6	<.0001
Sedentary Occupational physical activity	25.7(13.5)	16.1(10.7)	6.0	<.0001
Transportation physical activity	1.7(3.4)	1.1(1.7)	1.9	.060
Household physical activity	23.6(14.2)	58.5(33.1)	-10.1	<.0001
Recreational physical activity	25.8(13.4)	20.8(11.4)	3.1	.003
Lifetime Physical activity intensity levels (Hr/wk/yr)				
Low-intensity activity (<3 METs)	6.7(5.9)	12.0(8.3)	-5.3	<.0001
Moderate-intensity activity (3-6 METs)	17.1(10.5)	18.1(10.9)	-0.78	.460
Vigorous-intensity activity (≥ 6 METs)	1.8(1.9)	2.2(3.5)	-0.86	.300
Time Periods of Physical activity (MET-hr/wk/yr)				
0-20 years old	71.1(31.8)	65.6(31.8)	1.3	.190
21-35 years old	112.9(72.7)	139.2(63.3)	-2.9	.004
36-50 years old	112.8(71.1)	147.5(66.5)	-3.8	<.001
51-65 years old	103.4(56.2)	118.5(65.8)	-1.9	.066

Abbreviations: MET(s) = metabolic equivalent

[¥]P-values are comparing differences between males and females.

Table 10. Robust regression result for the association between lifetime physical activity and global cognition.

	Global Cognitive Performance	
Predictor	**Regression Coefficients (SE)**	**p-value**
Lifetime total PA	**0.40(0.20)**	**0.045***
Age	0.038(0.40)	0.920
Sex	62.26(37.26)	0.096
NAART	0.62(0.078)	0.000
$\dot{V}O_2$max	0.077(0.14)	0.590
BMI	0.21(0.15)	0.180
Age-Sex	-0.93(0.20)	0.097
Age-Lifetime PA	-0.0063(0.0031)	0.045
Sex-Lifetime PA	-0.55(0.29)	0.056
Age-Sex-Lifetime PA interaction	0.0087(0.0044)	0.047
Constant	-78.08(29.77)	0.009

Abbreviations: PA= physical activity; NAART= North American Adult Reading Test; $\dot{V}O_2$max= maximal aerobic capacity; BMI= body mass index.

Multivariable adjusted for age at the time of LTPAQ interview, sex, NAART, $\dot{V}O_2$max, BMI, age-sex, age-lifetime PA, sex-lifetime PA and age-sex-lifetime PA.

R^2 attributable to lifetime PA= 18.4%, Adjusted model R^2=34.7%

*p<0.05 for the overall relationship between lifetime PA and global cognitive performance.

Table 11. Adjusted models for the relation between type, intensity and life periods of physical activity and cognition.

Predictor	Outcome Variable	Regression Coefficients (SE)	p-value	Model R^2 %
Type (MET-hour/week/year)				
Non-sedentary Occupational physical activity	Global Cognition	0.42(0.23)	0.074	34.7
Household physical activity		-0.51(0.50)	0.310	34.6
Recreational physical activity		1.18(0.49)	0.021*	35.0
Intensity (Hour/week/year)				
Low (0-3 METs)	Global Cognition	-0.97(1.0)	0.330	34.6
Moderate (3-6 METs)		0.43(0.69)	0.530	34.0
Vigorous (>6 METs)		9.85(3.36)	0.004 $^{\delta}$*	36.0
Life Periods (MET-hour/week/year)				
Age 0 to 20	Global Cognition	0.47(0.23)	0.036*	35.3
Age 21 to 35		0.36(0.099)	0.000 $^{\delta}$*	36.1
Age 36 to 50		0.059(0.10)	0.570	34.2
Age 51 to 65		-0.13(0.12)	0.280	34.7

Abbreviations: MET(s) = metabolic equivalent;
Multivariable adjusted for age at the time of LTPAQ interview, NAART, $\dot{V}O_2$max, BMI and interaction terms (age, sex, exposure). All models adjusting for age at the time of LTPAQ interview, sex, NAART, $\dot{V}O_2$max, BMI and interaction terms (age-sex, age-lifetime PA predictor, sex-lifetime PA predictor, age-sex-lifetime PA predictor).
*$p<0.05$
$^{+}$*$p<0.01$
$^{\delta}$*$p<0.005$ (Bonferroni corrected p-value)

Table 12. Adjusted models for the relation between type, intensity and life periods of physical activity and global cognition when also adjusting for respective types, intensities or life periods.

Predictor	Regression Coefficients (SE)	p-value	Model R^2 %
[€]***Type (MET-hour/week/year)***			
Non-sedentary Occupational physical activity	0.42(0.23) *	0.072	35.2
Household physical activity	-0.50(0.50)	0.320	34.6
Recreational physical activity	1.19(0.51)	0.019*	35.6
[€]***Intensity (Hour/week/year)***			
Low (0-3 METs)	-0.85(0.99)	0.390	35.3
Moderate (3-6 METs)	0.33(0.69)	0.640	34.7
Vigorous (>6 METs)	8.93(3.47)	0.011*	35.9
[€]***Life Periods (MET-hour/week/year)***			
Age 0 to 20	0.46(0.23)	0.053	35.1
Age 21 to 35	0.33(0.10)	0.001 [δ]*	36.6
Age 36 to 50	0.056(0.11)	0.600	34.4
Age 51 to 65	-0.11(0.13)	0.390	35.3
[¥]***Life Periods (MET-hour/week/year)***			
Age 0 to 20	0.48(0.23)	0.038*	35.2
Age 21 to 35	0.36(0.10)	0.000 [δ]*	36.1
Age 36 to 50	0.052(0.11)	0.630	34.2
Age 51 to 65	-0.16(0.13)	0.210	35.0

Abbreviations: MET(s) = metabolic equivalent

[€]Multivariable adjusted for age at the time of LTPAQ interview, sex, NAART, $\dot{V}O_2$max, BMI, respective physical activity groupings and interaction terms (age-sex, age-predictor, sex-predictor, age-sex-predictor).

[¥] Multivariable adjusted for age at the time of LTPAQ interview, sex, NAART, $\dot{V}O_2$max, BMI, past year PA and interaction terms (age-sex, age-predictor, sex-predictor, age-sex-predictor).

*p<0.05

[+]*p<0.01

[δ]*p<0.005 (Bonferonni corrected p-value)

Table 13. Adjusted overall model for associations between past year physical activity and global cognition and current fitness ($\dot{V}O_2$max) and global cognition.

		Global Cognitive Performance
Predictor	**Regression Coefficients (SE)**	**p-value**
Past year PA	0.018(0.008)	**0.019**
Sex	3.50(1.45)	0.016
NAART	0.60(0.10)	0.000
Waist Circumference	0.030(0.060)	0.62
Blood Pressure	0.10(0.081)	0.20
Smoking Status	1.74(1.29)	0.18
Alcohol Consumption	0.024(0.57)	0.97
Constant	-81.07(13.27)	0.000
$\dot{V}O_2$ max	0.57(0.15)	**0.000**
Sex	7.80(1.77)	0.000
NAART	0.58(0.098)	0.000
Waist Circumference	0.14(0.068)	0.042
Blood Pressure	0.082(0.080)	0.30
Smoking Status	1.74(1.26)	0.16
Alcohol Consumption	-0.038(0.56)	0.95
Constant	-102.42(14.61)	0.000

Abbreviations: PA= physical activity; NAART= North American Adult Reading Test; $\dot{V}O_2$ max = maximal aerobic capacity.
Multivariable adjusted for sex, NAART, waist circumference, blood pressure, smoking status and alcohol consumption.

R^2 attributable to Past year PA= 0.15%, Adjusted model R^2=21.4%
R^2 attributable to $\dot{V}O_2$ max = 0.44%, Adjusted model R^2=23.6%

3.8 Manuscript Online Supplements

Supplemental Cerebrovascular Blood Flow Testing Methods

Participants underwent a two-hour assessment administered by trained staff. Two hours prior to testing, participants fasted and refrained from exercising. Blood flow velocity of the middle cerebral artery (MCAv) was measured non-invasively using a 2-MHz pulsed transcranial Doppler ultrasound system (TCD; Toc Neurovision™, Multigon Industries, Inc., Yonkers, NY) (Aaslid et al., 1982; Poulin et al., 1996; Poulin & Robbins, 1996). Peak MCAv, heart rate, beat-by-beat blood pressure measurements using finger pulse photoplethysmography; corroborated with three resting brachial measurements, and arterial O_2 saturation (finger pulse oximetry) were measured continuously throughout the protocol, as previously described (Brown et al., 2010). Dedicated software (Chamber, University Laboratory of Physiology, Oxford, UK) recorded end-tidal P_{CO2} and P_{O2} (PET_{CO2} and PET_{O2}) during 10 minutes of seated rest. Each participant had their nose occluded and breathed room air through a mouthpiece. A fine capillary line inserted in a port immediately distal to the mouthpiece and connected to a mass spectrometer (AMIS 2000, Innovision, Odense, Denmark) measured the concentration of CO_2 and O_2 continuously at the mouth, and breath-by-breath values for end tidal CO_2 (PET_{CO2}) and O_2 (PET_{O2}) were determined. These end-tidal responses (PET_{CO2} and PET_{O2}) were averaged over 10 minutes of seated rest and were used to determine the desired PET_{CO2} and PET_{O2} to assess the cerebrovascular response to the euoxic hypercapnia testing. Accurate control of desired PET_{CO2} and PET_{O2} values were continuously achieved using customized software (BreatheM v2.40, University Laboratory of Physiology, Oxford, UK), using the dynamic end-tidal forcing techniques (Poulin et al., 1996; Poulin, Liang, & Robbins, 1998), and experimental protocols (Brown et al., 2010, Tyndall et al., 2013), as previously described. The euoxic hypercapnia test lasted 12 minutes and included two 3-minute step increases in PET_{CO2} as previously described (Brown et al., 2010; Tyndall et al.,

2013). Physiological responses were calculated as the mean response over the final 30 seconds of each stage during the hypercapnic challenge.

This protocol produced four measures of cerebrovascular function for analysis including peak velocity of blood moving through the MCA ($\bar{V}_P$), cerebrovascular conductance (CVC*; MCAv/Mean Arterial Pressure*) and $\bar{V}_P$ and CVC reactivity during the hypercapnic challenge. Specifically $\bar{V}_P$ reactivity was calculated as the change in $\bar{V}_P$ divided by the change in PET_{CO2} from +1 to +8 mmHg while CVC reactivity is the change in CVC divided by the change in PET_{CO2} from +1 to +8 mmHg. These measures are widely used in the cerebrovascular literature employing transcranial Doppler ultrasound techniques (Aengevaeren et al., 2013; Ainslie et al., 2008; Bailey et al., 2013; Barnes et al., 2013; Brown et al., 2010; Demirkaya et al., 2008; Murrell et al., 2013; Zhu et al., 2013)

Table 14. Raw test scores for cognitive sub-domains for male and female participants (n=226) in the *Brain in Motion* Study, Calgary, Alberta.

Cognitive Test	Males (n=108) M (SD)	Females (n=118) M (SD)	T-statistic	p-value[¥]
Verbal Memory				
Buschke Selective Reminding Test Delayed Recall	7.23(2.41)	8.64(2.06)	-4.8	<.0001
Buschke Selective Reminding Test Immediate Recall	44.68(7.62)	50.41(6.83)	-6.0	<.0001
Figural Memory				
Medical College of Georgia Complex Figures Test Delayed	27.61(6.06)	27.13(5.96)	0.60	.55
Medical College of Georgia Complex Figures Test Immediate	28.31(6.09)	27.75(5.47)	0.74	.46
Processing Speed				
D-KEFS Color Word Interference Color time	40.44(93.14)	38.34(89.17)	1.7	.09
D-KEFS Color Word Interference Word time	31.59(93.88)	22.57(3.94)	-0.011	.99
Symbol-Digit Modalities Test Oral score	62.57(91.40)	56.57(8.45)	-2.1	.04
Symbol-Digit Modalities Test Written score	47.48(9.25)	49.42(7.02)	-1.8	.08
Executive Function				
D-KEFS Color Word Interference Switch time	73.77(91.40)	64.86(17.18)	0.12	.91
D-KEFS Color Word Interference Inhibit time	71.47(91.50)	60.49(11.71)	1.2	.23
D-KEFS Verbal Fluency Category Switching	13.78(2.39)	14.94(2.67)	-3.4	<.001
D-KEFS Verbal Fluency Test Target Words Correctly Produced	41.34(10.55)	43.27(11.80)	-1.3	.20
D-KEFS Card Sorting Recognition Description score	18.35(6.08)	18.87(6.04)	-0.65	.52
D-KEFS Card sorting Free Sort Description score	18.35(6.08)	18.87(6.04)	-0.65	.52
D-KEFS Card Sorting Free Sort: Number of Correct Sorts	5.10(1.37)	5.01(1.51)	0.49	.63
Complex Attention				
ACT Perseverations	6.57(4.39)	6.14(3.94)	0.79	.43
ACT Total Correct	47.88(6.72)	48.25(5.91)	-0.45	.66
Verbal Knowledge				
D-KEFS Verbal Fluency Test: Category Fluency Score	38.65(7.57)	43.36(6.99)	-4.9	<.0001
Spatial Reasoning				
Medical College of Georgia Complex Figures Test: Copy	35.47(1.11)	35.56(0.86)	-0.66	.51
Global Cognition z-score	-1.48(10.72)	2.20(8.45)	-2.87	.004

Abbreviations: D-KEFS = Delis-Kaplan Executive Function System; ACT= Auditory Consonant Trigrams
[¥]P-values are comparing differences between males and females.

Table 15. Adjusted models assessing the relations between $\dot{V}O_2$max and cerebrovascular health indices.

Outcome Variable	Predictor	Regression Coefficients (SE)	p-value	Model R^2 %
$\bar{V}$P	$\dot{V}O_2$max	0.60(0.21)	0.004	14.9
	Sex	9.96(2.41)	0.000	
	NAART	-0.032(0.13)	0.81	
	Waist Circumference	-0.043(0.091)	0.64	
	Blood Pressure	-0.14(0.11)	0.20	
	Smoking Status	1.73(1.70)	0.31	
	Alcohol Consumption	0.32(0.75)	0.69	
	Constant	48.19(19.68)	0.015	
CVC	$\dot{V}O_2$max	0.0080(0.0024)	0.001	31.6
	Sex	0.13(0.027)	0.000	
	NAART	0.000029(0.0015)	0.99	
	Waist Circumference	0.00040(0.0010)	0.70	
	Blood Pressure	-0.0087(0.0012)	0.000	
	Smoking Status	-0.0098(0.0031)	0.20	
	Alcohol Consumption	0.00071(0.0086)	0.93	
	Constant	0.89(0.22)	0.000	
$\bar{V}$P reactivity	$\dot{V}O_2$max	0.021(0.017)	0.21	5.1
	Sex	0.33(0.19)	0.092	
	NAART	-0.16(0.011)	0.14	
	Waist Circumference	0.00020(0.0073)	0.98	
	Blood Pressure	-0.0066(0.0087)	0.45	
	Smoking Status	-0.078(0.14)	0.57	
	Alcohol Consumption	0.0014(0.060)	0.98	
	Constant	3.64(1.58)	0.022	
CVC reactivity	$\dot{V}O_2$max	0.00020(0.00015)	0.16	4.8
	Sex	0.0016(0.0017)	0.35	
	NAART	-0.00014(0.000093)	0.12	
	Waist Circumference	0.0000055(0.000064)	0.93	
	Blood Pressure	-0.00011(0.000076)	0.16	
	Smoking Status	-0.00052(0.0012)	0.66	
	Alcohol Consumption	-0.00067(0.00053)	0.20	
	Constant	0.030(0.013)	0.029	

Abbreviation: $\bar{V}$P = blood flow velocity at +1 mmHg; CVC = cerebrovascular conductance at +1 mmHg; $\bar{V}$P reactivity= blood flow reactivity to a hypercapnic challenge from +1 mmHg to +8 mmHg; CVC reactivity= cerebrovascular conductance reactivity to a hypercapnic challenge from +1 mmHg to +8 mmHg.
Multivariable adjusted for sex, NAART, waist circumference, blood pressure, smoking status and alcohol consumption.

Table 16. Adjusted overall models for associations between $\bar{V}$P and CVC and the outcome of global cognition.

	Global Cognition		
Predictor	**Regression Coefficients (SE)**	**p-value**	**Model R^2 %**
$\bar{V}$P	0.14(0.055)	0.014	21.3
Sex	2.27(1.51)	0.14	
NAART	0.60(0.10)	0.000	
Waist Circumference	0.021(0.060)	0.73	
Blood Pressure	0.095(0.082)	0.25	
Smoking Status	0.92(1.28)	0.48	
Alcohol Consumption	0.033(0.57)	0.95	
Constant	-82.03	0.000	
CVC	13.31(4.63)	0.005	22.3
Sex	2.08(1.48)	0.16	
NAART	0.60(0.099)	0.000	
Waist Circumference	0.030(0.059)	0.61	
Blood Pressure	0.19(0.087)	0.032	
Smoking Status	0.89(1.27)	0.49	
Alcohol Consumption	0.023(0.56)	0.97	
Constant	-91.37	0.000	

Abbreviation: CVC = cerebrovascular conductance at +1 mmHg; $\bar{V}$P = cerebral blood flow at +1 mmHg; NAART= North American Adult Reading Test; BMI= body mass index.
Multivariable adjusted for sex, NAART, waist circumference, blood pressure, smoking status and alcohol consumption.

Chapter Four: **Secondary Analysis**

4.1 Secondary Analysis Results and Discussion

4.1.1 Results

In a series of secondary analyses, we examined the relation between measures of lifetime PA and executive functioning, processing speed, figural memory and verbal memory, adjusting for age, sex, and age-sex-lifetime PA predictor interactions (age-sex, age-lifetime PA predictor, sex-lifetime PA predictor, age-sex-lifetime PA predictor), NAART, $\dot{V}O_2$max and BMI (Table 17). Better processing speed scores were associated with lifetime recreational PA, vigorous intensity PA over lifetime and PA between the ages of 21 and 35 years old (Table 18). For every unit increase in MET-hours/week/year of lifetime recreational PA there was a 0.40 increase in processing speed scores (p=0.03). For every hour/week of increased vigorous intensity PA over lifetime there was a 3.55 increase in processing speed scores (p=0.005) and for every unit increase in MET-hours/week/year of PA between the ages of 21 and 35 years old there was a 0.10 increase in processing speed scores (p=0.006).

Better executive functioning scores were associated with lifetime recreational PA, and vigorous intensity PA over lifetime, with a trend towards significance for PA between the ages of 0 and 20 years old and 21 and 35 years old (Table 19). For every unit increase in MET-hours/week/year of lifetime recreational PA there was an increase of 0.74 in executive functioning score (p=0.002), and for every increase in hours/week of vigorous intensity PA performed over lifetime a 4.36 increase in executive functioning was observed (p=0.009). There

was a trend towards statistical significance for MET-hours/week/year of PA between early childhood and 20 years old (p=0.054) and 21 and 35 years old (p=0.058).

Figural memory scores increased by 0.12 for every unit increase in MET-hours/week/year of PA done between early childhood and 20 years old (p=0.048) (Table 20). No associations were observed with verbal memory and lifetime measures of PA (Table 21). All analyses were repeated controlling for all other types of activity, all other intensities, and all other life periods in the same multivariate model and the relationships remained statistically significant. There were no statistically significant mediating effects of cerebrovascular regulation ($\bar{V}$P, CVC, $\bar{V}$P reactivity, CVC reactivity) on the association between all significant PA measures and cognition sub-domain scores (Table 17).

4.1.2 Discussion

Generally, previous studies have performed analyses using a composite score of cognition and have less often differentiated between specific domains for analysis to assess what domain may be the most influenced by PA. Processing speed, executive function and memory were specifically chosen based on prior research indicating the effects fitness and PA have on these cognitive sub-domains (Chang et al., 2010; Eskes et al., 2010). The secondary analyses revealed that lifetime recreational and vigorous intensity PA were associated with better processing speed and executive function, while activity done between childhood and 20 years of age was associated with better figural memory and PA between the ages of 21 and 35 years was associated with better processing speed.

Our findings that lifetime recreational PA and vigorous intensity PA are associated with processing speed and executive function provide support to previous findings from our group indicating that higher levels of $\dot{V}O_2$max were associated with better scores on processing speed

and executive function domains (Brown et al., 2010; Eskes et al., 2010). Interestingly, no relations were observed between $\dot{V}O_2$max and domains of memory in previous research from our group using the same neuropsychological test battery, whereas we observed relations between PA done from childhood to age 20 and figural memory. This result suggests that PA done earlier in life may have more influential effects on figural memory and development of this domain than acute fitness in later life.

Further, a large prospective cohort with a 26-year follow up found associations between higher levels of PA and processing speed, executive function and memory, with no associations observed for those who took part in no sport PA (Chang et al., 2010). Additionally, Tarumi et al. (2013) looked at memory and attention-executive functioning and found a correlation with both domain scores and cardiopulmonary fitness. It is possible that our lack of findings for the verbal memory domain is a result of the neuropsychological test used. Verbal memory was assessed using the Buschke Selective Reminding Test to test both immediate and delayed recall of a 12-item word list, a rote memorization task. In contrast, Chang et al. (2010) used the California modified Verbal Learning Test (CVLT) consisting of a 16-item word list to assess verbal memory and found associations between PA levels and memory scores. In our highly educated sample many individuals scored highly on the verbal memory assessment, decreasing the variability in scores and limiting our ability to find a statistically significant difference between individual verbal memory scores in relation to PA levels. Therefore, it is possible we observed no associations because our results were less variable than if a longer item list was used, as in the assessment performed by Chang et al. (2010). Furthermore, there is potential that an individual would realize that the CVLT word list could be divided into four sub-lists (words that fall into

similar categories) and it is possible that an individual's executive functioning could play a role in improving performance on the CVLT if they remember the words based on the sub-groupings.

In the future, when assessing memory in a highly educated sample, it would be beneficial to administer a different neuropsychological test such as the Logical Memory Subtest of the Wechsler Memory Scale-Revised (WMS-R/LM-R). The Logical Memory Subtest assesses both immediate and delayed recall of a short story. Participants are read a short story containing 25 discrete chunks of information and are asked to repeat the story with as much detail as possible (Wechsler & Scale-Revised, 1981). There is no concern that other cognitive domains will influence this memory assessment. Finally, the Logical Memory Subtest is more applicable to memory used in daily living, versus rote memorization and is a more sensitive measure for a healthy, educated population (Strauss, Sherman, & Spreen, 2006).

4.2 Chapter Four Tables

Table 17. Summary of adjusted models for lifetime physical activity, cognitive sub-domains (processing speed, executive function, figural memory and verbal memory) and indices of cerebrovascular health for mediation analysis.

Exposure Variable	Outcome Variable	Regression Coefficients (SE)	p-value	Model R^2 %
Total Lifetime Physical Activity (Mediation Steps 1-3)				
Lifetime total physical activity (MET-hr/wk/yr)	Processing Speed	0.13(0.074)	0.077	18.9
	Executive Function	0.14(0.097)	0.15	30.6
	Figural Memory	-0.0075(0.056)	0.90	8.8
	Verbal Memory	0.058(0.046)	0.21	23.4
Lifetime total physical activity (MET-hr/wk/yr)	$\bar{V}$P	-0.35(0.31)	0.26	18.7
	CVC	-0.0036(0.004)	0.37	21.3
	$\bar{V}$P reactivity	-0.009(0.025)	0.70	5.5
	CVC reactivity	-0.0002(0.0002)	0.35	4.6
$\bar{V}$P	Processing Speed	0.031(0.19)	0.87	19.5
CVC		7.80(17.65)	0.66	20.4
$\bar{V}$P reactivity		1.16(2.81)	0.68	18.5
CVC reactivity		23.56(341.43)	0.95	17.9
$\bar{V}$P	Executive Function	-0.030(0.24)	0.90	31.0
CVC		-6.34(22.97)	0.78	31.0
$\bar{V}$P reactivity		2.02(3.61)	0.58	31.1
CVC reactivity		136.11(440.05)	0.76	30.5
$\bar{V}$P	Figural Memory	-0.21(0.15)	0.16	7.9
CVC		-8.67(13.71)	0.53	8.1
$\bar{V}$P reactivity		-2.68(2.15)	0.21	8.6
CVC reactivity		-365.62(262.32)	0.17	7.7
$\bar{V}$P	Verbal Memory	-0.049(0.12)	0.67	21.9
CVC		3.10(11.06)	0.78	22.2
$\bar{V}$P reactivity		-0.84(1.72)	0.63	22.5
CVC reactivity		-17.40(208.00)	0.93	22.8

Abbreviations: MET(s) = metabolic equivalent; $\bar{V}$P = blood flow velocity at +1 mmHg; CVC = cerebrovascular conductance at +1 mmHg; $\bar{V}$P reactivity= blood flow reactivity to a hypercapnic challenge from +1 mmHg to +8 mmHg; CVC reactivity= cerebrovascular conductance reactivity to a hypercapnic challenge from +1 mmHg to +8 mmHg.

Multivariable adjusted for age at the time of LTPAQ interview, sex, NAART, $\dot{V}O_2$max, BMI and interaction terms (age-sex, age predictor, sex-predictor, age-sex-predictor).

Table 18. Adjusted models for type, intensity and life periods of physical activity and processing speed.

Exposure Variable	Outcome Variable	Regression Coefficients (SE)	p-value	Model R^2 %
Type (MET-hour/week/year)				
Non-sedentary Occupational physical activity	Processing Speed	0.12(0.084)	0.15	17.5
Household physical activity		-0.073(0.18)	0.69	16.5
Recreational physical activity		0.40(0.19)	0.03	17.4
Intensity (Hour/week/year)				
Low (0-3 METs)	Processing Speed	-0.61(0.37)	0.097	17.7
Moderate (3-6 METs)		0.25(0.25)	0.33	16.3
Vigorous (>6 METs)		3.55(1.25)	0.005	19.1
Life Periods (MET-hour/week/year)				
Age 0 to 20	Processing Speed	0.13(0.084)	0.13	16.6
Age 21 to 35		0.10(0.037)	0.006	17.9
Age 36 to 50		-0.0010(0.038)	0.98	16.5
Age 51 to 65		-0.0048(0.043)	0.92	17.1

Abbreviations: MET(s) = metabolic equivalent;

Multivariable adjusted for age at the time of LTPAQ interview, NAART, $\dot{V}O_2$max, BMI and interaction terms (age-sex, age predictor, sex-predictor, age-sex-predictor).

Relationship between recreational PA, vigorous intensity PA and cerebrovascular indices presented in Appendix C, Table 24.

Table 19. Adjusted models for type, intensity and life periods of physical activity and executive functioning.

Exposure Variable	Outcome Variable	Regression Coefficients (SE)	p-value	Model R^2 %
Type (MET-hour/week/year)				
Non-sedentary Occupational physical activity	Executive functioning	0.020(0.11)	0.86	29.9
Household physical activity		-0.21(0.24)	0.38	30.7
Recreational physical activity		0.74(0.24)	0.002	31.9
Intensity (Hour/week/year)				
Low (0-3 METs)	Executive functioning	-0.63(0.47)	0.18	31.6
Moderate (3-6 METs)		-0.071(0.33)	0.83	30.2
Vigorous (>6 METs)		4.36(1.64)	0.009	32.5
Life Periods (MET-hour/week/year)				
Age 0 to 20	Executive functioning	0.21(0.11)	0.054	30.9
Age 21 to 35		0.092(0.048)	0.058	31.9
Age 36 to 50		-0.0055(0.050)	0.91	30.2
Age 51 to 65		-0.054(0.056)	0.34	30.8

Abbreviations: MET(s) = metabolic equivalent;
Multivariable adjusted for age at the time of LTPAQ interview, NAART, $\dot{V}O_2$max, BMI and interaction terms (age-sex, age predictor, sex-predictor, age-sex-predictor).
Relationship between recreational PA, vigorous intensity PA and cerebrovascular indices presented in Appendix C, Table 24.

Table 20. Adjusted models for type, intensity and life periods of physical activity and figural memory.

Exposure Variable	Outcome Variable	Regression Coefficients (SE)	p-value	Model R^2 %
Type (MET-hour/week/year)				
Non-sedentary Occupational physical activity	Figural Memory	0.045(0.066)	0.50	7.3
Household physical activity		-0.33(0.14)	0.81	8.9
Recreational physical activity		0.053(0.14)	0.72	7.2
Intensity (Hour/week/year)				
Low (0-3 METs)	Figural	0.25(0.28)	0.37	8.1
Moderate (3-6 METs)	Memory	-0.088(0.19)	0.64	8.7
Vigorous (>6 METs)		0.31(0.98)	0.75	7.4
Life Periods (MET-hour/week/year)				
Age 0 to 20	Figural	0.12(0.063)	0.048	11.0
Age 21 to 35	Memory	0.035(0.28)	0.21	9.7
Age 36 to 50		0.0080(0.029)	0.79	7.6
Age 51 to 65		-0.061(0.033)	0.068	9.8

Abbreviations: MET(s) = metabolic equivalent;

Multivariable adjusted for age at the time of LTPAQ interview, NAART, $\dot{V}O_2$max, BMI and interaction terms (age-sex, age predictor, sex-predictor, age-sex-predictor).

Relationship between PA done between ages 0 and 20 and cerebrovascular indices presented in Appendix C, Table 24.

Table 21. Adjusted models for type, intensity and life periods of physical activity and verbal memory.

Exposure Variable	Outcome Variable	Regression Coefficients (SE)	p-value	Model R^2 %
Type (MET-hour/week/year)				
Non-sedentary Occupational physical activity	Verbal Memory	0.083(0.053)	0.12	23.0
Household physical activity		-0.036(0.11)	0.75	22.7
Recreational physical activity		0.095(0.11)	0.41	22.3
Intensity (Hour/week/year)				
Low (0-3 METs)	Verbal Memory	-0.16(0.23)	0.50	22.3
Moderate (3-6 METs)		0.28(0.16)	0.071	23.0
Vigorous (>6 METs)		-0.21(0.78)	0.79	23.8
Life Periods (MET-hour/week/year)				
Age 0 to 20	Verbal Memory	-0.0038(0.052)	0.94	22.5
Age 21 to 35		0.036(0.023)	0.11	23.1
Age 36 to 50		0.019(0.023)	0.42	23.8
Age 51 to 65		0.012	0.65	23.2

Abbreviations: MET(s) = metabolic equivalent;
Multivariable adjusted for age at the time of LTPAQ interview, NAART, $\dot{V}O_2$max, BMI and interaction terms (age-sex, age predictor, sex-predictor, age-sex-predictor).

Chapter Five: **Summary and Conclusions**

5.1 Summary of Main Findings

The overall goal of this thesis was to explore the relations between measures of lifetime PA and global cognition scores, while addressing the role of cerebrovascular health in this association. This study adds to previous evidence suggesting that PA protects against poor cognitive functioning in later life while providing new insight into the importance of lifetime PA and the potential mediating effects of cerebrovascular health. We found that greater total lifetime PA was associated with better global cognitive performance in middle aged and older individuals (≥55 years old). Further, the timing and intensity of activity are important in the relation between PA and cognitive performance. Specifically, vigorous intensity and recreational PA done across the lifespan appear to have the greatest impact on global cognition in older adults. When considering the amount of PA done in different life periods (childhood to age 20, age 21 to 35, age 36 to age 50 and age 51-65) an association between PA done in early life (childhood to age 20 and age 21 to age 35) and improved cognitive performance later in life was found. These significant relations between measures of lifetime PA (i.e. total, recreational, vigorous intensity, early life periods) and cognitive performance were not mediated by current indices of cerebrovascular health.

The secondary analyses revealed no associations between total lifetime PA and the sub-domains of executive function, processing speed, verbal memory or figural memory. However, lifetime recreational and vigorous intensity PA was associated with better processing speed and executive function, while PA done before age 20 years was associated with better figural memory and PA between the ages of 21 and 35 years was associated with better processing

speed. No associations were observed between any measures of lifetime PA and figural memory. Finally, these significant relations were not mediated by indices of cerebrovascular health.

Our lack of evidence showing associations between cerebrovascular health, lifetime PA and cognition, in conjunction with current evidence suggesting cerebrovascular function is a factor contributing to cognitive ability (at least in part) and is affected by PA and exercise resulted in *post-hoc* analyses. We wanted to determine if recent PA or acute fitness levels were associated with better cerebrovascular function, supporting our *post-hoc* hypothesis that current PA levels or fitness may be more important for acute measures of cerebrovascular health than lifetime measures of PA. We assessed the relation between both past year PA and current fitness level and global cognitive performance. Past year PA and acute fitness levels were associated with greater global cognitive scores. In addition, indices of cerebrovascular health partially mediate only the relation between current fitness and global cognition. These findings indicate that acute measures of cerebrovascular health may have a more important role in mediating the relation between acute measures of fitness and cognition versus PA measures over longer time periods.

5.2 Biological Mechanisms

A number of biological mechanisms have been proposed to explain the observed effect PA has on cognitive functioning. Both animal and human models have contributed to the development of these plausible biological pathways. The proposed mechanisms are related to the impact of increased PA or cardiovascular fitness on physiological functions that may contribute to increasing or decreasing cognitive function. These pathways are summarized in Figure 8.

Before considering the physiological impact of PA it is important to consider the lifestyle and behavioural factors that may influence PA levels. We hypothesize that favourable lifestyle behaviours may contribute to increased levels of PA and fitness. These lifestyle factors include improved sleep and diet quality, lower levels of stress, alcohol and tobacco misuse and decreased obesity. Further, it is also likely that behavioural factors play a role in the level of PA an individual chooses to sustain. Specifically, increased cognitive activities, education, social support, social activities, psycho-social function and decreased depression are likely to result in an individual's desire and/or understanding to increase PA levels. Although the majority of these factors were not addressed in this study we acknowledge the important role they may play in affecting PA levels.

Increased PA positively impacts many of the body's physiological functions. Cardiovascular disease and cognitive decline share similar vascular risk factors, with increasing evidence suggesting a link between cardiovascular and cerebrovascular health (Qiu & Fratiglioni, 2015). Hypertension, arterial stiffness, oxidative stress and vascular inflammation have been identified as being associated with brain health and cognitive deficits (Davenport et al., 2012; Qiu & Fratiglioni, 2015). Increased levels of PA or improved cardiovascular fitness have the ability to counteract these potentially damaging effects, thus improving the likelihood of cerebrovascular integrity and cognitive abilities.

As demonstrated by the *post-hoc* analyses from this study and previously in the literature, acute measures of increased PA and cardiovascular fitness are related to increased measures of cerebrovascular blood flow (Ainslie et al., 2008; Bailey et al., 2013; Brown et al., 2010; Burdette et al., 2010; Chapman et al., 2013; Murrell et al., 2013). Improved blood perfusion within the brain likely results in increased oxygen transport, endothelial function, capillary recruitment and

angiogenesis, all of which contribute to improved tissue health and functioning (Bloor, 2005; Brown et al., 2013; Davenport et al., 2012). This has also been demonstrated in findings from animal studies (Kleim, Cooper, & VandenBerg, 2002; Swain et al., 2003; Voss, Nagamatsu, Liu-Ambrose, & Kramer, 2011).

Improved vasculature within the brain is thought to be integrated with neural functioning due to the structural makeup of the neurovascular unit (Davenport et al., 2012). Enhanced neurogenesis and extended survival of existing neurons has been proposed as a potential mechanism for delaying cognitive decline (Palmer, Willhoite, & Gage, 2000; Pereira et al., 2007; Voss et al., 2014). Brain-derived neurotropic factor (BDNF) has been identified as an important growth factor for neurogenesis because it supports neural survival and growth (Brown et al., 2013; Voss et al., 2011). It has been demonstrated that PA induces BDNF production (Baker et al., 2010; Brown et al., 2013; Prakash et al., 2015; Rasmussen et al., 2009; Voss et al., 2011) supporting the hypothesis of increased neurogeneration with PA. Other growth factors such as insulin-like growth factor 1 (IGF-1) and vascular endothelial growth factor (VEGF) have also been identified to promote exercise induced cognition benefits. Specifically, with exercise IGF-1 has been shown to mediate angiogenesis and neurogenesis, and it appears a symbiotic relationship exists between BDNF and IGF-1 signalling (Brown et al., 2013; Prakash et al., 2015). Additionally, VEGF promotes angiogenesis, has been identified as a mediator of neurogenesis through the action of IGF-1, and finally increased levels of VEGF are observed with increased levels of PA (Prakash et al., 2015; Voss et al., 2011).

In addition to the vascular and neural improvements that have been observed with increasing fitness and PA levels, decreased deposition of amyloid-β (Aβ) plaques has also been proposed as a mechanism that contributes to improve cognitive functioning. In animal studies Aβ

plaque deposition was significantly lower in the frontal cortex and hippocampus in mice that were pre-disposed to Aβ deposition after 5 months of voluntary exercise on a treadmill (Adlard, Perreau, Pop, & Cotman, 2005). Additionally, human studies have also identified increased levels of exercise resulted in decreased Aβ deposition (Baker et al., 2010; Brown et al., 2013; Liang et al., 2010).

Brain atrophy, a hallmark of advanced aging, has been identified as yet another physiological change that can be reduced with increasing activity level leading to improved cognitive benefits (Brown et al., 2013; Prakash et al., 2015). One study observed increasing levels of grey and white matter after a 6-month aerobic exercise intervention (Colcombe et al., 2006), while another identified larger frontal lobe volume with increased levels of exercise (Bugg & Head, 2011). Further, it has been demonstrated by Colcombe et al. (2004), Prakash et al. (2011) and Erickson et al. (2009) that increased levels of PA or fitness may result in increased neural plasticity resulting in improved cognitive abilities (Voss et al., 2011).

Finally, individual genetic effects must also be considered when assessing the underlying biological mechanisms. Of special interest is the potential impact *APOE* ε4 genotype has on both the physiological adaptations, such as its effect on amyloid clearance, neuronal repair and redistributing lipids among the central nervous system, in addition to changes in cognitive function (Brown et al., 2013; Prakash et al., 2015). Individuals with the ε4 allele have approximately four times the risk of developing cognitive deficits, potentially leading to late onset AD, than non-carries (Farrer et al., 1997). There is increasing evidence suggesting that increased levels of PA provide more benefit for ε4 carriers to prevent cognitive decline (Prakash et al., 2015; Voss et al., 2011). Therefore, it is important to account for the effect of APOE ε4 in the overall biological mechanism.

Together these factors paint a very intriguing picture of what might contribute to the cognitive improvements observed with increased levels of PA or fitness. It is clear that we cannot only consider one piece of evidence and must take a multi-disciplinary approach for greater understanding.

5.3 Strengths

This study is the first to investigate the relation between total lifetime PA and cognitive functioning using a retrospective measure of lifetime PA, and only one other study has examined lifetime recreational aerobic PA (confirmed by $\dot{V}O_2max$) and cerebrovascular functioning in older adults. Previous research examining PA and cognition generally assessed only past month or past year PA, and was restricted to recreational/leisure activities (Carvalho et al., 2014). A comprehensive assessment of total lifetime PA has not been previously done in studies that investigated the association between PA and cognition. A major strength of this study is the comprehensive and reliable measure of total lifetime PA (Friedenreich et al., 1998) that captured all types, intensities and time periods in life when PA could be most beneficial for reducing cognitive decline associated with aging. Additionally, the LTPAQ is interviewer-administered using cognitive interview techniques that permitted a more reliable and complete assessment of PA than would have been possible with a self-administered questionnaire. The use of a trained interviewer and two recall calendars allowed the participants to identify all activities and reduce the effect of recall error normally associated with self-reported questionnaire data collection.

An additional strength was the extensive neuropsychological test battery used to assess cognitive functioning. Our test battery provided a thorough evaluation of a range of cognitive abilities allowing us to assess cognition on a ‘global’ scale. The unique testing protocol used to

determine cerebrovascular functioning is an additional strength (Brown et al., 2010; Tyndall et al., 2013). Previously established, non-invasive methods were used for obtaining measures of cerebrovascular blood flow and conductance through the Laboratory for Human Cerebrovascular Physiology at the University of Calgary.

The quality and extent of participant information collected permitted a full assessment of covariates in the statistical analysis. It was determined that lifetime PA explained between 34.0% and 36.1% of the variance in global cognition when adjusting for age, sex, NAART, $\dot{V}O_2$max, BMI and age-sex-PA predictor interaction terms. We were able to determine that other important factors such as blood pressure, smoking status, income, *APOE* ε4 genotype and blood cholesterol levels did not substantially improve the model's variance.

Finally, the extent of information obtained at baseline for the BIM study allowed us to develop *post-hoc* hypotheses and perform additional analyses based on our primary findings that cerebrovascular function was not a mediator of the relation between lifetime PA and cognition. Having information on past year PA and current fitness levels allowed us to explore the indices of cerebrovascular health further and expand our understanding of the role cerebrovascular health plays in the relation between PA and cognition.

5.4 Limitations

Foremost, a cross-sectional study design cannot assess causality. All of our measures were obtained at the same point in time and therefore we cannot assume that the associations observed are causal. Since we obtained a retrospective lifetime PA assessment this limitation is somewhat mitigated since we were able to examine some temporal associations given the extensive retrospective assessment of activity that was captured in this study. However, recent

research by Belsky et al. (2015) demonstrate that children with higher levels of cognitive ability choose healthier lifestyles, and also had improved cognitive functioning later in life. These findings suggest that causality cannot be concluded, however future research is warranted to confirm these findings. As with many other smaller epidemiological samples, the results obtained may have limited generalizability to the general population of older adults given since it is based on a highly educated, healthy, and mostly Caucasian volunteer sample.

There is the possibility of misclassification of lifetime PA since participants may not have recalled their activities accurately. However, given that the LTPAQ has high reproducibility (Friedenreich et al., 1998) and we were interested in the relative ranking of activities, we anticipate the effect of this measurement error to be minimal. Any misclassification that is present would be non-differential with the effect of reducing our ability to show a relation between PA and cognition, suggesting that our results are conservative estimates of the true effect. Further, the questionnaire has not been tested for validity given the complexity of such a validation study that would have required historical PA data on a cohort of study participants who would have been assessed repeatedly over their lifetimes to capture the same data as are assessed in the LTPAQ used here. Hence, it is possible that PA from earlier in life is not accurately captured.

Although lifetime PA and other factors explain between 34.0% and 36.1% of the variance in global cognition, it is possible that a better model fit could be obtained. If we had consider the collection of additional data on factors such as current social activities, history of depression, family history of disease, and more detailed smoking history (packs per year), these variables could have been included as covariates in our models. It is possible that these other factors could improve the amount of variance explained by the model (i.e. make our findings more clinically

relevant). Additionally, we did not collect information on hormone levels and therefore were unable to fully explore the sex differences observed for the main relation between lifetime PA and global cognition.

It is possible that factors, other than cerebrovascular functioning may mediated the relation between lifetime PA and cognitive functioning. In the future it would be beneficial to explore non-physiological mediators that may have impact over one's lifetime such as history of socio-economic status (impacting opportunities over one's lifetime) or intellectual ability in the individual's youth (impacting decisions to participate in PA). Finally, a Bonferroni correction was used for multiple regression comparisons to reduce the risk of type I error. Using this correction resulted in loss of significance for some findings. Although we reduced type I error with a conservative α level, these corrections may lead to reduced statistical power and increase the risk of type II error and therefore the corrected α level should be interpreted with caution (Rothman, 1990).

5.5 Future Directions

In conjunction with previous research, this study suggests that higher levels of PA (recent or lifetime) or fitness are associated with cognitive abilities in later life. Although our study provides novel insight for the effects of lifetime PA on cognition, we did not address its impact on the development of dementia or AD. It would be beneficial to extend this research with a follow-up period to obtain information on diagnosis of these diseases. Such a design would allow us to relate measures of lifetime PA with disease onset versus the precursors of disease onset, cognitive ability and cerebrovascular health. Further, more research should be conducted to

determine if there is a dose-response relation between PA (total, recreational and vigorous) and cognitive performance, and to determine the possibility of a threshold effect.

5.6 Chapter Five Figure

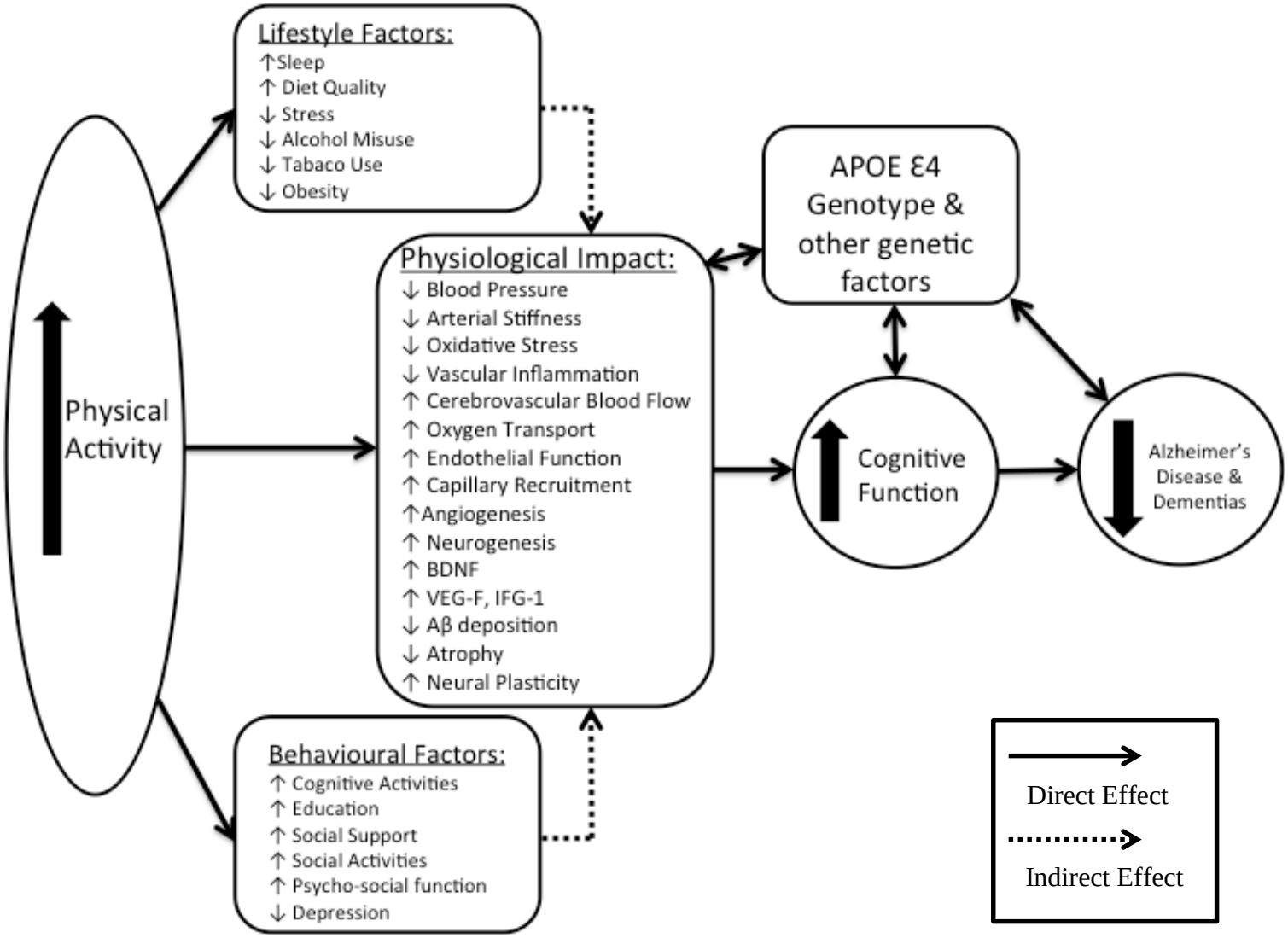


Figure 8. Proposed Biological Mechanism

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APPENDIX A: LIFETIME PHYSICAL ACTIVITY QUESTIONNAIRE

LIFETIME TOTAL PHYSICAL ACTIVITY QUESTIONNAIRE

These questions will be about your physical activity patterns over your lifetime. Specifically, I will be asking you about your occupational, household and recreational activities.

1. OCCUPATIONAL & VOLUNTEER ACTIVITIES

*Starting with your occupational activities, please tell me what jobs (paid or volunteer) you have done for at least **8 hours per week for 4 months** of the year (**128 hours** total per year or **2.5 hours** per week per year) over your lifetime starting with your first job.*

Please tell me about each job that you had. I need to know how old you were when you started and stopped working at each job and the number of months per year, days per week, hours per day that you worked at each job. Finally, I need to know what kind of physical effort you had for each job. Please choose one intensity level from the list on this separate page that defines each level.

LIFETIME RECORD OF OCCUPATIONAL & VOLUNTEER ACTIVITIES

No. of Rows _____

No.	Job Title	Description of Occupational Activity	Age Started	Age Ended	No. of Mos/ Yr.	No. of Days/ Wk.	Time/Day Hrs.	Time/Day Mins.	Intensity of Activity (1,2,3,4)	Did you ever walk, bike, rollerblade, or run to this job?	Which ones did you normally do? (*Check all that apply.*)	No. of Mos/ Yr.	No. of Days /Wk.	Time/Day Hrs.	Time/Day Mins.
1										[1]○ yes [2]○ no (**next job**) [97]○ Ref (**next job**) [99]○ DK (**next job**)	[1]○ walk [2]○ bike [3]○ rollerblade [4]○ run [5]○ other_____ [97]○ Ref (**next job**) [99]○ DK (**next job**)	…… …… …… …… ……	…… …… …… …… ……	…… …… …… …… ……	…… …… …… …… ……
2										[1]○ yes [2]○ no (**next job**) [97]○ Ref (**next job**) [99]○ DK (**next job**)	[1]○ walk [2]○ bike [3]○ rollerblade [4]○ run [5]○ other_____ [97]○ Ref (**next job**) [99]○ DK (**next job**)	…… …… …… …… ……	…… …… …… …… ……	…… …… …… …… ……	…… …… …… …… ……
3										[1]○ yes [2]○ no (**next job**) [97]○ Ref (**next job**) [99]○ DK (**next job**)	[1]○ walk [2]○ bike [3]○ rollerblade [4]○ run [5]○ other_____ [97]○ Ref (**next job**) [99]○ DK (**next job**)	…… …… …… …… ……	…… …… …… …… ……	…… …… …… …… ……	…… …… …… …… ……

No.	Job Title	Description of Occupational Activity	Age Started	Age Ended	No. of Mos/ Yr.	No. of Days/ Wk.	Time/Day Hrs.	Time/Day Mins.	Intensity of Activity (1,2,3,4)	Did you ever walk, bike, rollerblade, or run to this job?	Which ones did you normally do? (*Check all that apply.*)	No. of Mos/ Yr.	No. of Days /Wk.	Time/Day Hrs.	Time/Day Mins.
4										[1]○ yes [2]○ no (**next job**) [97]○ Ref (**next job**) [99]○ DK (**next job**)	[1]○ walk [2]○ bike [3]○ rollerblade [4]○ run [5]○ other_____ [97]○ Ref (**next job**) [99]○ DK (**next job**)	……. ……. ……. ……. …….	……. ……. ……. ……. …….	……. ……. ……. ……. …….	……. ……. ……. ……. …….
5										[1]○ yes [2]○ no (**next job**) [97]○ Ref (**next job**) [99]○ DK (**next job**)	[1]○ walk [2]○ bike [3]○ rollerblade [4]○ run [5]○ other_____ [97]○ Ref (**next job**) [99]○ DK (**next job**)	……. ……. ……. ……. …….	……. ……. ……. ……. …….	……. ……. ……. ……. …….	……. ……. ……. ……. …….
6										[1]○ yes [2]○ no (**next job**) [97]○ Ref (**next job**) [99]○ DK (**next job**)	[1]○ walk [2]○ bike [3]○ rollerblade [4]○ run [5]○ other_____ [97]○ Ref (**next job**) [99]○ DK (**next job**)	……. ……. ……. ……. …….	……. ……. ……. ……. …….	……. ……. ……. ……. …….	……. ……. ……. ……. …….
7										[1]○ yes [2]○ no (**next job**) [97]○ Ref (**next job**) [99]○ DK (**next job**)	[1]○ walk [2]○ bike [3]○ rollerblade [4]○ run [5]○ other_____ [97]○ Ref (**next job**) [99]○ DK (**next job**)	……. ……. ……. ……. …….	……. ……. ……. ……. …….	……. ……. ……. ……. …….	……. ……. ……. ……. …….
8										[1]○ yes [2]○ no (**next job**) [97]○ Ref (**next job**) [99]○ DK (**next job**)	[1]○ walk [2]○ bike [3]○ rollerblade [4]○ run [5]○ other_____ [97]○ Ref (**next job**) [99]○ DK (**next job**)	……. ……. ……. ……. …….	……. ……. ……. ……. …….	……. ……. ……. ……. …….	……. ……. ……. ……. …….

No.	Job Title	Description of Occupational Activity	Age Started	Age Ended	No. of Mos/ Yr.	No. of Days/ Wk.	Time/Day Hrs.	Time/Day Mins.	Intensity of Activity (1,2,3,4)	Did you ever walk, bike, rollerblade, or run to this job?	Which ones did you normally do? (*Check all that apply.*)	No. of Mos/ Yr.	No. of Days /Wk.	Time/Day Hrs.	Time/Day Mins.
10										[1]○ yes [2]○ no (**next job**) [97]○ Ref (**next job**) [99]○ DK (**next job**)	[1]○ walk [2]○ bike [3]○ rollerblade [4]○ run [5]○ other_____ [97]○ Ref (**next job**) [99]○ DK (**next job**)	……. ……. ……. ……. …….	……. ……. ……. ……. …….	……. ……. ……. ……. …….	……. ……. ……. ……. …….
11										[1]○ yes [2]○ no (**next job**) [97]○ Ref (**next job**) [99]○ DK (**next job**)	[1]○ walk [2]○ bike [3]○ rollerblade [4]○ run [5]○ other_____ [97]○ Ref (**next job**) [99]○ DK (**next job**)	……. ……. ……. ……. …….	……. ……. ……. ……. …….	……. ……. ……. ……. …….	……. ……. ……. ……. …….
12										[1]○ yes [2]○ no (**next job**) [97]○ Ref (**next job**) [99]○ DK (**next job**)	[1]○ walk [2]○ bike [3]○ rollerblade [4]○ run [5]○ other_____ [97]○ Ref (**next job**) [99]○ DK (**next job**)	……. ……. ……. ……. …….	……. ……. ……. ……. …….	……. ……. ……. ……. …….	……. ……. ……. ……. …….
13										[1]○ yes [2]○ no (**next job**) [97]○ Ref (**next job**) [99]○ DK (**next job**)	[1]○ walk [2]○ bike [3]○ rollerblade [4]○ run [5]○ other_____ [97]○ Ref (**next job**) [99]○ DK (**next job**)	……. ……. ……. ……. …….	……. ……. ……. ……. …….	……. ……. ……. ……. …….	……. ……. ……. ……. …….
14										[1]○ yes [2]○ no (**next job**) [97]○ Ref (**next job**) [99]○ DK (**next job**)	[1]○ walk [2]○ bike [3]○ rollerblade [4]○ run [5]○ other_____ [97]○ Ref (**next job**) [99]○ DK (**next job**)	……. ……. ……. ……. …….	……. ……. ……. ……. …….	……. ……. ……. ……. …….	……. ……. ……. ……. …….

No.	Job Title	Description of Occupational Activity	Age Started	Age Ended	No. of Mos/ Yr.	No. of Days/ Wk.	Time/Day Hrs.	Time/Day Mins.	Intensity of Activity (1,2,3,4)	Did you ever walk, bike, rollerblade, or run to this job?	Which ones did you normally do? (*Check all that apply.*)	No. of Mos/ Yr.	No. of Days /Wk.	Time/Day Hrs.	Time/Day Mins.
16										[1]○ yes [2]○ no (**next job**) [97]○ Ref (**next job**) [99]○ DK (**next job**)	[1]○ walk [2]○ bike [3]○ rollerblade [4]○ run [5]○ other_____ [97]○ Ref (**next job**) [99]○ DK (**next job**)	……. ……. ……. ……. …….	……. ……. ……. ……. …….	……. ……. ……. ……. …….	……. ……. ……. ……. …….
17										[1]○ yes [2]○ no (**next job**) [97]○ Ref (**next job**) [99]○ DK (**next job**)	[1]○ walk [2]○ bike [3]○ rollerblade [4]○ run [5]○ other_____ [97]○ Ref (**next job**) [99]○ DK (**next job**)	……. ……. ……. ……. …….	……. ……. ……. ……. …….	……. ……. ……. ……. …….	……. ……. ……. ……. …….
18										[1]○ yes [2]○ no (**next job**) [97]○ Ref (**next job**) [99]○ DK (**next job**)	[1]○ walk [2]○ bike [3]○ rollerblade [4]○ run [5]○ other_____ [97]○ Ref (**next job**) [99]○ DK (**next job**)	……. ……. ……. ……. …….	……. ……. ……. ……. …….	……. ……. ……. ……. …….	……. ……. ……. ……. …….
19										[1]○ yes [2]○ no (**next job**) [97]○ Ref (**next job**) [99]○ DK (**next job**)	[1]○ walk [2]○ bike [3]○ rollerblade [4]○ run [5]○ other_____ [97]○ Ref (**next job**) [99]○ DK (**next job**)	……. ……. ……. ……. …….	……. ……. ……. ……. …….	……. ……. ……. ……. …….	……. ……. ……. ……. …….
20										[1]○ yes [2]○ no (**next job**) [97]○ Ref (**next job**) [99]○ DK (**next job**)	[1]○ walk [2]○ bike [3]○ rollerblade [4]○ run [5]○ other_____ [97]○ Ref (**next job**) [99]○ DK (**next job**)	……. ……. ……. ……. …….	……. ……. ……. ……. …….	……. ……. ……. ……. …….	……. ……. ……. ……. …….

2. HOUSEHOLD ACTIVITIES

*Now I am going to ask you to tell me about your patterns of household and gardening activities over your lifetime. Again, we will start with your past activity and then continue up to your reference year. Please include only those activities that you have done at least **7 hours per week 4 months** of the year (**112 hours** total per year or **2.15 hours** per week per year).*

*It may help you to consider what a typical day or week was for you. Then think about how many hours of household, gardening, yard work or do-it-yourself jobs around your home that you did in a typical day or week. For seasonal activities, such as gardening, you can report those separately from all other household activities that are done all year. Seated activities (such as sewing or paying bills) are not included. **Childcare** and **housework** are included.*

LIFETIME RECORD OF HOUSEHOLD ACTIVITIES

No. of Rows ____

No.	Age Started	Age Ended	Number of Months/Yr.	Number of Days/Wk.	Time per day Hrs. Mins		Hours per day spent in activities that were in category: 2	3	4
1									
2									
3									
4									
5									
6									
7									
8									
9									

No.	Age Started	Age Ended	Number of Months/Yr.	Number of Days/Wk.	Time per day Hrs. Mins		Hours per day spent in activities that were in category: 2	3	4
14									
15									
16									
17									
18									
19									
20									
21									
22									
23									
24									
25									
26									
27									
28									
29									

3. EXERCISE & SPORTS ACTIVITIES

*Now I would like to know all your exercise or sports activities that you did during your lifetime starting with your childhood and continuing to your reference year. Please report the activities that you have done at least **2 hours per week for 4 months** of the year (**32 hours** total per year or **40 minutes** per week per year).*

*Please tell us what exercise and sports activities you have done at least **10 times during your lifetime**. Besides sports and exercise, we are also interested in knowing whether you **walked, biked, ran or rollerbladed to school**. If you have done this, please report all the information as for the other sports activities. Please begin by telling me the activities that you did during your school years including your physical education (**gym**) classes.*

LIFETIME RECORD OF EXERCISE & SPORTS ACTIVITIES

No. of Rows ____

No.	Description of Exercise/Sports Activity	Code	Age Started	Age Ended	Frequency of Activity				Time per Activity		Intensity of Activity (2,3,4)
					Day	Week	Month	Year	Hrs.	Mins.	
1											
2											
3											
4											
5											
6											
7											
8											
9											

No.	Description of Exercise/Sports Activity	Code	Age Started	Age Ended	Frequency of Activity				Time per Activity Hrs. Mins.		Intensity of Activity (2,3,4)
					Day	Week	Month	Year			
14											
15											
16											
17											
18											
19											
20											
21											
22											
23											
24											
25											
26											
27											
28											

APPENDIX B: SELF REPORT INTENSITY DOCUMENTS

Lifetime Total Physical Activity Questionnaire
Intensity Levels

Category	Description
Occupation	
1	Jobs that require only sitting with minimal walking.
2	Jobs that require a minimal amount of physical effort such as standing and slow walking. There is no increase in heart rate and there is no perspiration.
3	Jobs that require carrying light loads and continuous walking. These activities would increase the heart rate slightly and may cause some light perspiration.
4	Jobs that require carrying heavy loads, brisk walking, and climbing. These jobs would increase the heart rate substantially and cause heavy sweating.
Household	
2	Activities that require minimal physical effort such as those activities that are done standing or with slow walking.
3	Activities that are not exhausting, that increase the heart rate slightly and may cause some light perspiration.
4	Activities that increase the heart rate and cause heavy sweating. These activities include those that require lifting, moving heavy objects, rubbing vigorously for fairly long periods, activities that cause sweating or faster heartbeat.
Exercise/ Sports	
2	Activities that require minimal physical effort.
3	Activities that are not exhausting, that increase the heart rate slightly and may cause some light perspiration.
4	Activities that increase the heart rate and cause heavy sweating.

Lifetime Total Physical Activity Questionnaire
Household Intensity Levels

CATEGORY	Description of Household Activity	MET level
Home activities		
2	**Home activities, light** (sweeping, vacuuming, dusting, washing dishes, cooking, food preparation standing or sitting, putting away groceries, shopping, ironing, laundry), light effort.	**2.5**
3	**Home activities, moderate** (general house cleaning, food shopping with grocery cart, standing-packing/unpacking boxes, occasional lifting of household items, child care - light effort), moderate effort.	**3.5**
4	**Home activities, heavy** (major cleaning e.g. wash car, windows, mop, clean garage, sweeping sidewalk, scrubbing floors vigorous effort, moving household items, furniture, boxes), child care - moderate to heavy effort (e.g. walk/run-playing with children)	**5**
Home Repair		
2	**Home repair, light** (automobile repair, wiring, plumbing, carpentry, workshop).	**3**
3	**Home repair, moderate** (automobile body work, finishing or refinishing cabinets or furniture, caulking, laying tile or carpet, painting, papering, plastering, scraping, sanding floors, washing/waxing/painting a car or boat, washing fence).	**4.5**
4	**Home repair, heavy** (outside carpentry, installing gutters, roofing, sawing hardwood, spreading dirt with a shovel, painting outside house).	**6**
Lawn & Garden		
2	**Lawn and garden, light** (watering lawn, fertilizing or seeding lawn, standing or walking in garden, mowing lawn on a rider mower).	**2.5**
3	**Lawn and garden, moderate** (mowing lawn by walking with a power mower, trimming shrubs or trees, operating a snow blower, planting seedlings, shrubs, trees, weeding, cultivating a garden, general gardening, sacking leaves, grass).	**4.5**
4	**Lawn and garden, heavy** (carrying, stacking wood, lumber, chopping wood, splitting logs, clearing land, hauling branches, digging, spading, filling garden, laying sod, rock, mowing lawn with a push mower, shoveling snow by hand).	**6**

APPENDIX C: TABLES NOT INCLUDED IN MANUSCRIPT

Table 22. Adjusted overall models for associations between lifetime physical activity and indices of cerebrovascular health.

Outcome Variable	Regression Coefficients (SE)	p-value	Model R^2 %
$\bar{V}$P	-0.35(0.31)	0.26	18.7
CVC	-0.0036(0.0040)	0.37	21.3
$\bar{V}$P reactivity	-0.0095(0.025)	0.70	5.5
CVC reactivity	-0.00020(0.00022)	0.35	4.6

Abbreviations: $\bar{V}$P = blood flow velocity at +1 mmHg; CVC = cerebrovascular conductance at +1 mmHg; $\bar{V}$P reactivity= blood flow reactivity to a hypercapnic challenge from +1 mmHg to +8 mmHg; CVC reactivity= cerebrovascular conductance reactivity to a hypercapnic challenge from +1 mmHg to +8 mmHg.

Multivariable adjusted for age at the time of LTPAQ interview, sex, NAART, $\dot{V}O_2$max, BMI, and interaction terms (age-sex, age predictor, sex-predictor, age-sex-predictor).

Displaying further interaction terms were not useful for interpreting these relations.

Table 23. Summary of adjusted models for lifetime physical activity, global cognition and indices of cerebrovascular health to fulfill mediation analysis.

Predictor	Outcome Variable	Regression Coefficients (SE)	p-value	Model R^2 %
Total Lifetime Physical Activity (Mediation Steps 1-3)				
Lifetime total physical activity (MET-hr/wk/yr)	Global Cognition	0.40(0.20)	0.045	34.7
Lifetime total physical activity (MET-hr/wk/yr)	$\bar{V}$P	-0.35(0.31)	0.26	18.7
	CVC	-0.0036(0.004)	0.37	21.3
	$\bar{V}$P reactivity	-0.009(0.025)	0.70	5.5
	CVC reactivity	-0.0002(0.0002)	0.35	4.6
$\bar{V}$P	Global Cognition	-0.36(0.52)	0.49	35.2
CVC		-17.26(48.81)	0.72	34.8
$\bar{V}$P reactivity		-2.82(7.69)	0.71	34.3
CVC reactivity		-401.59(930.58)	0.67	34.6

Abbreviations: MET(s) = metabolic equivalent; $\bar{V}$P = blood flow velocity at +1 mmHg; CVC = cerebrovascular conductance at +1 mmHg; $\bar{V}$P reactivity= blood flow reactivity to a hypercapnic challenge from +1 mmHg to +8 mmHg; CVC reactivity= cerebrovascular conductance reactivity to a hypercapnic challenge from +1 mmHg to +8 mmHg.
Multivariable adjusted for age at the time of LTPAQ interview, sex, NAART, $\dot{V}O_2$max, BMI and interaction terms (age-sex, age predictor, sex-predictor, age-sex-predictor).

Table 24. Adjusted models for type, intensity and life periods of physical activity, cognition and cerebrovascular health.

Exposure Variable	Outcome Variable	Regression Coefficients (SE)	p-value	Model R^2 %
Type (MET-hour/week/year)				
Non-sedentary Occupational physical activity	Global Cognition	0.42(0.23)	0.074	34.7
Household physical activity		-0.51(0.50)	0.31	34.6
Recreational physical activity		1.18(0.49)	0.021	35.0
Recreational physical activity	$\bar{V}$P	-1.10(0.77)	0.15	20.1
	CVC	-0.013(0.0099)	0.18	22.2
	$\bar{V}$P reactivity	-0.055(0.060)	0.36	7.5
	CVC reactivity	-0.0010(0.00055)	0.065	6.0
Intensity (Hour/week/year)				
Low (0-3 METs)	Global	-0.97(1.0)	0.33	34.6
Moderate (3-6 METs)	Cognition	0.43(0.69)	0.53	34.0
Vigorous (>6 METs)		8.72(3.42)	0.012	35.8
Vigorous (>6 METs)	$\bar{V}$P	-7.2(5.38)	0.18	18.1
	CVC	-0.10(0.068)	0.14	21.6
	$\bar{V}$P reactivity	-0.48(0.41)	0.24	7.2
	CVC reactivity	-0.0065(0.0038)	0.086	5.3
Life Periods (MET-hour/week/year)				
Age 0 to 20	Global	0.47(0.23)	0.036	35.3
Age 21 to 35	Cognition	0.36(0.099)	0.000	36.1
Age 36 to 50		0.059(0.10)	0.57	34.2
Age 0 to 20	$\bar{V}$P	-0.45(0.35)	0.20	20.2
	CVC	-0.0062(0.045)	0.17	22.7
	V_p reactivity	-0.018(0.028)	0.51	5.7
	CVC reactivity	-0.00048(0.00024)	0.052	6.5
Age 21 to 35	$\bar{V}$P	-0.074(0.16)	0.64	18.8
	CVC	-0.0012(0.0020)	0.57	21.2
	V_p reactivity	0.0026(0.012)	0.83	6.1
	CVC reactivity	-0.0000011(0.00011)	0.93	4.2

Abbreviations: MET(s) = metabolic equivalent; $\bar{V}$P = blood flow velocity at +1 mmHg; CVC = cerebrovascular conductance at +1 mmHg; $\bar{V}$P reactivity= blood flow reactivity to a hypercapnic challenge from +1 mmHg to +8 mmHg; CVC reactivity= cerebrovascular conductance reactivity to a hypercapnic challenge from +1 mmHg to +8 mmHg.
Multivariable adjusted for age at the time of LTPAQ interview, NAART, $\dot{V}O_2$max, BMI and interaction terms (age, sex, exposure).

Table 25. Adjusted overall model for association between past year physical activity and global cognition.

Variable	Regression Coefficients (SE)	p-value	Model R^2 %
Global Cognition			
Past year PA	0.018(0.008)	0.019	21.4
Sex	3.50(1.45)	0.016	
NAART	0.60(0.10)	0.000	
Waist Circumference	0.030(0.060)	0.62	
Blood Pressure	0.10(0.081)	0.20	
Smoking Status	1.74(1.29)	0.18	
Alcohol Consumption	0.024(0.57)	0.97	
Constant	-81.07(13.27)	0.000	

Abbreviations: PA= physical activity; NAART= North American Adult Reading Test; Multivariable adjusted for sex, NAART, waist circumference, blood pressure, smoking status and alcohol consumption.

Table 26. Adjusted overall model for association between current fitness and global cognition.

Variable	Regression Coefficients (SE)	p-value	Model R^2 %
$\dot{V}O_2$max	0.57(0.15)	0.000	23.6
Sex	7.80(1.77)	0.000	
NAART	0.58(0.098)	0.000	
Waist Circumference	0.14(0.068)	0.042	
Blood Pressure	0.082(0.080)	0.30	
Smoking Status	1.74(1.26)	0.16	
Alcohol Consumption	-0.038(0.56)	0.95	
Constant	-102.42(14.61)	0.000	

Abbreviations: $\dot{V}O_2$max = maximal aerobic capacity; NAART= North American Adult Reading Test.
Multivariable adjusted for sex, NAART, waist circumference, blood pressure, smoking status and alcohol consumption.

APPENDIX D: PUBLICATION ACCEPTANCE EMAIL

JINS - Decision on Manuscript ID JINS#-15-128-SIPA.R2

@manuscriptcentral.com on behalf of

Thu 8/27/2015 12:53 PM

27-Aug-2015

Dear Dr.

Thank you for resubmitting your manuscript, "Association Between Lifetime Physical Activity and Cognitive Functioning in Middle-aged and Older Community Dwelling Adults: Results from the Brain in Motion Study" (JINS#-15-128-SIPA.R2) to JINS. The manuscript is now acceptable for publication as a Special Issue: Physical Activity and Brain Plasticity.

Therefore, it is with great pleasure that I can tell you that the paper will appear in the journal. In the near future, Cambridge University Press will be forwarding galley proofs to you. Please review the proofs carefully, since you will be the only person proofreading your manuscript for "content." In order to facilitate our being able to get the Journal out on schedule, PLEASE RETURN YOUR PROOFS TO THE PUBLISHER WITHIN 48 HOURS. As a contingency plan, please recommend a co-author who can make necessary corrections in case you are unavailable when the galley proofs arrive. Please e-mail Lauren Marra, lmarra@cambridge.org with this information immediately. Delay in returning manuscripts to the publisher may delay the publication of your manuscript.

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