PHYSICAL ACTIVITY AS MEDICINE: AGEING, LIFESTYLE AND COGNITIVE FUNCTION

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A DISSERTATION SUBMITTED TO THE FACULTY OF GRADUATE STUDIES IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

GRADUATE PROGRAM OF KINESIOLOGY AND HEALTH SCIENCE

YORK UNIVERSITY

TORONTO, ONTARIO

JUNE 2016

ABSTRACT

As the world's population grows older, cognitive disorders are becoming more common. It is estimated that to date more than 20 million people worldwide have dementia, and the total prevalence of dementia is predicted to quadruple by 2040 due to demographic changes as well as increasing longevity. Currently, there is no cure for cognitive decline or dementia; therefore, finding lifestyle interventions which decrease the risk of cognitive decline or preserve cognitive function are of the utmost importance. This thesis comprises four manuscripts that explore the inter-relationships between physical activity, various lifestyle factors and cognitive function at different points across the lifespan.

Studies one and two used data from the 2012 annual component of the Canadian Community Health Survey and studies three and four used data from the Midlife in the US (MIDUS) survey. The first study assessed the associations between physical activity, sedentary time, obesity (body mass index), and cognitive function in younger and older Canadian adults. The second study explored the relationships between physical activity, daily fruit and vegetable consumption, obesity (body mass index), and cognitive function in younger and older Canadian adults. The third study evaluated the inter-relationships between physical activity, number of medications used (type II diabetes, high blood pressure, high cholesterol), obesity (waist-to-hip ratio) and cognitive function in adults between the ages of 25 to 84 years. The fourth study considered the relationships between physical activity, engagement in cognitively stimulating activities, obesity (waist-to-hip ratio) and cognitive function in adults between the ages of 25 to 84 years.

Collectively, the findings of these studies contribute to a better understanding of the relationships that exist between lifestyle variables and cognitive function across the adult lifespan.

Acknowledgements

First and foremost, I'd like to thank my incredible supervisors, Dr. Chris Ardern and Dr. Joe Baker, for all of their support, guidance, and assistance over the last few years. I have really enjoyed working with and learning from the both of you throughout this demanding, challenging, and rewarding process. I will forever appreciate your willingness to accept me as one of your doctoral students; thank you for your confidence in me. I feel truly privileged to have had the opportunity to work under the supervision of two of the most brilliant researchers and people that I've ever met. Thank you both so much for making this such a wonderful experience for me!

Dr. Rebecca Bassett-Gunter and Dr. Gary Turner, thank you both so much for being so helpful, approachable, and supportive throughout this process. I truly appreciate your thorough and informative feedback on my work. I learned a lot from both of you, thank you!

Dr. Susan Murtha and Dr. Laura Middleton, thank you both so much for being a part of my doctoral examination committee. The feedback that you have provided me with has really helped strengthen my dissertation. Thank you!

My Family, mom, dad, Bethany, I love you all so very much. Thank you for your undying support and never-ending confidence in me. Thank you for believing in me even in times when I stopped believing in myself. Thank you for your words of encouragement and for always being there for me. I could not have accomplished any of this without you. Thank you!

Mirka, you have seen me through both my Master's degree and now my PhD, I know I say this to you all the time, but I'm going to say this once more, I truly appreciate all of your help. Thank you for making statistics less daunting and much more pleasant. I learned a lot from you. Thank you!

Finally, my lab mates from both the Ardern and Baker labs, thank you all for your support and help throughout this process. It was really amazing getting to know all of you and going through this process with you. Thank you!

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CHAPTER 6: GENERAL DISCUSSION

CHAPTER 1: GENERAL INTRODUCTION

As people age, they change in numerous ways, both biologically and psychologically. There is sufficient evidence that alterations in brain structure and function are closely tied to alterations in cognitive function (Raz, 2000). Age-related changes in cognitive function vary considerably across individuals and across cognitive domains, with some cognitive functions appearing more susceptible to the effects of ageing than others (Raz, 2000). The basic cognitive functions that seem most affected by age are attention and memory, although higher-level functions such as language processing and decision making, may also be affected (Verhaeghen & Cerella, 2002). Moreover, complex cognitive tasks may also depend on a set of executive functions (controls goal oriented behaviors such as problem solving, multitasking, and plan making) (Verhaeghen & Cerella, 2002). Evidence points to executive functioning impairments as contributors to declines in cognitive functioning that may result in a Mild Cognitive Impairment (MCI) or a dementia spectrum disorder (Bishop et al., 2010; Hedden & Gabrieli, 2004). Bearing in mind the increase in the proportion of older adults, it is important to identify a means for maintaining cognitive integrity by protecting against, or even counteracting, some of the adverse effects of the ageing process (Bishop et al., 2010; Hedden & Gabrieli, 2004).

Dementia means “loss of mind” and is a neurological condition characterized by both cognitive as well as functional impairments; individuals eventually lose their independence and become unable to perform the typical activities of daily living (Gelder et al., 2006). Dementia is a syndrome that is affecting an ever-increasing number of people due to the ageing of populations globally. According to Alzheimer’s Disease International (ADI), 24.3 million people were living with dementia in 14 World Health Organization (WHO) regions in 2001, and this is estimated to reach 81.1 million by 2040, with the number doubling every 20 years (Prince et al., 2013). In 2010, the global prevalence of dementia for age 60y+ was 4.7% with a regional prevalence of 2.6% in Africa, 4.0% in Asia, 6.2% in Europe and 6.9% in North America (Sosa-Ortiz et al., 2012). *The Global Burden of Disease* has estimated that dementia accounts for 11.2% of disability years in people over 60 years, a value higher than stroke (9.5%), cardiovascular diseases (5.0%), musculoskeletal disorders (8.9%) and all forms of cancer (2.4%) (Ferri et al., 2005). These facts and figures emphasize the importance of developing preventative strategies in order to reduce the burden of this disease on society as well as ease the suffering of those affected both directly and indirectly (e.g. family members).

Cognitive Function

Cognitive function is brain function. An adult human brain weighs approximately 3 pounds (Clarke & Sokoloff, 1999; Kramer & Erickson, 2007), is smaller in women than men, and encompasses about 2% of total body mass. As people age, the weight and volume of their brains decreases, with a loss of between 5%-10% in their later years (Clarke & Sokoloff, 1999; Kramer & Erickson, 2007). The brain works even when the individual is at rest, although it works harder when the individual thinks, speaks, reads, plans or acts. All that work depends on the body's ability to deliver oxygen and glucose to the cerebrovascular system and on that system's ability to route blood to the active neurons. The brain's functioning depends heavily on cardiovascular, respiratory, and metabolic health (Kramer & Erickson, 2007; Cotman et al., 2007; Hillman et al., 2008; Kumari et al., 2000; Spiro et al., 2008).

Human brains age at different rates due to factors such as genetic make-up and environmental variables (Clarke & Sokoloff, 1999; Kramer & Erickson, 2007). To a large degree, lifestyle behaviors define the non-genetic elements that affect the brain. If the ageing process in the brain is accelerated for any reason, neurons are damaged and dementia emerges

(Kramer & Erickson, 2007).

Research has shown that dementia spectrum disorders are characterized by varying patterns of impairment. Alzheimer's Disease is characterized by impairment of episodic memory (verbal and non-verbal) initially, followed by dysfunctions in judgment and abstract reasoning, visual construction, verbal fluency and naming (Gelder et al., 2006). Patients with vascular dementia tend to be significantly more impaired than patients with AD on tests of executive function such as verbal fluency, and their level of memory impairment usually tends to be less severe (Gelder et al., 2006). In fronto-temporal dementia, letter fluency and executive function are usually worse than in AD, while memory performance is usually better. Dementia with lewy bodies is characterized by a dysfunction in attention, visuospatial tasks, letter fluency, mental tracking and abstract reasoning (Gelder et al., 2006).

Successful cognitive ageing is defined as:

‘‘Not just the absence of cognitive impairment, but the development and preservation of the multi-dimensional cognitive structure that allows the older adult to maintain social connectedness, and ongoing sense of purpose, and the abilities to function independently, to permit functional recovery from illness and injury, and to cope with residual cognitive deficits (Hendrie & Albert, 2006).’’

The main elements of this definition are that successful cognitive ageing combines multiple cognitive domains, extending beyond traditional neuropsychological abilities, such as memory and executive functions, to more esoteric constructs such as wisdom and resilience. In addition, this definition considers the link between cognitive health with functional independence and engagement with life (Hendrie & Albert, 2006).

Risk Factors

Genetics.

The apolipoprotein E (APOE) e4 allele is the main genetic risk factor for AD. The APOE e4 allele increases the risk for AD in a dose-response manner, where those with homozygous e4 allele have a higher risk than individuals with heterozygous e4 allele, who in turn have a higher risk than individuals with no e4 copies (Qiu et al., 2004). It has been estimated that 15%-20% of dementia and AD are attributable to the APOE e4 allele (Frikke-Schmidt et al., 2001). Genetic causes of AD include autosomal-dominant mutations in three genes (Presenilin 1 (PSEN1), Presenilin 2 (PSEN2) and the amyloid precursor protein (APP), which are implicated in early-onset AD and account for approximately 1% of all cases (Solomon et al., 2014; Wu et al., 2012)

Age.

Age is the leading risk factor for cognitive decline and dementia, with risk for both Alzheimer's disease (AD) and vascular dementia (VaD) doubling every 5 years over the age of 65 (Wimo & Prince, 2010; Lobo et al., 2000). Age-dependent associations with dementia/AD have been suggested for several ageing-related medical conditions. For example, elevated blood pressure, body mass index (BMI: kg/m^2), and total cholesterol levels at a young age and in middle age (<65 years) are associated with an increased risk of dementia and AD, and having lower values in late life (>75 years) is also associated with subsequent development of dementia/AD (Qiu et al., 2005; Qiu et al., 2010; Kivipelto et al., 2005). Diabetes mellitus has also been associated with increased risk of dementia and AD throughout adulthood, but the risk is stronger when diabetes occurs in mid-life compared to late-life (Arvanitakis et al., 2004).

Obesity.

Among older adults, a low or declining BMI is generally indicative of an unhealthy loss of muscle, bone density, and an increase in body fat resulting from inactivity, poor nutrition, and an accumulation of chronic conditions (Dziura et al., 2004; Kahng et al., 2004). However, the relationship between BMI and cognitive decline and dementia is largely dependent on the time of onset as well as duration of BMI and body weight change. Compared to normal BMI (18.5-24.9), underweight was not significantly associated with AD (Anstey et al., 2011; Xu et al., 2011; Fitzpatrick et al., 2009; Beydoun et al., 2008; Whitmer et al., 2007). Additionally, obesity (BMI ≥30) in later life (≥60 years of age) appears to be inversely associated with dementia compared to normal weight, reducing the risk of dementia by 21% (Luchsinger et al., 2012). Among seniors who have been overweight or obese for a long period of time, remaining so may be a relatively good sign for cognitive function (Kuo et al., 2006). For middle-aged adults, however, higher BMI is associated with lower cognitive function and faster subsequent decline (Cournot et al., 2006; Sabia et al., 2009). Cournot and colleagues (2006) found that a higher BMI was associated with lower cognitive scores after adjustment for age, sex, educational level, blood pressure, diabetes, and other psychosocial factors. A higher BMI was also associated with a higher cognitive decline at follow-up, after adjustment for confounders (Cournot et al., 2006). Sabia and colleagues (2009) found that both underweight and obesity were associated with lower cognition in late midlife and with early adulthood, early midlife, and late midlife measures of BMI. Being obese on two or three occasions was associated with lower Mini-Mental State Examination scores, scores of memory and executive function in analyses adjusted for age, sex, and level of education compared with the normal-weight group. Participants who were underweight on two or more occasions from early adulthood to late midlife had lower executive function. Further, a large increase in BMI from early to late midlife was associated with lower executive function (Sabia et al., 2009). Compared to normal weight individuals, obese individuals in midlife (40-59 years of age) had a nearly twofold, greater risk for all types of any dementia, and a modestly higher risk for AD (Xu et al., 2011; Fitzpatrick et al., 2009; Beydoun et al., 2008; Whitmer et al., 2005; Whitmer et al., 2008; Rosengren et al., 2005; Wimo & Prince, 2010; Whitmer et al., 2007).

Obesity and a sedentary lifestyle are believed to accelerate ageing in all of the body's organs, including the brain. In general, weight is gained over the life span, but this weight increase is considered to level off around the age of 65–70 years, and weight loss is associated with an increased risk of death in late life (Dziura et al., 2004; Kahng et al., 2004). However, older adults today are heavier and have been overweight for a longer period of time than in previous generations (Hedley et al., 2004). Given that excess body weight is a global health problem, with more than 60% of the US and European adult populations being overweight or obese, even a small adverse effect on cognitive abilities might have a detrimental effect on public health (Hedley et al., 2004).

Excess adiposity with many measures of physiological dysfunction may be associated with poorer cognitive functioning (Abraham et al., 2007; Kumari et al., 2000). Moreover, BMI is related to other factors such as high blood pressure, high ratios of low-density to high-density lipoprotein, type II diabetes, insulin resistance and high blood glucose, heart disease, stroke, and signs of the inflammatory processes that contribute to the formation of atherosclerotic plaques and embolisms that may weaken cognitive functioning (Hillman et al., 2008; Abraham et al., 2007; Haffner, 2006; Ogden et al., 2007). Poor cognitive function is related to type II diabetes and the metabolic syndrome (a cluster of metabolic risk factors), particularly in the presence of inflammation (Morley, 2004; Arvanitakis et al., 2004). Any three of the following traits in the same individual meet the criteria for the metabolic syndrome: abdominal obesity (a waist circumference of 102 cm or more in men and 88 cm or more in women), serum triglycerides (150 mg/dl or above), HDL cholesterol (40mg/dl or lower in men and 50mg/dl or lower in women), blood pressure (of 130/85 or more), and fasting blood glucose (of 100 mg/dl or above) (Morley, 2004). Excess adiposity is associated with decreased levels of physical activity engagement, which also contributes to cognitive decline, partly due to low aerobic capacity (Kramer & Erickson, 2007; Angevaren et al., 2008). Additionally, vascular risk factors such as type II diabetes and high blood pressure are recognized factors that influence cognition and are implicated in the evolution toward dementia (Xu et al., 2004; Shah et al., 2006).

Type II Diabetes.

Type II diabetes has increasingly been identified as a risk factor for cognitive impairment and dementia (Biessels et al., 2006; Luchsinger, 2008; Euser et al., 2010). Individuals with diabetes, even without a diagnosis of dementia, report poorer cognitive function when compared to those without diabetes in global tests of cognition, attention, executive function, processing speed, memory, and language, independent of other factors (Arvanitakis et al., 2004; Cukierman et al., 2005; Euser et al., 2010; Manschot et al., 2006; Verdelho et al., 2007).Type II diabetes promotes neuronal degeneration and increases risk of brain atrophy, the development of cognitive issues as well as dementia (Folch et al., 2013; Hayden et al., 2006; MacKnight et al., 2002). Furthermore, it is a risk factor for AD, even more so when it is combined with smoking, high blood pressure or heart disease (Luchsinger et al., 2005; Arvanitakis et al., 2004; Abraham et al., 2007). The inter-relationship between blood glucose and insulin levels may also play a role in the development of dementia, as insulin appears to affect amyloid deposition, memory and cognitive processes (Luchsinger et al., 2005; Arvanitakis et al., 2004; Abraham et al., 2007).

Hypertension.

Hypertension in midlife has been consistently associated with later development of cognitive decline and dementia (Hénon et al., 2006; Qiu et al., 2009). High blood pressure alone damages the brain and speeds up the ageing process, possibly because it damages the small blood vessels, particularly in the white matter, producing innumerable silent "mini-strokes" and ischemic changes (Goldstein et al., 2005). The large blood vessels that supply the brain (i.e. carotid arteries) and the large and small blood vessels within the brain are also affected by hypertension. Such damage can disrupt the blood-brain barrier, thus allowing the entry of toxic substances into the brain. Other structural changes to the blood vessels that are common in hypertension decrease the blood supply to the brain. Healthy older adults who experience small increases in blood pressure over a five-year period displayed greater brain atrophy and white matter vascular lesions (Goldstein et al., 2005). The higher the systolic blood pressure in a patient, the more brain damage was seen. High blood pressure in midlife is a major risk factor for dementia, but plays a prominent role at any point. Even minor elevations may negatively impact the brain (Goldstein et al., 2005).

High Cholesterol.

High cholesterol in midlife has also been associated with an increased risk of developing cognitive decline and dementia (Kivipelto et al., 2001), via atherosclerosis and CVD, as well as greater amyloid deposition in brain (Van Vliet et al., 2009; Solomon et al., 2007). Though, it is known that cardiovascular risk factors may contribute to cognitive decline, it remains unclear whether the medications used to treat these conditions may also be contributing to cognitive decline.

Sedentary Time.

Sedentary behavior is distinct from physical activity in that it is "any waking behaviour characterised by an energy expenditure ≤1.5 METs whilst in a sitting or reclining posture". This definition includes activities such as sitting, lying down, watching television, reading, screen-based entertainment and driving a vehicle (Ainsworth et al., 2000; Ainsworth et al., 2011). A growing body of epidemiological evidence has linked sedentary behaviour to health risks including an increased risk of type II diabetes (Proper et al., 2011; Van Uffelen et al., 2010), metabolic syndrome (Edwardson et al., 2012), cancer (Lynch, 2010), and all-cause and CVD mortality (Proper et al., 2011; Van Uffelen et al., 2010). These associations are usually shown to be at least partially independent of levels of physical activity suggesting that sedentary behaviours have the potential to influence risk of disease, independent of physical activity levels typically recommended for good health. To date, the exact effects of sedentary time on cognitive functioning are unknown.

Protective Factors

Several protective factors for cognitive decline and dementia/AD have also been identified: these include higher socioeconomic status in early life and attaining a high level of education as well as a number of factors in adult life such as high work complexity, having a rich social network, mentally stimulating activity, non-smoking, and engagement in regular physical activity (Qiu et al., 2009; Karp et al., 2009; Rovio et al., 2005). Living with a partner during mid-life has also been associated with reduced risk of cognitive impairment and dementia later in life, suggesting that being in a relationship entails cognitive and social challenges that can increase the cognitive reserve, the ability of the human brain to cope with damage by using different brain processes to retain the ability to function well. Cognitive reserve is developed through intellectual stimulation and translates into a higher volume of connections between neurons and stronger rates of cerebral blood flow (Hakansson et al., 2009). Even at older ages, active engagement in mental, physical, and social activities may postpone the onset of dementia by increasing the cognitive reserve (Paillard-Borg et al., 2009).

Physical Activity & Cognitive Function.

Physical activity refers to body movement that is produced by the contraction of skeletal muscles and that increases energy expenditure. Exercise refers to planned, structured, and repetitive movement to improve or maintain one or more components of physical fitness (Chodzko-Zajko et al., 2009). Physical activity is an independent contributing factor of disability and mortality, with estimates of 5-10% of deaths worldwide being due to physical inactivity (World Health Organization, 2002). The benefits of physical activity are numerous and well established. These include a reduction in the risk of cardiovascular disease, hypertension, stroke, type II diabetes, obesity, osteoporosis, some forms of cancer as well as improvements in aspects of mental health (Haskell et al., 2007). In addition, for older adults there is a growing body of evidence that physical activity reduces the risk of falls, reduces functional limitations and prevents or delays cognitive decline (Nelson et al., 2007).

Physical activity is important at every stage of life, but perhaps more so as people age (Kumari & Heese, 2010; Uchida et al., 2006; Joyner & Green, 2009; Biessels et al., 2006). Because of the positive effects listed above, risk of strokes, coronary artery disease, and all-cause mortality are decreased by engaging in physical activity (Abbott et al., 2004; Weuve et al., 2004; Biessels et al., 2006; Middleton et al., 2008). Endorphin levels are also elevated by aerobic exercise, reducing depression and anxiety (Abbott et al., 2004; Weuve et al., 2004; Van Gelder et al., 2004; Laurin et al., 2001; Cotman & Berchtold, 2002). Only recently, however, have investigators realized that physical activity also offers protection against cognitive decline and dementia, with an inverse correlation between the amount of exercise a person engages in and the possibility of experiencing cognitive decline. Studies have reported that people who regularly exercise have faster reaction times than those who do not, are able to discriminate between multiple stimuli better, can outperform those who are not physically active on tasks involving reasoning, working memory, and fluid intelligence tests (Abbott et al., 2004; Sun et al., 2010; Kramer et al., 1999). Current physical activity guidelines recommend engaging in moderate-intensity aerobic activities for at least 30 or up to 60 (for greater benefit) minutes/day in bouts of at least 10 minutes each to total 150-300 minutes/week; or at least 20-30 minutes/day or more of vigorous-intensity activities to total 75-150 minutes/week (American College of Sports Medicine, 2010). As well as resistance training (progressive weight training program or weight bearing calisthenics) (8-10 exercises involving the major muscle groups of 8-12 repetitions each) should be performed at least twice per week between a moderate and vigorous intensity (American College of Sports Medicine, 2010).

In addition, frontal lobe functions, mainly executive ability, which deteriorate disproportionately with age, have been shown to improve in individuals on a walking regimen (Abbott et al., 2004; Sun et al., 2010; Kramer et al., 1999). The Canadian Study of Health and Ageing, a large-scale population-based study, found reduced risk for AD with exercise and reported physical activity as a means to reduce risk for cognitive decline and dementia (Laurin et al., 2001; American College of Sports Medicine, 2010). Laurin and colleagues (2001) found that compared with no exercise, physical activity was associated with lower risks of cognitive impairment, AD and dementia. High levels of physical activity were associated with reduced risks of cognitive impairment, AD, and dementia of any type (Laurin et al., 2001). Larson and colleagues (2006) followed 1,740 older adults over a mean follow-up period of 6.2 years and found that the incidence rate of dementia was 13.0 per 1,000 person years for participants who exercised 3 or more times per week compared with 19.7 per 1,000 person years for those who exercised fewer than 3 times per week. Findings indicate that participants who exercised 3 or more times per week had a higher probability of being dementia-free than those who exercised fewer than 3 times per week (Larson et al., 2006). This can be interpreted to mean that there is an inverse relationship between levels of activity and risk of cognitive decline.

The Nurse's Health Study involving 18,766 women from 70 to 81 years of age showed that higher levels of activity were associated with better cognitive performance (Weuve et al., 2004). Compared with women in the lowest physical activity quintile, a 20% lower risk of cognitive impairment was found for women in the highest quintile of activity. Among women performing the equivalent of walking at an easy pace for at least 1.5 hours/week, mean global scores were 0.06 to 0.07 units higher compared with walking less than 40 min/week ($P \leq 0.003$). Less cognitive decline was also observed among women who were more active, especially those in the 2 highest quintiles of energy expenditure (Weuve et al., 2004). The Honolulu-Asia Aging study reported similar findings. This study which involved 2,257 men, age 71 to 93 years, who were physically capable and cognitively intact on a screening test found an increased incidence of dementia in those who walked the shortest distance daily (Abbott et al., 2004). After adjusting for age, men who walked the least (<0.25 mile/day) experienced a 1.8-fold excess risk of dementia compared with those who walked more than 2 miles per day. As well, compared with men who walked the most (>2 mile/day), an excess risk of dementia was observed in those who walked 0.25-1 miles per day (Abbott et al., 2004). A recent longitudinal examination of approximately 13,000 individuals at least 70 years of age in the Nurses' Health Study revealed that mid-life physical activity rates were significantly associated with higher survival rates (Sun et al., 2010). After adjustment for covariates, higher physical activity levels at midlife, as measured by metabolic-equivalent tasks, were associated with greater odds of successful survival. Increasing energy expenditure from walking was associated with a similar elevation in odds of successful cognitive ageing (Sun et al., 2010). Physical activity engagement prevents cognitive decline; this holds true for males and females, irrespective of study design.

There are several ways in which physical activity helps protect and improve brain function. First, aerobic exercise reduces vascular risk factors including diabetes, hypertension, hyperlipidemia and coronary artery disease. The amount and intensity of physical activity is also linked with the decrease that occurs in these risk factors. This makes it less likely that a person who is physically active will experience a stroke or significant cerebrovascular disease (Lee et al., 2003). There have been a number of studies suggesting that physical activity also exerts an effect on the brain, producing anatomic changes while augmenting memory (Van Pragg, 2009). It has been suggested that physical activity could preserve neuronal structure and promote the expansion of neural fibers, synapses and capillaries (Abbott et al., 2004; Van Pragg, 2009); for example, in laboratory animals who were placed on an exercise program, those who were the most active had larger hippocampi (Van Pragg, 2009; Romano, 2004). Physical activity seems to enhance neurogenesis in the brains of young rats as well as older ones, and may moderate age-related decline in neural structures, as well as increase neuron proliferation (Van Pragg, 2009; Churchill et al., 2002). Neurogenesis has been demonstrated specifically in the hippocampus and cerebral cortex, and an increase in synaptic connections between neurons has also been shown. In addition, cardiovascular fitness appeared to be correlated with the thickness of the brain's cortical tissue (the gray matter where the neurons are located) (Van Pragg, 2009; Romano, 2004; Radak et al., 2007; Stranahan et al., 2009).

Finally, physical activity promotes angiogenesis, the growth of new capillaries from preexisting arteries, which has been found to occur in the brains of laboratory animals exposed to exercise (Van Pragg, 2009; Churchill et al., 2002). This may begin days after an exercise regimen is initiated, supporting heightened neuronal activity via increased blood flow and delivery of oxygen, glucose and other nutrients to brain tissue. It should also be noted that physical activity might improve cognitive function because of its overall impact on vitality and biological ageing. People who are physically active are generally healthier than their peers who are not.

These findings indicate that engagement in physical activity contributes to improvements to cognitive functioning domains. However, all of the research to date is focused on an older adult population, and it is unclear if the benefits of physical activity and cognitive function extend to younger adults, and whether there are critical time points across the lifespan.

Fruit and Vegetable Consumption & Cognitive Function.

Diets that are high in fruits and vegetables are widely recommended due to their health promoting properties. Fruits and vegetables are rich sources of antioxidant nutrients and bioactive compounds (e.g., vitamin E, vitamin C, carotenoids, flavonoids). As well, epidemiological and laboratory studies, show that these micronutrients have been related to cognitive benefits (Lindeman et al., 2000; Morris et al., 2001; Cotman et al., 2002; Vermeer et al., 2002; Floyd & Hensley, 2002; Proteggente et al., 2002). As well, laboratory data suggest that the combinations of nutrients available in fruits and vegetables might have greater health benefits than single-vitamin supplements (Joseph et al., 1999). Animal studies have shown that antioxidants prevent neuronal damage and improve cognitive performance (Cotman et al., 2002; Joseph et al., 1999). For example, Joseph and colleagues (1999) found that rats who were given spinach, strawberries, or vitamin E, in doses with equivalent antioxidant potency, exhibited superior neuronal function compared to control animals.

Consumption of fruit and vegetables has been strongly associated with reduced risk of CVD, cancer, diabetes, and age-related functional decline (Hung et al., 2004; Temple, 2000; Willett, 1994). In a population-based cohort study in The Netherlands, higher consumption of fruits and vegetables was found to be protective against the incidence of coronary heart disease (CHD) (Oude et al., 2010). Coronary heart disease incidence was 34% lower for individuals with a high intake of total fruit and vegetables compared to those with a low total fruit and vegetable consumption (Oude et al., 2010). A systematic review and meta-analysis of fruit and vegetable intake and the incidence of type II diabetes showed that a greater intake of vegetables was associated with a 14% reduction in risk of type II diabetes ($P = 0.01$). As well, higher intakes of fruit were associated with a lower risk of type II diabetes (Carter et al., 2010; Wedick et al., 2012). In another systematic review, the relationship between fruit and vegetable intake and adiposity was explored (Ledoux et al., 2011). It was determined that an inverse relationship exists between fruit and vegetable intake and adiposity (Ledoux et al., 2011). The study of the relationship between the consumption of vegetables and fruits on human health is greatly complicated by many factors, including varying dietary patterns and interactions with other dietary elements and to date the associations between the consumption of fruit and vegetables and cognitive function remain unclear.

Cognitive Stimulation & Cognitive Function.

Longitudinal studies assessing the associations between cognitively stimulating activities and the incidence of dementia have shown that engaging in complex mental activities is protective against the development of dementia (Verghese, 2003). A systematic review of observational studies evaluated population-based cohorts and showed that higher educational attainment, cognitively stimulating lifestyle activities, and greater occupational complexity offered protection against the development of dementia (Valenzuela & Sachdev, 2006). The ACTIVE trial, a key study in this field, randomized individuals into four groups: a 10-session group training for i) memory (verbal episodic memory), ii) reasoning (ability to solve problems that follow a serial pattern), iii) speed of processing (visual search and identification) or iv) a control group (n = 704). Results indicated significant improvements in 87% of participants trained in processing speed, 74% of participants trained in reasoning, and 26% of memory-trained participants and demonstrated reliable cognitive improvement immediately after the intervention period. Cognitive improvements were maintained at the second year of follow-up

(Ball, 2002). A 5-year follow-up of the same population showed that cognitively trained subjects had improved cognitive abilities specific to the abilities trained that persisted after the intervention was stopped, compared to the control group (Willis, 2006).

Although the mechanisms are not completely understood, engagement in cognitively stimulating activities may contribute to an increase in cognitive reserve. Cognitive reserve describes the notion that a greater number of neurons and higher intelligence can protect an individual from faster cognitive decline or a dementia spectrum disorder (Valenzuela, 2008). Cognitive reserve involves neuro-flexibility where the end goal is adaption. Individuals with a higher cognitive reserve have a larger repertoire of strategies to resolve complicated tasks. Therefore, when a particular neuronal network malfunctions, other networks can be used to solve the same problems (Stern, 2002).

CONCEPTUAL FRAMEWORK

A well-known theoretical model depicting the inter-relationships between physical activity, cognitive function, and lifestyle factors across the lifespan does not exist; hence, this dissertation proposes and implements such a model. This framework proposes a life-course approach and indicates that interactions and joint effects exist between physical activity and lifestyle variables, anthropometry, and age. In this project the lifestyle variables that are explored are sedentary time, fruit and vegetable consumption, the number of medications used, and engagement in cognitively stimulating activities. Anthropometry refers to overweight/obesity status, which will be measured as body mass index (BMI) or waist-to-hip-ratio (WHR). Finally, life cycle refers to age. Further, this model also indicates that an interaction exists between physical activity and cognitive function. The lifestyle variables that were selected in this project were chosen because they are all modifiable and can all be performed and accomplished by the individual. As well, the obesity variable was included in each of the projects because of the increasing prevalence in both the American and Canadian populations. Obesity is a disease but it also serves as a risk factor for other conditions. However, it was considered separately from physical activity and the lifestyle variables because its relationship with ageing is a unique one- its changing relationship with cognitive function (i.e. being overweight/obese at midlife is bad for cognitive function, whereas in late life it is protective). As people age, they tend to accumulate risk factors and develop unhealthy habits which tend to contribute to poor health. The concept of disease prevention implies the acquirement of behaviors and habits which would subsequently reduce the risk of disease. Although dementia is viewed as a disease of older adults, because symptoms manifest themselves in later years, cognitive declines may be occurring years or decades prior to when the overt symptoms become present.

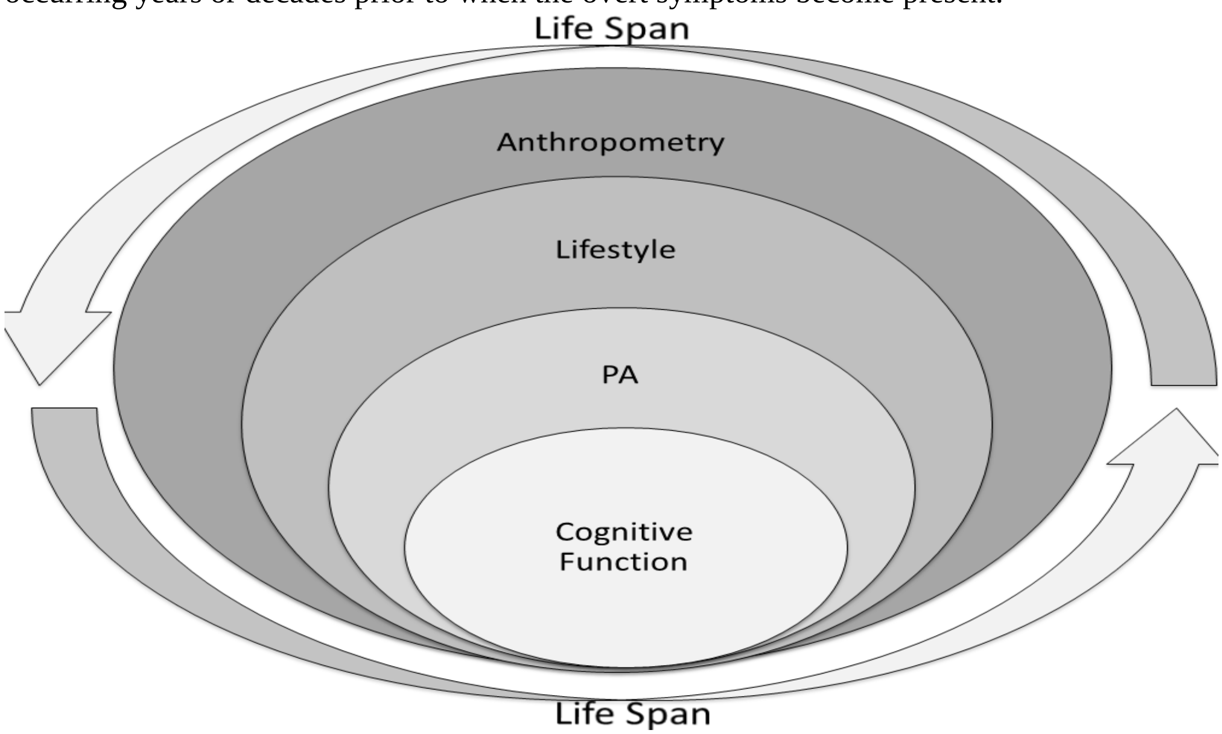

Figure 1-1: General theoretical model illustrating the potential relationships between lifestyle, anthropometry, physical activity and cognitive health, across the lifespan.

This thesis is presented in manuscript format and consists of four manuscripts. The manuscripts are followed by a general discussion of the main findings, public health implications, strengths and limitations of the research, as well as future directions.

Specific Objectives

Study 1: To determine the associations between physical activity, sedentary time, obesity, and cognitive functioning in younger and older Canadian adults. In this study, lifestyle will be captured using sedentary time; anthropometry will be captured using body mass index (BMI), and; physical activity will be captured using the physical activity index (PAI).

Study 2: To determine the associations between physical activity, total daily fruit and vegetable consumption, obesity, and cognitive functioning in younger and older Canadian adults. In this study, lifestyle will be captured using total daily fruit and vegetable consumption; anthropometry will be captured using body mass index (BMI), and; physical activity will be captured using the physical activity index (PAI).

Study 3: To determine the inter-relationships between increased medication use (for conditions such as high blood pressure, type II diabetes, and high cholesterol), physical activity, obesity, and cognitive function in younger, middle-aged and older American adults. In this study, lifestyle will be captured using medication use; anthropometry will be captured using waist-to-hip ratio (WHR), and; physical activity will be captured using a series of question regarding the frequency of engagement in moderate-to-vigorous physical activity (MVPA).

Study 4: To determine the inter-relationships between cognitive stimulation (reading, attending lectures/courses, playing card games, playing word games), physical activity, obesity, and cognitive function in younger, middle-aged and older American adults. In this study, lifestyle will be captured using cognitive stimulation; anthropometry will be captured using waist-to-hip ratio (WHR), and; physical activity will be captured using a series of question regarding the frequency of engagement in moderate-to-vigorous physical activity (MVPA).

Data Sources

This project involved four secondary data analyses. The first two studies use data from the 2012 annual component of the Canadian Community Health Survey (CCHS). Briefly, the CCHS is a cross-sectional survey that collects information related to health status, health care utilization and health determinants for the Canadian population. It surveys a large sample of respondents and is designed to provide reliable estimates at the health region level.

Using computer-assisted interviews, the CCHS recruits persons aged 12 and over living in private dwellings in the 10 provinces and three territories, representing 98% of the population. Informed consent was obtained from each respondent by Statistics Canada, in accordance with Canadian federal legislative requirements. The analyses included all respondents between the ages of 30 to 80+ years of age, with complete data for all study variables (n = 48,041), representing an estimated 21,523,898 Canadians. For a full list of the CCHS variables that were used, please refer to Appendix A. Separate ethics approval was not required for the current project as it involved secondary analysis of publicly available data.

Studies three and four used data from MIDUS (Midlife in the U.S.) which is a national longitudinal study of the many factors (i.e. behavioral, social, psychological, biological, neurological) that come together to influence health and well-being as people age from early adulthood into midlife and old age. In 1995, MIDUS survey data were collected from a total of 7,108 participants. All eligible participants were non-institutionalized English speaking adults in the contiguous United States, aged 25-74. All respondents were asked to participate in a phone interview of approximately 30 minutes in length and complete 2 self-administered questionnaires. With funding from the National Institute on Aging, a longitudinal follow-up of MIDUS I began in 2004. Of the 7,108 in MIDUS I, 4,963 were successfully contacted to participate in MIDUS II. The overall response rate for the self-administered questionnaires was 81%. For a full list of the MIDUS variables that were used, please refer to Appendix B. Separate ethics approval was not required for the current project as it involved secondary analysis of publicly available data.

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CHAPTER 2: MANUSCRIPT 1

Exploring the Inter-Relationships between Physical Activity, Body Mass Index, SedentaryTime and Cognitive Functioning In Younger and Older Canadian Adults: Analysis of Cross-Sectional Data

This manuscript has been submitted to The Journal of Aging and Physical Activity, and is presented in a format that is consistent with journal requirements.

Abstract

Background: Engagement in leisure-time physical activity (LTPA) is protective against cognitive decline whereas obesity and leisure-time sedentary time (LTST) are associated with impairments in cognitive function. Currently, little is known about how these relationships vary across the lifespan.

Purpose: This study investigated the inter-relationships between LTPA, LTST, BMI and perceived cognitive functioning in younger and older Canadian adults.

Methods: Data from the 2012 annual component of the Canadian Community Health Survey (N=45,522; ≥30y) were used to capture self-reported LTPA (kcal/kg/day, KKD), BMI (kg/m^2), LTST, and perceived cognitive function. The inter-relationships were assessed using general linear models.

Results: Lower LTPA, higher BMI and LTST, were related to poorer cognitive functioning ($p<0.0001$). This relationship becomes more pronounced with age.

Conclusions: Across the lifespan Higher LTPA levels contribute to better perceived cognitive functioning both independently and by way of reducing BMI and LTST.

Introduction

Dementia is a syndrome characterized by progressive deterioration in multiple cognitive domains, affecting an ever-increasing number of people due to the ageing of populations around the world. According to Alzheimer's Disease International (ADI), 24.3 million people were living with dementia in 14 World Health Organization (WHO) regions in 2001, and this is estimated to reach 81.1 million by 2040, with the numbers doubling every 20 years (Prince et al., 2013). Age is the leading risk factor for cognitive decline and dementia, with risk for both Alzheimer's disease (AD) and vascular dementia (VaD) doubling every 5 years over the age of 65 (Wimo & Prince, 2010; Lobo et al., 2000). Among the factors that contribute to the onset of cognitive decline, excess adiposity, type II diabetes, elevated blood pressure, and mood disorder appear to be key (Qui et al., 2005; Kivipelto et al., 2005; Qui et al., 2010). Several protective elements have also been identified including attaining high levels of education, not smoking, and being married (Qui et al., 2009; Karp et al., 2009; Rovio et al., 2005).

Perhaps most consistently, epidemiological research shows a relationship between higher levels of leisure time physical activity (LTPA) and reduced risk of cognitive decline. A meta-analysis of 16 prospective studies examining the relationship between LTPA and risk of neurodegenerative disease reported that engaging in the highest LTPA category had a 28% lower risk of dementia, compared to inactivity, even after adjusting for possible confounding factors including age, education, vascular risk factors, and other medical conditions (Hamer & Chida, 2009). In a more recent meta-analysis of 15 prospective cohort studies, over thirty thousand healthy older adults were followed for periods of 1-12 years. Results showed that individuals who had higher levels of LTPA at baseline had a 38% lower risk of cognitive decline at follow-up compared to those who who were inactive (Sofi et al., 2010). As well, observational studies have linked low levels of walking, low LTPA and increased sedentary behaviors to declines in cognitive functioning (Scarmeas et al., 2001; Abbott et al., 2004). Sedentary behaviors are defined as activities that are performed in a seated or reclining posture, including television viewing, computer-use, game-console use and reading (Sedentary Behaviour Research Network, 2012). These activities are in the low energy expenditure range of 1.0 to 1.5 METs (Ainsworth et al., 2000). To make matters more complicated, adults can meet their public health guidelines on LTPA, but still be engaged in sedentary activities over prolonged periods of time throughout the day.

The prevalence of overweight and obesity has greatly increased in both developed and developing countries and increasing evidence suggests adiposity increases the risk of cognitive decline and dementia (Anstey et al., 2011; Ng et al., 2014). Studies have shown a negative association between BMI and cognitive performance (Elias et al., 2012), in particular with measures of executive function (Gunstad et al., 2007). The potential underlying mechanisms linking higher BMI to dementia may include direct effects of adiposity (hyperinsulinemia, advanced glycosylation end products, adipokines and cytokines), as well as indirect effects (increases in the prevalence of other vascular risk factors and related cerebrovascular disease) (Luchsinger & Gustafson, 2009).

Currently, it is unclear how factors such as LTPA, leisure time sedentary time (LTST), BMI, and cognitive functioning are inter-related, and whether these inter-relationships remain consistent with age. These relationships might be particularly relevant for older adults. Currently, people aged 65 years or older represent one of the fastest growing segments of the world's population (WHO, 2011), and determining how to delay cognitive decline will be important for keeping people physically independent throughout later life. As people age, levels of LTPA tend to decrease, whereas engagement in LTST activities as well as obesity prevalence tend to increase (Flegal et al., 2012; Seguin et al., 2012; Hamer & Stamatakis, 2013). Therefore, the aim of this study was to investigate the inter-relationships between LTPA levels, LTST, obesity, and perceived cognitive functioning scores in younger and older Canadian adults (30 years of age and older).

Methods

Sample

This study used data from the 2012 annual component of the Canadian Community Health Survey (CCHS), a cross-sectional survey that collects information related to health status, health care utilization and health determinants for the Canadian population. Using computer-assisted interviews, the CCHS recruits persons aged 12 and over living in private dwellings in the 10 provinces and three territories, representing 98% of the Canadian population. Informed consent was obtained from each respondent by Statistics Canada, in accordance with Canadian federal legislative requirements (Beland, 2002). To examine these relationships within a sample with adequate chronic disease risk factors, obesity, LTPA, and LTST to relate to cognitive functioning scores, the present analysis was limited to respondents 30 years of age and older. Respondents with answers of “not stated” or “refused” for other study variables were excluded, reducing the original sample size of 61 707 to a sample of n = 45 522 (representing a weighted sample of an estimated 21 million Canadians) with complete data for all study variables.

Measures

Leisure Time Physical Activity:

LTPA was assessed using an adaptation of the Minnesota Leisure Time Physical Activity Questionnaire (Taylor et al., 1978). Respondents were asked about their LTPA participation, indicating participation frequency within the past 3 months as well as average session duration. Average daily energy expended during LTPA was calculated, weighting activities by the associated metabolic equivalent of task (MET) value. Average daily energy expenditure was calculated by multiplying the number of times the activity was performed by the average duration of the activity by the energy cost. The energy expenditure of other activities was expressed in multiples of METs. For example, standing requires approximately 2 METs (Ainsworth et al., 2000; Ainsworth et al., 2011). Results were expressed in kilocalories per kilogram per day (KKD) and used to classify participants as active (≥3.0 KKD), moderately active (1.5–2.9 KKD), or inactive (<1.5 KKD). Here, the active category (3.0 KKD) reflects, on average, the equivalent of 60 minutes of moderate-intensity activity daily (Schmitz, Kruse & Tress, 2000). The Physical Activity Index demonstrates very good reliability (r=0.90) and criterion validity (r=0.36) when compared with physical activity measured by alternative questionnaire-based methods (r=0.77) (Craig, Russell & Cameron, 2002).

Leisure Time Sedentary Time:

LTST was assessed by self-report. Participants were asked how many hours per week (in the past 3 months) they typically spent doing the following 4 activities outside of work: watching TV, playing video games, using computers, or reading. This was a categorical variable that measured the total number of hours per week engaging in LTST activities ranging from less than 5 hours to 45 or more hours per week.

Anthropometry:

Height and weight were self-reported and BMI was calculated as weight (kg) per height (m^2). Participants were classified based on Canadian and World Health Organization guidelines as underweight (≤18.49 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), or obese (≥30 kg/m^2) (Health Canada, 2003; WHO, 2000).

Age:

Participants were asked to select their age from one of 16 possible categories. For the purposes of this analysis, only categories 6 (30-34 years of age) through 16 (80+ years of age) were analyzed.

Perceived Cognitive Functioning

Perceived cognitive functioning was measured using the Cognition Attribute of the Health Utilities Index (HUI). The HUI provides a standardized measure of health status and Health Related Quality of Life (HRQL) (Patrick & Erickson, 1993). It describes an individual's functional health status using eight basic attributes: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain. Each attribute has five or six levels, ranging from normal to severely limited (or the complete absence of) functioning. HUI has been used in a wide variety of populations and clinical studies including stroke (Pickard et al., 2004; Grootendorst et al., 2000), various cancers (Whitton et al., 1997), type II diabetes (Maddigan et al., 2004), Alzheimer disease (Neumann et al., 2000), and many others in a wide variety of pediatric and adult populations. Health status at a point in time is described by an 8-element vector, one level for each of the 8 attributes. Furthermore, correlations among attributes in HUI are very low (unlike other instruments), therefore each attribute contributes new information (Houle & Berthelot, 2000). The HUI system has strong test re-test reliability, validity and internal consistency (Cronbach's α=0.81), and it is a very good discriminator of disease-related quality of life at the population level (Horsman et al., 2003; Furlong et al., 2001). The cognition attribute of the HUI has 6 levels of ability/disability: level 1 (able to remember most things, think clearly and solve day-to-day problems), level 2 (able to remember most things, but have a little difficulty when trying to think and solve day-to-day problems), level 3 (somewhat forgetful, but able to think clearly and solve day-to-day problems), level 4 (somewhat forgetful, and have a little difficulty when trying to think and solve day-to-day problems), level 5 (very forgetful, and have great difficulty when trying to think or solve day-to-day problems), level 6 (unable to remember anything at all, and unable to think or solve day-to-day problems). A higher score indicates a poorer level of functioning.

Covariates:

Given the well-researched relationship between the primary exposure and outcome variables in these analyses, sex, marital status (married/common-law, widowed/separated/divorced, single/never married), level of education (less than secondary school grad, secondary school grad, some post-secondary school, post-secondary grad), smoking status (yes/no), high blood pressure (yes/no), diabetes (yes/no), and mood disorder (yes/no) were included as covariates (Barnes et al., 2004; Marx, 2005; Ngandu et al., 2007). Respondents with answers of ‘‘not stated’’ or ‘‘refused’’ for all study variables were excluded from the analyses.

Statistical Analysis

Participants were categorized into young-to-middle aged (30-59 y) and older (60-80+ y) groups on the basis of descriptive analyses that found that group differences in perceived cognitive functioning began to emerge at age 60 and above. Categorical variables are presented as frequencies and percentages, and continuous variables as means and standard deviations (SD).

General linear models were used to determine the associations between BMI, LTPA or LTST, and perceived cognitive functioning, after adjusting for sex, education, marital status, smoking status, high blood pressure, diabetes, and mood disorder with cognitive functioning scores. Regression diagnostics were assessed, revealing no influential outlier observations and a normal distribution of residuals. Because the interactions between LTPA, LTST, BMI, cognitive functioning and age were significant (all p=<0.001), analyses were further stratified by age.

Statistical analyses were performed using SAS v 9.4 (SAS Institute Inc., NC, USA) with statistical significance set at $\alpha<0.05$. To ensure representativeness of the results to the Canadian population, data were weighed using the master weight in SAS survey procedures.

Results

Demographic and health characteristics of the population are presented in **Table 1**.

Participants were on average overweight (younger: μ=27.09±5.36; Older: μ=27.01±4.85), with about 59% of the younger adult population and 62% of the older adult population overweight or obese. Nearly 47% of the younger adults and 53% of the older adults were inactive, whereas only 27% of the younger adults and 23% of the older adults were active. Overall, 23% of younger adults and 39% of older adults reported spending 30 or more hours per week engaged in LTST.

As presented in **Table 2**, individuals who were more active reported superior perceived cognitive functioning scores compared to those who were moderately active or inactive (Active: μ=1.58±0.078; Moderately Active: μ=1.70±0.085; Inactive: μ=1.86±0.067; $p<0.001$). As well, younger adults reported better perceived cognitive functioning scores compared to older adults (Younger: μ=1.68±0.060; Older: μ=1.87±0.060; $p<0.001$). In regards to BMI and LTST, though insignificant in the unadjusted model, they both become strongly significant in the final model. Normal weight and overweight individuals reported better perceived cognitive functioning than obese individuals (Normal weight: μ=1.75±0.090; Overweight: μ=1.70±0.060; Obese: μ=1.82±0.077). Participants who reported low and moderate levels of LTST reported better perceived cognitive functioning than those reporting high LTST (Low LTST: μ=1.74±0.078; Moderate LTST: μ=1.68±0.072; High LTST: μ=1.83±0.078). Also, individuals who were married/common-law, post-secondary graduates, non-smokers, and were otherwise healthy (i.e. non-diabetic, normotensive, and no reported mood disorder) reported better perceived cognitive functioning than individuals who were single/divorced/widowed, had lower levels of education, smokers, diabetics, hypertensive, and those who reported having a mood disorder.

As shown in **Figure 1**, younger adults who were normal weight active and moderately active, overweight active and moderately active, and obese active reported better perceived cognitive functioning scores than normal weight inactive, overweight inactive, and obese moderately active and inactive. In older adults, normal weight active, overweight moderately active, and obese active reported better perceived cognitive functioning scores than normal weight moderately active and inactive, overweight active and inactive, and obese moderately active and inactive (**Figure 1)**.

In regards to LTPA, in younger adults, lower levels of LTPA, higher BMI and LTST were associated with poorer perceived cognitive functioning scores. In older adults, this association was more pronounced (**Figure 2**).

Discussion

Age-related cognitive decline is an escalating worldwide public health concern. The prevalence of cognitive decline is expected to rise dramatically in the upcoming decades, predominantly due to demographic changes as well as increasing longevity (Moore, 2007). Therefore, understanding factors that may slow the rate of cognitive decline and provide some degree of protection against dementia, are of the utmost importance. This study examined the inter-relationships amongst LTPA, LTST, BMI and perceived cognitive functioning in younger and older Canadian adults. Overall, findings indicated that both younger and older individuals were generally overweight and inactive, no sex differences were observed. Results also showed that those who were more physically active and less sedentary reported better cognitive function and younger adults reported better perceived cognitive functioning compared to older adults.

In younger adults, findings suggest that normal weight active and moderately active overweight active and moderately active, as well as obese active younger adults reported better perceived cognitive functioning scores. On the other hand, normal weight inactive, overweight inactive, and obese moderately active and inactive reported poorer perceived cognitive functioning scores. In older adults, normal weight active and overweight moderately active reported better perceived cognitive functioning scores. Those who were normal weight moderately active, obese active as well as obese inactive reported poorer perceived cognitive functioning scores. However, obesity was associated with poorer perceived cognitive functioning scores in both younger and older adults as well as at all levels of PA. The poorer perception of cognitive functioning in individuals with obesity compared to normal weight may partly be explained by their increased disease risk, but other factors, such as negative perceptions of body weight, mild physical impairments and stigmatization may also play a role (Wilson, Latner & Hayashi, 2013).

The findings of this study indicate that higher levels of physical activity, reduced sedentary time and a BMI in the normal weight or overweight range, may contributed to a better perception of cognitive function. LTPA is a modifiable behavioral factor that is often the focus of health promotion initiatives and physically active adults have slower rates of cognitive decline than those who are inactive (Schuit, Feskens & Launer, 2001; Yaffe et al., 2001). Second, LTPA is independently related to disability and mortality, with estimates of 5-10% of deaths worldwide being due to physical inactivity (WHO, 2002). The benefits of LTPA are numerous and well established. These include a reduction in the risk of cardiovascular disease, hypertension, stroke, type II diabetes, obesity, osteoporosis, some forms of cancer as well as improvements in aspects of mental health (Haskell et al., 2007). LTPA has also been found to reduce functional limitations and delay cognitive decline by increasing cardiovascular fitness and cerebral perfusion (Nelson, Rejeski & Blair, 2007). On the other hand, a growing body of epidemiological evidence has linked sedentary behaviors to health risks including an increased risk of type II diabetes (Proper et al., 2011; Van Uffelen et al., 2010; Wilmot et al., 2012), metabolic syndrome (Edwardson et al., 2012), some cancers (Lynch, 2010), and all-cause and CVD mortality (Proper et al., 2011; Van Uffelen et al., 2010; Wilmot et al., 2012). In terms of BMI, for middle-aged adults, higher BMI is associated with lower cognitive function and faster subsequent decline (Cournot et al., 2006; Sabia et al., 2009). Cournot and colleagues (2006) found that a higher BMI was associated with lower cognitive scores after adjustment for age, sex, educational level, blood pressure, diabetes, and other psychosocial covariables (Cournot et al., 2006). In their study, higher BMI was also associated with a higher cognitive decline at follow-up, after adjustment for the confounding variables (Cournot et al., 2006). Thus, LTPA can be used as a tool to preserve cognitive functioning by way of reducing BMI and LTST.

There are several strengths and limitations to our investigation. The use of a large nationally representative Canadian population dataset, making the study findings highly generalizable to the Canadian population and measuring perceived cognitive functioning in both younger and older adults, represent the strengths of this study. Nonetheless, because the CCHS is a cross-sectional study, these data do not allow us to determine causality in the LTPA, sedentary time, BMI and perceived cognitive functioning relationship. Second, reliance on self-reported LTPA, LTST and BMI might have resulted in underestimations of BMI and LTST and overestimations of LTPA.

Conclusion

People today are less active than they were decades ago (Church et al., 2011). LTPA and PA associated with work, home, and transportation has declined due to economic growth, technological advancements, and social changes. Along with this decrease in PA there has been an increase in sedentary activities leading to an increased prevalence of obesity (Juneau & Potvin, 2010). Due to these demographic changes, the prevalence of cognitive decline is expected to rise dramatically in the upcoming decades. Therefore, interventions that decrease the risk of cognitive decline are critical. Increasing LTPA levels, reducing LTST and obesity are a few promising strategies that may contribute to a reduction in the prevalence of cognitive impairment.

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Table 1-1: Characteristics of Participants in the Canadian Community Health Survey, 2012.

Variable	**30-59 years**	**60-80+ years**
	n=23 633	n=20 889
Sex, Frequency (%)		
Male	11018 (46.62)	8903 (42.62)
Female	12615 (53.38)	11983 (57.38)
Marital Status, Frequency (%)		
Married/Common-Law	15562 (65.85)	11565 (55.36)
Widowed/Separated/Divorced	3438 (14.55)	7882 (37.73)
Single/Never Married	4633 (19.60)	1442 (6.90)
Education, Frequency (%)		
Less than secondary school grad	2299 (10.04)	5712 (28.61)
Secondary school grad	4030 (17.60)	3433 (17.19)
Some post-secondary	903 (3.94)	715 (3.58)
Post-secondary grad	15671 (68.42)	10107 (50.62)
BMI, Mean (SD)	27.09 (5.36)	27.01 (4.85)
BMI, Frequency (%)		
Normal Weight	9634 (40.77)	8015 (38.37)
Overweight	8305 (35.14)	8221 (39.36)
Obese	5694 (24.09)	4653 (22.27)
Smoking, Frequency (%)		
Yes	12893 (54.68)	11931 (57.28)
No	10684 (45.32)	8897 (42.72)
High BP, Frequency (%)		
Yes	3624 (15.38)	9465 (45.46)
No	19944 (84.62)	11357 (54.54)
Diabetes, Frequency (%)		
Yes	1205 (5.11)	3327 (15.94)
No	22395 (94.89)	17541 (84.06)
Mood Disorder, Frequency (%)		
Yes	2236 (9.48)	1405 (6.72)
No	21358 (90.52)	19441 (93.26)
Physical Activity, Frequency (%)		
Active	6355 (26.91)	4809 (23.05)
Moderately Active	6252 (26.47)	5096 (24.42)
Inactive	11010 (46.62)	10959 (52.53)
Cognition Attribute of HUI, Mean (SD)	1.74 (1.12)	1.91 (1.17)
Sedentary Time, Frequency (%)		
Low ST (<5-14 h)	10034 (42.46)	5394 (25.82)
Moderate ST (15-29 h)	8250 (34.91)	7324 (35.07)
High ST (30-45+ h)	5349 (22.63)	8170 (39.11)

Table 1-2: Mean Cognitive Functioning Scores Stratified by Socio-Demographics & Health History.

Variable	Mean (±SD)	F-Value	P-Value
Age			
Young (30-59y)	1.68 (0.060)	5.00	0.025
Old (60-80+y)	1.87 (0.060)		
Sex			
Male	1.74 (0.061)	0.01	0.910
Female	1.75 (0.066)		
BMI			
Normal Weight	1.75 (0.090)	0.72	0.486
Overweight	1.70 (0.060)		
Obese	1.82 (0.077)		
PAI			
Active	1.58 (0.078)	3.68	0.025
Moderately Active	1.70 (0.085)		
Inactive	1.86 (0.067)		
Marital Status			
Married/Common-Law	1.74 (0.055)	0.04	0.961
Widowed/Separated/Divorced	1.77 (0.107)		
Single/Never Married	1.73 (0.110)		
Education			
Less than secondary school grad	2.00 (0.097)	3.51	0.015
Secondary school grad	1.84 (0.100)		
Some post-secondary	1.73 (0.183)		
Post-secondary grad	1.65 (0.060)		
Sedentary Time (ST)			
Low ST (<5-14 h)	1.74 (0.078)	1.05	0.349
Moderate ST (15-29 h)	1.68 (0.072)		
High ST (30-45+ h)	1.83 (0.078)		
Smoking			
Yes	1.79 (0.063)	0.83	0.362
No	1.71 (0.064)		
High BP			
Yes	1.78 (0.067)	0.28	0.600
No	1.73 (0.055)		
Diabetes			
Yes	1.80 (0.198)	0.08	0.774
No	1.74 (0.045)		
Mood Disorder			
Yes	1.91 (0.194)	0.79	0.374
No	1.73 (0.046)		

*Physical Activity Post-Hoc Tests indicated significant differences between the active and inactive groups only (t=-2.69, p=0.007); Education Post-Hoc Tests indicated significant differences between those individuals with the lowest and the highest levels of education (t=3.13, p=0.002).
All values are weighted.

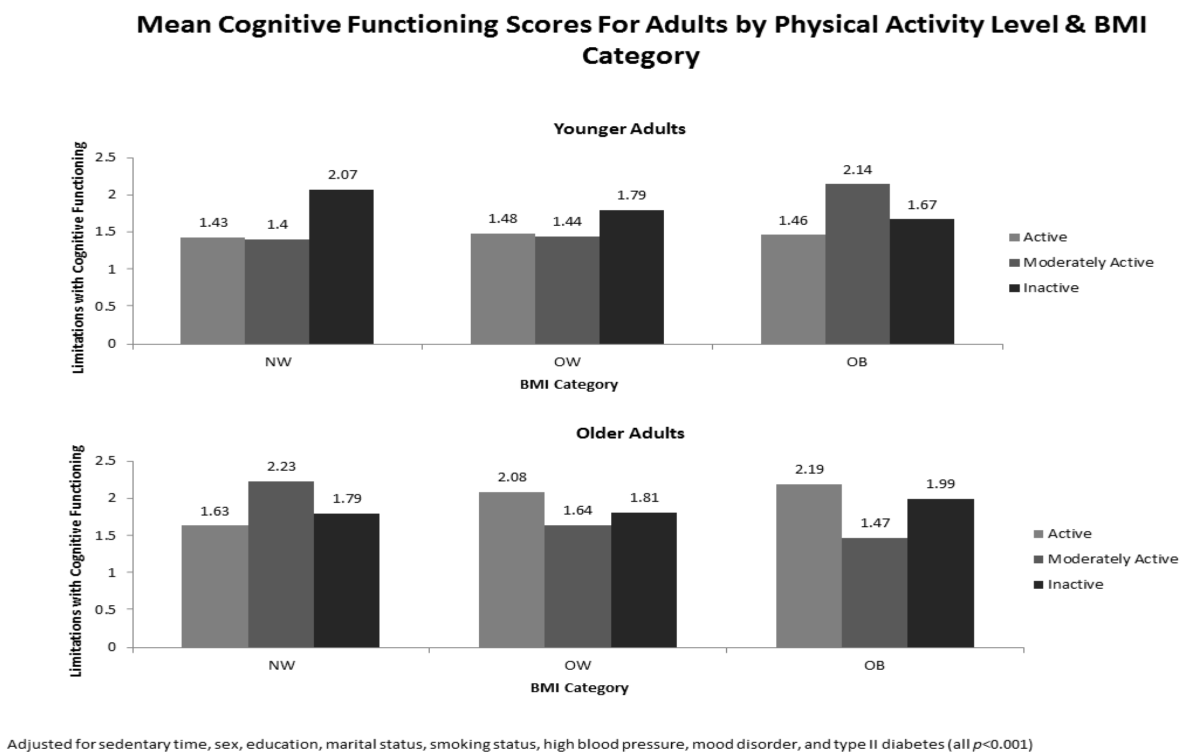

Figure 2-1: Mean Cognitive Functioning Scores for Younger & Older Adults by Physical Activity Level & BMI Category.

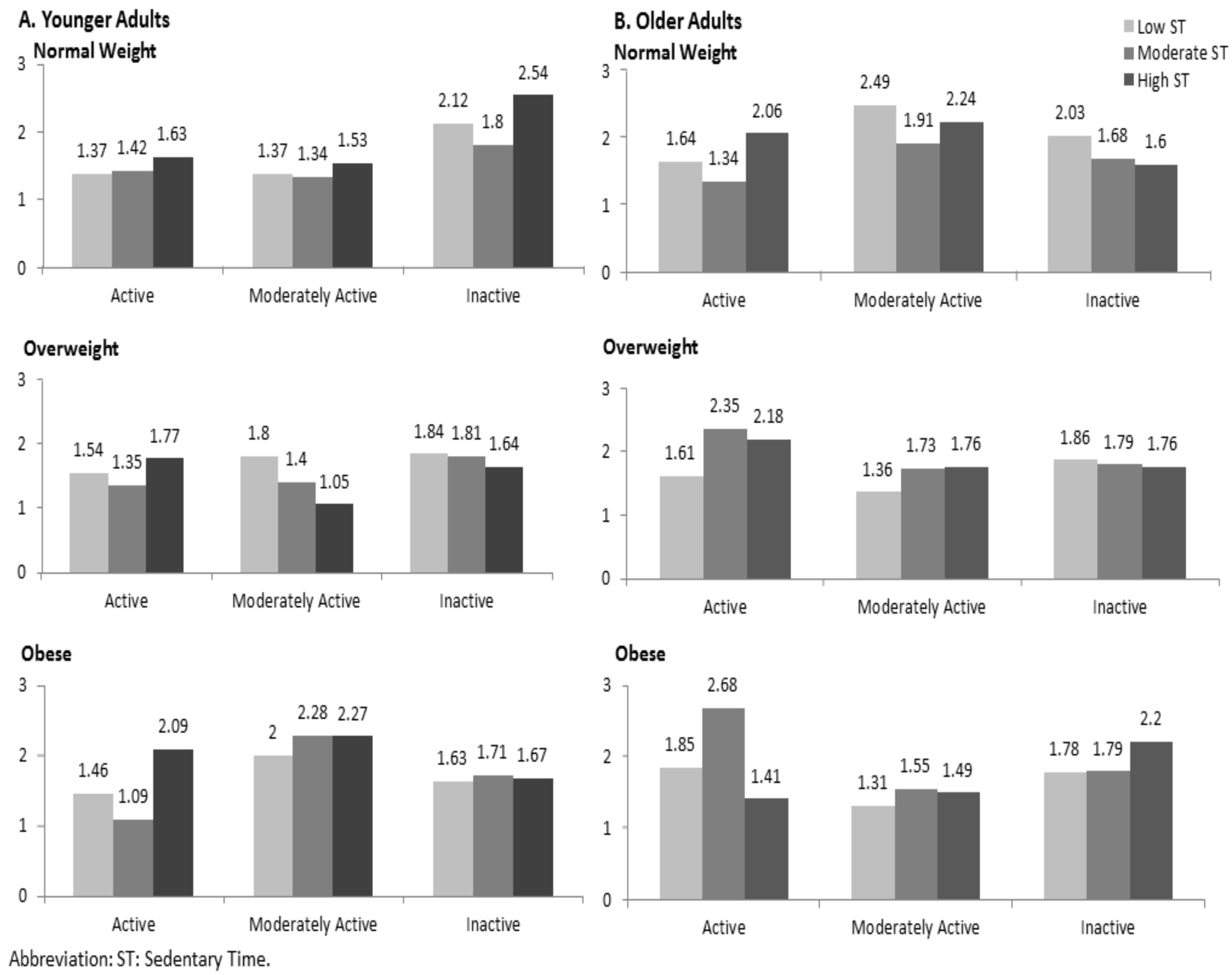

Figure 2-2: Mean Cognitive Functioning Scores for Younger & Older Adults by Physical Activity Level, BMI Category & Sedentary Time.

CHAPTER 3: MANUSCRIPT 2

Physical Activity Mediates the Relationship between Fruit and Vegetable Consumption and Cognitive Functioning: A Cross-Sectional Analysis

This manuscript has been submitted to The Journal of Public Health (Oxford), and is presented in a format that is consistent with journal requirements.

Abstract

Background: Excess adiposity is associated with impairments in cognitive functioning, whereas physical activity (PA) and fruit and vegetable consumption (FVC) may be protective against cognitive decline. Therefore, this study investigated the inter-relationships between FVC, BMI PA and perceived cognitive functioning in younger and older Canadian adults.

Methods: Cross-sectional data of 45,522 participants (≥30y) were examined from the 2012 annual component of the Canadian Community Health Survey. Perceived cognitive function was assessed using the cognitive attribute of the Health Utilities Index. PA was classified according to the Physical Activity Index; BMI was measured in kg/m^2; FVC per day was classified as Low: <5; Moderate: 5-10, and; High: ≥10. To assess the inter-relationship between FVC, BMI, PA, age and perceived cognitive functioning, general linear models were used.

Results: Higher BMIs, lower PA levels and a lower daily FVC contributed to worse cognitive functioning. This pattern persisted in younger and older adults (younger: μ=1.68±0.060, older: μ=1.87±0.060, p=0.03). As well, higher levels of education coupled with high daily FVC were associated with better perceived cognitive function (p<0.001).

Conclusion: Independent of age, higher FVC and PA were associated with better perceived cognitive functioning.

Key words: Physical activity, public health, food and nutrition

Background

Dementia is a clinical syndrome that is characterized by a decline in intelligence, memory, and perception (Hedden & Gabrieli, 2004) as well as in logical and critical thinking, judgment and short-term memory (Verhaeghen & Cerella, 2002). Non-modifiable risk factors for dementia include age and genetic susceptibility (Prince et al., 2013; Kramer & Erickson, 2007) in addition to modifiable vascular risk factors (e.g. type II diabetes, hypertension, and smoking) and the presence of cardio- and cerebrovascular diseases. Several protective factors for cognitive decline have also been identified: these include attaining a high level of education as well as high work complexity, and having a rich social network (Qiu et al., 2009). As well, from a primary prevention standpoint, engagement in physical activity (PA) is associated with reduced risk of a range of chronic conditions (Qiu et al., 2010). For older adults there is a growing body of evidence that PA may delay the onset of cognitive decline and dementia (Kivipelto et al., 2005; Qiu et al., 2007; Middleton & Yaffe, 2009). PA is an important modifiable behavioral factor and is often the focus of health promotion initiatives. More recently, researchers have begun to focus on whether PA could also contribute to healthy brain ageing and this has prompted calls that it should be investigated more closely as a potential protective factor against cognitive decline and dementia (Middleton & Yaffe, 2009).

On the other hand, overweight and obesity increase the risk of cognitive decline independent of other comorbidities (Whitmer et al., 2005). For example, Cournot and colleagues (2006) found that a higher body mass index (BMI) was associated with lower cognitive scores after adjustment for age, sex, educational level, blood pressure, diabetes, and other psychosocial factors (Cournot et al., 2006). Sabia and colleagues (2009) also found that both underweight and obesity were associated with poorer cognitive function (Sabia et al., 2009).

Although excess weight may have unfavorable effects on cognitive health, healthy behaviors such as daily fruit and vegetable consumption (FVC), may serve to preserve cognitive integrity. FVC may influence the pathology of dementia in several different ways: fruits and vegetables both contain high quantities of a vitamin C, vitamin E, dietary fiber, flavonoids, β-carotenes as well as other classes of phytochemicals (Vioque et al., 2008). These compounds exert their action via a host of different mechanisms; for instance, they can modulate detoxifying enzymes, stimulate the immune system, modulate cholesterol synthesis and act as antibacterial, antioxidant or neuroprotective agents (Lampe, 1999). To date, very few studies have investigated the associations between FVC and cognitive decline (Kuslansky et al., 2004, Ortega et al., 1997; Lee et al., 2001). Cross-sectional studies in Spain and Korea have shown that older adults with better cognitive performance consumed more servings of fruit and vegetables than older adults with impaired or poor cognitive performance (Ortega et al., 1997; Lee et al., 2001). For the Korean participants, males and females with poor cognitive function had significantly lower intakes of fruits and vegetables than those individuals with normal cognitive scores on the MMSE ($\geq$24, $p<0.05$) (Lee et al., 2001).

Given existing patterns of inactivity and obesity, there is an increasing need to understand how modifiable risk factors for cognitive impairment may act to oppose or reinforce each other. Due to increasing life expectancy in industrialized countries and the increase in the prevalence of dementia (Ferri et al., 2005) . Given these trends, there is a clear need to focus attention on strategies to preserve cognitive health. In contrast to the relative wealth of studies of cardiometabolic outcomes and mortality, less attention has been paid to the relationship between dietary patterns and cognitive outcomes in middle-aged and older people. Therefore, the aim of this study was to investigate the relationships that exist between FVC, BMI, PA and perceived cognitive functioning in younger (30-59y) and older (60-80+y) Canadian adults.

Methods

Sample

The 2012 annual component of the Canadian Community Health Survey (CCHS) was used in this study. It is a cross-sectional survey that collects information related to the health status of the Canadian population. The CCHS surveys a large sample of respondents and is designed to provide reliable estimates at the health region level. Using computer-assisted interviews, the CCHS recruits persons aged 12 and over living in private dwellings, representing 98% of the Canadian population. Informed consent was obtained from each respondent by Statistics Canada. The present analysis was limited to respondents 30 years of age and older. Respondents with answers of "not stated" or "refused" for other study variables were excluded, leaving a sample of n = 45 522, with complete data for all study variables. This study was part of a larger project exploring the influence of different physical activity, anthropometric, and lifestyle variables on cognitive functioning in younger and older Canadian adults (See Chapter 2: Study 1).

Measures

Total Fruit and Vegetable Consumption:

To determine total FVC, participants were asked how many servings of fruits and vegetables they consumed per day (<5, 5-10, and 10+). The measure assessing consumption of fruits and vegetables was established based on *Canada's Food Guide to Healthy Eating* which was in use from 1992 to 2007.

Physical Activity:

Physical activity was assessed using an adaptation of the Minnesota Leisure Time Physical Activity Questionnaire (Taylor et al., 1978). Respondents were asked about participation in 21 specified activities, plus up to three additional participant reported activities, indicating participation frequency within the past 3 months as well as average session duration. Average daily energy expended during leisure time PA was calculated, weighting activities by their metabolic equivalent (MET) values, a measure of energy expenditure (Ainsworth et al., 2000; Ainsworth et al., 2011). Results were expressed in kilocalories per kilogram per day (KKD). A Physical Activity Index categorized participants as active (≥3.0 KKD), moderately active (1.5–2.9 KKD), or inactive (<1.5 KKD). The CCHS Physical Activity Index demonstrates very good reliability (r=0.90) and validity when compared with physical activity measured by alternative questionnaire-based methods (r=0.77) (Craig et al., 2002).

Anthropometry:

BMI was calculated as kg/m^2 from self-reported height and weight. Participants were classified based on World Health Organization (WHO) guidelines as normal weight (18.5–24 kg/m^2), overweight (25–29.9 kg/m^2), or obese (≥30 kg/m^2) (WHO, 2002).

Age:

Age was self-reported as one of 16 possible categories. For the purposes of this analysis, only categories 6 (30-34 years of age) through 16 (80+ years of age) were analyzed.

Perceived Cognitive Functioning:

Perceived cognitive functioning was operationalized as a respondent's score on the Cognition Attribute of Health Related Health Utilities Index (HUI) (Patrick & Erickson, 1993). The HUI describes an individual's functional health status using eight attributes: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain. As well, it should be noted that correlations between the attributes in the HUI are very low thus each attribute contributes new information (Houle & Berthelot, 2000).The cognition attribute of the HUI has 6 levels of ability/disability, with level 1 indicating that individuals are able to remember most things, think clearly and solve day-to-day problems and level 6 indicating that individuals are unable to remember anything at all, and unable to think or solve day-to-day problems. Higher scores on the cognition attribute indicate poorer levels of functioning. The HUI has strong test re-test reliability, validity and internal consistency (Cronbach's α=0.81), and it is a very good discriminator of disease-related quality of life at the population level (Horsman et al., 2003; Furlong et al., 2001).

Covariates:

Given their previously established relationships with the primary variables examined in these analyses, the following variables were considered as covariates: sex, marital status, education, smoking status, hypertension, diabetes, and mood disorder (Barnes et al., 2004; Marx, 2005; Ngandu et al., 2007; Hayden et al., 2006; Goldstein et al., 2005; Barnes & Yaffe, 2011).

Statistical Analysis

Participants were categorized into younger/middle aged (30-59years) and older adult (60+ years) groups. Categorical variables are presented as frequencies and percentages, and continuous variables as means and standard deviations (SD).

The relationships between BMI, PA, daily FVC and perceived cognitive functioning scores in younger/middle aged and older Canadian adults were explored. General linear models were used to determine the associations between the variables of interest, after adjusting for covariates. As well, because the effect of education was significant, it was included in the final model. Regression diagnostics were assessed; there were no influential outliers and residuals were normally distributed. Because the interactions between PA, BMI, daily FVC, cognitive functioning scores and age were significant ($p<0.001$), analyses were further stratified by age.

Statistical analyses were performed using SAS v9.4 (SAS Institute Inc., NC, USA) with statistical significance set at an α of 0.05. To ensure representativeness of the results to the Canadian population, data were weighted using the master weight in SAS survey procedures.

Results

The demographic and health characteristics of the sample are presented in **Table 1**. Study participants were on average overweight (younger: μ=27.09±5.36; Older: μ=27.01±4.85), with about 59% of the younger adult population and 62% of the older adult population overweight or obese. Nearly 47% of the younger adults and 53% of the older adults were inactive, whereas only 27% of younger adults and 23% of older adults were active. Approximately 61% of younger adults and 59% of older adults reported a FVC of less than 5 servings per day; whereas, 39% of younger adults and 41% of older adults reported a daily FVC of more than 5 servings. Finally, 68% of younger adults and 51% of older adults were post-secondary graduates, whereas 32% of younger adults and 49% of older adults had not obtained a post-secondary school education.

As presented in **Table 2**, individuals who reported higher PA levels reported better perceived cognitive functioning compared to those who were moderately active or inactive (Active: μ=1.58±0.078; Moderately Active: μ=1.70±0.085; Inactive: μ=1.86±0.067; $p=0.03$). Younger adults reported better perceived cognitive functioning compared to older adults (Younger: μ=1.68±0.060; Older: μ=1.87±0.060; $p=0.03$). In regards to BMI, those who were normal-weight and overweight reported better perceived cognitive functioning than individuals with obesity. In terms of FVC, participants who consumed 10 or more servings had the best perceived cognitive functioning scores (<5: 1.75±0.058; 5 to 10: 1.68±0.078, and; 10+: 1.46±0.172). As well, individuals with higher levels of education reported better perceived cognitive functioning scores than those with lower levels of education (Less than secondary school grad: 2.00±0.097; secondary school grad: 1.84±0.100; some post-secondary: 1.73±0.183; post-secondary grad: 1.65±0.060). Also, individuals who were married/common-law, non-smokers, and were otherwise healthy (i.e. non-diabetic, normotensive, and no reported mood disorder) reported better perceived cognitive functioning than individuals who were single/divorced/widowed, smokers, diabetics, hypertensive, and those who reported having a mood disorder.

Individuals who were normal-weight or overweight and reported a FVC of more than 10 servings per day reported better perceived cognitive functioning scores than those who reported fewer than 10 servings, as well as those individuals with obesity (**Figure 1a**). As well, both active and inactive individuals who reported a FVC of more than 10 servings per day had better perceived cognitive scores than those who consumed fewer servings. However, in those who were moderately active, individuals with a daily FVC of less than 5 or 5-10 servings, reported better perceived cognitive functioning than those with a daily FVC of 10 or more servings; this may have resulted because of underestimations of the number of servings of fruits and vegetables actually consumed (**Figure 1b**).

Due to the significant interaction with age, analyses were stratified into younger adults and older adults. Younger adults with a daily FVC of more than 10 servings generally reported better perceived cognitive functioning scores at every BMI-category and PA-level than those who consumed fewer servings (**Figure 2**). Furthermore, those who reported consuming 5-10 servings had better cognitive scores than those who consumed less than 5 servings. Older adults, with a daily FVC of more than 10 servings, generally reported better perceived cognitive functioning. Finally, overweight and obese older adults with a daily FVC of less than 5 servings generally reported poorer perceived cognitive functioning scores.

Higher levels of education contributed to better perceived cognitive functioning scores. Findings indicate that individuals with a post-secondary education with a daily FVC of five or more servings reported better perceived cognitive functioning scores; conversely, those individuals who are normal-weight/inactive, overweight/inactive, and obese/inactive with a daily FVC of less than 5 servings reported poorer perceived cognitive functioning scores. As well, regardless of level of PA, individuals with higher levels of education who were normal-weight and overweight reported better perceived cognitive functioning than obese adults (**Figure 3**).

Discussion

Main Finding of this study

This study examined the inter-relationship between PA, total daily FVC, BMI and perceived cognitive functioning in younger and older Canadian adults. Overall, the prevalence of overweight and inactivity was high amongst both younger and older men. As expected, younger adults reported better cognitive functioning scores than older adults. Additionally, analyses revealed that individuals with a higher daily FVC and PA level, who were normal-weight or overweight, with higher levels of education reported better perceived cognitive functioning scores.

What is already Know on this topic

Currently, it is known that diets which are high in fruits and vegetables are widely recommended due to their health promoting properties. FVC has been strongly associated with reduced risk of cardiovascular disease (CVD), cancer, diabetes, and age-related functional decline (Temple, 2000; Willet, 1994). Currently, the association between FVC and cognitive function remains unclear, as very little research exists in this area (Kuslansky et al., 2004, Ortega et al., 1997; Lee et al., 2001). As well, although much work has been done to explore the relationship between PA on cognitive function, this relationship has been mainly explored in older adults (Qiu et al., 2010; Qiu et al., 2007; Kivipelto et al., 2005; Middleton & Yaffe, 2009). To date, very little is known about the inter-relationships between PA and FVC and perceived cognitive function, in both younger and older adults.

What this study adds

The findings of this study show that PA, FVC, and BMI in both younger and older adults impact perceived cognitive functioning. The results of this study indicate that younger adults with a daily FVC of 10 or more servings reported better perceived cognitive functioning scores at every BMI category irrespective of PA level. In older adults, however, those with a daily FVC of at least 5 daily servings generally reported better cognitive functioning scores, a relationship that also varied by BMI and PA. Excess adiposity, declining PA levels, as well as nutrition transition (the trend towards increased consumption of a diet high in saturated fat, sugar, and low in fiber) among communities are the top risk factors for morbidity and mortality worldwide[31]. Therefore, PA, BMI and FVC are important modifiable factors that can affect the maintenance of the healthy aging phenotype. Successful cognitive aging combines multiple cognitive domains, such as memory and executive functioning; this definition also encompasses the link between cognitive health with functional independence (Lim et al., 2012). Thus, increasing FVC and PA levels as well as having a healthy BMI, may aid in the delay of cognitive decline.

Results also indicated that higher levels of education along with a daily FVC of 5 or more servings contributed to better perceived cognitive functioning. Education may be assisting in the process of delaying cognitive decline be increasing cognitive reserve, the ability of the human brain to cope with damage by using different brain processes to retain the ability to function well. Cognitive reserve is developed through intellectual stimulation and translates into a higher volume of connections between neurons and stronger rates of cerebral blood flow (Mathers, 2013) .

The results of this study indicate that higher levels of physical activity, a higher daily intake of fruits and vegetables, as well as being normal weight or overweight might contribute to better perceived cognitive functioning. The benefits of regular PA are well documented in the clinical and public health literature and include reduced risk of many chronic diseases, stress and depression, and increased emotional well-being, energy level, self-confidence and satisfaction with social activity (Hakansson et al., 2009). Physically inactive people are more likely to be obese, which itself is an important risk factor for many chronic diseases (Brown et al. 2007; Warburton et al., 2006). Therefore, regular PA engagement along with a daily FVC of more than 5 servings and a healthy BMI may be beneficial to preserving cognitive integrity and delaying cognitive decline. If the onset of dementia can be delayed by 5 years, there would be a reduction in over a million cases after 10 years, and over 4 million cases after 50 years (Middleton & Yaffe, 2009). Thus, identifying potential strategies for the maintenance of cognitive health has considerable public health benefit.

Limitations of this study

This investigation was aimed at elucidating the inter-relationships between PA, BMI, FVC, and perceived cognitive functioning scores in younger and older Canadian adults. There are several strengths and limitations to our investigation. The strengths of our study include studying both younger and older adults, the use of a nationally representative Canadian dataset, the application of survey weights to ensure the findings are generalizable to the population, as well as adjustment for known confounding variables (Warburton et al., 2006; Costet et al., 1998). Nonetheless, because the CCHS is a cross-sectional study, no causal effects can be inferred. As well, reliance on self-reported PA, total FVC and BMI may have resulted in underestimations of BMI and overestimations of PA and total FVC.

Conclusion

Ageing is described as a continuous process that includes loss of functional capability as well as the increase in risk of morbidity and mortality (Wang et al., 1999). Although ageing is a risk factor for chronic diseases, it is not necessarily defined by the presence of morbidities but is instead a process that starts early in life, which is modulated by the accumulation of experiences and exposures throughout the life-course (Franco et al., 2009). Although life expectancy has increased in the past few decades, the years lived with disabilities and diseases are increasing (Salmon et al., 2012), and the prevalence of cognitive decline is expected to rise dramatically in the upcoming decades, predominantly due to demographic changes as well as increasing longevity. Therefore, identifying effective ways to delay the onset of cognitive decline is of great importance (Brookmeyer et al., 2007). The extent to which engagement in regular PA, daily FVC, and weight maintenance are sufficient to provide *clinically meaningful* reductions in the rate of cognitive decline is not yet known, and requires a longitudinal study in order to more fully explore the dose-dependent nature of these relationships.

Author's Contribution

Data were acquired by A.C and study was conceived by A.C., C.I.A. and J.B. A.C. performed the statistical analysis and drafted the manuscript. A.C., C.I.A. and J.B. interpreted the results and critically reviewed and edited the manuscript. All authors read and approved the final manuscript.

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Table 2-1: Characteristics of Participants in the Canadian Community Health Survey, 2012.

Variable	30-59 years	60-80+ years
	n=23 633	n=20 889
Sex, Frequency (%)		
Male	11018 (46.62)	8903 (42.62)
Female	12615 (53.38)	11983 (57.38)
Marital Status, Frequency (%)		
Married/Common-Law	15562 (65.85)	11565 (55.36)
Widowed/Separated/Divorced	3438 (14.55)	7882 (37.73)
Single/Never Married	4633 (19.60)	1442 (6.90)
Education, Frequency (%)		
Less than secondary school grad	2299 (10.04)	5712 (28.61)
Secondary school grad	4030 (17.60)	3433 (17.19)
Some post-secondary	903 (3.94)	715 (3.58)
Post-secondary grad	15671 (68.42)	10107 (50.62)
BMI, Mean (SD)	27.09 (5.36)	27.01 (4.85)
BMI, Frequency (%)		
Normal Weight	9634 (40.77)	8015 (38.37)
Overweight	8305 (35.14)	8221 (39.36)
Obese	5694 (24.09)	4653 (22.27)
Smoking, Frequency (%)		
Yes	12893 (54.68)	11931 (57.28)
No	10684 (45.32)	8897 (42.72)
High Blood Pressure, Frequency (%)		
Yes	3624 (15.38)	9465 (45.46)
No	19944 (84.62)	11357 (54.54)
Diabetes, Frequency (%)		
Yes	1205 (5.11)	3327 (15.94)
No	22395 (94.89)	17541 (84.06)
Mood Disorder, Frequency (%)		
Yes	2236 (9.48)	1405 (6.72)
No	21358 (90.52)	19441 (93.26)
Physical Activity, Frequency (%)		
Active	6355 (26.91)	4809 (23.05)
Moderately Active	6252 (26.47)	5096 (24.42)
Inactive	11010 (46.62)	10959 (52.53)
Cognition Attribute of HUI, Mean (SD)	1.74 (1.12)	1.91 (1.17)
Total Fruit/Vegetable Consumption, Frequency (%)		
Less than 5	13783 (60.77)	11313 (59.03)
5 to 10	8090 (35.67)	7345 (38.33)
10 or more	1760 (3.56)	506 (2.64)

Table 2-2: Mean Cognitive Functioning Scores Stratified by Socio-Demographics & Health History.

Variable	Mean (±SE)	F-Value	P-Value
Age			
Young (30-59y)	1.68 (0.060)	5.00	0.03
Old (60-80+y)	1.87 (0.060)		
Sex			
Male	1.74 (0.061)	0.01	0.91
Female	1.75 (0.066)		
BMI			
Normal Weight	1.75 (0.090)	0.72	0.49
Overweight	1.70 (0.060)		
Obese	1.82 (0.077)		
PAI			
Active	1.58 (0.078)	3.68	0.03
Moderately Active	1.70 (0.085)		
Inactive	1.86 (0.067)		
Marital Status			
Married/Common-Law	1.74 (0.055)	0.04	0.96
Widowed/Separated/Divorced	1.77 (0.107)		
Single/Never Married	1.73 (0.110)		
Education			
Less than secondary school grad	2.00 (0.097)	3.51	0.02
Secondary school grad	1.84 (0.100)		
Some post-secondary	1.73 (0.183)		
Post-secondary grad	1.65 (0.060)		
Total Fruit/Vegetable Consumption			
Low (Less Than 5)	1.75 (0.058)	1.44	0.24
Moderate (5 to 10)	1.68 (0.078)		
High (10 or more)	1.46 (0.172)		
Smoking			
Yes	1.79 (0.063)	0.83	0.36
No	1.71 (0.064)		
High Blood Pressure			
Yes	1.78 (0.067)	0.28	0.60
No	1.73 (0.055)		
Diabetes			
Yes	1.80 (0.198)	0.08	0.77
No	1.74 (0.045)		
Mood Disorder			
Yes	1.91 (0.194)	0.79	0.37
No	1.73 (0.046)		

All values are weighted.

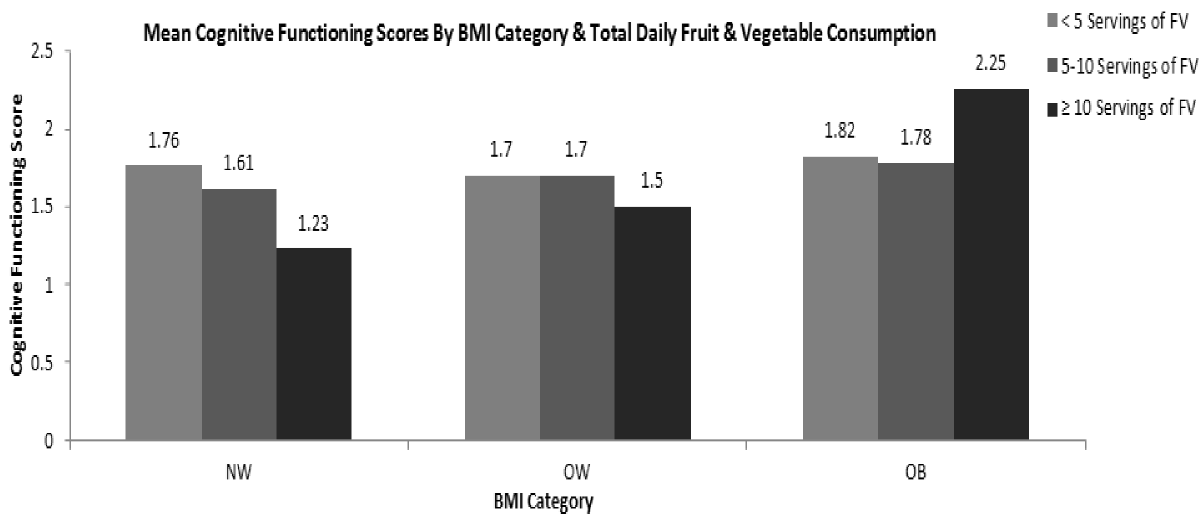


Figure 1a: Mean Cognitive Functioning Scores By BMI Category & Total Daily Fruit & Vegetable Consumption.

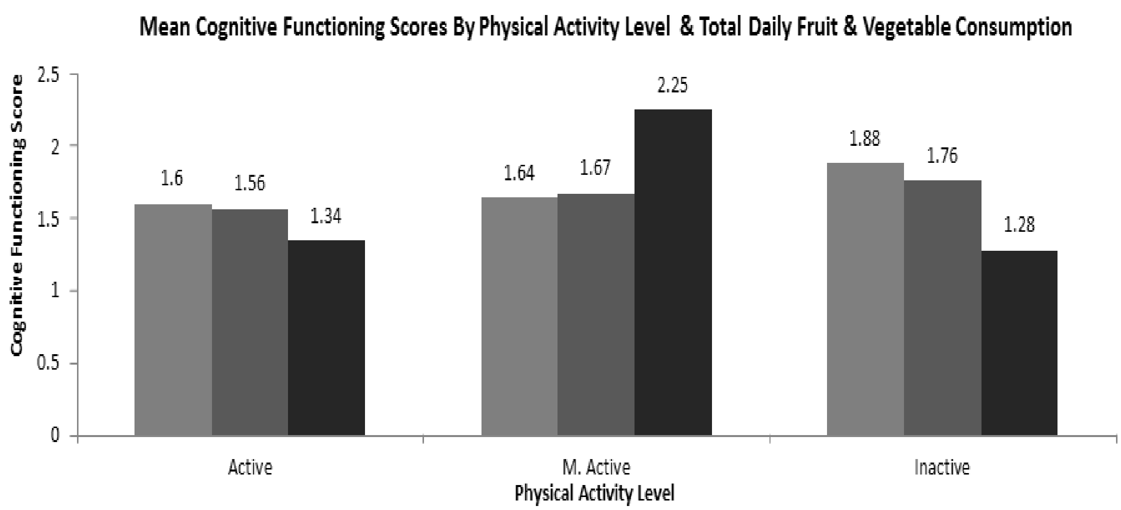
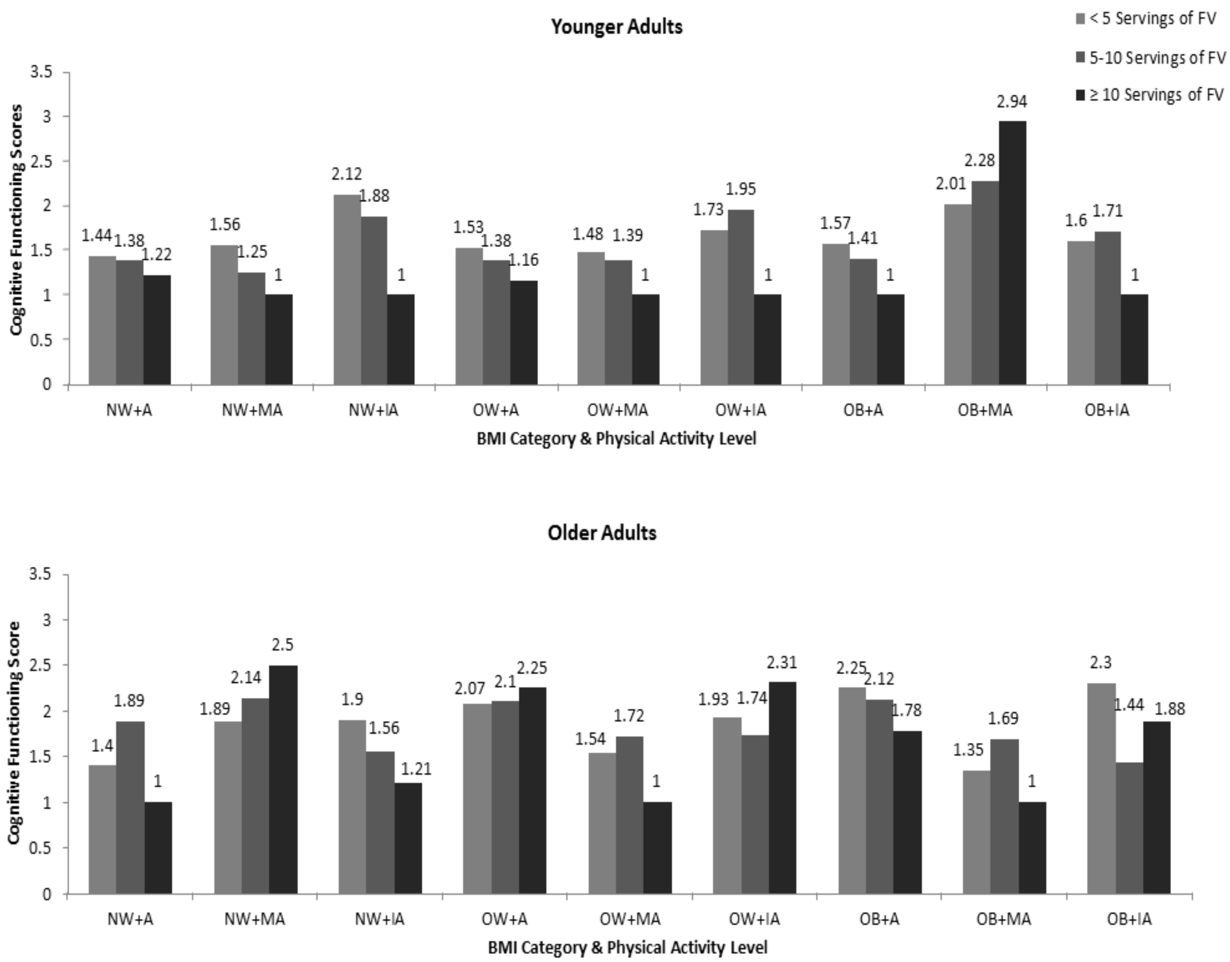


Figure 1b: Mean Cognitive Functioning Scores By Physical Activity Level & Total Daily Fruit & Vegetable Consumption.

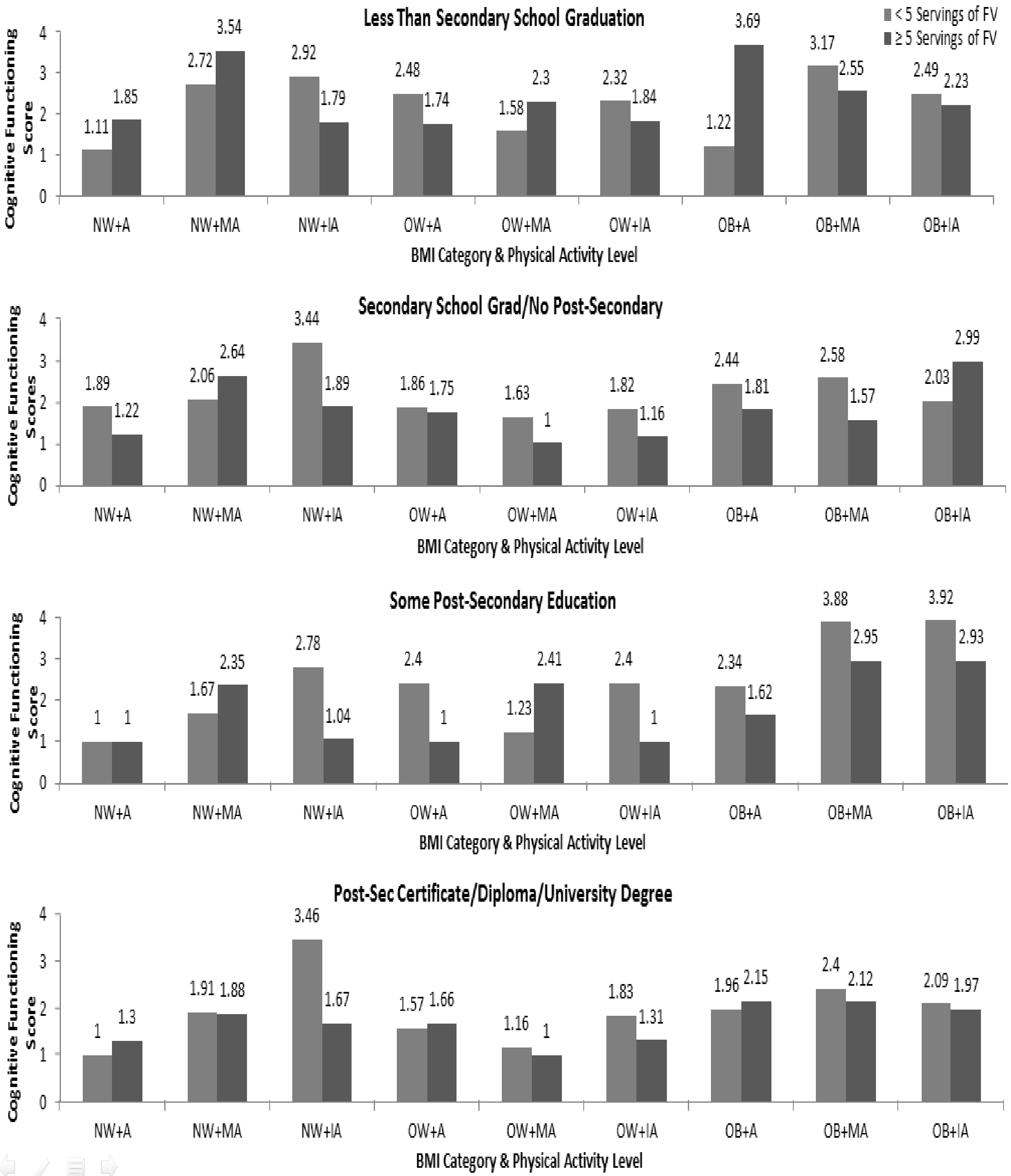
Abbreviations: FV: fruits and vegetables; NW: normal weight; OW: overweight; OB: obese; M. Active: moderately active.

Figure 3-1: Mean cognitive functioning scores by BMI & total daily fruit and vegetable consumption and PA level and total daily fruit and vegetable consumption.



Abbreviations: FV: fruits and vegetables; NW: normal weight; OW: overweight; OB: obese; A: active; MA: moderately active; IA: inactive.

Figure 3-2: Mean Cognitive Functioning Scores by BMI Category and PA level for Younger and Older Adults: Total Daily Fruit and Vegetable Consumption.



Abbreviations: FV: fruits and vegetables; NW: normal weight; OW: overweight; OB: obese; A: active; MA: moderately active; IA: inactive.

Figure 3-3: Mean Cognitive Functioning Scores by BMI/PA Category & Fruit/Vegetable Consumption: Level of Education.

CHAPTER 4: MANUSCRIPT 3

Physical Activity, Number of Medications Used & Cognitive Function in Younger, Middle-Aged & Older Adults: Analysis of the Midlife in the US Survey (MIDUS)

Abstract

Background: Prescription medication use is on the rise and the rates of cognitive decline are also expected to increase dramatically due to the ageing of the world's population. Given that the treatment options for Alzheimer's and dementia are limited, efforts to identify means of cognitive preservation are essential.

Purpose: The aim of this study was to explore the relationships between established risk factors (physical activity, medication use (number of medications taken), obesity (waist-to-hip ratio), age) and cognitive function (measured as episodic memory and executive function).

Methods: This study used data from the Midlife in the U.S. (MIDUS) a national longitudinal study of health and well-being as people age from early adulthood into midlife and old age. The inter-relationships between moderate to vigorous physical activity (MVPA), waist-to-hip ratio (WHR), medication use, and cognitive functioning were explored using ANCOVAs and general linear models after adjusting for covariates.

Results: Engagement in regular MVPA has a protective effect on cognitive function irrespective of the number of medications taken. However, lower levels of physical activity, higher medication use and WHR correspond with worse cognitive function scores ($p<0.001$); this relationship became more pronounced with age.

Conclusions: Regular engagement in physical activity may contribute to the preservation of cognitive performance as well as countering the adverse effects of prescription medication taken for chronic conditions, across the lifespan.

Introduction

Age related cognitive decline is an escalating worldwide public health concern (Prince et al., 2013). Cognitive functioning reflects the series of psychological processes involved in the acquisition, organization and application of knowledge. It includes short-term and long-term memory, attention and language (Verhaeghen & Cerella, 2002). Moreover, complex cognitive tasks depend on a set of executive functions (goal oriented behaviors such as problem solving, multitasking, and plan making) (Verhaeghen & Cerella, 2002). Evidence points to executive functioning impairments as contributors to declines in cognitive functioning that may result in a Mild Cognitive Impairment (MCI; cognitive problems that exceed the normal declines associated with aging but are not severe enough to meet the criteria for the diagnosis of dementia) or a dementia spectrum disorder (Bishop, Lu &Yankner, 2010; Hedden & Gabrieli, 2004). The prevalence of dementia is expected to rise dramatically in the coming decades, predominantly due to demographic changes and increasing longevity (Moore, 2007). Currently, there is no cure for cognitive decline or dementia, and pharmaceutical therapies have limitations in compliance due to adverse side effects and cost (Moore, 2007), for this reason other means of disease prevention or delay of disease onset are essential.

Cognitive decline may be exacerbated by cardiovascular risk factors (e.g., hypertension, type II diabetes, high cholesterol, overweight/obesity). As well, excess body weight is a global health problem, with more than 60% of the US and Canadian adult populations classified as overweight or obese. With numbers as high as these, if any of the above exert even a small adverse effect on cognitive abilities, it might have a detrimental effect on public health (Hedley et al., 2004). Impairments in attention, executive function (“higher level” cognitive functions involved in control and regulation of “lower level” cognitive processes and goal oriented and future oriented behaviors), and processing speed are common with cognitive decline (Cohen et al., 2009; Roberts et al., 2014; Yaffe et al., 2014). As well as, reduced episodic memory, episodic memories allow people to mentally travel back in time to an event from the recent or distant past; episodic memories include various details about these events, such as what happened, when it happened and where it happened, is also observed (Yaffe et al., 2014; Almaeida et al., 2012). Data from cross-sectional studies are reinforced by longitudinal analyses showing accelerated cognitive decline in individuals with type II diabetes, high blood pressure and high cholesterol within the domains of executive function and episodic memory (Dregan et al., 2013; Okonkwo et al., 2010). Cardiovascular risk factors have also been associated with reduced brain volume, decreased white matter integrity, and reductions in cerebral blood flow (Beason-Held et al., 2012). Moreover, structural and functional brain alterations associated with cardiovascular risk factors induce predictable cognitive impairments such as deficits in episodic memory and executive dysfunction (Alosco et al., 2013).

Physical activity plays an important role in reducing vascular risk factors, including blood pressure and total cholesterol (Kumari & Heese, 2010). As well, the chances of diabetes and insulin resistance are reduced and inflammatory elements in the blood appear to be lowered (Joyner & Green, 2009; Biessels et al., 2006). Only recently, however, have investigators realized that physical activity also offers protection against cognitive decline and dementia, with an inverse correlation between the amount of exercise a person engages in and the possibility of experiencing cognitive decline. Studies have reported that people who regularly exercise have faster reaction times than those who do not, are able to discriminate between multiple stimuli better and can outperform those who are not physically active on tasks involving reasoning, working memory, and fluid intelligence tests (Abbott et al., 2004; Sun et al., 2010). As a whole, cardiovascular risk factors negatively impact cognitive performance whereas physical activity may offer protection against cognitive decline.

Research indicates that certain classes of hypertension medication negatively affect cognition (e.g., beta-blockers) (Amenta et al., 2002; Muldoon et al., 2002; Murray et al., 2002). However, most of the research to date has been conducted on younger rather than older samples. As well, a drug interaction between metformin (a drug often used in individuals with type II diabetes) and the cubilin receptor inhibits the uptake of vitamin B_{12} thus lowering serum vitamin B_{12} levels. And reduced B_{12} levels are associated with neuropathy (Wile & Toth, 2010). Given the high prevalence of chronic conditions such as type II diabetes, hypertension and high cholesterol and the substantial evidence of the adverse impact of these conditions on cognition, it is somewhat surprising that the treatment status of these conditions is not regularly considered in the psychological literature on cognitive ageing. Individuals who have been diagnosed with hypertension, type II diabetes, and high cholesterol are on medications for years or even decades and though the literature on the adverse effects of these conditions on health is vast (Okonko et al., 210; Nwankno et al., 2013; Roberts et al., 2014). Currently, not much is known about the impact of medication use and whether as the number of medications used increases, cognitive performance declines. Therefore, the aim of this study is to explore the relationships between physical activity, obesity, medication use (number of medications taken), age and cognitive function.

Methods

This study used data from the Midlife in the U.S. survey (MIDUS; Brim, Ryff, & Kessler, 2004), a national longitudinal study of factors (behavioral, social, psychological, biological, neurological) influencing health and well-being as people age from early adulthood into midlife and old age. In 1995, MIDUS survey data were collected from a total of 7,108 participants. All eligible participants were non-institutionalized English speaking adults in the contiguous United States, aged 25-74 years. Respondents were asked to participate in a phone interview of approximately 30 minutes in length and complete 2 self-administered questionnaires. With funding provided by the National Institute on Aging, a longitudinal follow-up of MIDUS I began in 2004, with an added cognitive function component. Of the 7,108 in MIDUS I, 4,963 were successfully contacted to participate in MIDUS II. Separate ethics approval was not required, as the data were accessed using the Inter University Consortium for Political and Social Research (ICPSR), of which York University is an institutional member (http://www.icpsr.umich.edu/icpsrweb/landing.jsp).

Physical Activity

Physical activity was measured with 4 items assessing the participant's frequency of vigorous and moderate physical activity in the summer and winter months on a 6-point scale (1 = Several times a week or more, 2 = About once a week, 3 = Several times a month, 4 = About once a month, 5 = Less than once a month, 6 = Never): "During the summer, how often do you engage in vigorous physical activity (e.g. running or lifting heavy objects) long enough to work up a sweat?", "What about during the winter - how often do you engage in vigorous physical activity enough to work up a sweat?", "During the summer, how often do you engage in moderate physical activity (e.g. bowling or using a vacuum cleaner)?", "What about during the winter - how often do you engage in moderate physical activity?". The differences between physical activity intensities were assessed separately for the winter and summer months and no significant differences were observed between seasons. Therefore, a new variable was created called MVPA (moderate to vigorous physical activity) with response options of "often" "sometimes," or "rarely". Individuals who reported engaging in physical activity "several times per week or more" were categorized into the "often" group; those who reported physical activity engagement "about once per week" or "several times per month" were categorized into the "sometimes" group, and; those who reported physical activity engagement "about once a month" or “less than once a month” or “never” were categorized into the “rarely” group.

Cognitive Function

Cognitive functioning was tested using the Brief Test of Adult Cognition by Telephone (BTACT) (Tun & Lachman, 2006). The BTACT provides a brief battery for telephone assessment of key domains of cognitive function, including episodic memory (memory of experiences and specific events in time in serial form), working memory span (the number of items, usually words or numbers, that a person can retain or recall), executive function (goal oriented behaviors such as problem solving, multitasking, and plan making), reasoning and speed of processing (the ability to process information automatically and quickly, without intentional thinking through), using tests that are sensitive to performance in community-dwelling adults ranging from young to middle-aged and older. The BTACT is administered in <20 minutes, is easily scored and provides a composite measure of cognitive function. The BTACT composite score showed good internal consistency of α =0.82 (Tun & Lachman, 2006) and includes the following tests:

- two measures of episodic memory (immediate and delayed free recall of 15 words);
- attention switching and inhibitory control (the Stop and Go Switch Task);
- processing speed (the number of digits produced by counting backward from 100 in 30 seconds);
- working memory span (backward digit span—the highest span achieved in repeating strings of digits in reverse order);
- inductive reasoning (completing a pattern in a series of 5 numbers);
- verbal fluency (the number of words produced from the category of animals in 60 seconds).

Two factor scores episodic memory and executive function were calculated using the seven tests. Tests of immediate and delayed recall were used to calculate episodic memory and the remainders of the tests were used to calculate executive function (Tun & Lachman, 2006).

Medication Use

Number of medications used was assessed using a series of questions regarding diagnosis of and treatment for hypertension, high cholesterol, and type II diabetes. A new variable was created called "number of medications used" (no medications, 1 medication, 2-3 medications).

Age

Participants were asked to indicate the year of their birth which was then subtracted from the year that the interview was conducted. Subsequently, respondents were categorized into 4 groups: 25-44 years, 45-54 years, 55-64 years, 65-84 years.

Anthropometry

Participants were mailed a tape measure and asked to measure their waist circumference at the level of the navel to the nearest ¼ inch and hip circumference measurements were to be taken at the widest point. Waist-to-hip ratio (WHR) has been suggested to be superior to body mass index (BMI) in predicting metabolic syndrome and cardiovascular diseases (Janssen et al., 2004). WHR was subsequently classified as "healthy" (M: <0.95; F: <0.80) or "unhealthy" (M: ≥ 0.95; F: ≥ 0.80).

Covariates

Sex, marital status (married, separated/divorced/widowed, never married), level of education (some grade school-some high school, GED-graduated high school, some college/no bachelor's degree, college grad-doctorate/professional degree), and ethnicity/race (White or Non-White (African American, native American, Asian, native Hawaiian, pacific islander, other)) were adjusted for in the analyses. Respondents with answers of ''not stated'' or ''refused'' for other study variables were excluded.

Statistical Analysis

The final sample consisted only of participants who had participated in both MIDUS and completed the cognitive function measures. The inter-relationships between MVPA, obesity, medication use, and cognitive functioning were explored using ANCOVAs and general linear models after adjusting for covariates. Individual Z-scores for the cognitive measures of executive function and episodic memory were used in the data analysis (Tun & Lachman, 2006). Because the interactions between MVPA, obesity, medication use, cognitive functioning scores and age were significant ($p<0.001$), analyses were further stratified by age. Statistical analyses were performed using SAS v 9.4 (SAS Institute Inc., NC, USA) with statistical significance set at an α of 0.05.

Results

Over 46% of the sample reported that they rarely/never engage in moderate-to-vigorous physical activity (MVPA), whereas 12% reported engaging in MVPA sometimes, and 42% of the sample reporting that they engage in MVPA regularly/often. As well, 27% of males and 23% of females reported a healthy WHR, whereas 18% of males and 32% of females reported an elevated WHR. Approximately 22% of the sample also reported taking 1 medication and 12% reported taking 2-3 medications **(Table 1)**.

Younger adults reported better scores on both measures of cognitive function than older adults; executive function (25-44 years (Mean Z-Score, SD): 0.51 (0.88), 45-54 years: 0.27 (0.89), 55-64 years: -0.03 (0.94), 65-84 years: -0.61 (0.92)) and episodic memory (25-44 years: 0.40 (0.94), 45-54 years: 0.18 (0.92), 55-64 years: 0.01 (0.95), 65-84 years: -0.49 (0.98)). Individuals who engaged in MVPA often or sometimes reported better cognitive functioning scores on both executive function (MVPA (often): 0.27 (0.91), MVPA (sometimes): 0.12 (0.95), MVPA (never): -0.24 (0.99)) and episodic memory (MVPA (often): 0.17 (0.99), MVPA (sometimes): 0.12 (1.06), MVPA (never): -0.14 (0.97)) than those who engaged in MVPA rarely/never. As well, with regards to medication use, individuals who are taking fewer medications reported better cognitive function; executive function (no medication: 0.14 (1.01), 1 medication: -0.19 (0.97), 2-3 medications: -0.34 (0.87)) and episodic memory (no medication: 0.10 (0.99), 1 medication: -0.12 (1.01), 2-3 medications: -0.27 (0.96)). Finally, males and females with a healthy WHR reported better cognitive function, on both executive function and episodic memory measures, than males and females with an elevated WHR **(Table 2)**.

Figure 1 illustrates the relationships between the individual variables of interest and the cognitive function outcomes (executive function and episodic memory). Findings generally indicate that individuals who engage in MVPA often or sometimes, are younger, and are on fewer medications, report better scores on both executive function and episodic memory measures.

Figure 2 displays the inter-relationships between MVPA, age category, medication use and cognitive function. With regard to executive function, individuals who consumed no medications for type II diabetes, hypertension, or high cholesterol reported better scores than individuals who consumed 1 or 2-3 medications. Furthermore, individuals who reported engaging in MVPA often or sometimes had better scores than those who engaged in MVPA rarely. As well, scores declined with age, and the decline was more pronounced in individuals who were less active and consumed more medications **(Figure 2)**. Similar findings were observed with episodic memory **(Figure 3)**. Once again, individuals who consumed no medications for type II diabetes, hypertension, or high cholesterol reported better scores than individuals who consumed 1 or 2-3 medications. The decline in scores became more pronounced with increasing age and lower levels of MVPA.

The inter-relationships between MVPA, medication use, WHR, age and both cognitive function measures indicate that as people age engaging in MVPA often or sometimes as well as having a healthy WHR may offer protection against cognitive decline and preserve both executive function **(Table 3)** and episodic memory **(Table 4)**. On the other hand, taking a greater number of medications was associated with worse cognitive function.

Discussion

This study explored the relationships between MVPA, medication use, WHR, and age. The findings of this study indicate that lower levels of physical activity and higher WHR and number of medications used corresponded with worse cognitive function scores on both executive function and episodic memory measures; this relationship was consistent with age.

Prolonged use of one or multiple medications and the accumulation of their side effects as well as interactions may have negative consequences for cognitive functioning (Mirowsky & Ross, 2003). The findings of this study indicate that physical activity may counter some of the adverse effects of medication use and offer protection against cognitive decline. Physical activity may preserve cognitive function by way of improving cerebral circulation by increasing the blood flow and oxygen supply to the brain (Kivipelto et al., 2005). Regular physical activity lowers blood pressure and lipids, prevents metabolic syndrome, has a positive effect on inflammatory markers and improves endothelial function, all of which are risk factors for cardiovascular diseases and dementia (Kivipelto et al., 2005). Animal studies indicate that physical activity stimulates neuron proliferation in hippocampal regions (Hillman et al., 2008), and may even increase hippocampal volume in humans (Erickson et al., 2011). As well, the findings of this study indicate that MVPA at all ages may offer protection against cognitive decline and perhaps even counteract some of the adverse effects of medications used to treat type II diabetes, high blood pressure and high cholesterol. Additionally, significant differences were observed between individuals who engaged in MVPA regularly and consumed fewer medications versus those who engaged in MVPA rarely or never and consumed 1 and 2-3 medications on both measures of executive function and episodic memory; with individuals who engaged in MVPA more often and consumed fewer medications reporting better scores.

The prevalence of cognitive decline and dementia as well as prescription drug use are on the rise. Hypertension affects 70 million American adults and nearly 7.5 million Canadians (Nwankwo et al., 2013; Genest et al., 2009); nearly 29.1 million Americans and 3.4 million Canadians have diabetes (Centers for Disease Control and Prevention, 2014; Public Health Agency of Canada, 2011); and finally, high cholesterol affects 71 million Americans (33.5%) and 39% of Canadians (Centers for Disease Control and Prevention, 2011; Kappelle et al., 2012). Currently, nearly 60% of Americans taking prescription medication (Kantor & colleagues, 2015); indeed, almost 3 in 5 American adults take a prescription drug, up markedly since 2000. The most commonly used drugs being those for the treatment of high cholesterol, high blood pressure and type II diabetes (Kantor et al., 2015). The rise in the use of prescription medication might reflect the growing need for treatment of complications associated with the increase in overweight, obesity and a sedentary lifestyle and a decline in physical activity levels, and this elevation might in turn contribute to the increasing prevalence of cognitive decline.

This study has several strengths that should be noted. First, this is the first study to explore the relationship between the number of medications taken and the corresponding impact on cognitive function scores. Other strengths include the use of a large dataset exploring age-related variations in health and well-being across the lifespan; as well as, evaluating cognitive performance using both episodic memory and executive function measures. However, this study is not without its limitations. For example, it is unknown how long participants have been using prescription medication and which prescription medications they were on. Additionally, since it is unclear which medications were used, it is possible that more than 3 medications were being used and the number of medications used actually represents the number of chronic conditions an individual has. As well, due to the self-report nature of the data there may have been overestimations in physical activity and underestimations in the waist and hip circumference measures that were used to calculate WHR.

Conclusion

As the world's population grows older, the prevalence rates of both cognitive decline and prescription medication use are on the rise. Although ageing is a risk factor for chronic diseases, ageing is not necessarily defined by the presence of morbidities but as a process that starts early in life and is modulated by the accumulation of experiences and exposures throughout the life-course (Franco et al., 2009). Although life expectancy has increased in the past few decades, the years lived with disabilities and diseases are increasing (Salomon et al., 2012). Therefore, identifying effective ways to delay the onset of dementia is of great importance for alleviating the family and societal pressures of this syndrome (Brookmeyer et al., 2007). Physical activity may be useful means of preserving cognitive performance by countering the effects of prescription medication taken for chronic conditions, across the lifespan.

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Table 3-1: Demographic Characteristics of The Midlife in the U.S. Survey (MIDUS).

Variable	
	N=4 153
Age (Mean, SD)	55.99 (12.34)
Age Categories (Freq, %)	
1 (25-44 years)	857 (20.64)
2 (45-54 years)	1125 (27.09)
3 (55-64 years)	1058 (25.48)
4 (65-84 years)	1113 (26.80)
Sex (Freq, %)	
Male	1904 (45.85)
Female	2249 (54.15)
Waist-to-Hip Ratio (Freq, %)	
1 (Male, <0.95)	1074 (26.84)
2 (Male, ≥0.95)	737 (18.42)
3 (Female, <0.80)	925 (23.11)
4 (Female, ≥0.80)	1266 (31.63)
Marital Status (Freq, %)	
1 (Married)	2978 (71.71)
2 (Separated/ Divorced/ Widowed)	731 (17.60)
3 (Never Married)	444 (10.69)
Education (Freq, %)	
1 (Some Grade School- Some High School)	261 (6.30)
2 (GED-Graduated High School)	1151 (27.76)
3 (Some College/No Bachelors Degree)	1243 (29.98)
4 (College Grad-Doctorate/Professional Degree)	1491 (35.96)
Race (Freq, %)	
1 (White)	3819 (91.96)
2 (African American, Native American, Asian, Native Hawaiian/Pacific Islander, Other)	334 (8.04)
Number of Meds Used (RX Use) (Freq, %)	
0	2697 (64.94)
1	931 (22.42)
2+	525 (12.64)
MVPA (Freq, %)	
1 (Often)	1514 (41.50)
2 (Sometimes)	452 (12.39)
3 (Never)	1682 (46.11)

Table 3-2: Mean Cognitive Function Scores.

Variable	Executive Function (Mean, SD)	Episodic Memory (Mean, SD)
Sex		
Male	0.13 (1.00)	-0.24 (0.91)
Female	-0.10 (0.99)	0.21 (1.02)
Waist-To-Hip-Ratio		
Male (<0.95)	0.18 (1.00)	-0.20 (0.92)
Male (≥0.95)	0.06 (0.99)	-0.29 (0.90)
Female (<0.80)	-0.02 (1.04)	0.26 (1.00)
Female (≥0.80)	-0.16 (0.94)	0.16 (1.01)
Age		
1(25-44 years)	0.51 (0.88)	0.40 (0.94)
2(45-54 years)	0.27 (0.89)	0.18 (0.92)
3(55-64 years)	-0.03 (0.94)	0.01 (0.95)
4(65-84 years)	-0.61 (0.92)	-0.49 (0.98)
Race		
1(White)	0.04 (0.99)	0.02 (1.00)
2(African American, Native American, Asian, Native Hawaiian/Pacific Islander, Other)	-0.40 (0.98)	-0.24 (0.98)
Education		
1(Some Grade School-Some High School)	-0.92 (0.91)	-0.55 (0.94)
2(GED-Graduated High School)	-0.36 (0.90)	-0.18 (0.95)
3(Some College/No Bachelors Degree)	-0.05 (0.89)	0.02 (1.01)
4(College Grad-Doctorate/Professional Degree)	0.49 (0.92)	0.22 (0.97)
Marital Status		
1(Married)	0.03 (0.98)	0.01 (0.99)
2(Separated/ Divorced/ Widowed)	-0.28 (1.02)	-0.15 (1.01)
3(Never Married)	0.33 (0.97)	0.16 (1.01)
Number of Meds Used		
0	0.14 (1.01)	0.10 (0.99)
1	-0.19 (0.97)	-0.12 (1.01)
2-3	-0.34 (0.87)	-0.27 (0.96)
MVPA		
1(Often)	0.27 (0.91)	0.17 (0.99)
2(Sometimes)	0.12 (0.95)	0.12 (1.06)
3(Never)	-0.24 (0.99)	-0.14 (0.97)

Table 3-3: Differences in Executive Function by Medication Use, MVPA, WHR & Age.

	Number of Medications											
	25-44 y			45-54 y			55-64 y			65-84 y		
	0	1	2-3	0	1	2-3	0	1	2-3	0	1	2-3
Males												
Low WHR (<0.95)												
MVPA Often	0.37	0.12	*	0.26	0.27	0.23	-0.11	-0.16	-0.72	-0.60	-0.74	-0.83
MVPA Sometimes	0.08	*	*	0.05	0.44	-1.47	-0.08	0.34	*	-0.44	-0.69	-0.28
MVPA Rarely	0.07	-0.34	*	0.05	-0.45	-0.55	-0.23	-0.47	-0.69	-0.92	-0.89	-0.77
High WHR (≥0.95)												
MVPA Often	0.35	0.11	*	-0.01	0.08	-0.68	0.24	-0.33	-0.26	-0.58	-0.76	-0.99
MVPA Sometimes	0.44	*	*	0.04	0.30	-0.54	-0.92	-0.12	*	-0.53	-1.03	-0.69
MVPA Rarely	0.04	-0.13	*	-0.003	-0.30	0.17	-0.36	-0.42	-0.18	-0.79	-1.02	-0.66
Females												
Low WHR (<0.80)												
MVPA Often	0.18	0.20	*	0.01	-0.28	-0.08	-0.30	-0.27	-2.05	-0.36	-0.37	-0.20
MVPA Sometimes	0.07	*	*	-0.11	0.48	-0.02	-0.25	-0.66	*	-1.25	-1.13	-0.28
MVPA Rarely	0.21	-0.45	*	-0.03	0.10	-0.45	-0.51	-0.38	-1.00	-0.99	-0.89	-0.81
High WHR (≥0.80)												
MVPA Often	0.10	0.62	*	-0.09	-0.09	-0.55	-0.28	-0.40	-0.48	-0.59	-0.46	-0.82
MVPA Sometimes	0.09	*	*	0.05	-0.44	-0.43	-0.36	-0.57	*	-0.89	-0.68	-0.77
MVPA Rarely	-0.07	0.30	*	-0.29	-0.38	-0.03	-0.54	-0.47	-0.64	-1.02	-0.98	-0.93

*estimate is suppressed due to insufficient n

Table 3-4: Differences in Episodic Memory by Medication Use, MVPA, WHR & Age.

	Number of Medications											
	25-44 y			45-54 y			55-64 y			65-84 y		
	0	1	2-3	0	1	2-3	0	1	2-3	0	1	2-3
Males												
Low WHR (<0.95)												
MVPA Often	0.06	-0.29	*	-0.16	-0.02	-0.07	-0.48	-0.53	-0.67	-1.12	-0.95	-0.69
MVPA Sometimes	-0.45	*	*	-0.02	-0.27	-0.84	-0.25	0.10	*	-0.60	-0.56	-1.38
MVPA Rarely	0.002	0.40	*	-0.19	-0.14	-0.86	-0.70	-0.35	-0.35	-1.02	-1.04	-0.60
High WHR (≥0.95)												
MVPA Often	-0.21	0.11	*	-0.36	-0.51	-1.03	-0.14	-0.12	-0.62	-0.91	-0.99	-1.06
MVPA Sometimes	-0.05	*	*	-0.18	-0.36	-0.53	-0.61	-0.02	*	-0.50	-0.68	-1.34
MVPA Rarely	-0.06	0.46	*	-0.26	-0.65	0.07	-0.46	-0.59	-0.58	-0.99	-0.98	-0.61
Females												
Low WHR (<0.80)												
MVPA Often	0.36	0.38	*	0.19	0.80	-0.28	0.24	0.31	-1.43	-0.10	0.07	-0.78
MVPA Sometimes	0.74	*	*	0.28	0.74	1.63	0.15	1.50	*	-1.43	-0.78	0.91
MVPA Rarely	0.32	0.17	*	0.35	-0.23	-0.89	0.08	-0.10	-0.42	-0.28	-0.23	-0.19
High WHR (≥0.80)												
MVPA Often	0.38	0.24	*	0.29	0.70	-0.24	0.24	0.04	0.15	-0.45	-0.41	-0.19
MVPA Sometimes	0.31	*	*	0.40	0.48	0.11	0.67	0.33	*	-0.49	0.03	0.17
MVPA Rarely	0.24	0.79	*	0.08	-0.04	0.02	0.002	-0.13	-0.24	-0.51	-0.44	-0.47

*estimate is suppressed due to insufficient n

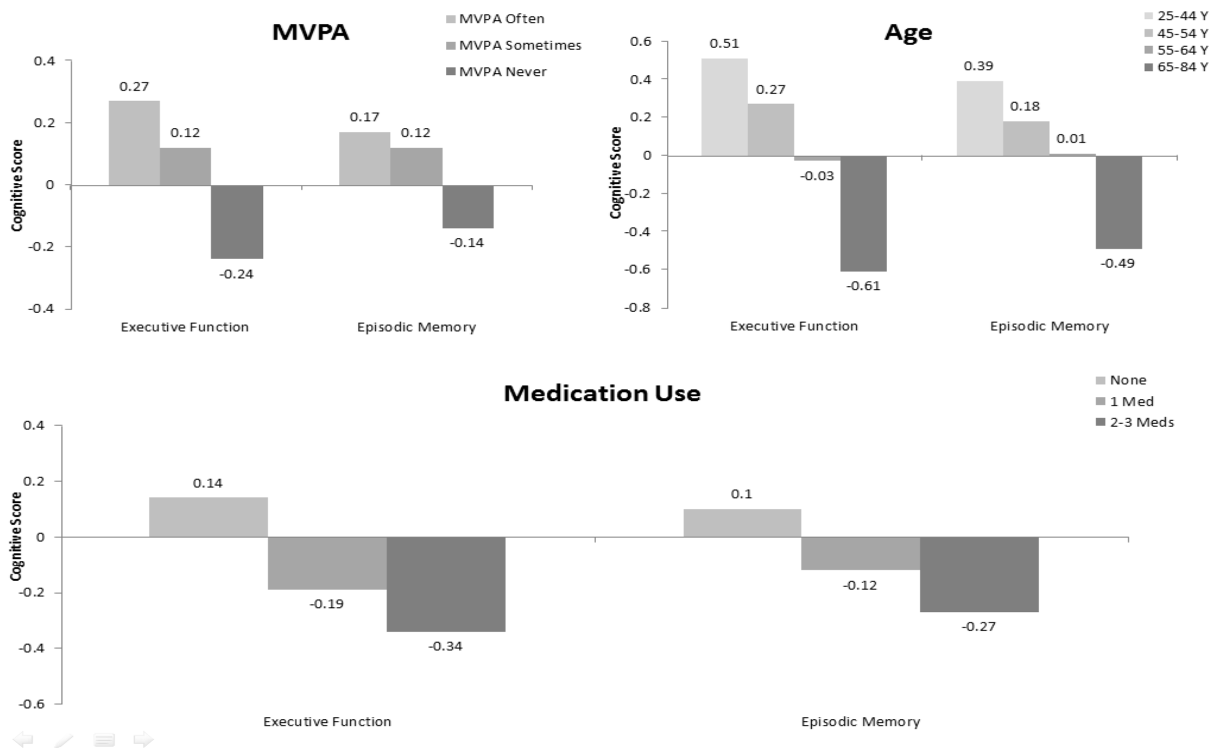
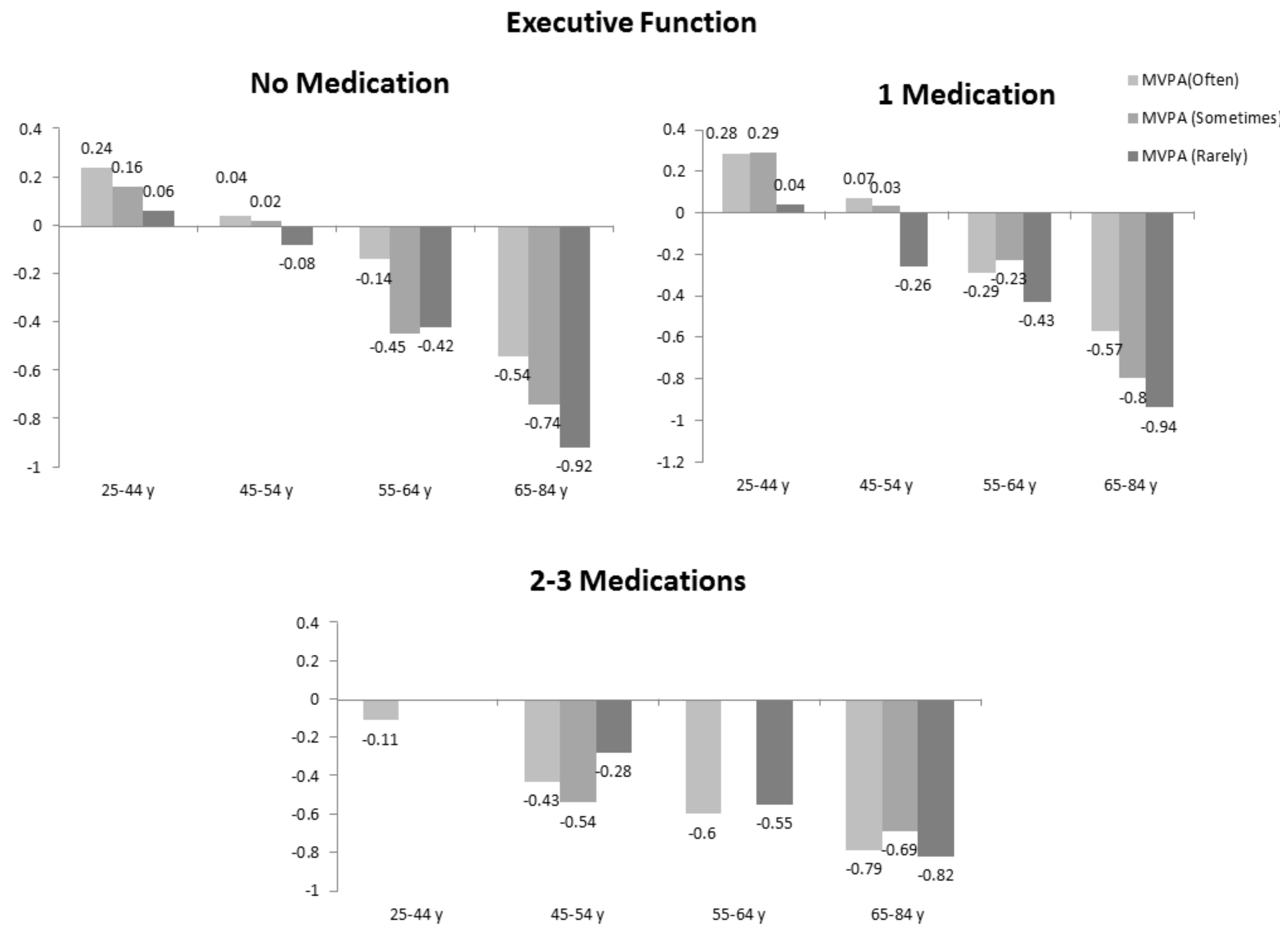
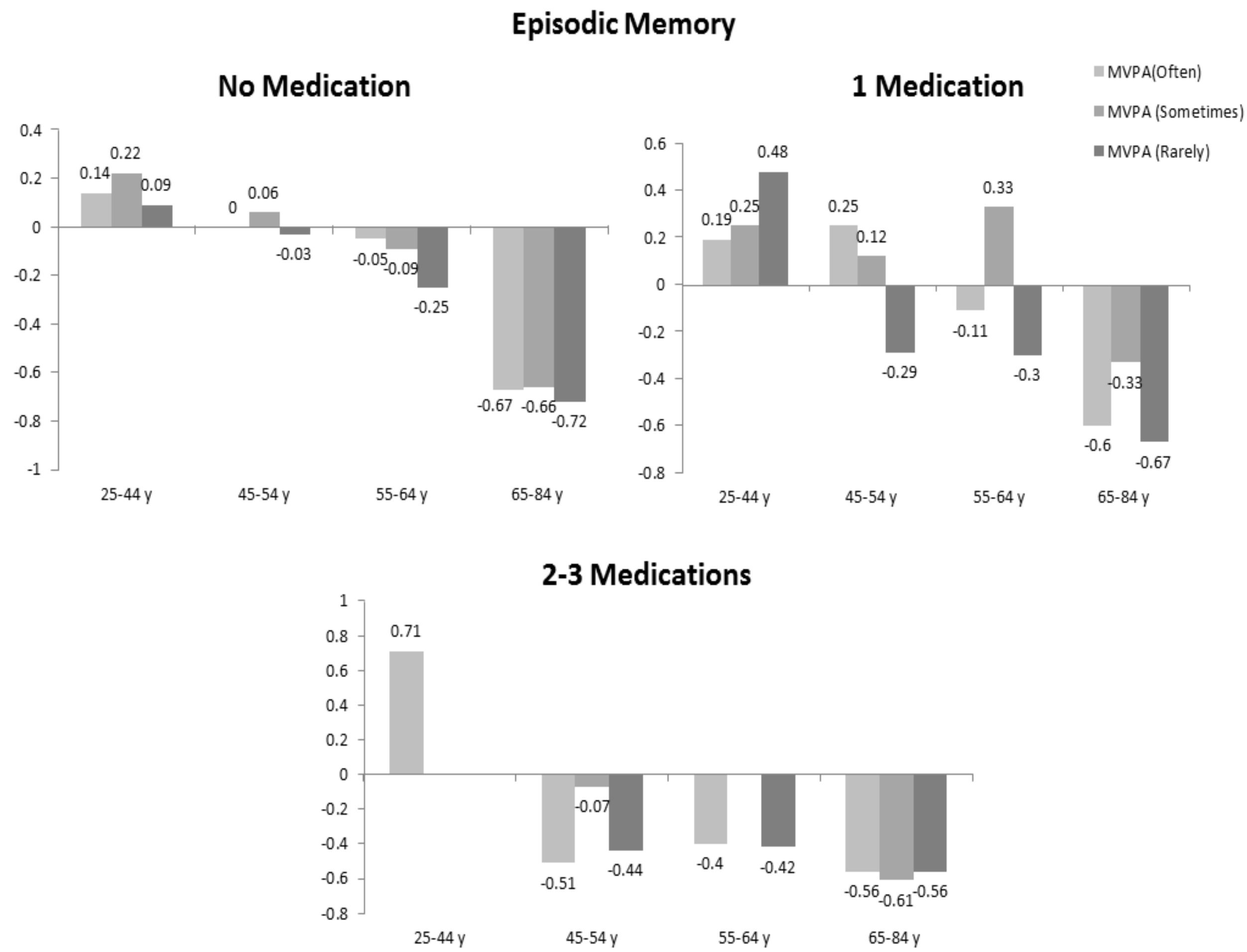


Figure 4-1: Relationships between individual variables of interest and cognitive function outcome variables.



Significant Differences: No medication: 25-44 years: MVPA(often) vs. MVPA(rarely) p<0.0001; MVPA(sometimes) vs. MVPA(rarely) p=0.001. 45-54 years: MVPA(often) vs. MVPA(rarely) p<0.0001; MVPA(sometimes) vs. MVPA(rarely) p=0.0052. 55-64 years: MVPA(often) vs. MVPA(rarely) p<0.0001; MVPA(often) vs. MVPA(sometimes) p=0.0013. 65-84 years: MVPA(often) vs. MVPA(rarely) p<0.0001. One medication: 45-54 years: MVPA(often) vs. MVPA(rarely) p=0.0339; 55-64 years: MVPA(often) vs. MVPA(rarely) p=0.0019; 65-84 years: MVPA(often) vs. MVPA(rarely) p<0.0001. 2-3 Medications: 65-84 years: MVPA(often) vs. MVPA(sometimes) p<0.0162.
Effect size (ω^2; 95% Confidence Interval): 0.22; 0.19, 0.24).

Figure 4-2: Executive function scores by medication use, level of physical activity and age.



Significant Differences: No medication: 25-44 years: MVPA(often) vs. MVPA(rarely) p=0.0147; 45-54 years: MVPA(often) vs. MVPA(rarely) p=0.0063; 55-64 years: MVPA(often) vs. MVPA(rarely) p=0.0028. One medication: 55-64 years: MVPA(often) vs. MVPA(rarely) p=0.0306; MVPA(sometimes) vs. MVPA(rarely) p=0.0433; 65-84 years: MVPA(often) vs. MVPA(rarely) p=0.0424; MVPA(sometimes) vs. MVPA(rarely) p=0.0462.

Effect size (ω^2; 95% Confidence Interval): 0.17; 0.15, 0.19).

Figure 4-3: Episodic memory scores by medication use, level of physical activity and age.

CHAPTER 5: MANUSCRIPT 4

Physical Activity, Cognitive Stimulation & Cognitive Function in Younger, Middle-Aged & Older Adults: Analysis of the Midlife in the US Survey (MIDUS)

Abstract

Background: Finding lifestyle variables that may preserve cognitive function or delay the onset of cognitive decline are of the utmost importance. Especially because the prevalence of cognitive decline continues to rise and effective treatment options remain elusive.

Purpose: The aim of this study was to explore the inter-relationships between physical activity (frequency, intensity, season), cognitive stimulation (reading, attending lectures, card games, word games), obesity (waist-to-hip ratio), age, and cognitive function (measured as episodic memory and executive function).

Methods: This study used data from the Midlife in the United States (MIDUS) national longitudinal survey conducted in 1995/1996 and 2004/2005. The inter-relationships between physical activity, obesity, cognitive stimulation, and cognitive functioning were explored using general linear models.

Results: Both executive function and episodic memory scores declined with age. However, at all ages, individuals who engaged in moderate to vigorous physical activity often or sometimes and regularly engaged in cognitively stimulating activities reported less cognitive decline ($p<0.001$).

Conclusions: The cumulative effects of physical activity and cognitive stimulation appear to be effective means for maintaining cognitive function as well as reducing the risk for cognitive decline, at every age group.

Introduction

Dementia is a neurological condition involving global impairment of cognitive ability that interferes with normal activities and everyday functioning, with notable deficits in a person's episodic (short-term) memory and executive functioning, the cognitive processes involved in planning and organization of one's resources in pursuit of a goal (Budson & Price, 2005). In 2010, there were an estimated 36 million people living with dementia and with increasing life expectancy, these numbers are expected to reach 66 million in 2030 and 115 million by 2050 (World Health Organization, 2012). Therefore, identifying early intervention opportunities to offset the risk of cognitive decline is a public health priority. Factors that may protect against cognitive decline include moderate-to-vigorous physical activity (MVPA) (Laurin et al., 2001; Abbott et al., 2004) and cognitively stimulating activities such as reading, learning a new skill or partaking in a new activity, or playing card or word games (Kramer et al., 2004).

Despite the well-known benefits of MVPA, physical activity levels tend to decrease, and the prevalence of overweight and obesity tends to increase, with age, which may exacerbate existing difficulties in normal functioning and instrumental activities of daily life (Kostic et al., 2011). Indeed, frontal lobe functions, particularly executive ability, tend to deteriorate disproportionately with age, and may be improved with a regular program of walking (Abbott et al., 2004). The Canadian Study of Health and Aging, a large-scale population-based study of individuals 65 years and older, also found that higher levels of MVPA were associated with reduced risk of cognitive impairment, Alzheimer's disease, and dementia of any type (Laurin et al., 2001).

Evidence suggests that complex mental activities and learning can also offer protection against cognitive decline; thus, higher levels of education, occupational complexity, and higher

IQ all offer protection against cognitive decline (Valenzuela & Sachdev, 2005). As well, leading a mentally active lifestyle (e.g., learning a new language or playing card games) has been shown to positively influence cognitive functioning (Hultsch et al., 1999; Kramer et al., 2004; Wilson et al., 2002). Thus, participation in cognitively stimulating leisure activities (i.e. reading) may be effective means by which to preserve cognitive function and delay cognitive decline.

It is known that both physical activity and cognitive stimulation individually exert positive effects on cognitive function. However, the combined effects and relative importance of each is not well understood, and it is currently unclear whether there are critical time points from early adulthood into midlife and old age for optimal benefit. Therefore, the aim of this study was to explore the inter-relationships between physical activity, cognitive stimulation (i.e. reading, attending lectures/courses, playing cards games, playing word games), obesity, age, and cognitive function in adults between the ages of 25 to 84 years of age.

Methods

The present study used data from the Midlife in the United States (MIDUS; Brim, Ryff, & Kessler, 2004) national longitudinal survey conducted in 1995/1996 and 2004/2005. MIDUS was designed to explore the role of various behavioral, social, psychological, biological, and neurological factors in physical and mental health as people age. It was based on a nationally representative sample (random-digit-dial) of non-institutionalized, English-speaking adults aged 25 to 74 (wave I) years, selected from working telephone banks in the contiguous United States in 1995. With support from the National Institute on Aging, a longitudinal follow-up (wave II, which took place 10 years later) of the original MIDUS national probability sample was conducted in 2005 and included a cognitive function component (Ryff et al., 2012)
Data were obtained using the Inter University Consortium for Political and Social Research (ICPSR), of which York University is an institutional member (http://www.icpsr.umich.edu/icpsrweb/landing.jsp) and a separate ethics approval was not

required. This study was part of a larger project exploring the influence of different physical activity, anthropometric, and lifestyle variables on cognitive functioning in younger, middle-aged, and older Canadian adults (See Chapter 4: Study 3).

Physical Activity

An index of physical activity was derived from items that assessed frequency, intensity (vigorous, moderate) and season (summer, winter). First, participants were asked: "How often do you engage in vigorous PA that causes your heart to beat so rapidly that you can feel it in your chest and you perform the activity long enough to work up a good sweat and to breath heavily?" This question was asked and answered twice (once for summer and once for winter). Second, participants were asked: "How often do you engage in moderate PA, that is not physically exhausting, but it causes your heart rate to increase slightly and you typically work up a sweat?" This question was also asked and answered twice (once for summer and once for winter). After examining the differences between PA intensities and seasons, no significant differences were observed between the winter and summer months, allowing for moderate and vigorous physical activity (MVPA) information to be pooled and categorized as "often" "sometimes," or "rarely". Individuals who answered "several times per week or more" were categorized into the "often" group; those who answered "about once per week" or "several times per month" were categorized into the "sometimes" group and; those who responded "about once a month," "less than once a month," or "never" were categorized into the "rarely/never" group.

Cognitive Stimulation

Participants were asked about frequency of engagement in mental activities such as reading, doing word games, playing cards, and attending lectures. Each participant indicated the frequency of engaging in these activities using a 6-point ordinal scale ranging from 1 (daily) to 6 (never) (Lachman et al., 2011). A new variable was created called cognitive stimulation with response options of "regularly" or "sometimes," on the basis of participation in these activities. Individuals who reported engaging in any of these activities "daily" were categorized into the "regularly" group, and everyone else was categorized in to the "sometimes" group.

Cognitive Function

Cognitive function was measured using the Brief Test of Adult Cognition by Telephone (BTACT), a neuropsychological battery of six cognitive tests, including measures of episodic verbal memory (Word List Immediate and Delayed), working memory span (Digits Backward), verbal fluency (Category Fluency), inductive reasoning (Number Series), and processing speed (Backward Counting) (Tun & Lachman, 2006). Participants also completed the Stop and Go Switch Task testing their attention switching and inhibitory control (Tun & Lachman, 2008). Two factor scores, episodic memory (EM) and executive function (EF), were derived using the seven cognitive tests (Lachman et al., 2011).

Anthropometry

Waist-to-hip ratio (WHR) was measured as the ratio of waist to hip circumference. Participants were asked to measure their waist circumference at the level of the navel and hip circumference at the widest point, using a tape measure that was mailed to them. WHR is often used as a crude estimate of body fat distribution, with elevated WHR defined as ≥0.80 and ≥0.95 in women and men, respectively.

Covariates

Marital status (married, separated/divorced/ widowed, never married), sex, level of education (some grade school-some high school, GED-graduated high school, some college/no bachelor's degree, college grad-doctorate/professional degree), and ethnicity (White or non-White (African American, native American, Asian, native Hawaiian, pacific islander, other)) were treated as potential confounders and adjusted for in all analyses. Respondents with answers of ''not stated'' or ''refused'' for other study variables were excluded.

Statistical Analysis

Participants were classified into four separate groups on the basis of their age (25-44 years of age, 45-54 years of age, 55-64 years of age, and 65-84 years of age). The final sample was comprised solely of individuals who had completed MIDUS I, MIDUS II, and the cognitive component. Participants' Z-scores for episodic memory and executive function were used in the data analysis. The inter-relationships between MVPA, obesity, cognitive stimulation, and cognitive functioning were explored using general linear models and ANCOVAs after adjusting for covariates. Because the interactions between MVPA, obesity, cognitive stimulation, cognitive functioning scores and age were significant ($p<0.001$), analyses were further stratified by age. Statistical analyses were performed using SAS v 9.4 (SAS Institute Inc., NC, USA) with statistical significance set at an α of 0.05.

Results

About 42% of the sample indicated they engaged in regular MVPA often, 12% of the sample reported engaging in MVPA sometimes, and 46% of the sample reported engaging in MVPA rarely/never. As well, nearly 72% of the sample reported engaging in cognitively stimulating activities regularly (i.e. reading, attending courses/lectures, playing card games, playing word games), and approximately 29% of the sample reported engaging in cognitively stimulating activities sometimes **(Table 1)**.

With regards to executive function, z-scores appear to decline with age. Older adults reported worse scores than younger adults (25-44 years (mean z-score, SD): 0.51 (0.88), 45-54 years: 0.27 (0.89), 55-64 years: -0.03 (0.94), 65-84 years: -0.61 (0.92)). As well, individuals who engaged in MVPA often or sometimes reported better scores compared to those who engaged in MVPA rarely/never (MVPA (often): 0.27 (0.91), MVPA (sometimes): 0.12 (0.95), MVPA (never): -0.24 (0.99)). Also, individuals with a healthy WHR (both males and females) reported better scores (males: 0.18 (1.00), females: -0.02 (1.04)) than those with an unhealthy WHR (males: 0.06 (0.99), females: -0.16 (0.94)). Finally, individuals who reported regular engagement in cognitively stimulating activities reported better executive function scores compared to those individuals who only engaged in these activities sometimes (regularly: 0.06 (0.97), sometimes:-0.10 (1.02)) **(Table 2)**.

Similarly, episodic memory scores also declined with age (25-44 years: 0.40 (0.94), 45-54 years: 0.18 (0.92), 55-64 years: 0.01 (0.95), 65-84 years: -0.49 (0.98)) **(Table 2)**. As expected, those who engaged in (MVPA (often): 0.17 (0.99), MVPA (sometimes): 0.12 (1.06), MVPA (never): -0.14 (0.97)) and had a healthy WHR reported better episodic memory scores (healthy WHR males: -0.20 (0.92), females: 0.26 (1.00)), than those with an elevated WHR (unhealthy WHR males: -0.29 (0.90), females: 0.16 (1.01)). Finally, those individuals who engaged in cognitively stimulating activities regularly also reported better scores than those who engaged in these activities only sometimes (males: 0.03 (1.01), females: -0.03 (0.98)).

Engaging in cognitively stimulating activities regularly contributed to better scores on both cognitive function measures (executive function: 0.06; episodic memory 0.03) than engaging in cognitively stimulating activities sometimes (executive function: -0.1; episodic memory -0.03) **(Figure 1)**. Further, regular engagement in cognitively stimulating activities contributes to superior scores on both executive function and episodic memory measures and this relationship became more pronounced with age. Individuals who engaged in these activities often reported better scores and lower levels of decline in comparison to individuals who only engaged in these activities sometimes **(Figure 2)**. Finally, individuals who engaged in cognitively stimulating activities often and participated in MVPA regularly (often or sometimes) reported better cognitive functioning than those who engaged in cognitively stimulating activities sometimes and MVPA rarely **(Figure 3)**.

Figure 4 illustrates the inter-relationship between MVPA, cognitive stimulation, age, and executive function. Findings indicate that regular/frequent engagement in cognitively stimulating activities along with regular engagement in MVPA (often or sometimes) may contribute to superior executive functioning, a relationship that became more pronounced with age.

Figure 5 illustrates the inter-relationship between MVPA, cognitive stimulation, age, and episodic memory. Similar to executive function, regular/frequent engagement in cognitively stimulating activities along with regular engagement in MVPA (often or sometimes) may contribute to better episodic memory. This relationship became more pronounced with age.

Discussion

This study examined the relationships between MVPA, cognitive stimulation, obesity, age and cognitive function. Results indicated that engaging in cognitively stimulating activities along with regular MVPA, results in better cognitive functioning scores on both executive function and episodic memory in every age group. However, in this study, elevated WHR was not related to poorer cognitive function.

Research to date suggests that ageing is associated with declines in cognitive functioning and brain structural changes. In particular, life-span studies have reported cognitive decline in both executive functions and episodic memory (especially delayed recall) (Keys & White, 2000; Luo & Craik, 2008; Salthouse, 2009). Results from the present study indicate that although episodic memory and executive functioning decline with age, the decline is less pronounced in individuals who lead physically and cognitively active lifestyles. Specifically, in all age groups, individuals who regularly or sometimes engaged in MVPA and cognitively stimulating activities regularly. In the absence of a cure, preventing or delaying the onset of dementia is a critical public health priority. Among the mechanisms proposed, brain reserve, the ability to withstand damage and continue to function normally, may be increased by way of MVPA (Raz & Lindenberger, 2005). Normal ageing is associated with global volumetric shrinkage in brain structures (i.e. hippocampus, prefrontal areas) leading to potential adverse consequences on cognitive functioning (Raz & Lindenberger, 2005). Brain reserve has been most commonly used to provide an explanation describing a subset of individuals who, at autopsy, have the hallmarks of Alzheimer's disease including amyloid plaques and yet during their life did not show clinical symptom manifestations of the disease (Snowden, 2003). The incongruity between having extensive brain neuropathology without cognitive impairment has contributed to the belief that a larger brain volume, larger neurons, and more synaptic connections can act as a buffer, or protective factor in preventing or slowing down cognitive decline.

Cognitive reserve, on the other hand, which involves active compensation, can be increased by regular engagement in cognitively stimulating activities. One potential strategy that has been noted in functional imaging studies is that prefrontal activity during cognitive performance tends to be less localized, to the right or left side of the brain specifically, in older compared to younger adults (Cabeza & Anderson, 2002). This indicates that the ageing brain, uses more of its resources in an attempt to compensate for both structural and functional decline. Brain reserve and cognitive reserve are two parallel processes that help to explain that there is more than one pathway to maintaining cognitive health as people age from early adulthood into midlife and old age.

This study aimed to build on previous research by exploring lifestyle means that may preserve cognitive function at various stages of life, ranging from early adulthood into midlife and old age. Exploring a wider age range is a key strength of this work because most of the existing literature is focused on older adults. Other strengths include the use of a large dataset focused specifically on variables that influence health and using a valid and reliable tool to measure cognitive function. Nonetheless, the limitations of this study include overestimations of physical activity and underestimations of both waist and hip circumference measures that were used to calculate WHR, which may have occurred due to the self-report nature of the data.

Conclusion

The findings of this study indicate that those who engage in moderate-to-vigorous physical activity and cognitively stimulating activities have superior episodic memory and executive function, a trend that becomes more pronounced with age. Due to the ageing of the population and the relative scarcity of effective treatment options for cognitive decline, cognitive health will have an increasing impact on the health and independence of older adults. Thus, interventions that determine lifelong strategies to delay or even prevent cognitive decline and dementia are imperative.

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Table 4-1: Demographic Characteristics of the Midlife in the U.S. Survey (MIDUS).

Variable	
	N=4 153
Age (Mean, SD)	55.99 (12.34)
Age Categories (Freq, %)	
25-44 years	857 (20.64)
45-54 years	1125 (27.09)
55-64 years	1058 (25.48)
65-84 years	1113 (26.80)
Sex (Freq, %)	
Male	1904 (45.85)
Female	2249 (54.15)
Waist-to-Hip Ratio (Freq, %)	
Healthy Male, <0.95	1074 (26.84)
Elevated Male, ≥0.95	737 (18.42)
Healthy Female, <0.80	925 (23.11)
Elevated Female, ≥0.80	1266 (31.63)
Marital Status (Freq, %)	
Married	2978 (71.71)
Separated/ Divorced/Widowed)	731 (17.60)
Never Married	444 (10.69)
Education (Freq, %)	
Some Grade School- Some High School	261 (6.30)
GED-Graduated High School	1151 (27.76)
Some College/No Bachelors Degree	1243 (29.98)
College Grad-Doctorate/ Professional Degree	1491 (35.96)
Race (Freq, %)	
White	3819 (91.96)
Non-White	334 (8.04)
Cognitive Stimulation (Freq, %)	
Regularly	2610 (71.55)
Sometimes	1038 (28.45)
MVPA (Freq, %)	
Regularly/Often	1514 (41.50)
Sometimes	452 (12.39)
Rarely/Never	1682 (46.11)

Table 4-2: Mean cognitive functioning scores.

Variable	**Executive Function (Mean, SD)**	**Episodic Memory (Mean, SD)**
Sex		
Male	0.13 (1.00)	-0.24 (0.91)
Female	-0.10 (0.99)	0.21 (1.02)
Waist-To-Hip-Ratio		
Healthy Male, <0.95	0.18 (1.00)	-0.20 (0.92)
Elevated Male, ≥0.95	0.06 (0.99)	-0.29 (0.90)
Healthy Female, <0.80	-0.02 (1.04)	0.26 (1.00)
Elevated Female, ≥0.80	-0.16 (0.94)	0.16 (1.01)
Age		
25-44 years	0.51 (0.88)	0.40 (0.94)
45-54 years	0.27 (0.89)	0.18 (0.92)
55-64 years	-0.03 (0.94)	0.01 (0.95)
65-84 years	-0.61 (0.92)	-0.49 (0.98)
Race		
White	0.04 (0.99)	0.02 (1.00)
Non-White	-0.40 (0.98)	-0.24 (0.98)
Education		
Some Grade School-Some High School	-0.92 (0.91)	-0.55 (0.94)
GED-Graduated High School	-0.36 (0.90)	-0.18 (0.95)
Some College/No Bachelors Degree	-0.05 (0.89)	0.02 (1.01)
College Grad Doctorate/ Professional Degree	0.49 (0.92)	0.22 (0.97)
Marital Status		
Married	0.03 (0.98)	0.01 (0.99)
Separated/ Divorced/ Widowed	-0.28 (1.02)	-0.15 (1.01)
Never Married	0.33 (0.97)	0.16 (1.01)
Cognitive Stimulation		
Regularly	0.06 (0.97)	0.03 (1.01)
Sometimes	-0.10 (1.02)	-0.03 (0.98)
MVPA		
Regularly/Often	0.27 (0.91)	0.17 (1.00)
Sometimes	0.12 (0.95)	0.12 (1.06)
Rarely/Never	-0.24 (0.99)	-0.14 (0.97)

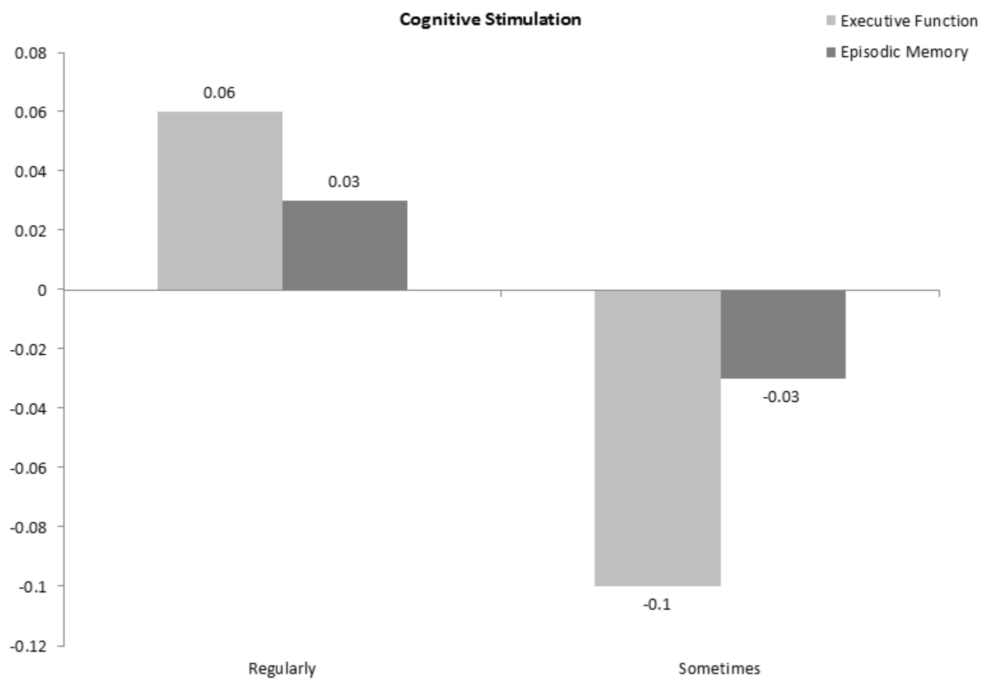


Figure 5-1: Relationship between cognitive stimulation participation frequency and cognitive function.

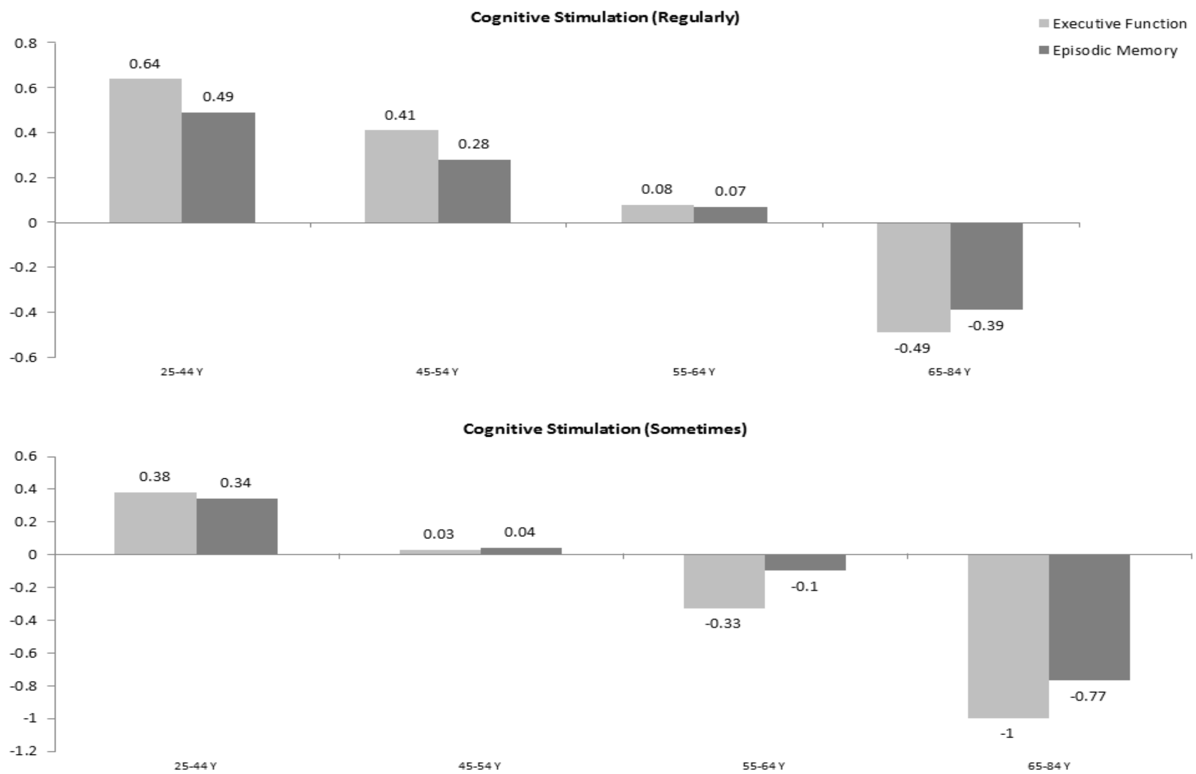


Figure 5-2: Cognitive stimulation frequency and cognitive function scores in different age groups.

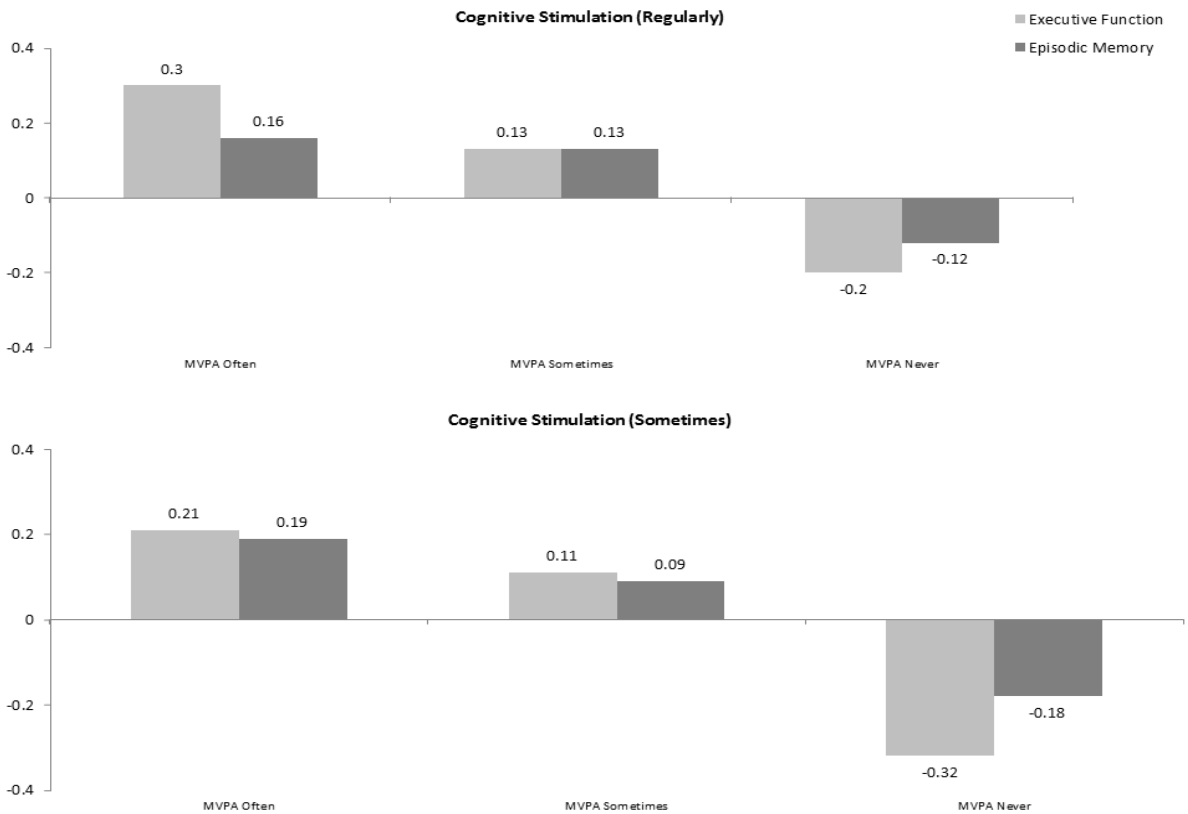
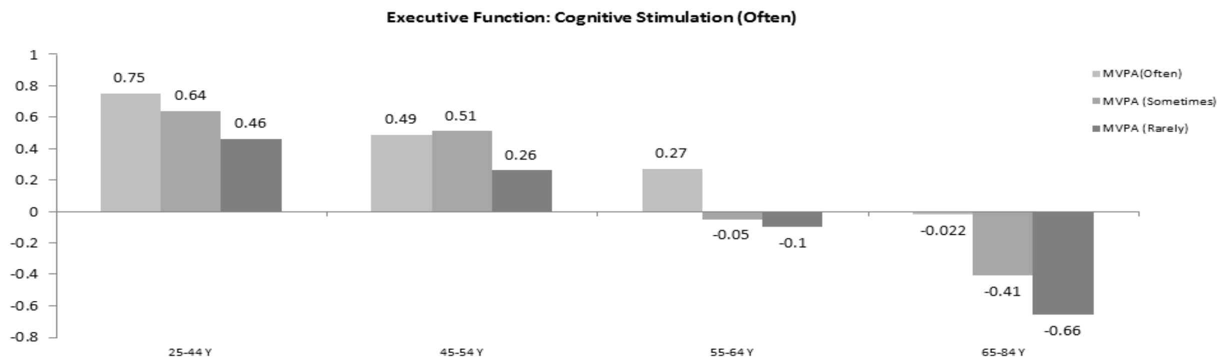
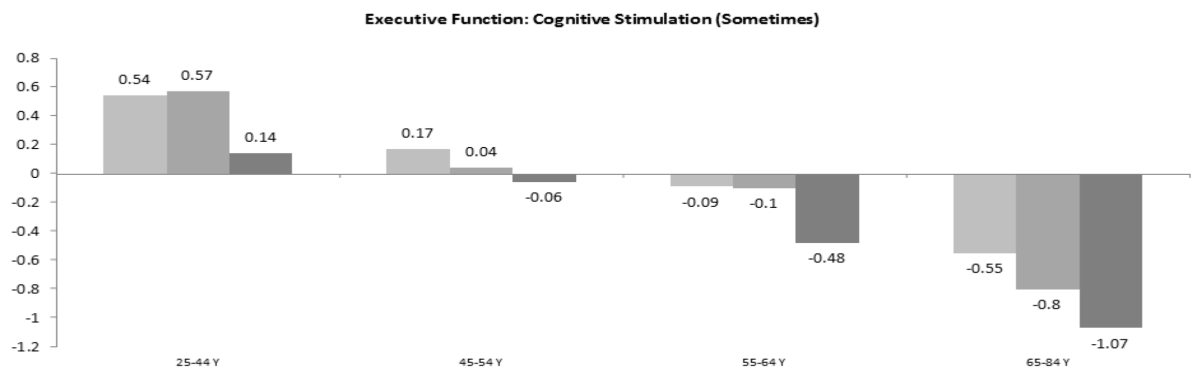


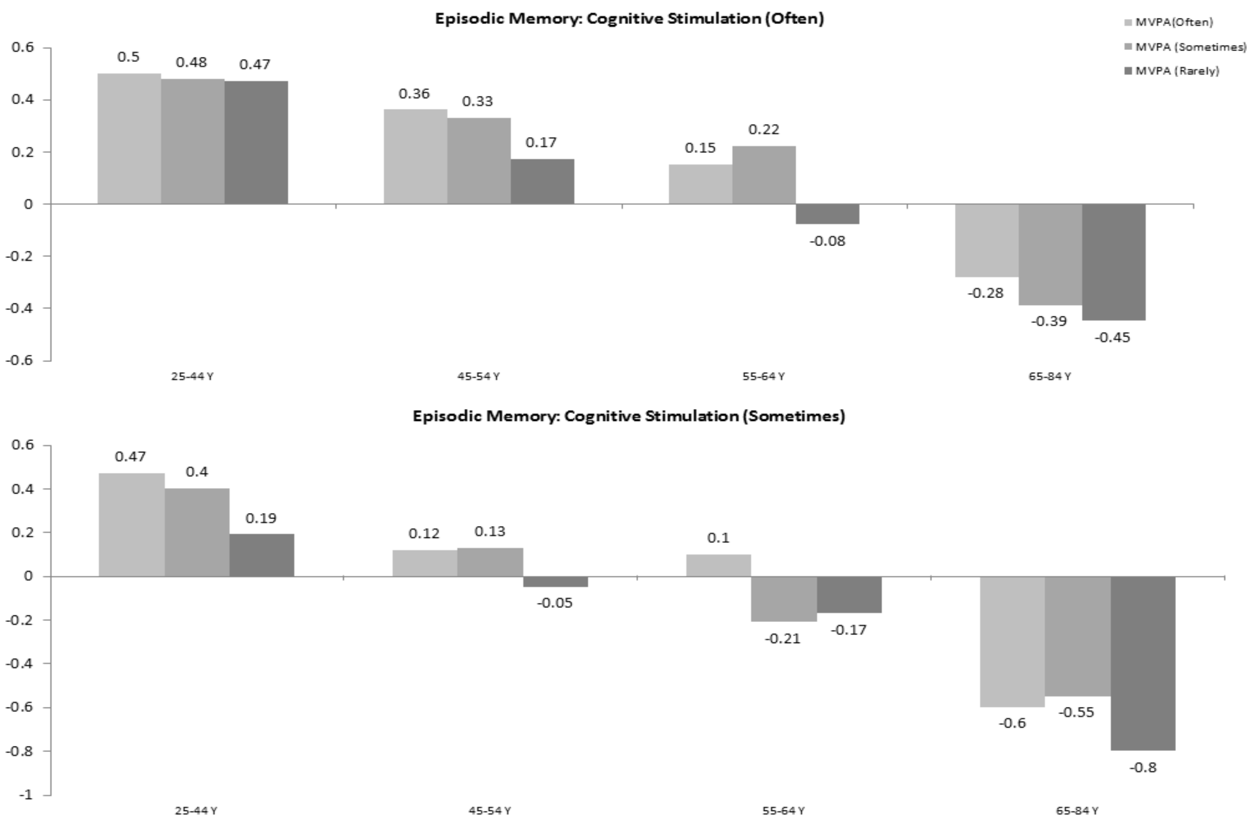
Figure 5-3: Cognitive stimulation frequency and cognitive function scores at different levels of MVPA.





Significant Differences: Cognitive Stimulation Regularly: 25-44 years: MVPA(often) vs. MVPA(rarely) p=0.0030; MVPA(sometimes) vs. MVPA(rarely) p=0.001. 45-54 years: MVPA(often) vs. MVPA(rarely) p=0.0014; MVPA(sometimes) vs. MVPA(rarely) p=0.0131. 55-64 years: MVPA(often) vs. MVPA(rarely) p<0.0001; MVPA(often) vs. MVPA(sometimes) p=0.0037. 65-84 years: MVPA(often) vs. MVPA(rarely) p<0.0001; MVPA(sometimes) vs. MVPA(rarely) p=0.0117. Cognitive Stimulation Sometimes: 25-44 years: MVPA(often) vs. MVPA(rarely) p=<0.0001; MVPA(sometimes) vs. MVPA(rarely) p=0.0052. 45-54 years: MVPA(often) vs. MVPA(rarely) p=0.0406; 55-64 years: MVPA(often) vs. MVPA(rarely) p=0.0024; MVPA(sometimes) vs. MVPA(rarely) p=0.0444. 65-84 years: MVPA(often) vs. MVPA(rarely) p=0.0092.
Effect size (ω^2; 95% Confidence Interval): 0.22; 0.20, 0.24).

Figure 5-4: Cognitive stimulation frequency and executive function scores at different levels of MVPA and different age groups.



Significant Differences: Cognitive Stimulation Regularly: 45-54 years: MVPA(often) vs. MVPA(rarely) p=0.0161; MVPA(sometimes) vs. MVPA(rarely) p=0.0131. 55-64 years: MVPA(often) vs. MVPA(rarely) p=0.0033; MVPA(sometimes) vs. MVPA(rarely) p=0.0100. 65-84 years: MVPA(often) vs. MVPA(rarely) p<0.0001 p=0.0253. Cognitive Stimulation Sometimes: 25-44 years: MVPA(often) vs. MVPA(rarely) p=0.0116; MVPA(sometimes) vs. MVPA(rarely) p=0.0052. 55-64 years: MVPA(often) vs. MVPA(rarely) p=0.0443.
Effect size (ω^2; 95% Confidence Interval): 0.11; 0.10, 0.13).

Figure 5-5: Cognitive stimulation frequency and episodic memory scores at different levels of MVPA and different age groups.

CHAPTER 6: GENERAL DISCUSSION

There are several important reasons for the increasing relevance of studying, understanding and working to preserve cognitive health. A hundred years ago, the leading causes of death were infectious diseases, with approximately 40% of people unable to survive beyond childhood (Fogel, 2005). However, with access to clean drinking water, and improvements in the practices targeting both prevention and treatment of infectious diseases, the leading causes of death have been dramatically altered. Today, people are living longer, and in developed regions, there has been a marked shift towards more age-related causes of death. In the past several decades, brain illnesses, dementias in particular, have begun to increase as the leading causes of mortality (Steenland et al., 2009). Indeed, the prevalence of cognitive decline and dementia is expected to rise dramatically over the coming decades due to demographic changes and increasing longevity (Moore, 2007). At the present time, there is a much larger inventory of treatment strategies for cardiovascular conditions than there are for cognitive decline.

Levels of physical activity in all facets of life (i.e. work, leisure/recreational, transportation) have declined over the past century (Church et al., 2011; Mirowsky & Ross, 2010; Wyatt & Hecker, 2006). Along with these decreasing levels of physical activity, simultaneous decreases in the consumption of fruits and vegetables and increases in food intake and the prevalence obesity have been observed (Kessler, 2009; Cook & Deponte, 2008). As well, a great number of individuals spend many of their early adult and middle-age years (prior to reaching old age) living with severe problems controlling their blood glucose levels, cholesterol and blood pressure (Bray & Bellanger, 2006; Centers for Disease Control and Prevention, 2010; Duncan et al., 2004; Ford et al., 2004; Mensah et al., 2004). On a population level, medical interventions have not been able and probably will not be able to eliminate the adverse physiological consequences of physical inactivity throughout the lifespan; and these accumulating adverse physiological effects will eventually contribute to the degradation of cognitive performance (Grodstein et al., 2001; Morley, 2004; Cournot et al., 2006; Sabia et al., 2009). Thus, identifying effective strategies for preservation of cognitive health in older age are important. Therefore, the four projects composing this dissertation are modeled in such a way that the existing inter-relationships between cognitive function, physical activity and other lifestyle and health variables can be evaluated at various points during the lifespan. This model insinuates that at every stage of life, cognitive health is determined by complex interactions between physical activity, lifestyle factors, anthropometry, and age.

This project explored the following lifestyle variables: sedentary time, daily fruit and vegetable consumption, the number of medication used, and engagement in cognitively stimulating activities; BMI and WHR were the anthropometric measures used; finally, age groups were categorized as younger versus older and as younger, middle aged and older adulthood (**Figure 1**). The conceptual model that was implemented in this project informs us of the existing inter-relationships between various lifestyle variables and cognitive function. What it does not inform us of is the factors that might contribute to behavior change in the population. The next logical step would be to implement or develop a model that does.

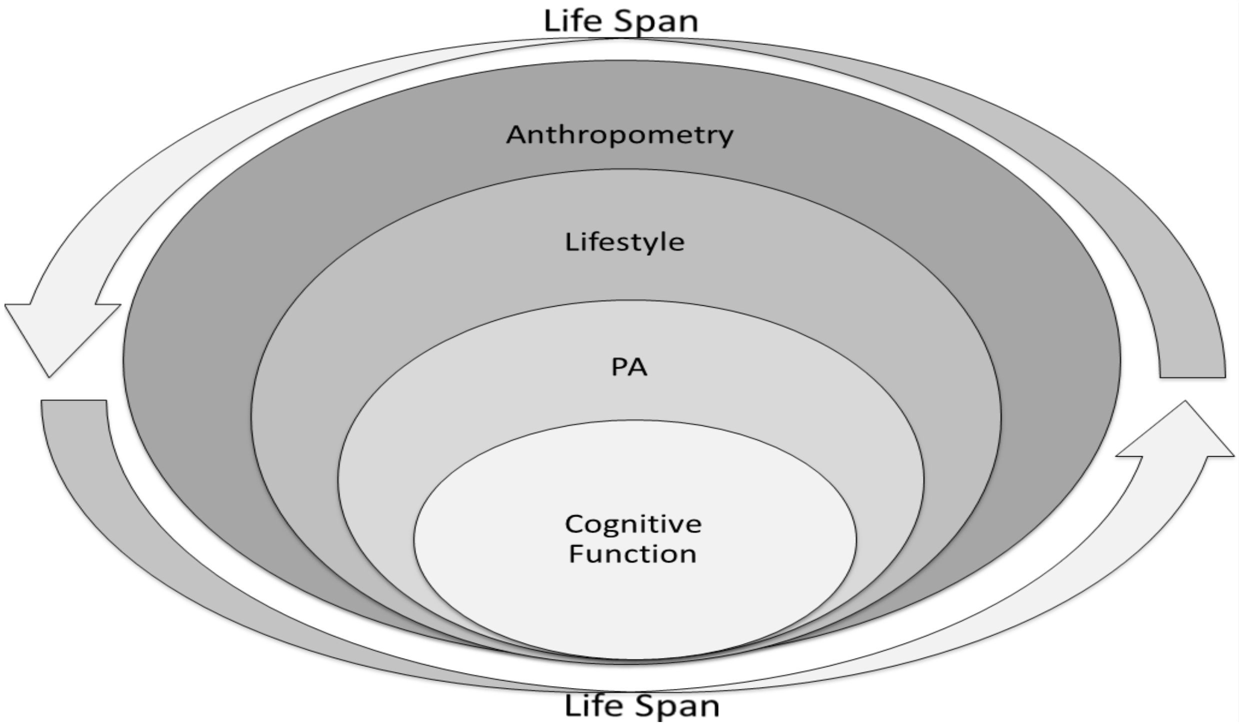


Figure 6-1: General theoretical model illustrating the potential relationships between lifestyle, Anthropometry, physical activity and cognitive health, across the lifespan.

Summary of Key Findings

The first study explored the inter-relationships between physical activity, sedentary time, obesity, and cognitive function in younger and older Canadian adults using data from the 2012 annual component of the Canadian Community Health Survey (CCHS); including only respondents 30 years of age and older with complete data for all study variables. The findings of this study indicate that lower levels of physical activity, along with higher BMIs and higher sedentary times contribute to poor cognitive functioning scores; a relationship that was found to become more pronounced with age.

Study two, using the same data set as study one, evaluated the associations between physical activity, daily fruit and vegetable consumption, obesity, and cognitive function in younger and older Canadian adults. The results of this study indicate that lower levels of physical activity, along with lower daily fruit and vegetable consumption and higher BMI, contribute to poorer cognitive function scores.

Study three examined the relationships between moderate to vigorous physical activity (MVPA) engagement frequency, obesity, number of medications used (for type II diabetes, high blood pressure, and high cholesterol), and cognitive function in individuals between the ages of 25-84 years. This study used data from the Midlife in the U.S. Survey (MIDUS), which evaluates health and well-being as people age from early adulthood into midlife and old age. The findings of this study indicate that regular engagement in MVPA may offer some protection against, or at the very least, slow the rate of cognitive decline. However, as people age, and risk factors accumulate, cognitive function worsens on both episodic memory and executive function measures.

Last, study four, using the same data set as study three, investigated the inter-relationships between MVPA engagement frequency, obesity, cognitive stimulation (reading, attending lectures/courses, playing card games, playing word games), and cognitive function in individuals between the ages of 25-84 years. The findings of this study indicate that regular engagement in MVPA and cognitively stimulating activities contribute to the preservation of cognitive functions. This relationship persists with age and was observed on both measures of episodic memory and executive functions. Obesity did not influence this relationship in this study.

Interestingly, no sex differences were found in any of the performed studies. This was surprising and there are no clear explanations for this finding. It may have been the result of the self-report nature of the datasets that were used or due to the unique makeup of the samples in these studies (e.g., they were healthier and more highly educated sample then previous samples). Additionally, the lack of sex differences may be because both younger and older adults were studied, and perhaps when looking across the life span sex is not the most important variable that contributes to differences in cognitive performance and physical activity, lifestyle variables, education, and anthropometrics all play a bigger role. However, these explanations are entirely speculative and would need to be evaluated in future research.

Public Health Implications

The purpose of this dissertation was to develop a better understanding of the factors that may impact the cognitive ageing process across the lifespan; the decline which occurs in various cognitive domains from early adulthood to old age. The existing literature has mainly focused on older adults, a population that is known to be affected by dementia; however, cognitive decline can develop over years or decades prior to symptom manifestation (Nelson et al., 2009). Therefore, it is pertinent that we develop a better understanding of the lifelong behavioral factors that may contribute to cognitive decline in late life and we believe that this can only be effectively achieved by implementing a life-span approach where various behavioral risk factors are evaluated prior to a diagnosis of dementia.

It appears that increasing age is greatly accompanied by an accumulation of poor lifestyle practices. As people age, they tend to exercise their minds and bodies less, engage in sedentary activities such as television watching, and consume fewer daily servings of fruits and vegetables (Brownson et al., 2005; Stamatakis et al., 2007; Juneau & Potvin, 2010), all of which may contribute to weight gain and the development of chronic conditions. All of these negative behaviors, in turn, either individually or collectively, may contribute to the increasing prevalence of cognitive impairment (Abraham et al., 2007; Luchsinger et al., 2005).

Over the past few decades, the way in which we live our daily lives has changed dramatically. Technological advances, societal influences and environmental attributes have significantly influenced the way we spend our leisure, work and travel time, and how we live our lives at home and in our communities, resulting in substantial proportions of the day spent in sedentary pursuits, or sitting (Church et al., 2011; Juneau & Potvin, 2010). However, the findings of this dissertation indicate that maintaining a physically active lifestyle at every stage of life, might contribute to the preservation of cognitive functions in old age.

Physical activity plays an important role in reducing vascular risk factors (Kumari & Heese, 2010; Joyner & Green, 2009); thus, reducing the need for medications, which negatively impact cognitive function (a relationship that is indicated by our findings). In addition, research findings indicate that individuals who exercised 3 or more times per week had a higher probability of being dementia-free than those who exercised fewer than 3 times per week. This suggests an inverse relationship between levels of activity and risk of cognitive decline (Laurin et al., 2001; Middleton et al., 2008). The cognitive benefits of physical activity have been observed in laboratory animals and older adults; however, more research needs to be done in younger adult populations in order to determine if there is a cumulative effect of physical activity on cognition over time. Perhaps, the earlier in their lifecycle an individual becomes physically active, maintains a healthy body weight (normal weight to overweight range) and leads a healthy lifestyle (low sedentary time, high daily intake of fruits and vegetables), the greater their brain reserve will be when they reach old age, and their risk of developing cognitive decline may be alleviated

As well, along with leading a physically active lifestyle, individuals also need to ensure that they maintain a mentally stimulating one. Physical activity increases brain reserve by increasing blood flow, the number of existing capillaries and neurons and therefore reduces volumetric shrinkages that occur with age. Mentally stimulating activities such as reading, attending lectures/courses, playing card games and word games, on the other hand, may contribute to an increase in cognitive reserve. Cognitive reserve refers to the ability of the brain to tolerate the age-related changes and disease related pathology in the brain without developing clinical symptoms or signs of disease (Kramer et al., 2004). It is known that higher levels of education and occupational complexity increase cognitive reserve but our findings indicate that regular engagement in cognitively stimulating leisure activities might offer protection against cognitive decline.

Due to the ageing of the world's population, dementia prevalence will continue to increase. Effective strategies to prevent cognitive decline are imperative to face the oncoming epidemic of dementia and cognitive diseases. Merely delaying the onset of dementia by as little as a year, could conceivably alleviate social and economic burdens associated with the disease. Lifestyle modifications, such as adhering to a healthy lifestyle including a diet that is rich in essential nutrients, regular exercise engagement, an adequate cardiovascular profile as well as challenging the brain with new information and new experiences seem to all be effective ways by which to preserve cognitive function and delay cognitive decline. As well, the findings of this dissertation also reinforce that cognitive decline is a complicated matter and needs to be studied as such.

Strengths and Limitations

The use of large Canadian and American datasets focused on variables that influence health and well-being as people age from early adulthood to old age, to explore the inter-relationships of interest represents one of the strengths of this project. The exploration of cognitive performance at various age-groups ranging from early adulthood to old age is one of the key strengths of this project. Dementia is a condition that develops gradually and decline may be occurring years or even decades prior to symptom manifestation. Therefore, having a clearer picture of which behaviors across the lifespan may be associated with cognitive performance might allow for earlier intervention and thus delay of disease onset or even disease prevention.

As well, the evaluation of the relationships between various lifestyle behavioral clusters (physical activity, a wide array of lifestyle and health indicators, anthropometry) and cognitive performance across the adult life-span all represent the strengths of this project.

This project is not without its limitations. First, the cross-sectional nature of the CCHS data prohibits the inference of causality, and only allows us to speculate on the existence of the various associations that exist between variables. Second, the reliance on self-reported measures of physical activity and anthropometry from both the CCHS and MIDUS datasets may have resulted in overestimations of physical activity and underestimations of anthropometry. Third, because cognitive measures were only added in the second wave of MIDUS, although differences between MIDUS I sample characteristics and MIDUS II sample characteristics were studied, longitudinal analyses could not be performed. The impact of these limitations on the overall findings from this dissertation is an important area for future work.

Future Directions

It is hoped that the findings contained within this dissertation will set the stage for future research, both by building on the current findings as well as exploring new questions which might now be generated. First and foremost, the opinion that dementia is a concern of the old, is a notion that needs to change. Instead, it needs to be perceived as a condition that develops over many years or decades prior to the manifestation of symptoms. Therefore, cognitive function needs to be studied across the lifespan in individuals of all ages so that we might be able to pinpoint the critical points in the life cycle during which cognitive performance is impacted. More longitudinal studies spanning early adulthood to old age are needed, including larger sample sizes and ideally followed for longer time frames. Future research should also include objective measures of overweight/obesity status and physical activity, with multiple measures of exposures in order to assess changes across time, as well as both survey and neuro-imaging measures of cognitive function. While the implementation of survey based measures allows for larger sample sizes (and thus more data) and are excellent for longitudinal studies and for tracking change; these tests only provide a snapshot of the current state of one's functioning (Cullen et al., 2007). On the other hand, the advantages of neuro-imaging techniques are clear: they allow for early detection of cognitive decline and they are able to differentiate between the different types of dementia (Cullen et al., 2007). Therefore, a combination of both survey-based and neuroimaging measures will contribute to a more conclusive result.

Additionally, the development of interventions that decrease the risk of cognitive decline is critical. These interventions must include adults of all ages, young and old, in order to determine whether leading a physically active lifestyle along with eating a healthy diet, reducing sedentary time, keeping a sharp mind, maintaining a healthy body weight and so on contribute to the preservation of cognitive performance. These interventions must be comprehensive and consider a large number of variables at one time. Cognitive decline is a complicated phenomenon that occurs due to malfunctions that may occur via many different pathways including inactive lifestyle, consumption of medications, genetics or some combination of all of the above; therefore variables cannot be studied in isolation or individually.

Finally, theory and theoretical constructs should be explored and potentially implemented in future interventions aimed at preserving cognitive function in order to influence behavior modification. Theoretical principles should inform and guide the design and development of interventions for encouraging the engagement in any behavior, including mind-body exercise for several reasons (Glanz & Bishop, 2010). First, they indicate which variables are important, and which might exhibit a certain effect from an intervention. As well, from a more theoretical perspective, practically applying theories is important for testing their effectiveness in real world settings (Glanz & Bishop, 2010).

Conclusion

This work provides new insight into the lifestyle factors as well as the important inter-relationships that contribute to the maintenance of cognitive integrity throughout the adult lifespan. It also contributes to a better understanding of the means by which to delay cognitive decline, which might help in identifying key opportunities for early intervention efforts within asymptomatic individuals in order to preserve cognitive function and delay cognitive decline. Thus, modifying perceptions that cognitive decline is a concern of the old, as well as informing the public of the significance of adopting and leading physically and mentally healthy lifestyles at every age, is of the utmost importance in the pursuit for the preservation of cognitive function and the slowing of the progression of cognitive decline.

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APPENDIX A

Canadian Community Health Survey (CCHS) Variables

Age Question: What is your age?

12 To 14 Years
15 To 17 Years
18 To 19 Years
20 To 24 Years
25 To 29 Years
30 To 34 Years
35 To 39 Years
40 To 44 Years
45 To 49 Years
50 To 54 Years
55 To 59 Years
60 To 64 Years
65 To 69 Years
70 To 74 Years
75 To 79 Years
80 Years Or Older

Sex - 1 Male 2 Female

Concept: Marital Status
Question: What is your marital status? Are you married, living common-law, widowed, separated, divorced, or single, never married?
Married
Common-Law
Widowed / Separated / Divorced
Single, Never Married
Not Stated

Concept BMI class
Underweight 1
Normal Weight 2
Overweight 3
Obese 4

Concept Has high blood pressure
Question Do you have high blood pressure? (diagnosed by a health professional and are expected to last or have already lasted 6 months or more)
1 Yes 2 No

Concept Ever diagnosed with high blood pressure
Question Have you ever been diagnosed with high blood pressure?
1 Yes 2 No
Concept Has diabetes
Question (diagnosed by a health professional 6 months or more.) Do you have diabetes?
1 Yes 2 No

Concept Has a mood disorder
Question (conditions diagnosed by a health professional and that are expected to last or have already lasted 6 months or more. Do you have a mood disorder such as depression, bipolar disorder, mania or dysthymia?
1 Yes 2 No

1 Yes (Or Sometimes) 2 No

Concept Daily Consumption - Total Fruits And Vegetables
Less Than 5 Times / Servings Per Day 1
5 To 10 Times / Servings Per Day 2
More Than 10 Times / Servings Per Day 3

Concept Leisure physical activity index
Active 1
Moderately Active 2
Inactive 3

Concept Type of smoker
Question At the present time, do you smoke cigarettes daily, occasionally or not at all?
Daily 1
Occasionally 2
Not At All 3

Concept Ever Smoked Cigarettes Daily
Question Have you Ever Smoked Cigarettes Daily?
1 Yes 2 No

Concept: Highest level of education
Less Than Secondary School Graduation 1
Sec. School. Gra,,, No Post-Sec. 2
Some Post-Secondary Education 3
Post-Sec Cert./Dip Or Univ. Deg 4

Concept: Cognition problems (cognitive attribute of health utilities index)
Cognition Attribute - Level 1
Cognition Attribute - Level 2
Cognition Attribute - Level 3
Cognition Attribute - Level 4
Cognition Attribute - Level 5
Cognition Attribute - Level 6

APPENDIX B

Midlife in the US (MIDUS) Variables

Respondent's Year of Birth: Range Of Valid Values: 1920 – 1975

Gender of Respondent:
1 Male 2 Female

Education Categories
1 Some Grade School To Some High School
2 Ged To Graduated High School
3 Some College (No Bachelors Degree)
4 Grad College To Doctorate Or Professional Degree

High Blood Pressure
Question: In the past twelve months, have you experienced or been treated for any of the following – High Blood Pressure Or Hypertension?
1 Yes 2 No

Diabetes Or High Blood Sugar
Question: In the past twelve months, have you experienced or been treated for any of the following -
Diabetes Or High Blood Sugar?
1 Yes 2 No

Rx For Hypertension
Question: During the past 30 days have you taken prescription medicine for any of the following conditions - Hypertension?
1 Yes 2 No

Rx For Diabetes
Question: During the past 30 days have you taken prescription medicine for any of the following conditions - Diabetes?
1 Yes 2 No

Rx For High Cholesterol
Question: During the past 30 days have you taken prescription medicine for any of the following conditions - High Cholesterol?
1 Yes 2 No

Summer Vigorous Activity
Question: During the summer, how often do you engage in VIGOROUS physical activity (for example, running or lifting heavy objects) long enough to work up a sweat?
1 Several Times A Week Or More
2 About Once A Week
3 Several Times A Month
4 About Once A Month
5 Less Than Once A Month
6 Never

Summer Moderate Phy Activity
Question: During the summer, how often do you engage in MODERATE physical activity (for example, bowling or using a vacuum cleaner)?
1 Several Times A Week Or More
2 About Once A Week
3 Several Times A Month
4 About Once A Month
5 Less Than Once A Month
6 Never

Winter Moderate Phy Activity
Question: What about during the winter -- how often do you engage in MODERATE physical activity?
1 Several Times A Week Or More
2 About Once A Week
3 Several Times A Month
4 About Once A Month
5 Less Than Once A Month
6 Never

Times/Month Moderate Activity
Range of valid values: 0 – 14
Mean: 9.345±5.122

Weight In Pounds
Question: How much do you currently weigh?
Range of valid values: 63 – 415
Mean: 172.033±39.487

Body Mass Index
Range of valid values: 9 – 64
Mean: 26.665±5.292

High Blood Pressure Ever Diagnosed
Question: Has a doctor ever told you that you have or had high blood pressure?
1 yes
2 no

Ever Taken High Blood Pressure Medicine
Question: Have you ever taken medicine prescribed by a doctor for your high blood pressure?
1 yes
2 no

Now Taking High Blood Pressure Medicine
Question: Are you CURRENTLY taking any prescription medications for your high blood pressure?

1 yes
2 no

Ever Smoked Cigarettes Regularly
Question: Have you ever smoked cigarettes regularly -- that is, at least a few cigarettes every day?
1 yes
2 no

Now Smoke Cigarettes Regularly
Question: Do you smoke cigarettes regularly now?
1 yes
2 no

High Blood Press/Hypertensn Ever (12 Mo)
Question: In the past twelve months, have you experienced or been treated for any of the following – High Blood Pressure Or Hypertension?
1 Yes
2 No

Diabetes/High Blood Sugar Ever (12 Mo)
Question: In the past twelve months, have you experienced or been treated for any of the following -
Diabetes Or High Blood Sugar?
1 Yes
2 No

Rx Hypertension Ever
Question: During the past 30 days have you taken prescription medicine for any of the following conditions - Hypertension?
1 Yes
2 No

Rx Diabetes Ever
Question: During the past 30 days have you taken prescription medicine for any of the following conditions - Diabetes?
1 Yes
2 No

Rx Cholesterol Ever
Question: During the past 30 days have you taken prescription medicine for any of the following conditions - High Cholesterol?
1 Yes
2 No

Do Word Games Frequency

Question: How often do you...do word games such as crossword puzzles or scrabble?
1 Daily
2 Several Times A Week
3 Once A Week
4 Several Times A Month
5 Once A Month
6 Never

Play Cards/Other Games Frequency
Question: How often do you...play cards or other games such as bridge or chess?
1 Daily
2 Several Times A Week
3 Once A Week
4 Several Times A Month
5 Once A Month
6 Never

Attend Lectures/Courses Frequency
Question: How often do you...Attend Educational Lectures or Courses?
1 Daily
2 Several Times A Week
3 Once A Week
4 Several Times A Month
5 Once A Month
6 Never

Waist Around Navel (Inches)
Pre-question: The next questions are about body measurements. We have enclosed a tape measure to help you. It is yours to keep. The information will be more accurate if you follow these suggestions: Make
measurements while standing. Avoid measuring over clothing (even thin clothing can add a 1/4 inch). Try to record answers to the nearest quarter (1/4) inch.
Question: What is your waist size--that is, how many inches around is your waist? Please measure at the level of your navel.
Range: 18-65
Mean: 37.282±5.897

Hips At Widest Point (Inches)
Question: What is your hip size--that is, how many inches do your hips measure at the widest point? Measure at the widest point between your waist and your thighs.
Range: 15-72
Mean: 41.087±5.392

Waist-To-Hip Ratio
Range: 0.5-1.617
Mean: 0.903±0.104

Weight Current (Pounds)
Question: How much do you currently weigh?
Range: 85-450
Mean: 178.428±42.155

APPENDIX C

Additional Information Regarding the Statistical Models

In Studies 1 & 2

Study 1:

The SURVEYREG Procedure

Regression Analysis for Dependent Variable hui_cog

Data Summary

Number of Observations	2310
Sum of Weights	631156.1
Weighted Mean of hui_cog	1.74560
Weighted Sum of hui_cog	1101749.2

Fit Statistics

R-square	0.2059
Root MSE	1.0362
Denominator DF	2309

Class Level Information

CLASS Variable	Levels	Values
age_cat	2	1 2
bmi	3	2 3 4
pai	3	1 2 3
ST	3	1 2 3

Tests of Model Effects

Effect	Num DF	F Value	Pr > F
Model	181	11414.4	<.0001
Intercept	1	23.38	<.0001
age_cat	1	0.96	0.3275
bmi	2	1.83	0.1607
pai	2	3.35	0.0023
ST	2	2.43	0.0097
age_cat*bmi	2	2.01	0.1342
age_cat*pai	2	0.37	0.6909

Tests of Model Effects

Effect	Num DF	F Value	Pr > F
age_cat*ST	2	1.77	0.0685
bmi*pai	4	0.06	0.9927
bmi*ST	4	1.55	0.0651
pai*ST	4	3.04	<.0001
age*bmi*pai	4	1.38	0.1932
age_cat*bmi*ST	4	2.56	0.0003
age_cat*pai*ST	4	4.18	<.0001
age_cat*bmi*pai*ST	16	2.71	<.0001

After finding a significant relationship between age*bmi*pai*ST; analyses were further stratified by age.

Younger Adults

Data Summary

Number of Observations	1215
Sum of Weights	425539.1
Weighted Mean of hui_cog	1.68413
Weighted Sum of hui_cog	716663.1

Fit Statistics

R-square	0.2100
Root MSE	1.0015
Denominator DF	1214

Class Level Information

CLASS Variable	Levels	Values
bmi	3	2 3 4
pai	3	1 2 3
ST	3	1 2 3

Tests of Model Effects

Effect	Num DF	F Value	Pr > F
Model	81	9.55	<.0001
Intercept	1	2014.60	<.0001
bmi	2	0.58	0.5593
pai	2	5.79	0.0031
ST	2	1.96	0.0403
bmi*pai	4	3.52	0.0072
bmi*ST	4	2.70	0.0002
pai*ST	4	4.62	<.0001
bmi*pai*ST	8	3.68	<.0001

Older Adults

Data Summary

Number of Observations	1095
Sum of Weights	205617.0
Weighted Mean of hui_cog	1.87283
Weighted Sum of hui_cog	385086.0

Fit Statistics

R-square	0.1645
Root MSE	1.1105
Denominator DF	1094

Class Level Information

CLASS Variable	Levels	Values
bmi	3	2 3 4
pai	3	1 2 3
ST	3	1 2 3

Tests of Model Effects

Effect	Num DF	F Value	Pr > F
Model	81	10.20	<.0001
Intercept	1	2024.22	<.0001
bmi	2	2.04	0.1303
pai	2	3.44	0.0097
ST	2	1.71	0.0815
bmi*pai	4	3.20	0.0127
bmi*ST	4	1.90	0.0128
pai*ST	4	3.10	<.0001
bmi*pai*ST	8	2.09	0.0003

The means for the figures 1 and 2 were obtained via Proc survey reg procedure in SAS, using the LSMEANS options.

Study 2:

The SURVEYREG Procedure

Regression Analysis for Dependent Variable hui_cog

Data Summary

Number of Observations	2130
Sum of Weights	598552.2
Weighted Mean of hui_cog	1.71955
Weighted Sum of hui_cog	1029240.5

Fit Statistics

R-square	0.1859
Root MSE	1.0362
Denominator DF	2129

Class Level Information

CLASS Variable	Levels	Values
age_cat	2	1 2

Class Level Information

CLASS Variable	Levels	Values
bmi	3	2 3 4
pai	3	1 2 3
education	4	1 2 3 4
fvtot	3	1 2 3

Tests of Model Effects

Effect	Num DF	F Value	Pr > F
Model	129	2368529	<.0001
Intercept	1	2175.39	<.0001
age_cat	1	10.10	0.0015
bmi	2	17.61	<.0001
pai	2	18.42	<.0001
education	3	8.34	<.0001
fvtot	2	12.21	<.0001
age_cat*bmi	2	0.18	0.8351
age_cat*pai	2	3.05	0.0474
age_cat*education	3	2.30	0.0753
age_cat*fvtot	2	3.74	0.0239
bmi*pai	4	3.38	0.0091
bmi*education	6	7.67	<.0001
bmi*fvtot	4	4.68	0.0009
pai*education	6	2.44	0.0236
pai*fvtot	4	2.16	0.0711
age_cat*bmi*education	6	1.35	0.2305
age_cat*pai*education	6	3.14	0.0046
age_cat*education*fvtot	11	8.66	<.0001
bmi*pai*education	12	6.82	<.0001
age_cat*bmi*pai	4	15.88	<.0001

Tests of Model Effects

Effect	Num DF	F Value	Pr > F
age_cat*bmi*fvtot	4	1.61	0.1692
age_cat*pai*fvtot	4	6.08	<.0001
age_cat*bmi*pai*fvtot	15	6.28	<.0001
age_cat*bmi*pai*education*fvtot	62	5.45	<.0001

After finding a significant relationship between age*bmi*pai*fvtot and age*bmi*pai*fvtot*ecucation; analyses were further stratified by age.

Younger Adults

Data Summary

Number of Observations	1150
Sum of Weights	411837.4
Weighted Mean of hui_cog	1.66103
Weighted Sum of hui_cog	684074.1

Fit Statistics

R-square	0.1870
Root MSE	1.0041
Denominator DF	1149

Class Level Information

CLASS Variable	Levels	Values
bmi	3	2 3 4
pai	3	1 2 3
education	4	1 2 3 4
fvtot	3	1 2 3

Tests of Model Effects

Effect	Num DF	F Value	Pr > F
Model	63	17.54	<.0001

Tests of Model Effects

Effect	Num DF	F Value	Pr > F
Intercept	1	1616.55	<.0001
bmi	2	11.71	<.0001
pai	2	12.85	<.0001
education	3	8.24	<.0001
fvtot	2	16.38	<.0001
bmi*pai	4	7.71	<.0001
bmi*education	6	3.20	0.0040
bmi*fvtot	4	3.77	0.0047
pai*education	6	1.65	0.1295
pai*fvtot	4	8.47	<.0001
bmi*pai*education	12	3.01	0.0004
bmi*pai*fvtot	7	2.59	0.0118
bmi*pai*education*fvtot	29	5.63	<.0001

Older Adults

Data Summary

Number of Observations	980
Sum of Weights	186714.7
Weighted Mean of hui_cog	1.84863
Weighted Sum of hui_cog	345166.3

Fit Statistics

R-square	0.1689
Root MSE	1.1008
Denominator DF	979

Class Level Information

CLASS Variable	Levels	Values

Class Level Information

CLASS Variable	Levels	Values
bmi	3	2 3 4
pai	3	1 2 3
education	4	1 2 3 4
fvtot	3	1 2 3

Tests of Model Effects

Effect	Num DF	F Value	Pr > F
Model	64	16.07	<.0001
Intercept	1	931.85	<.0001
bmi	2	6.45	0.0017
pai	2	0.87	0.4196
education	3	5.26	0.0013
fvtot	2	4.28	0.0141
bmi*pai	4	6.54	<.0001
bmi*education	6	4.74	<.0001
bmi*fvtot	4	3.44	0.0083
pai*education	6	4.23	0.0003
pai*fvtot	4	5.46	0.0002
bmi*pai*education	12	9.80	<.0001
bmi*pai*fvtot	8	3.17	0.0015
bmi*pai*education*fvtot	32	7.59	<.0001

The means for the figures 1, 2 and 3 were obtained via Proc survey reg procedure in SAS, using the LSMEANS options.

APPENDIX D

Additional Information Regarding the Statistical Models

In Studies 3 & 4

Study 3: Episodic Memory

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	139	714.047663	5.137034	6.16	<u><.0001</u>
Error	3346	2788.994504	0.833531		
Corrected Total	3485	3503.042167			

R-Square	Coeff Var	Root MSE	episodic_memory Mean
<u>0.203836</u>	3937.261	0.912979	0.023188

Source	DF	Type III SS	Mean Square	F Value	Pr > F
Whr	3	72.4646375	24.1548792	28.98	<.0001
Age	3	83.7849990	27.9283330	33.51	<.0001
Meds	2	4.2654145	2.1327073	2.56	0.0776
Mvpa	2	6.6656476	3.3328238	4.00	0.0184
age*mvpa	6	9.5323602	1.5887267	1.91	0.0761
meds*mvpa	4	0.5068300	0.1267075	0.15	0.9622
whr*mvpa	6	8.2960041	1.3826673	1.66	0.1270
whr*meds	6	1.4153120	0.2358853	0.28	0.9452
age*meds*mvpa	18	33.3633520	1.8535196	10.22	0.0022
whr*age*meds*mvpa	89	105.2283136	1.1823406	13.42	0.0006

After a significant interaction was found between whr*age*meds*mvpa; analyses were further stratified by age.

Study 3: Executive Function

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	139	839.650026	6.040648	7.99	<u><.0001</u>
Error	3353	2534.556631	0.755907		
Corrected Total	3492	3374.206656			

R-Square	Coeff Var	Root MSE	executive_function Mean
<u>0.248844</u>	6108.037	0.869429	0.014234

Source	DF	Type III SS	Mean Square	F Value	Pr > F

R-Square Coeff Var		Root MSE	executive_function Mean		
whr	3	9.6267983	3.2089328	4.25	0.0053
age	3	101.9026966	33.9675655	44.94	<.0001
meds	2	9.5658695	4.7829348	6.33	0.0018
mvpa	2	16.6967596	8.3483798	11.04	<.0001
age*mvpa	6	7.4422289	1.2403715	1.64	0.1317
meds*mvpa	4	5.2101401	1.3025350	1.72	0.1420
whr*mvpa	6	3.4660835	0.5776806	0.76	0.5980
whr*meds	6	1.8365400	0.3060900	0.40	0.8762
age*meds*mvpa	18	19.2062064	1.0670115	5.41	0.0024
whr*age*meds*mvpa	89	68.6964664	0.7718704	14.33	<.0001

After a significant interaction was found between whr*age*meds*mvpa; analyses were further stratified by age.

The means for the figures 2-3 were obtained via Proc Proc GLM in SAS, using the LSMEANS options.

Study 4: Episodic Memory

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	23	432.349666	18.797812	21.13	<.0001
Error	3592	3195.540316	0.889627		
Corrected Total	3615	3627.889982			

R-Square	Coeff Var	Root MSE	episodic_memory Mean
0.119174	4363.574	0.943200	0.021615

Source	DF	Type III SS	Mean Square	F Value	Pr > F
mvpa	2	19.8354892	19.9177446	19.15	<.0001
cog_stim	1	17.4448382	12.4448382	11.61	<.0001
age	3	156.5165268	52.1721756	58.64	<.0001
mvpa*age	6	0.9924522	0.1654087	8.19	0.0098
cog_stim*age	3	1.0566820	0.3522273	6.40	0.0176
mvpa*cog_stim	2	0.8206186	0.4103093	7.46	0.0063
mvpa*cog_sti*age	6	4.1958438	0.6993073	13.67	0.0011

After a significant interaction was found between age*cog_stim*mvpa; analyses were further stratified by age.

Study 4: Executive Function

Source	**DF**	**Sum of Squares**	**Mean Square**	**F Value**	**Pr > F**
Model	23	780.340039	33.927828	45.05	<.0001
Error	3600	2711.245431	0.753124		
Corrected Total	3623	3491.585469			

R-Square	**Coeff Var**	**Root MSE**	**executive_function Mean**
0.223492	4409.834	0.867827	0.019679

Source	**DF**	**Type III SS**	**Mean Square**	**F Value**	**Pr > F**
mvpa	2	68.5843358	38.2921679	51.17	<.0001
cog_stim	1	38.5354243	34.5354243	45.43	<.0001
age	3	248.6557100	82.8852367	110.06	<.0001
mvpa*age	6	4.4023150	0.7337192	9.97	0.0044
cog_stim*age	3	2.6611737	0.8870579	7.35	0.0166
mvpa*cog_stim	2	0.8684397	0.4342199	7.50	0.0156
mvpa*cog_stim*age	6	3.1749155	0.5291526	15.70	0.0003

After a significant interaction was found between age*cog_stim*mvpa; analyses were further stratified by age.

The means for the figures 2-5 were obtained via Proc Proc GLM in SAS, using the LSMEANS options.