Association of Objectively Measured Physical Activity with Cognitive Function in Black and White Older Adults: Reasons for Geographic and Racial Differences in Stroke (REGARDS) study

by

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ABSTRACT

Background and purpose: Regular physical activity (PA) provides benefits for cognitive health and helps to improve or maintain quality of life among older adults. Objective PA measures have been increasingly used to overcome limitations of self-report measures. The purpose of this study was to investigate the association of objectively measured PA and sedentary time with cognitive function among older adults.

Methods: Participants were recruited from the parent REasons for Geographic and Racial Differences in Stroke (REGARDS) Study. Actical^{TM} accelerometers provided estimates of PA variables, including moderate-to-vigorous PA (MVPA), high light PA (HLPA), low light PA (LLPA) and sedentary time, for 4-7 consecutive days. Prevalence and incidence of cognitive impairment were defined by the Six-Item Screener. Letter fluency, animal fluency, word list learning and Montreal Cognitive Assessment (orientation and recall) were conducted to assess executive function and memory.

Results: Of the 7,339 participants who provided accelerometer wear data $\geq$ 4 days (70.1 ± 8.6 yr, 54.2% women, 31.7% African American), 320 participants exhibited impaired cognition. In cross-sectional analysis, participants in the highest MVPA% quartile had 39% lower odds of cognitive impairment than those in the lowest quartile (OR: 0.61, 95% C.I.: 0.39-0.95) after full adjustment. Further analysis shows most quartiles of MVPA% and HLPA% were significantly associated with executive function and memory ($P<0.01$). During 2.7 ± 0.5 years of follow-up, 3,385 participants were included in the longitudinal analysis, with 157 incident cases of cognitive impairment. After adjustments, participants in the highest MVPA% quartile had 51% lower hazards of cognitive impairment (HR: 0.49, 95% C.I.: 0.28-0.86). Additionally, MVPA% was inversely associated with change in memory z-scores ($P<0.01$), while the highest quartile of HLPA% was inversely associated with change in executive function and memory z-scores ($P<0.01$).

Conclusion: Higher levels of objectively measured MVPA% were independently associated with lower prevalence and incidence of cognitive impairment, and better memory and executive function in older adults. Higher levels of HLPA% were also independently associated with better memory

and executive function. The amount of MVPA associated with lower risk of cognitive impairment (259 min/week) is >70% higher than the minimal amount of MVPA recommended by PA guidelines.

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CHAPTER 1

A growing body of evidence indicates increasing prevalence and incidence of cognitive impairment among older adults in the United States (Thies, Bleiler, & Alzheimer's Association, 2013). A national study (Plassman et al., 2008) reported an estimated 5.4 million people in the United States age >70 years had mild cognitive impairment (MCI). Among those who completed follow-up assessments in the study, 11.7% with MCI progressed to dementia annually. The annual death rate was 8% among those with MCI. A more recent study (Hurd, Martorell, & Langa, 2013) showed the estimated prevalence of dementia among older adults in the United States in 2010 was 14.7%. The total monetary cost of dementia in 2010 was between 157 - 215 billion dollars, with approximately 11 billion dollars associated with direct medical care. Dementia represents a substantial financial burden on society, and one that is similar to heart disease and cancer. Effective prevention strategies will have significant public health implications by improving quality of life and reducing economic cost and social burden.

Regular physical activity (PA) provides benefits for cognitive health and helps to improve or maintain quality of life among older adults (Buchman et al., 2012; Liu et al., 2012; Sofi et al., 2011). Studies in humans suggest more active individuals may have reduced risks of cognitive impairment and dementia (Geda et al., 2010). Higher self-reported PA levels at early or midlife were associated with reduced risk of MCI in later life (Etgen et al., 2010; Middleton, Barnes, Lui, & Yaffe, 2010). A meta-analysis (Hamer & Chida, 2009) of 16 prospective studies using self-reported PA reported the relative risks of dementia and Alzheimer’s disease in the highest PA category compared with the lowest were reduced by 28% and 45%, respectively.

Methodological differences in PA assessment and analysis preclude comparisons among studies of the optimal pattern of PA required to reduce the risk of cognitive decline. Most previous studies were based on self-reported PA assessments (Aarsland, Sardahaee, Anderssen, Ballard, & Alzheimer's Society Systematic Review group, 2010; Angevaren, Vanhees, Nooyens, Wendel-Vos, & Verschuren, 2010; Geda et al., 2010; Hamer & Chida, 2009; Middleton et al., 2010). These measures are easy to administer and can provide information on the types of activities performed,

but may not capture activity patterns throughout the day (Davis & Fox, 2007). Some measures also include calculations to estimate energy expenditure based on the duration and frequency of reported activity participation. However, there are some disadvantages to using self-report measures such as recall bias and social desirability. In older adults in particular, self-report may also be influenced by fluctuations in health status and mood, depression, anxiety, or cognitive ability (Davis & Fox, 2007; Rikli, 2000). In addition, self-report PA measures designed for younger adults have been shown to be inaccurate when given to older adult samples, particularly underestimating the performance of light and moderate intensity activities (Washburn, Heath, & Jackson, 2000). Objective PA measures have been increasingly used to overcome limitations of self-report measures. Accelerometers, in particular, provide information on the amount, frequency, and duration of PA. Data can be obtained about daytime and nighttime activity patterns and activity intensity (including estimates of energy expenditure) as they occur in people's daily lives (Plasqui & Westerterp, 2007).

Recently, a few studies with objectively measured data in humans have reported active older adults may have lower risks of cognitive impairment and dementia. One cross-sectional study (Barnes et al., 2008) of 2735 older women showed daytime PA measured by accelerometers was associated with better cognitive function and lower odds of cognitive impairment in women >80 years old. Another study (Kerr et al., 2013) with a smaller sample of 217 older adults indicated a dose response relationship between objectively measured PA intensity and cognitive function with a stronger association existing between moderate to vigorous PA (MVPA) and cognitive function. A higher level of total daily PA, measured continuously for 10 days with accelerometers, was reported to be significantly associated with a reduced risk of Alzheimer's disease among 716 white older adults during 4 years of follow up (Buchman et al., 2012). Higher levels of aerobic fitness predicted better performance on measures of attention and executive function, whereas self-reported PA was not predictive of cognition six years later (Barnes, Yaffe, Satariano, & Tager, 2003). Recently, one study (Burzynska et al., 2014) examined the association of both accelerometer measured PA and cardiorespiratory fitness with measures of white matter integrity

in 88 healthy low-fit adults (age 60-78). The investigators concluded it is important to engage in PA of varying intensity while avoiding being sedentary for maintaining white matter integrity of the brain in older age. However, to date, there are no national-level data to examine the association between objectively measured PA and sedentary behavior and cognitive function among a diverse population of older adults.

Important differences exist in PA across different sex and race groups (Malmstrom, Wolinsky, Andresen, Miller, & Miller, 2005; Masel, Raji, & Peek, 2010), and women and blacks have been significantly understudied in terms of the association between PA and cognitive function (Bopp et al., 2006). To our knowledge, the relationship between PA and cognitive function remain robust in older adults when adjusted for different confounders, such as race, sex, education, age (Bowen, 2012; Obisesan, Umar, Paluvoi, & Gillum, 2012; Scarmeas et al., 2009). However, few investigations have explored the relationship between PA and cognitive function among the African American population. With an objective measure of PA via accelerometers, our study enabled a more detailed investigation of the dose response relationship between time spent being sedentary and various PA components and selected measures of cognitive function in a nationally representative sample of both white and black older adults.

Specific Aims.

The purpose of this study was to investigate the cross-sectional and longitudinal association of objectively measured PA and sedentary time with cognitive function among older adults defined by sex and race. This was conducted by pursuing the following specific aims:

Study 1.

Aim 1.1: To examine the **cross-sectional** relationship between objectively measured PA, including **MVPA and light PA (LPA)** and cognitive function (including global cognitive function, memory and executive function) in white and black older adults.

Aim 1.2: To examine the **cross-sectional** relationship between objectively measured **sedentary time** and cognitive function (including global cognitive function, memory and executive function) in white and black older adults.

Aim 1.3: To examine whether the cross-sectional relationship between objectively measured PA, including **MVPA and LPA**, and cognitive function is moderated by **race and sex**.

Aim 1.4: To examine whether the cross-sectional relationship between **sedentary time** and cognitive function is moderated by **race and sex**.

Study 2.

Aim 2.1: To examine the **longitudinal** relationship between objectively measured PA, including **MVPA and LPA,** and cognitive function (including global cognitive function, memory and executive function) in white and black older adults.

Aim 2.2: To examine the **longitudinal** relationship between objectively measured **sedentary time** and cognitive function (including global cognitive function, memory and executive function) in white and black older adults.

Aim 2.3: To examine whether the longitudinal relationship between objectively measured PA, including **MVPA and LPA,** and cognitive function is moderated by **race and sex**.

Aim 2.4: To examine whether the longitudinal relationship between **sedentary time** and cognitive function is moderated by **race and sex**.

Hypothesis (Null).

Study 1.

1.1: There is no significant **cross-sectional** relationship between objectively measured PA, including **MVPA and LPA,** and cognitive function (including global cognitive function, memory and executive function) in white and black older adults.

1.2: There is no significant **cross-sectional** relationship between objectively measured **sedentary time** and cognitive function (including global cognitive function, memory and executive function) in white and black older adults.

1.3: The relationship of **PA** and **prevalent cognitive impairment** is not significantly moderated by race and sex.

1.4: The relationship of **sedentary time** and **prevalent cognitive impairment** is not significantly moderated by race and sex.

Study 2.

2.1: There is no significant **longitudinal** relationship between objectively measured PA, including **MVPA and LPA,** and cognitive function (including global cognitive function, memory and executive function) in white and black older adults.

2.2: There is no significant **longitudinal** relationship between objectively measured **sedentary time** and cognitive function (including global cognitive function, memory and executive function) in white and black older adults.

2.3: The relationship of **PA** and **incident cognitive impairment** is not significantly moderated by race and sex.

2.4: The relationship of **sedentary time** and **incident cognitive impairment** is not significantly moderated by race and sex.

CHAPTER 2

REVIEW OF LITERATURE

What is Cognitive Impairment?

Prevalence and incidence of mild cognitive impairment, dementia and Alzheimer's disease.

Improvements in health care over the past 50 years have extended average life expectancy, which has resulted in a substantial increase in the numbers of individuals over 65 years of age. Cognitive impairment has become an issue in the field of public health. Generally, cognitive impairment includes mild cognitive impairment (MCI) without dementia, dementia, and Alzheimer's disease (AD). A growing body of evidence (Alzheimer's Association, 2013) has shown the global prevalence and incidence of cognitive impairment and the associated mortality. A national study (Plassman et al., 2008) reported that an estimated 5.4 million people (22.2%) age 71 years or older in the United States had MCI. Among participants who completed follow-up assessments, 11.7% with MCI progressed to dementia annually. The annual death rate was 8% among those with MCI. The prevalence of dementia among individuals aged 71 and older was 13.9%, comprising about 3.4 million individuals in the USA in 2002. According to the 2013 AD facts and figures (Alzheimer's Association, 2013), an estimated 5.2 million Americans have AD. AD is the sixth leading cause of death in the United States and the fifth leading cause of death in Americans age 65 years or older. In 2012, more than 15 million family members and other unpaid caregivers provided an estimated 17.5 billion hours of care to people with AD and other dementias, a contribution valued at more than $216 billion. Medicare payments for services to beneficiaries age 65 years and older with AD and other dementias are three times as great as payments for beneficiaries without these conditions. Total payments in 2013 for health care, long-term care, and hospice services for people age 65 years and older with dementia are $203 billion (not including the contributions of unpaid caregivers). Similarly, a recent study (Hurd et al., 2013) showed the estimated prevalence of dementia among older adults in the United States in 2010 was 14.7%. The total monetary cost of dementia in 2010 was between $157-215 billion, with approximately $11

billion associated with direct medical care. Dementia represents a substantial financial load on society, and one that is similar to heart disease and cancer. Effective prevention strategies will have significant public health implications by improving quality of life and reducing economic cost and social burden.

Cognitive decline with normal aging.

Normal aging is associated with structural and neurophysiological changes in the brain as well as a decline in cognitive function. Age has been correlated with a loss of cerebral cortical tissue and cerebrospinal fluid (CSF), most consistently in the frontal cortex and hippocampus (Jernigan et al., 2001). A longitudinal analysis of adults age 64 to 86 showed a decline over 10 years in brain volume of all regions scanned by magnetic resonance imaging (MRI). Mild cognitive impairment is associated with a unique pattern of structural vulnerability reflected in differential volume loss in specific regions, which included the ventricular CSF, frontal gray matter, and areas of the frontal and parietal lobes (Driscoll et al., 2009).

Brain tissue atrophy and neurophysiological changes occur with aging and may be related to changes in cognitive function (Gregory, Parker, & Thompson, 2012). Hippocampal volume loss in older subjects may be related to cognitive impairments. When compared to young subjects (age 20-39), Older subjects (age 60–85) demonstrated impaired memory task performance, smaller hippocampal volumes, and decreased hippocampal NAA/Cre ratios, which imply neuronal loss and/or decrease in neuronal density (Driscoll et al., 2003). Research has suggested that hippocampus undergoes structural and biochemical changes with normal aging and that these changes may represent an important component of age-related deterioration in hippocampus-dependent cognition.

The age-related changes in brain appears to be region-specific. The hippocampus has been studied intensively because of its important role in facilitating memory-related tasks. Blood flow measured by positron emission tomography increased to the medial temporal lobe, which includes the hippocampus, during episodic memory recall in middle-aged subjects (Piolino et al., 2008), and hippocampal volume was associated with performance on tests of memory (Driscoll et

al., 2003). Furthermore, prospective study with nine years of follow-up demonstrated that greater gray matter volume in the hippocampus, frontal gyrus, and supplementary motor area was associated with a lower risk of developing MCI (Erickson et al., 2010). Hippocampal atrophy, which occurs normally with aging, may be accelerated in those who progress from MCI to dementia (Eckerstrom et al., 2008). These findings suggest that interventions aimed at preventing hippocampal atrophy and neurodegeneration may prevent age-related cognitive impairments and associated structural and function brain changes.

Cognitive decline in patients with cognitive impairment.

MCI, dementia, and AD are three phases of cognition decline with aging. MCI refers to the clinical condition between normal aging and AD in which persons experience memory loss to a greater extent than one would expect for age, yet they do not meet currently accepted criteria for clinically probable AD. When these persons are observed longitudinally, they progress to clinically probable AD at a considerably accelerated rate compared with healthy age-matched individuals (Petersen et al., 2001). Gradual decline in cognitive ability is characteristic in longitudinal studies of older adults (Wilson, Beckett, Bennett, Albert, & Evans, 1999). However, differences between individual trajectories of change suggest that there was little evidence of cognitive decline during a 3.5-year period among persons who remained free of AD, and much of the age-related cognitive decline reflects the inclusion of individuals with dementia and AD. The notion that dementia is common among older individuals is further supported by neuropathological studies that reveal evidence of AD years before clinical symptoms present. Extensive AD pathology can rarely be found in individuals with no detectable symptoms. AD pathology is, however, more common in individuals with cognitive impairment who are not demented. Clinical studies of older individuals with cognitive impairment also reveal a rapid rate of conversion to AD, reaching as high as 15% per year. They almost always have the neuropathologic features of AD. MCI generally represents early-stage AD (J. C. Morris et al., 2001). Significant cognitive impairment in older people may be a transition phase between the normal aging process and AD. Not all MCI patients go on to develop AD, particularly when MCI is studied in the general population. Recognition that MCI may represent

a transition state between normal cognitive decline due to aging and dementia offers possibilities for early diagnosis and potential treatment with the aim of delaying the onset or preventing dementia (Petersen et al., 2001).

Care for cognitive impairment and possible strategies for prevention.

People with cognitive impairment and their families face significant financial impact from the cost of providing health and social care and from reduction or loss of income. Cognitive impairment also has an immense impact on the lives of the family, and particularly the person who takes the primary role in providing care. Most care is provided by family and other informal support systems in the community and most caregivers are women. However, changing population demographics may reduce the availability of informal caregivers in the future. The provision of care to a person with cognitive impairment can result in significant strain for those who provide most of that care. The stressors are physical, emotional and economic. The challenges to policy-makers and public health workers to respond to the growing numbers of people with cognitive impairment are substantial. A broad public health approach is needed to improve the care and quality of life of people with cognitive impairment and family caregivers. The aims and objectives of the approach should either be articulated in a stand-alone cognitive impairment policy or plan or be integrated into existing health, mental health or old-age policies and plans (Panza et al., 2005).

The implementation of preventive measures in cognitively healthy individuals offers the best hope against the onset of cognitive impairment. There is a large body of literature on primary prevention strategies for cognitive impairment. Modifiable risk factors are well known including smoking, hypertension, type 2 diabetes, insulin resistance, hypercholesterolemia, and obesity. Higher education, physical exercise, and mental exercise are well established as important pro-cognitive attributes and behaviors. Dietary measures, such as high intake of fish, fruit and vegetables suggest a positive role for omega-3 fatty acids, antioxidants (vitamin E and flavonoids), and B group vitamins such as folate, B6, and B12 (Daviglus et al., 2011; M. C. Morris, 2012).

Measurements of Cognitive Function

Domains of cognitive function.

Cognition is the process by which the sensory input is transformed, reduced, elaborated, stored, recovered, and used. It includes several specific cognitive functional domains, such as attention and concentration, executive functioning, memory and learning, emotional/personality functioning, etc (Stopford, Thompson, Neary, Richardson, & Snowden, 2012).

For example, executive functioning is an umbrella term for the management (regulation, control) of cognitive processes, including working memory, reasoning, task flexibility, and problem solving as well as planning and execution (Chan, Shum, Toulopoulou, & Chen, 2008). It answers the question of how or whether one will do something, involving the capacity to initiate activity and the process of self- monitoring and interpreting feedback. Executive functions include the planning and sequencing strategies that facilitate goal-directed behaviors. Assessment of executive functioning includes testing at varying levels of complexity to obtain an adequate picture of the mental flexibility of subject.

Memory is the process in which information is encoded, stored, and retrieved. Memory assessment is at the core of most neuropsychological evaluations of the older adults. A complete evaluation examines verbal memory (contextual and non- contextual) and visual memory (independent of constructional ability), and addresses acquisition, retention and recognition through somewhat independent means. The distinction between deficits in encoding and deficits in retrieval of newly-learned information can be crucial in differential diagnosis of the various dementias (Stopford et al., 2012).

Neuropsychological assessment.

Neuropsychological assessments, such as screening instruments, are routinely used to as a screener in normal population, or quantify the degree of cognitive impairment in patients with dementia and are likely to be particularly helpful early in a dementing illness, when functional and behavioral disturbances are absent (Pasquier, 1999). The value of neuropsychological measures in helping to identify early cases of dementia has been documented by cross-sectional and

longitudinal studies. Cross-sectional comparisons of patients clinically diagnosed as having MCI compared with older healthy persons who have shown that patients with MCI consistently perform worse than their comparison subjects (Panza et al., 2005).Patients with early AD are impaired on tests of memory, including tests of delayed recall, and often on tests of new learning. Deficiencies in language, executive function, and attention are also present in many patients with mild AD, and deficits in more than one cognitive domain are a better indicator of MCI than memory impairment alone. These data indicate that sensitive neuropsychological measures can help identify cases of AD at early stages. Longitudinal studies (Dartigues et al., 1997; Masur, Sliwinski, Lipton, Blau, & Crystal, 1994) of older healthy persons at high risk for developing dementia because of advanced age have shown that persons who later develop AD perform more poorly on cognitive tests at baseline compared with those who remain free of dementia. These longitudinal data indicate that neuropsychological tests may help to identify persons likely to convert to MCI or AD before they meet conventional diagnostic criteria.

For example, the Mini-Mental State Examination (MMSE) is a 10-minute measure of impaired thinking in undeveloped, uneducated, diseased, or old populations (Folstein, Folstein, & McHugh, 1975). The summed score of the individual items indicates the current severity of cognitive impairment. Deterioration in cognition is indicated by decreasing scores of repeated tests. Scores are reliable between tests and between raters and correlate with other mental tests, computerized tomography, and magnetic resonance imaging. The items of the MMSE include tests of orientation, registration, recall, calculation and attention, naming, repetition, comprehension, reading, writing and drawing. If all items are answered correctly, the score is 30. The mean score for a community-dwelling population over 65 years of age is 27, with a standard deviation of 1.71. The score is lower in those who completed comparatively fewer years of education and who have diagnosable diseases. Alzheimer's disease patients lose 3–4 points per year of illness after the onset of memory disturbance, although there is wide variability in this phenomenon (Tombaugh & McIntyre, 1992).

Alzheimer's disease and MCI cannot be diagnosed by neuropsychological tests alone, and clinical judgment is always required (Panza et al., 2005; Petersen et al., 2001). First, performance on neuropsychological tests is affected by many factors, including education, age, cultural background, and illnesses other than AD. Second, neuropsychological measures cannot fully distinguish among different types of dementia, because there is substantial overlap in neuropsychological profiles. The usefulness of any battery for identifying cases of MCI will depend on its composition, size, and supporting data. A brief battery, including measures of new learning, delayed recall, attention, and executive function, could provide valuable information for screening and diagnosis if interpreted properly (Petersen et al., 2001).

Neuroimaging.

Neuroimaging is a powerful tool for the differential diagnosis of cognitive impairment and for monitoring change. Both cross-sectional and longitudinal studies have used structural and functional modalities in the evaluation of MCI (Jack et al., 1997; Jack et al., 1999). Neuroimaging studies support the view that MCI shares features with AD, such as hippocampal atrophy, so that the presence or development of atrophy will therefore predict conversion to clinical AD. More and more studies began to concentrate on measuring rates of change on neuroimaging studies and on finding the shortest intervals necessary to demonstrate significant changes. Attributes of neuroimaging that make it superior to neuropsychological tests include increased diagnostic accuracy, freedom from ethnic/cultural bias for interpretation, independence from level or quality of education, and rater-independent objective measures of brain anatomy and function (Petersen et al., 2001). Neuroimaging with amyloid tags can potentially test hypotheses about disease pathogenesis in vivo-tasks not otherwise possible using clinical or neuropsychological assessments.

Structural neuroimaging can also identify anatomical changes specifically associated with AD. Atrophy on MRI from normal to mildly cognitively impaired to demented individuals parallels progressive neurofibrillary degeneration (Studholme, Cardenas, Maudsley, & Weiner, 2003). Longitudinal studies has shown progressive atrophy and the rates of hippocampal volume loss

increase with disease severity (Jack et al., 2000). Neuroimaging can reveal the structural and metabolic substrates of memory deficits at different stages. Functional neuroimaging may also increase diagnostic accuracy. Functional imaging may accurately identify rapid converters from MCI to AD and may predict subsequent development of dementia in normal aging or those with questionable symptoms (Petersen et al., 2000).

A main criticism of neuroimaging is the cost of measurements and operation training. To date, there have been no cost-effectiveness studies of neuroimaging as a predictor of AD, yet. In the future, enriching study populations using risk factors such as age and family history of AD, and using biomarkers such as genetic markers (e.g. Apolipoprotein E4), markers of neuronal toxicity or other markers might result in further controlled trial of time and cost savings.

Prevention and Treatment of Cognitive Impairment in Older Adults

Neural plasticity.

Previous research has indicated that PA, learning and social factors exert alterations in gene expression, giving rise to changes in patterns of neural connectivity and functionality throughout life (Burke, Hickie, Breakspear, & Gotz, 2007). These changes are achieved through mechanisms of neural plasticity, synaptogenesis, angiogenesis and possibly neurogenesis. Studies have demonstrated neurogenesis in the healthy adult human brain, in the hippocampus (Draganski et al., 2004) and in the olfactory bulb (Bedard & Parent, 2004).

Neural plasticity, synaptogenesis and neurogenesis all require parallel angiogenesis. New vessels develop in response to tissue demands, mediated principally by vascular endothelial growth factor, which responds to some local factors such as inflammation, blood pressure, oxygen saturation, lipid levels, insulin levels and tissue perfusion (Fam, Verma, Kutryk, & Stewart, 2003). Many vascular risk factors may therefore modify and promote these processes of neural plasticity, synaptogenesis, angiogenesis and neurogenesis (Burke et al., 2007).

Cardiovascular disease and cognitive function.

The respective associations between cardiovascular disease, cerebrovascular disease and cognitive impairment are well known (Burke et al., 2007). The risk factors for cardiovascular disease - hypertension, diabetes, obesity, smoking, low levels of high-density lipoprotein (HDL), high levels of low-density lipoprotein (LDL), high concentrations of fibrinogen and of homocysteine, and alcohol misuse - are also risk factors for cerebrovascular disease. Additional risk factors for cerebrovascular disease include metabolic syndrome, cardiac arrhythmia, carotid atheroma, hypotension, transient ischaemic attacks, coronary artery bypass grafts, angioplasty, and ischaemic heart disease and. These can all then be considered to be risk factors for cognitive impairment and most of the dementias (O'Brien, 2006).

Mechanisms of neurovascular change.

Vascular risk factors lead directly or indirectly to oxidative stress and a cascade of inflammatory events that result in vascular damage in the brain, compromising neural activity and hence causing cognitive impairment (K. Yaffe et al., 2004). Oxidative stress may occur peripherally in response to obesity, smoking, alcohol, inactivity, atherosclerosis, hyperlipidaemia and psychosocial stress, and centrally in response to hypertension, diabetes, hyperhomocysteinaemia, protein aggregation in Alzheimer's disease and ischaemia (McEwen, 2002). Oxidative stress then leads to inflammation, and results in a loss of endothelial wall integrity, further compromising perfusion and leading to increased surrounding cell damage and loss. It would therefore seem reasonable to speculate that repair of cell damage in the brain caused by oxidative stress, inflammation and vascular damage can be expected if the conditions promoting the latter events are treated or prevented, and the potential for angiogenesis, neural plasticity, synaptogenesis and neurogenesis is maximized (Burke et al., 2007).

Possibilities for treatment and prevention.

PA and engagements in exercise has been shown to be associated with enhanced reaction time and a variety of cognitive executive control processes in retrospective, prospective and meta-analysis studies (Gregory et al., 2012). Observational studies suggest the cognitive benefits of exercise are achievable in young and old individuals with and without preexisting cognitive

impairment (Larson et al., 2006). Similarly, cognitive training interventions in targeted cognitive abilities has been approved to be effective for cognition improvement in a sustained manner, including in the domains of verbal episodic memory, reasoning and speed of information processing (Ball et al., 2002). Additionally, complex environments that stimulate problem-based learning promote structural and functional neuronal changes, and older people responded by recruiting neural circuitry in a fashion that is different from younger individuals (Grady et al., 2003).

Social engagement is associated with positive effects on cognition in humans, and similar positive effects have been observed in relation to supportive psychotherapy and problem-solving therapy, social relations and social support, social ties and marital status, and living arrangements and social network indices (Alexopoulos, Raue, & Arean, 2003).The biological mechanism is proposed to be neural plasticity (the cognitive reserve hypothesis), neurogenesis and vasculogenesis (the vascular hypothesis) and cortisol regulation (the stress hypothesis) (Fratiglioni, Paillard-Borg, & Winblad, 2004).

Diet and supplementation could also be reasonably expected to play a part in providing the chemical substrates necessary to improve neurovascular function. Increased HDL and decreased LDL concentrations and marine omega-3 polyunsaturated fatty acid consumption are associated with better cognitive function (Kalmijn et al., 2004). It is well established that caloric restriction could be used to promote successful brain aging. Data from randomized controlled trials in humans are limited. No positive effect on cognitive impairment was found probably due to methodological limitations. The long-term effects of caloric restriction in adults must be clarified before engaging in such preventive strategy (Gillette-Guyonnet & Vellas, 2008). Antioxidant compounds, contained in fruit, vegetables and tea, have been postulated to have a protective effect against age-related cognitive decline by combating oxidative stress. However, recent research on this subject has been conflicting. Future intervention trials are warranted to elucidate the effects of a high intake of dietary antioxidants on cognitive functioning, and to explore effects within a whole dietary pattern (Crichton, Bryan, & Murphy, 2013). Medical interventions including cessation of smoking, treatment of depression, control of hypertension, folic acid plus vitamin B12 supplementation sufficient to reduce

raised homocysteine levels and melatonin may provide reduction of risk for cardiovascular, cerebrovascular and depressive illness (Hickie et al., 2005).

Influences of PA on the Health of Older Adults

Engagement in PA is a health behavior that can positively impact the severity and course of chronic diseases. The health benefits include decreased mortality rates; lower incidence of developing diseases; maintenance of conditions such as hypertension, diabetes, and obesity; reduction of fall risk; improvement in mood and well-being; and the lessening of functional decline, especially among older adults (Nelson et al., 2007). Centers for Disease Control and Prevention (CDC) and the American College of Sports Medicine (ACSM) (Centers for Disease Control and Prevention (CDC), 2005; Haskell et al., 2007) recommend that adults engage in at least 30 minutes of moderate-intensity PA on most days, preferably all days, to have a beneficial effect on their health. Two Healthy People 2010 objectives of CDC are to increase the proportion of adults who engage in regular moderate or vigorous activity to at least 50% and to decrease the proportion of adults who engage in no leisure-time PA to 20%.

PA levels of older adults.

Data from the Behavioral Risk Factor Surveillance System (BRFSS) surveys for 2001 and 2003 indicated that more than half of U.S. adults continue not to participate in PA at a level recommended as beneficial to health (Centers for Disease Control and Prevention (CDC), 2005). There remains a broad range of evidence to underscore concern that US adults are still not active enough. For example, data from 2005 indicate that less than half (49.1%) of U.S. adults met the CDC/ACSM PA recommendation (Centers for Disease Control and Prevention (CDC), 2005). Men were more likely to meet the recommendation (50.7%) than women (47.9%). For men and women combined, younger people were more likely to be active than older people, with the prevalence of those meeting the recommendation declining from 59.6% among those 18–24 yr of age to 39.0% among those 65 years and older. White, non-Hispanics (51.1%) were most likely to meet the

recommendation followed by ‘‘other’’ racial or ethnic groups (46.3%), Hispanics, (44.0%) and African-Americans (41.8%). Persons with a college degree were the most likely to meet the recommendation (53.2%) followed by those with some college education (50.2%), a high school education (45.9%), and less than high school (37.8%).

According to data obtained from the 2003-2004 National Health and Nutritional Examination Survey (NHANES) (Troiano et al., 2008), adherence to PA recommendations according to accelerometer-measured activity is substantially lower than according to self-report. Males are more physically active than females. PA declines dramatically across age groups between childhood and adolescence and continues to decline with age. For example, 42% of children ages 6-11 yr obtain the recommended 60 min per day of PA, whereas only 8% of adolescents achieve this goal. Among adults, adherence to the recommendation to obtain 30 min per day of PA is less than 5%. Great care must be taken when interpreting self-reported PA in clinical practice, public health program design and evaluation, and epidemiological research.

PA and health in older adults.

To date, disease outcomes inversely related to regular PA in prospective observational studies include cardiovascular disease, thromboembolic stroke, hypertension, type 2 diabetes mellitus, osteoporosis, obesity, colon cancer, breast cancer, anxiety and depression. Scientific evidence continues to accumulate, with more recent efforts focused on the nature of the relation between PA and health, rather than trying to determine if such a relation exists (Kesaniemi et al., 2001; Warburton, Nicol, & Bredin, 2006). This additional evidence includes compelling new data on women, and more conclusive evidence on stroke, some cancers, and cognitive function. Generally, participants engaging in regular PA display more desirable health outcomes across a variety of physical conditions. Similarly, participants in randomized clinical trials of physical-activity interventions show better health outcomes, including better general and health-related quality of life, better functional capacity and better mood states. Assessment and promotion of exercise and PA may be beneficial in achieving desired benefits across several populations (Penedo & Dahn, 2005).

The primary limitation of much of the data linking PA to morbidity and mortality due to chronic diseases is that for many conditions few randomized trials of adequate design have been conducted. However, this situation is not all that different from data regarding the relation between some other health-related behaviors and clinical outcomes, such as cigarette smoking or saturated fat intake and coronary heart disease. No adequately designed randomized controlled study in the general population has shown that stopping smoking or decreasing saturated fat or trans-fatty acid intake significantly decreases CHD mortality yet getting the public to stop smoking or reduce their intake of saturated fat or trans-fatty acids are major components of national public health campaigns (Haskell et al., 2007).

Based on the recommendation of ACSM (Haskell et al., 2007), frequent PA is an important behavior for individual and population health. To promote and maintain health, all healthy adults need to engage in moderate-intensity aerobic PA for a minimum of 30 min per day on 5 days per week or vigorous-intensity aerobic activity for a minimum of 20 min per day on 3 days per week. Combinations of moderate- and vigorous-intensity activity can be performed to meet the guidelines. Moderate-intensity aerobic PA, which is generally equivalent to a brisk walk and noticeably accelerates the heart rate, can be accumulated toward the 30-min minimum from bouts lasting 10 or more minutes. Vigorous-intensity activity is exemplified by jogging, and causes rapid breathing and a substantial increase in heart rate. This recommended amount of aerobic activity is in addition to routine activities of daily living that tend to be of light intensity or last less than 10 min in duration. In addition, every adult should perform activities that maintain or increase muscular strength and endurance a minimum of two days each week. It is recommended that 8–10 exercises be performed on two or more nonconsecutive days each week using the major muscles of the body. Such activities include lifting weights, weight bearing calisthenics or similar resistance exercises that use the major muscle groups of the body. Because of the dose-response relation between PA and health, persons who wish to further improve their personal fitness, reduce their risk for chronic diseases and disabilities or prevent unhealthy weight gain may benefit by exceeding the minimum recommended amounts of PA.

For old adults, there is substantial evidence that PA reduces risk of falls and injuries from falls (Panel on Prevention of Falls in Older Persons, American Geriatrics Society and British Geriatrics Society, 2011), prevents or mitigates functional limitations (Keysor, 2003), and is effective therapy for many chronic diseases. Clinical practice guidelines also identify a role for PA in the management of depression and anxiety disorders (Brosse, Sheets, Lett, & Blumenthal, 2002), cognitive impairment (Larson et al., 2006) and improves sleep (Pa et al., 2014).

All older adults should be physically active (Nelson et al., 2007). An older adult with a medical condition for which activity is therapeutic should perform PA in a manner that treats the condition, and reduces risk of developing other chronic diseases. PA should be one of the highest priorities for preventing and treating disease and disablement in older adults. Effective interventions to promote PA in older adults deserve wide implementation.

Sedentary time and health in older adults

Data of participants (N=6,329) from the 2003-2004 National Health and Nutrition Examination Survey aged >=6 years (C. E. Matthews et al., 2008) indicated Americans spent 54.9% of their monitored time, or 7.7 hours/day, in sedentary behaviors. The most sedentary groups in the United States were older adolescents and adults aged >/=60 years, and they spent about 60% of their waking time in sedentary pursuits. Females were more sedentary than males before age 30 years, but this pattern was reversed after age 60 years. Mexican-American adults were significantly less sedentary than other US adults, and white and black females were similarly sedentary after age 12 years. These data provide the first objective measure of the amount of time spent in sedentary behavior in the US population and indicate that Americans spend the majority of their time in behaviors that expend very little energy.

Even for adults who meet PA guidelines, sitting for prolonged periods can still compromise metabolic health. TV time and objective-measurement studies show deleterious associations, and breaking up sedentary time is beneficial. Sitting time, TV time, and time sitting in automobiles increase premature mortality risk (Owen, Healy, Matthews, & Dunstan, 2010).

Sedentary behaviors (typically in the contexts of TV viewing, computer and game-console use, workplace sitting, and time spent in automobiles) have emerged as a new focus for research on PA and health. Research indicates that too much sitting is distinct from too little exercise. For example, one study (Hamilton, Hamilton, & Zderic, 2004) provides a compelling body of evidence that the chronic, unbroken periods of muscular unloading associated with prolonged sedentary time may have deleterious biological consequences. It has been suggested that the loss of local contractile stimulation induced through sitting leads to both the suppression of skeletal muscle lipoprotein lipase activity, which is necessary for triglyceride uptake and HDL-cholesterol production, and reduced glucose uptake. These findings suggest that standing, which involves isometric contraction of the anti-gravity (postural) muscles and only low levels of energy expenditure, elicits EMG and skeletal muscle LPL changes. However, in the past, this form of standing would be construed as a "sedentary behavior" because of the limited amount of bodily movement and energy expenditure entailed. Within this perspective, standing would not be a sedentary activity and may have more potential health benefits.

Findings on the metabolic correlates of prolonged TV viewing time have been confirmed by recent objective-measurement studies, which also show that breaking up sedentary time can be beneficial for metabolic health (Healy, Dunstan, Salmon, Cerin et al., 2008). Furthermore, recent studies have shown prospective relationships of sedentary behaviors with premature mortality (Matthews et al., 2008; Proper, Singh, van Mechelen, & Chinapaw, 2011). There is a growing body of evidence that sedentary behavior may be a distinct risk factor, independent of PA, for multiple adverse health outcomes in adults (Thorp, Owen, Neuhaus, & Dunstan, 2011). The study of Healthy Aging cycle of the Canadian Community Health Survey (Dogra & Stathokostas, 2012) also reported that older adults who were moderately (2–4 hours/day) and least sedentary (<2 hours/day) were 38% (OR: 1.38; CI: 1.12–1.69) and 43% (OR: 1.43; CI: 1.23–1.67) more likely to age successfully, respectively. Among middle-aged adults, those who were least sedentary were 43% (OR: 1.43; CI: 1.25–1.63) more likely to age successfully. Sedentary activities are significantly associated with lower odds of SA among middle-aged and older adults, potentially in a dose-

dependent manner. Importantly, adults can meet public-health guidelines on PA, but if they sit for prolonged periods of time, their metabolic health is compromised. Among these healthy, physically-active adults, significant detrimental dose-response associations of TV time were observed with waist circumference, systolic blood pressure, and 2-h plasma glucose in both men and women, as well as fasting plasma glucose, triglycerides, and HDL-cholesterol in women only (Healy, Dunstan, Salmon, Shaw et al., 2008). This observation named as “the Active Couch Potato phenomenon” is important. The particular metabolic consequences of time spent watching TV are adverse, even among those considered to be sufficiently physically active to reduce their chronic disease risk. This finding reinforces the potential importance of the deleterious health consequences of prolonged sitting time, which may be independent of the protective effect of regular moderate-intensity PA. This is a new and challenging area for exercise science, behavioral science, and population-health research.

Measurement of PA and Sedentary Time

Subjective and objective PA measurement.

PA is often assessed using self-report measures. These measures are easy to administer and can provide information on the types of activities performed, but may not capture activity patterns throughout the day (Murphy, 2009). Some measures include calculations to estimate energy expenditure based on the duration and frequency of reported activity participation (Stewart et al., 2001). However, there are some disadvantages to using self-report measures such as recall bias, and in older adults in particular. Self-report may also be influenced by fluctuations in health status and mood, depression, anxiety, or cognitive ability. In addition, self-report PA measures designed for younger adults have been shown to be inaccurate when given to older adult samples, particularly underestimating the performance of light and moderate intensity activities (Washburn, 2000).

Objective PA measures have been increasingly used to overcome limitations of self-report measures (Davis & Fox, 2007). Accelerometer, in particular, provides information on the amount,

frequency, and duration of PA. Data can be obtained about daytime and nighttime activity patterns and activity intensity (including estimates of energy expenditure) as they occur in people's daily lives. The results has been proven to correlate reasonably with doubly labeled water-derived energy expenditure (Plasqui & Westerterp, 2007). Objective PA measurement techniques can assess free-living activity which, similar to structured exercise, has been shown to have health benefits. It was recently shown that participation in non-exercise PA (such as housework or climbing stairs) improves mortality risk (C. E. Matthews et al., 2007). Interventions that are designed to build PA (such as walking and stair climbing) into daily routines have shown effects of improved physical fitness in diverse population (Rikli, 2000). Incorporating free-living activity into the daily routines of older adults is one potential way to promote long-term adoption of PA engagement (Murphy, 2009).

Objective measurements of PA in older adults.

There are several issues concerning PA measurement that are unique to the older adult population. First, older adults differ from younger adults and children in the type and intensity of activities in which they engage. Compared to the other age groups, older adults spend a higher percentage of their day performing low intensity activities and a lower percentage performing high intensity activities (Westerterp, 2008). These patterns may be due to age-related changes which include loss of flexibility, decreased bone and muscle mass, and decreased ability of the cardiac and respiratory systems to adapt to more intense PA. Second, age-related declines in basal metabolic rate and decreased fat free mass may contribute to errors in energy expenditure calculations that were developed using younger adult samples. Third, chronic conditions increase in prevalence with aging and can affect PA levels. Fourth, problems with memory and recall among older adults may affect compliance of wearing monitors over a series of days (Murphy, 2009).

Appropriate strategies of data proceeding in accelerometer.

Protocol decisions made by researchers may affect the validity of the output. Accelerometer-based activity assessments requires careful planning and the use of appropriate strategies to increase compliance. For example, the type of monitor or monitors chosen depends

on the motion of interest and the investigator's primary outcome variables. Whole body movement can be measured by a three dimensional monitor or by multiple monitors. Often one monitor is placed near the center of mass to approximate whole body movement and energy expenditure. However, the output of monitors depends on placement and is activity-specific (Murphy, 2009). For example, upper extremity movement of stroke survivors has been assessed using a wrist-worn monitor. Gait and balance have been assessed using hip or trunk worn accelerometers and a combination of monitors have been used to distinguish sit to stand movements in the clinic. In addition, sleep and wake patterns are often measured using wrist-worn activity monitors (Morgenthaler et al., 2007). Another consideration for using accelerometers is the length of time they are worn. For adults, 3-5 d of monitoring is required to reliably estimate habitual PA. Among children and adolescents, the number of monitoring days required ranges from 4 to 9 d, making it difficult to draw a definitive conclusion for this population (Trost, McIver, & Pate, 2005). If nighttime activity, such as sleep patterns, is of interest, recent practice parameters recommend at least 3 days of monitor wear (Morgenthaler et al., 2007). Some investigators (Gretebeck & Montoye, 1992) suggested that at least 5 or 6 d are needed to minimize the intra-individual variance a reasonable degree. Weekdays as well as weekend days need to be included.

Compliance by participants wearing accelerometers may also be inconsistently reported in the research literature (Murphy, 2009). Several different approaches can be undertaken by researchers to promote compliance including a daily monitoring log filled out by participants, reminder phone calls, adequate education about the monitor and its proper wear, and identification of potential barriers to wearing with each participant (Trost et al., 2005). Concrete instructions about compliance may be particularly important to provide for older adults given issues with memory and recall. Based on personal experience using accelerometers with older adults, the daily logs are a fundamental tool for data analysis to determine times when the watch was not worn and have been consistently completed by participants. We should also include compliance instructions in the daily logs. There are no universal guidelines for data manipulation in the accelerometer literature, however, for study comparability, it is important that researchers clearly state their protocol for

monitor wear and their decision rules for handling missing and spurious data (Masse et al., 2005). Researchers are encouraged to take advantage of software to implement missing value imputation, as estimates of activity are more precise and less biased in the presence of intermittent missing accelerometer data than those derived from an observed data analysis approach (Catellier et al., 2005). Consistency in using one monitor in studies of older adults could help build the evidence base along with standard protocols.

A recent systematic review (Gorman et al., 2014) identified 59 articles with cut-points ranging between 574 and 3,250 counts/min for MVPA and 50 and 500 counts/min for sedentary time. By choosing a cut-point that is either too high or too low could either over or under estimate who meets the 30 min/day of MVPA depending on the group of older adults under investigation. The most commonly used cut-point of ≥1,952 for MVPA was able to best distinguish between participants who would likely meet the 30 min of MVPA/day. However, there were little differences between this value and cut-points within close proximity (≥1,566, ≥2,000, ≥2,020). It appears that 1,566 to 2,020 counts/min (with 1,952 appearing to be the optimal) may provide the greatest differences across age groups and potentially physical capacity. Although there is currently no consensus on the optimal cut-points for older adults, the majority of studies use the same cut-points for MVPA (1,952 counts/min) and sedentary time (100 counts/min), and this allows for comparison between the studies. However, these cut-points are not specific to older adults; the most commonly reported cut-point of 1,952 counts/ min was validated in young adults (Freedson, Melanson, & Sirard, 1998). Older adults may have a different capacity for activity, and may expend more energy to complete a task compared with a fitter, younger adult. Therefore, a lower cut-point for MVPA than what is used in adult research may be appropriate due to the age related decline in fitness, if present. Copeland and colleagues' (Copeland & Esliger, 2009) cut-point of 1041 counts/min from Actigraph accelerometer was developed specifically for older adults, and using this cut-point resulted in 64 % of the older women in our dataset meeting PA guidelines compared with 33 % meeting guidelines using the most commonly reported cut-point of 1,952 counts/min. Hooker and colleagues (Hooker et al., 2011) reported that cut-point of 1065 yielded similar accuracy in

predicting light and moderate intensity activity for Actical accelerometer in middle-aged and older adults, and can be used to determine light and moderate intensity PA in this population. More studies are needed to validate the exact cut-points for different activity monitor for older adults.

For sedentary time, the range of cut-points resulted in a difference of 25%, or over 3 h/day, which is important as older adults could spend a large proportion of their day in sedentary activities. It is promising that the majority of studies are using the same cut-points (100 counts/min) for sedentary time (Winkler et al., 2012). This is an emerging area of research, and older adult specific validation is needed (Gorman et al., 2014).

Another issue that can affect the accuracy of reported sedentary time is the ability to differentiate between non- wear time and sedentary time. This is of particular concern for older adults' accelerometer data because the large amount of time they spend in sedentary behaviors can potentially lead to the misclassification of sedentary time as non- wear time (Winkler et al., 2012). The most common criteria for non-wear time was based on the NHANES recommended protocol for the removal of 60 min or more of continuous zeros with allowance of 1–2 min with counts between 1 and 100 (Troiano et al., 2008). One study suggests 90 min may be more appropriate (Choi, Ward, Schnelle, & Buchowski, 2012) for some older populations with limited mobility. Another recent study (Hutto et al., 2013) reported that the 60-min and 90-min methods substantially overestimated number of non-wear bouts per week and underestimated time spent in sedentary behavior. Utilization of at least 120 minutes of consecutive zero counts will provide dependable population-based estimates of wear and non-wear time, and time spent being sedentary and active in older adults.

Limitations of accelerometers.

Accelerometers can be used to approximate energy expenditure, however, they do not capture the full energy cost of certain activities, such as walking while carrying a load or walking uphill, because acceleration patterns do not change under these conditions (Gorman et al., 2014; Murphy, 2009). PA may also be underestimated depending upon the placement of the monitor. Other limitations include the financial cost of monitors, staff time to process and analyze data, and

problems with monitor placement when data are collected over a number of days. In addition, although raw activity counts are frequently reported in studies, they are not easily interpretable.

To date, there is not a standardized method to quantifying accelerometer-based PA and sedentary time in older adults. Different strategies can produce markedly different results, and using too low or too high cut-points may obscure important group or treatment differences. Standard reporting should include specific data assumptions for analysis. Also studies is needed to determine which assumptions are most appropriate for older adults, taking into account their physical capacity. For future research, estimates of the patterns of modes of PA may be a new direction. Research (Pober, Staudenmayer, Raphael, & Freedson, 2006) has shown novel approach of estimating activity mode, rather than activity levels separated by cut-points, may allow for more accurate field-based estimates of PA using accelerometer data, and this approach warrants more study in a larger and more diverse population of subjects and activities.

The Association between PA and Cognitive Function

Animal Studies.

Animal models of PA and exercise training have demonstrated beneficial effects on cognitive function. For instance, daily wheel running for 2 weeks promotes memory acquisition, memory retention, and reversal learning in rodents. A decrease in neurogenesis might be a prerequisite for optimal memory retrieval (Van der Borght, Havekes, Bos, Eggen, & Van der Zee, 2007). Furthermore, aerobic training program with the treadmill running in rats showed regular and chronic aerobic exercise has time and dose-dependent, neuroprotective and restorative effects on physiological brain aging, and reduces anxiety-related behaviors (Pietrelli, Lopez-Costa, Goni, Brusco, & Basso, 2012). Animal models also report protective effects of exercise on cognitive function. Age-related impairments in memory and spatial learning were reversed by increased PA in older mice (Yau et al., 2011). These collective findings indicate that PA may improve or reverse impairment in hippocampal-related cognitive tasks (i.e., memory and learning), and provide the framework for the human studies of the relationship between PA and cognitive function.

Human studies.

Cross-sectional and longitudinal studies.

The exercise-cognition relation in older adults has been strengthened by recent epidemiological studies. Cross-sectional studies in humans suggest that more active individuals may have reduced risk of cognitive impairment and dementia. Women who reported being physically active at any point over the life course, especially as teenagers, had a lower likelihood of cognitive impairment in late life. Interventions should promote PA early in life and throughout the life course (Middleton et al., 2010). Moreover, a history of high PA is associated with better cognitive performance among old adults living in the community (Landi et al., 2007). Compared to controlled cohort, active elderly marathon runners or bicyclists older than 60 years had better performance in cognitive tests. Extensive endurance exercise training may be beneficial for maintaining cognitive function in older adults (Winker et al., 2010). While moderate activity may be protective, long-term strenuous activity before menopause may lower cognitive performance later in life (Tierney, Moineddin, Morra, Manson, & Blake, 2010).

Prospective longitudinal investigations have attempted to determine the effects of PA or fitness on cognitive decline or incident dementia over follow-up periods of several years. One study (K. Yaffe, Barnes, Nevitt, Lui, & Covinsky, 2001) in 5925 predominantly white community-dwelling women (aged above 65 years) has shown women with a greater PA level at baseline were less likely to experience cognitive decline during the 6 to 8 years of follow-up. After adjustment for age, educational level, comorbid conditions, smoking status, estrogen use, and functional limitation, women in the highest quartile remained less likely than women in the lowest quartile to develop cognitive decline. Similarly, the Nurses' Health Study (Weuve et al., 2004), which included 18 766 US women aged 70 to 81 years, also indicated higher levels of activity were associated with better

cognitive performance. Long-term regular PA, including walking, is associated with significantly better cognitive function and less cognitive decline in older women.

For both older women and men, the Canadian Study of Health and Aging (Middleton, Mitnitski, Fallah, Kirkland, & Rockwood, 2008) of 8403 participants who had measurements of cognition and self-reported PA reported that high exercisers had more frequent stable or improved cognition (42.3%, 95% CI: 40.6-44.0) over 5 years than did low/no exercisers (27.8%, 95% CI: 26.4-29.2). People who did not exercise were also more likely to die (37.5%, 95% CI: 36.0-39.0) versus 18.3% (95% CI: 16.9-19.7)). Exercise is strongly associated with improving cognition. As the majority of mortality benefit of exercise is at the highest level of cognition, and declines as cognition declines, the net effect of exercise should be to improve cognition at the population level. In another community-based prospective cohort study in Germany (Etgen et al., 2010), 3903 participants older than 55 years were enrolled. Self-reported PA (classified as no activity, moderate activity, and high activity), cognitive function (assessed by the 6-Item Cognitive Impairment Test), and potential confounders were evaluated. After a 2-year follow-up, 207 of 3485 initially unimpaired subjects (5.9%) developed incident cognitive impairment. Compared with participants without PA, fully adjusted multiple logistic regression analysis showed a significantly reduced risk of incident cognitive impairment for participants with moderate or high PA at baseline (odds ratio [OR], 0.57; 95% confidence interval [CI], 0.37-0.87, and OR, 0.54; 95% CI, 0.35-0.83, respectively). Further sub-analysis including participants without functional impairment and without prodromal phase of dementia resulted in an even higher reduction of risk of incident cognitive impairment for participants with moderate or high PA (OR, 0.44; 95% CI, 0.24-0.83, and OR, 0.46; 95% CI, 0.25-0.85, respectively) compared with no activity. Moreover, a meta-analysis review (Hamer & Chida, 2009) of 16 prospective studies reported a reduction in relative risk for dementia in the highest PA category when compared to the lowest, suggesting that PA is inversely associated with risk of dementia.

The association between objectively-measured PA and cognitive function in older adults are consistent. Middleton et al. (Middleton et al., 2011) used activity energy expenditure (AEE) as

90% of total energy expenditure (assessed during 2 weeks using doubly labeled water) minus resting metabolic rate (measured using indirect calorimetry) in 197 men and women (mean age, 74.8 years) who were free of mobility and cognitive impairments at baseline. Cognitive function was assessed at baseline and 2 or 5 years later using the Modified Mini-Mental State Examination. After adjustments, older adults in the highest sex-specific tertile of AEE had lower odds of incident cognitive impairment than those in the lowest tertile (OR: 0.09, 95% CI: 0.01-0.79). There was also a significant dose response between AEE and incidence of cognitive impairment (P = 0.05 for trend over tertiles). These findings indicate that greater AEE may be protective against cognitive impairment in a dose-response manner.

In one prospective study named Rush Memory and Aging Project, total daily PA was objectively measured continuously for up to 10 days with Actigraph from 716 older individuals without dementia participating, (Buchman et al., 2012). All participants underwent structured annual clinical examination including a battery of 19 cognitive tests. After an average follow-up of about 4 years, a Cox proportional hazards model adjusting for age, sex, and education indicated that total daily PA was associated with incident AD (hazard ratio = 0.477; 95% confidence interval 0.273-0.832). The association remained after adjusting for self-report physical, social, and cognitive activities, as well as current level of motor function, depressive symptoms, chronic health conditions, and APOE allele status. In a linear mixed-effect model, the level of total daily PA was associated with the rate of global cognitive decline (estimate 0.033, SE 0.012, p = 0.007).

Comparison of cross-sectional and prospective analyses is made difficult by differences in the method used to measure PA level: questionnaire, self-reported activities, and more objective measures, including active energy expenditure, accelerometer, or cardiorespiratory fitness. In addition, different PA status classifications have been used, such as dichotomizing the sample into active and inactive subjects based on arbitrary cut points, differentiating between levels of PA (i.e., low, moderate, and high), or establishing percentiles (Gregory et al., 2012). Studies also differ in the dependent variable measured (i.e., cognitive performance, dementia development, Alzheimer's risk or mortality) and measurement technique (i.e., cognitive test battery used, criteria for dementia

or cognitive impairment). Such differences make it difficult to compare studies and draw firm conclusions. These cross-sectional and prospective analyses suffered from the heterogeneous methods for measuring and quantifying PA, fitness level, and cognitive impairment, and the likeliness of a bidirectional relationship between cognitive impairment and PA (Erickson, Weinstein, & Lopez, 2012; Gregory et al., 2012).

In a large prospective investigation (Liu et al., 2012), individuals in the middle and highest tertiles of cardiorespiratory fitness had a reduced risk for dementia-related mortality over an average follow-up period of 17 years when compared to the lowest tertile. The most significant reduction in risk was seen between the lowest and middle fitness tertiles, and each 1-metabolic equivalent (MET) improvement in fitness reduced the relative risk of dementia-related mortality by 14%. Investigations measuring cardiorespiratory fitness by maximal oxygen consumption have the advantage of presumably assessing PA level by more objective and reliable methods when compared to retrospective PA questionnaires or recall methods. The results of these investigations may therefore provide more reliable evidence of the relationship between PA and brain health. However, it is important to consider that although cardiorespiratory fitness logically relates to PA level, it is not necessarily reflective of PA levels, as cardiorespiratory fitness can be influenced by other factors such as chronic disease, especially in older, untrained populations. The relationships reported may simply describe the likelihood that those with cognitive impairment and increased dementia risk are also those most likely to have physical limitations, chronic disease, or psychological issues that reduce their PA level and/or measured cardiorespiratory fitness. Furthermore, physical impairments that limit mobility may reduce access to social interaction with family and peers, which may influence cognitive function (Erickson et al., 2012).

Exercise intervention studies.

Research designs employing exercise interventions provide the ability to examine a causal relationship between exercise training and cognitive function. A recent meta-analysis (Smith et al., 2010) of 29 studies involving aerobic exercise interventions reported modest but significant

improvements in attention and processing speed, executive function, and memory in exercise-trained subjects.

Improvements in cognitive performance have been reported after non-supervised exercise interventions. Older adults who were unsupervised but encouraged to increase their current PA level by 150 min per week for 6 months improved performance on delayed recall and on the cognitive section of the Alzheimer Disease Assessment Scale. Improvements in cognition occurred in the whole exercise group, including those exercisers with MCI at baseline, and maintained during the 18 months follow-up (Lautenschlager et al., 2008).

The effect of exercise on cognitive function have also been reported from supervised aerobic training interventions. Previously sedentary older adults with mild amnestic cognitive impairment at baseline improved performance on a series of tasks related to executive processing, but not short-term memory, after 6 months of aerobic training (4 days per week at 75% to 85% heart rate reserve) (L. D. Baker et al., 2010a). The control group that performed stretching and balance exercises showed no improvements in cognitive function. The intervention successfully improved cardiorespiratory fitness measured by maximal oxygen consumption in the training group (+11%) compared to the control group (−7%). Interestingly, the treatment effect was larger in women for several executive function tests implying gender differences may exist in the response to exercise training. The same research group reported in another paper (L. D. Baker et al., 2010b) that improved executive function in cognitively normal older adults with impaired glucose tolerance relative to a stretching control group after a 6-month aerobic training intervention. Comparatively, Erickson and colleagues (Erickson et al., 2011) reported that aerobic exercise training increases the size of the anterior hippocampus, leading to improvements in spatial memory. Exercise training increased hippocampal volume by 2%, effectively reversing age-related loss in volume by 1 to 2 years. Hippocampal volume declined in the control group, but higher pre-intervention fitness partially attenuated the decline, suggesting that fitness protects against volume loss. These findings support the benefits of exercise training for improving and maintaining cognitive function as indicated by improved performance on tests of memory task and executive function, and reduced

risk of cognitive decline and dementia-related mortality in fitter and more active individuals. Problems with available interventional studies include the use of different tests for cognitive function, variability in the exercise training program, and an inability to examine the effects of lifelong PA patterns on dementia risk and cognitive function.

In summary, although there are a multitude of unanswered questions regarding PA and cognition in older adults, there is evidence of a relationship between PA and improvements in various aspects of cognition across a broad range of ages. Future research are necessary to determine if the threshold of exercise to predict changes in brain function, specifically in the form of type, intensity, duration and frequency of exercise. It remains to be clarified if physical activities requiring higher levels of motor complexity or that require more memory function will differentially impact cognitive function or brain physiology. Thus, it might be necessary to compare relative simple motor tasks, such as walking, with activities that are more complex, such as dancing, game playing and resistance training.

Potential Mechanism of the Effect of PA on Cognition

A growing body of literature suggests that PA beneficially influences brain function during adulthood, particularly frontal lobe-mediated cognitive processes (executive function), such as planning, scheduling, inhibition, and working memory. The sedentary lifestyle that pervades modern society has overridden the necessity for a physically active lifestyle. The impact of inactivity on disease processes has been the focus of much attention; the growing understanding that PA also has the benefit of enhancing cognitive performance strengthen the imperative for interventions that are successful in increasing PA, with the outcomes of promoting health and productivity. Cardiorespiratory fitness may mediate the relationship and improve the cognitive function in adults.

Animal Studies.

Brain plasticity, also called neuroplasticity refers to the brain's ability to change at any age, for better or worse. Several studies in animals have examined changes in brain physiology in response to PA. In mice, expression of brain-derived neurotrophic factor (BDNF) increased in the

hippocampus after level and downhill running (Aguiar, Speck, Prediger, Kapczinski, & Pinho, 2008). Others studies (Lou, Liu, Chang, & Chen, 2008; Nakajima, Ohsawa, Ohta, Ohno, & Mikami, 2010) have indicated that exercise improves possible mediators of neurodegeneration, and suggest that anti-inflammatory and antioxidant effects as well as neurochemical alterations in the hippocampus and cortex could mediate changes in neurologic function induced by exercise in humans.

Compelling findings from animal studies also suggest exercise training may prevent or reverse age-related changes in brain tissue associated with dementia (Lou et al., 2008). Chronic exercise may be protective against age-related changes in neurobiology, including altered expression of neurotrophic factors and neurotransmitters (Latimer et al., 2011), and enhanced or maintained neuronal proliferation and maturation in the hippocampus (Yau et al., 2011).

Human Studies.

Cross-sectional and prospective studies.

Cross-sectional and prospective human investigations suggest a relationship between fitness/PA level and brain health. In cross-sectional analyses, aerobic fitness was associated with gray matter volume and white matter integrity in females with relapsing-remitting multiple sclerosis (Prakash, Snook, Motl, & Kramer, 2010) and with parietal and medial temporal volume in early-stage AD patients (Honea et al., 2009). In a prospective analysis of older adults (Erickson et al., 2010), PA level at baseline predicted gray matter volume changes over 9 years of follow-up. Greater amounts of walking are associated with greater gray matter volume, which is in turn associated with a reduced risk of cognitive impairment. Moreover, cardiorespiratory fitness was a significant predictor of right and left hippocampal volume in a group of older adults aged 59 to 81 years (Erickson et al., 2009). Higher aerobic fitness was associated with greater right and left hippocampal volumes, but only left hippocampal volume was reported to be a significant partial mediator of the relationship between aerobic fitness and memory. These cross-sectional investigations indicate a relationship between higher aerobic fitness level, larger hippocampal volume, and improved neuronal health, and suggest that improvements in cognitive function with aerobic activity may be mediated by neurophysiological and structural changes in the brain.

Exericse intervention studies.

Intervention studies indicate aerobic exercise training increases regional brain volumes. Regional gray and white matter volumes increased and relative risk of brain tissue loss decreased in older non-demented adults performing aerobic exercise training for 6 months when compared to a control group that performed stretching and toning exercises (S. J. Colcombe et al., 2006). In a large sample (n = 120) of cognitively normal older adults, left and right anterior hippocampal volumes increased after 1 year of aerobic exercise training (walking 4 days per week at 60%–75% Heart Rate Reserve) (Erickson et al., 2011). Improvements were relative to a control group that performed toning and stretching exercises. However, the changes in left (+2.12% in aerobic vs. −1.40% in control) and right (+1.97% vs. −1.43%) hippocampal volumes were modest. In addition, the standard deviation for volume measurements was 3–4 folds larger than the reported mean difference between groups indicating that the treatment effect was not large and there may be considerable intra-individual variability in the response. The large variability in hippocampal volume measurements is likely attributable to the multitude of biological and environmental factors that influence human brain physiology.

There appears to be a relationship between fitness improvements and hippocampal volume changes with exercise training. After 1 year of aerobic training, greater improvements in aerobic fitness were moderately but significantly associated with greater changes in left and right hippocampal volumes (Williamson et al., 2009). Similarly, Modest but significant associations between changes in cardiorespiratory fitness and changes in left hippocampal volume after a 10-week aerobic exercise intervention (3 days per week for 40 min at a moderate intensity) in 13 healthy men and women (age 23–45). Right and left hippocampal volume did not change, which may be related to the heterogeneous fitness improvements observed (change in VO_{2peak} range: 0 to 22%) (Parker et al., 2011). The relationship between changes in cardiorespiratory fitness and increased hippocampal volume suggest that a longer duration intervention more likely to induce more uniform and substantial improvements in fitness may increase hippocampal volume. Together these findings suggest that improvements in cardiorespiratory fitness may mediate the effects of

exercise training on brain volume, and suggest that exercise interventions that result in greater fitness improvement will elicit greater changes in brain volume.

Regional brain activity

Regional brain activity, measured by changes in the blood oxygen level dependent signal intensity during functional MRI, is altered in those at risk for MCI and AD (Erickson et al., 2012). Higher fit and aerobically trained participants demonstrated increased prefrontal and parietal cortical activity and decreased activity in the anterior cingulate gyrus during a flanker task designed to elicit activation in the frontal and parietal lobes (S. J. Colcombe et al., 2004). Greater activity in a large neural network associated with memory and learning, including the hippocampus, was associated with individual cardiorespiratory fitness level before and after a 6-month cycling program, but only in a group that also performed spatial navigation training (Holzschneider, Wolbers, Roder, & Hotting, 2012). Improvements in cardiorespiratory fitness with training correlated with increased activity in the frontal cortex, the cingulate gyrus, the insula, and the parahippocampal gyrus. Changes in regional brain activity may be related to structural and neurophysiological changes in the brain and may contribute to the cognitive benefits of exercise training (Gregory et al., 2012).

Resistance training.

Several studies have examined the effects of resistance training on cognitive function. Improvements in cognitive function were reported in randomized clinical trials of older adults after full-body resistance training programs lasting 8 weeks, 24 weeks or 1 year (Cassilhas et al., 2007; Liu-Ambrose et al., 2010; Perrig-Chiello, Perrig, Ehrsam, Staehelin, & Krings, 1998). Improvements were independent of frequency (one or two sessions per week) and intensity (moderate versus high-intensity). Only one study assessed changes in brain volume, and reported a small reduction in whole brain volume after resistance training (−0.43 to −0.32%) (Liu-Ambrose et al., 2010). These limited studies and their divergent results suggest that the relationship between chronic resistance training and brain function has not been adequately studied to draw conclusions.

In conclusion, current research suggests that active individuals and those prescribed structured exercise regimes demonstrate improved cognitive function and reduced brain atrophy and/or neurodegeneration, particularly in the hippocampus. The potential for exercise training to delay or attenuate age-related decrements in cognitive performance and neurobiology is an important field of study because of the possible benefit to the health and independence of a growing elderly population and to the larger social and economic environment. Longer-term exercise studies are necessary to determine whether exercise can reduce loss of brain tissue volume and cognitive decline with aging, and whether exercise leads to lasting improvements in brain function. Directions for future research include targeting vulnerable clinical populations, and optimizing exercise training variables.

CHAPTER 3

METHODS

REasons for Geographic and Racial Differences in Stroke Study (REGARDS)

REGARDS was an ongoing, national, population-based, longitudinal study of blacks and whites, aged ≥ 45 years, enrolled January 2003-October 2007 (Howard et al., 2005). REGARDS was designed to investigate causes of regional and black-white disparities in stroke mortality, oversampling blacks and residents of the Stroke Belt. The Stroke Belt was first identified in 1965 as a region of high stroke mortality in the Southeastern US (Borhani, 1965), and it is frequently defined as including 8 southern states: North Carolina, South Carolina, Georgia, Tennessee, Mississippi, Alabama, Louisiana, and Arkansas. Within the Stroke Belt, a Buckle region along the coastal plain of North Carolina, South Carolina, and Georgia has been identified with a higher stroke mortality rate than the remainder of the Stroke Belt.

The organization of REGARDS comprised an Operations Center and the Survey Research Unit (SRU) at the University of Alabama at Birmingham (UAB), a Central Laboratory at the University of Vermont, an Electrocardiogram (ECG) Reading Center at Wake Forest University, an in-home exam component provided by Examination Management Services, Inc. (EMSI), and a medical monitoring and stroke adjudication center at Alabama Neurological Institute, Inc. An Executive Committee comprising the principal investigator of each study center and a National Institute of Neurological Disorders and Stroke representative assisted the principal investigator at the UAB in the scientific leadership of the study. Study methods were reviewed and approved by all involved institutional review boards, as well as an external observational study monitoring board appointed by the funding agency.

Sampling, Recruitment, and Initial Telephone Interview.

The REGARDS sample was selected from a commercially available nationwide list purchased through Genesys Inc.. Sample listings were purchased in batches of 50,000 households to ensure the most current telephone numbers and addresses. Criteria for inclusion in the sample included having a name, telephone number and address in the Genesys database. The recruitment

goal of 30,000 participants included 30% from the Stroke Belt, 20% from the Stroke Buckle, and the remainder from elsewhere in the continental United States. Within each region, approximately one half was white and one half African-American, and within each region-race stratum, approximately one half male and one half female.

A letter and study brochure were sent to each potential participant approximately 2 weeks prior to attempting telephone contact. Initially, only the individual listed in the database was considered a potential participant. After recruitment of approximately 25% of the sample, because of concerns that non-heads-of-household could be underrepresented by the commercially available list, a household enumeration approach and selection of a 'random' household member was implemented. Trained interviewers made up to 15 contact attempts during day, evening, weekday and weekend calling shifts. Upon reaching a household resident, the household was enumerated and one resident aged above 45 was randomly selected and screened for eligibility. Exclusion criteria included race other than African-American or white, active treatment for cancer, medical conditions that would prevent long-term participation, cognitive impairment judged by the telephone interviewer, residence in or inclusion on a waiting list for a nursing home, or inability to communicate in English. Potential participants who respond 'don't know' to questions about medical conditions were considered eligible.

Once eligibility was established, respondents were asked for their verbal informed consent. Prior to agreeing to participate in the study, the participant was told that he/she would be contacted to arrange a convenient time and place (usually in their home) to collect physical measurements, blood and urine samples. Following verbal consent, the medical history, including risk factor evaluation, was collected by computer-assisted telephone interviewing (CATI). CATI (rather than in-home interview) was used to collect these data in order to provide a higher level of quality control and standardization by the use of trained, certified and monitored staff of the SRU. It also allowed for the assessment of differences in the characteristics of participants completing and not completing the in-home exam.

In-Home Exam.

Following the telephone interview, the participant's contact information was transmitted to EMSI for scheduling of the in-home visit. During scheduling, the participant was reminded to fast overnight for 10–12 hours before the visit and was asked to have medications available for recording at the time of the visit. The visit took place on Monday–Thursday mornings to permit fasting status and allow time for specimen processing and shipping for receipt the following day at the central laboratory. EMSI technicians who were trained on methods for the REGARDS protocol completed the in-home visits and shipped samples to the central laboratory. If the participant changed his/her mind or for some other reason the in-home visit was not completed, he/she was then classified as a partial participant.

At the in-home visit, trained EMSI personnel reviewed and obtained written informed consent from the participant. Physical measurements, a resting ECG, medication inventory, phlebotomy and urine collection were performed using standardized methods. If the participant was willing to provide it, the social security number was obtained for tracking purposes. Self-administered questionnaires were left with the participant to gather information on additional demographic and risk factor characteristics. These questionnaires were completed by the participant after the home visit and were returned to the Operations Center by self-addressed prepaid envelopes. Any problems (e.g. missing or incomplete data) were resolved via follow-up telephone contact. Participants were mailed a thank-you letter and a $30 check approximately 6–8 weeks following the in-home visit.

Data Collected.

Components of the baseline evaluation were provided in **Table 1**. Variables include age, race, and sex of the participant, history of heart disease, kidney disease, reproductive history (if female), aspirin use, cigarette smoking (including smoking status, pack-years exposure, and exposure to passive cigarette smoke), alcohol intake, PA level, general health (MOS Short Form-12), access to care, insurance status, marital status, measures of socioeconomic status (education and income) and social network, psychosocial factors (social network, depressive symptoms, and stress), and history of cardiovascular procedures (endarterectomy, coronary artery bypass surgery,

peripheral vascular surgery, and percutaneous transluminal coronary angioplasty), myocardial infarction or stroke. Previous stroke symptoms were assessed using the Questionnaire for Verifying Stroke-Free Status (Jones, Williams, & Meschia, 2001). Depressive symptoms were assessed by the Center for Epidemiologic Studies Depression Scale (Orme, Reis, & Herz, 1986) and Cohen's Perceived Stress Scale (Cohen, Kamarck, & Mermelstein, 1983).Cognitive function was assessed by the Six-Item Cognitive Screener (Callahan, Unverzagt, Hui, Perkins, & Hendrie, 2002). The duration of the telephone interview was 30–45 min.

During the in-home visit, EMSI personnel took two blood pressure measurements utilizing a standard aneroid sphygmomanometer. Blood pressure quality control was monitored by central examination of digit preference, and retraining of technicians took place if necessary. Height was obtained utilizing an 8-foot metal tape measure and a square, and weight (without shoes) was obtained using a standard 300-lb calibrated scale. Venipuncture was performed using standardized methods and a random urine samples was collected. Quality control of the samples was monitored as in other large cohort studies (Cushman, Cornell, Howard, Bovill, & Tracy, 1995). Samples were immediately placed in a cooler with ice packs for transport to the local EMSI field office. A 12-lead ECG was obtained using several electrocardiograph models available from EMSI. The ECGs were recorded at standard 25 mm/s speed and calibrated to 10 mm = 1 mV.

The EMSI examiner records prescription and nonprescription medications were taken within the previous 2 weeks, and left the self-administered questionnaires with the participant. These included a 'Places You Have Lived' questionnaire, the Block 98 Food Frequency Questionnaire, a family history questionnaire for stroke, heart attack, and death in parents and siblings, and a contact information questionnaire. Tracking information, including contact information for two relatives or friends not living with the participant, was requested. In the residential history questionnaire, the participant records the city and state of birth, and all other cities and states in which he/she has lived (including dates) up to the present residence.

The length of the in-home visit was 45–60 min. All appropriate paperwork was completed, verified and reviewed with the participant to ensure accuracy. The EMSI staff reminded the

participant to complete and mail the self-administered questionnaires and reiterates that he or she can be contacted by telephone every 6 months. A card including his/her height, weight, blood pressure and pulse, and a brochure on stroke warning signs were given to the participant during the in-home examination. For questions, the participant was encouraged to contact the Operations Center through a toll-free number.

Table 1

Components of the REGARDS telephone and in-home baseline examination

Component	Telephone interview	In-home exam	Self-administered
Medical history	X		
Demographic data	X		
Stroke-free status	X		
Physical activity	X		
Depression	X		
Cognitive screening	X		
Health/quality of life	X		
Social support	X		
Social network	X		
Potential caregiver	X		
Laboratory assays		X	
Urine		X	
Height, weight, waist circumference		X	
Blood pressure, pulse		X	
Electrocardiography		X	
Medications in the past 2 weeks		X	
Residential history			X
Dietary intake			X
Family history			X

Personnel Training and Quality Control.

Approximately 100 telephone interviewers, approximately half of whom were African-American, were carefully trained and closely monitored for sensitivity to the attitudes, abilities, and limitations of study participants. Training of telephone interviewers and the more than 6,500 EMSI examiners emphasizes the importance of participant privacy and the confidentiality of personal information. An interviewer's performance was continuously monitored by SRU supervisors, and group meetings were held periodically with the REGARDS Operations Center personnel to discuss frequently asked questions and to resolve unusual circumstances. EMSI examiners were trained at their local offices by centrally-trained supervisors. Training includes a web-based REGARDS-specific program that was also available for continuing reference and retraining if needed. Feedback was provided at periodic intervals and when needed, based on review of data.

A single data management system integrates data from all sources. Interview information collected during the telephone contact was entered as part of the CATI system. Data from the in-home and self-administered questionnaires were scanned and processed by an in-house system similar to the Teleform ® system. Data from the Central Laboratory, the ECG Reading Center and EMSI were transmitted daily by internet.

PA Ancillary Study

An ancillary study proposal for an accelerometer supplement to REGARDS was approved by the REGARDS Executive Committee and developed into a research application that was funded by NIH to the University of South Carolina (USC) in October 2008 for implementation into the ongoing REGARDS follow-up. Consent was obtained verbally by phone. The ancillary study was approved by the IRBs at all participating institutions.

Recruitment for the accelerometer ancillary study occurred May 2009-January 2013. Participant characteristics, collected at time of enrollment into the parent REGARDS study, were used to describe the participants. Age, race, sex, highest education level, annual household income, smoking (current, never, past), PA, physician diagnosis of stroke, history of diabetes,

history of kidney disease/kidney failure and self-rated health status ("In general, would you say that your health is excellent, very good, good, fair, or poor?) were defined by self-report. PA level was defined by numeric response to the open-ended question "How many times per week do you engage in intense PA, enough to work up a sweat?" categorized as 4 or more times per week, 1-3 times a week or none. History of heart disease was defined as self-reported myocardial infarction (MI), coronary artery bypass surgery, coronary angioplasty or stenting, or evidence of MI from study ECG. Body mass index (BMI) was determined as a function of measured height and weight.

PA Measurement.

The accelerometers used were Actical™ activity monitors (Mini Mitter Respironics, Inc., Bend, OR). The choice was based on several factors: validity and reliability, goals of the study (to quantify the frequency, duration, and intensity of PA), cost/convenience in that the investigators had an initial supply on hand to start with (including peripherals such as computer interface and software), cost of supplies to attach the monitor, familiarity with the technology and feasibility/acceptability of use in older adults (Hutto et al., 2013).The initial supply of devices was 600, but with some budget readjustment and additional unrestricted funds, an additional 550 devices were purchased in year 2 to accelerate enrollment.

All active members of the cohort were targeted to be invited to wear an accelerometer. Accelerometer study recruitment began at a slow rate to allow for an assessment of staffing needs, participant cooperation and communication needs, and database systems refinement for tracking of devices, critical dates, supplies, and communications among the SRU, Operations, and USC for data transfer. During one of the participant's routine biannual follow-up telephone calls, when an accelerometer was available, a screening question was asked: "on a typical day, were you physically able to go outside where you live and walk, whether or not you actually do?" When there were no devices currently available, the "switch" was turned off such that the screening question was not asked, and that participant was deferred to potentially be screened on their next follow-up call. If the participant response was "yes," a brief explanation of the purpose of the study was given and the participant was asked if he/she was willing to wear the accelerometer for seven consecutive

days and complete a daily log sheet. If the response was “no,” the participant could be screened again on a subsequent call.

Participants who answered “yes,” to the screening question were invited to participate; they were told it did not matter what their current level of PA was, that the device would arrive in the mail within the next week, and they would need to start wearing the device the day after receipt. Response options were “yes,” a definitive “no” or “not now, maybe later,” i.e., deferred. “Deferred”, indicated that the participant either was not interested or not available at that time to wear the device, and could be asked again on a subsequent follow-up call. If the participant agreed to wear the device (i.e., verbal consent) and indicated availability to do so immediately upon receipt, the SRU notified UAB staff responsible for implementing the accelerometer protocol. Staff initialized the Actical™, attached it to an adjustable nylon belt, and mailed it via regular US mail to the participant along with a cover letter, written and pictorial wear instructions, daily log sheet, protocol check list, and pre-addressed postage-paid, padded, return envelope (also by regular US mail). Instructions included: to wear the device the day after receipt, remove it at bedtime and reattach upon awakening, place the device over the right hipbone crest, make sure the belt was snug around the waist, complete the daily log sheet with start date and time the device was put on and taken off each day, and return the device immediately after wearing for the seven day period. Participants were encouraged to call the REGARDS toll-free telephone number for any questions or concerns. Reminder post cards were mailed two to three days following the initial mailing of the device to encourage compliance including recording and return of log sheet. Additional return efforts included staff initiated follow-up postcards and telephone calls if the device was not received back at UAB within 45 and 65 days, respectively.

Upon return of a device, any available data were downloaded using a serial port computer interface and transferred from UAB to USC. The reusable belts were sent to commercial laundry for cleaning/sanitizing. Batteries in devices were checked and changed if necessary and the device was re-initialized for re-use. Within a few weeks of return of the device, to provide feedback to the

participant, USC performed a preliminary examination of the data to obtain an approximate estimate of wear time and minutes of MVPA (Hutto et al., 2013).

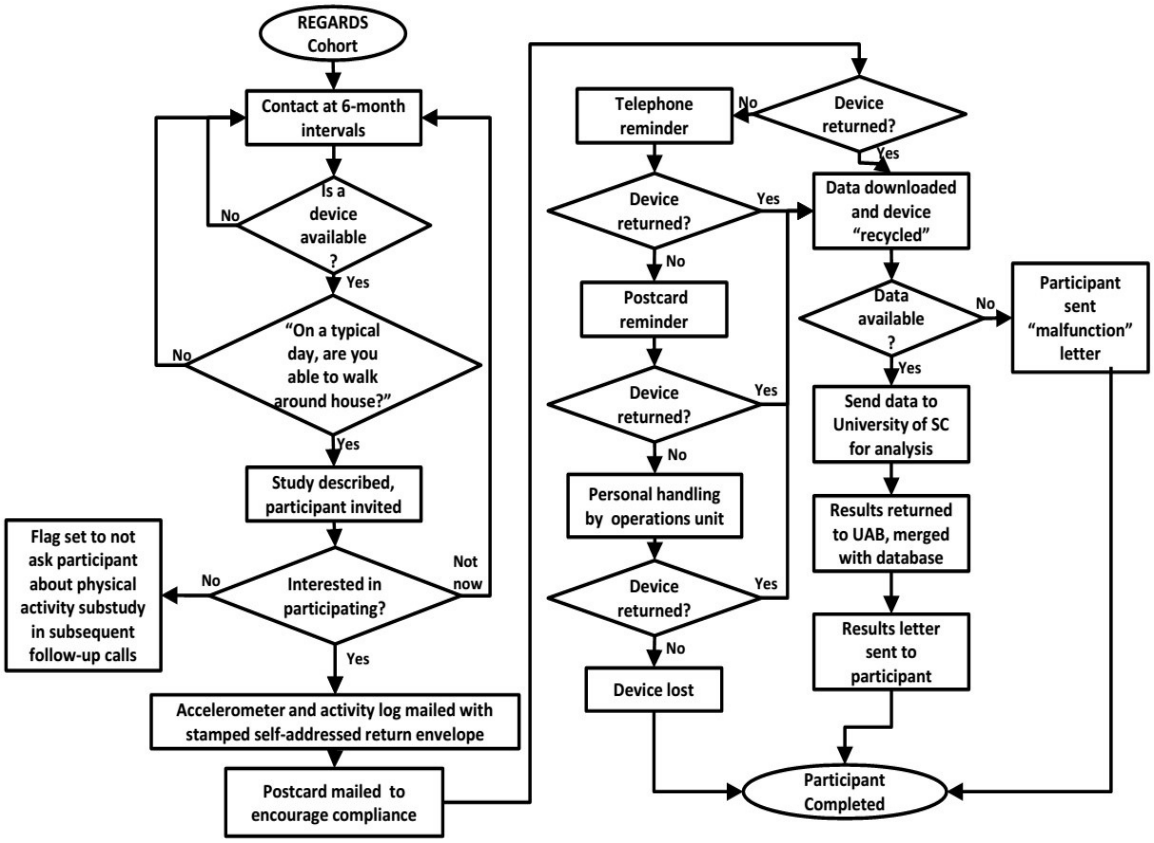


Figure 1. **Processing Flow of REGARDS-PA Study**

Accelerometer data processing.

Participants were asked to complete a one-page daily PA log sheet with two key elements: the date the Actical™ was first worn, and the time(s) put on and taken off for each of the following seven days. As needed, times reported by the internal Actical™ clock were adjusted by 1-3 hours to account for differences in Actical™ time (reset to central time during each battery change) and the time zone in which the participant was living.

A record was excluded for any of the following: (1) missing or illegible time(s) or date(s); (2) uncertainty in the number of hours to adjust the internal Actical™ time-stamp; or (3) self-reported wear dates not corresponding with valid data in the Actical™ file. Some data were also excluded due to device failure or errors (e.g. spurious activity counts >20,000 or lengthy strings of repeated activity counts). Compliant participants wore the device $\geq$10 hours/day on at least four of the seven days (Tudor-Locke, Camhi, & Troiano, 2012). Non-wear periods were defined as times during which no movement was detected for 120 consecutive minutes, and activity count cut-points of 50 counts per minute (cpm) and 1065 cpm were applied to differentiate between sedentary behavior and LPA and LPA and MVPA, respectively (Hooker et al., 2011; Hutto et al., 2013). Additionally, LPA was divided into high light PA (HLPA) and low light PA (LLPA) using the cut-point of 557 cpm, which was the median of between 50 and 1065 cpm.

Sample size.

Of the 20,076 participants who were invited to wear an accelerometer, 12,146 (60.5%) agreed, 7,312 (36.4%) declined, and 618 (3.1%) were deferred and did not have the opportunity to be asked again during the enrollment period. Participation rates did not differ substantially by race-sex groups: black women 58.6%, black men 59.6%, white women 62.3%, and white men 60.5% (Tables 2 and 3.). Of the devices that were mailed, 972 (8.0%) were lost/not returned, 1,187 (9.8%) were returned not worn, 14 (0.11%) were returned and found to be defective such that no data could be downloaded, and 9,973 (82.1%) were returned with data. Of the 9,973 participants who returned and wore the accelerometer, 8,096 (81.1%) provided usable data after exclusions for device error, missing log sheet, and wear time < 4 days with $\geq$ 10 hr/day. Using the denominator of

accelerometers mailed out to 12,146 participants, 66.7% (8,096) provided usable data with the highest yield from white men (74.5%) and lowest from black women (56.1%) (Table 3). Further analysis showed participants who provided valid data were more likely to be well-educated, non-smoker, without diabetes and hypertension, and cognitive impairment, and lower in BMI and systolic and diastolic blood pressure.

Table 2

Final Response to Invitation to Participate in REGARDS Accelerometer Study by Race-Sex Groups (N=20,076)

Sex-Race Group	Asked to wear accelerometer (N=20,076)	Responded Positively (n=12,146)	Responded Not Now and not recontacted (n=618)	Declined to participate (n=7,312)
Black women	4840	2835 (58.6%)	180 (3.7%)	1825 (37.7%)
Black men	2749	1638 (59.6%)	101 (3.7%)	1010 (36.7%)
White women	6411	3995 (62.3%)	185 (2.9%)	2231 (34.8%)
White men	6076	3678 (60.5%)	152 (2.5%)	2246 (37.0%)

Table 3
Tracking of Returned Accelerometers and Usable Data by Race-sex Groups, N=12,146

Accelerometer Return and Usability Category	Total (12,146)	Black Women (2835)	Black Men (1638)	White Women (3995)	White Men (3678)
Lost/not returned	972 (8.0%)	346 (12.2%)	232 (14.2%)	227 (5.7%)	167 (4.5%)
Returned not worn	1,187 (9.8%)	346 (12.2%)	140 (8.5%)	410 (10.3%)	291 (7.9%)
Returned Defective	14 (0.1%)	5 (0.2%)	1 (0.1%)	4 (0.1%)	4 (0.1%)
Returned and worn	9,973 (82.1%)	2138 (75.4%)	1265 (77.2%)	3354 (84.0%)	3216 (87.4%)
• Less those with device errors	231	53	31	85	62
• Less those missing log sheet	952	275	161	287	229
• Less those with < 4 days wear time	694	220	104	186	184
• Final: those with usable data (% of those who wore it)	8,096 (81.1%)	1,590 (74.4%)	969 (76.6%)	2,796 (83.4%)	2,741 (85.2%)

Cognition Assessments

The REGARDS cognitive assessment was designed to be: 1) sensitive to Vascular Cognitive Impairment (VCI), 2) consistent with the goals of the National Institute of Neurological Disorders and Stroke and the Canadian Stroke Network (NINDS-CSN) VCI Harmonization Standards (Hachinski, 2006), 3) brief (gathered in under 15 minutes), and 4) amenable to telephone administration using customized technology. The measures can be combined to form composite indices representing cognitive domains affected by VCI.

The cognitive assessments being performed included two groups (Table 4):

1. The Six-item Screener (SIS) provided a screening assessment of global cognitive function. It resulted in a dichotomous outcome (impaired versus not impaired).

2. Four expanded cognitive battery tests demonstrated usefulness in the early identification of Alzheimer's disease or dementia (J. C. Morris et al., 1989). These tests were Word List Learning (WLL) and semantic fluency (animals fluency, AF) from the Consortium to Establish a Registry for Alzheimer's Disease battery (CERAD), and letter fluency (LF), recall and orientation items from Montreal Cognitive Assessment (MoCA). These tests assessed domains of memory (WLL, MoCA-recall and orientation) and executive function (AF, LF). Acceptable reliability and validity of these cognitive battery tests have been previously reported (J. C. Morris et al., 1989).

Table 4

Summary of Cognitive Function Assessment

	Measure	Score	Occasions of Measurement
Screener of Overall Cognitive Function			
Global Cognitive Status	Six-item Screener (SIS)	Number correct (0-6) Dichotomous categorization (intact, impaired)	Measured on an annual basis (months 12, 24, 36 …)
Expanded Battery of Cognitive Domains			
Memory	Word List Learning (WLL)	Sum of 3 learning trials (0-30)	Measured on a biennial basis starting with month 18 (months 18, 42, 66, 90, 114)
	Montreal Cognitive Assessment (MoCA) - Recall	Number correct (0-5)	
	MoCA -Orientation	Number correct (0-6)	
Executive function	Animal Fluency (AF)	Number correct in 60 seconds	
	MoCA -Letter Fluency (LF)	Number correct in 60 second	

Six-item Screener.

The Six-item Screener (SIS) (Callahan et al., 2002) was administered by telephone in REGARDS. It consisted of 3-item recall and 3-item temporal orientation. For telephone administration, we modified the instructions for 3-item recall to include "please do not write anything down," and for the orientation items, we modified the instruction by prefacing each item with the phrase, "Without looking at a calendar or a watch," "what [year/month/day of the week] is this?" The SIS was performed during baseline telephone interviews beginning in December, 2003 (11 months after enrollment began) and during the follow-up period on an annual basis. Scores on the SIS range from 0 to 6, with a score of 4 or fewer correct responses indicating cognitive impairment. The SIS has been validated in both community and clinical samples and among both black and white adults (Callahan et al., 2002). Its sensitivity and specificity to a combined endpoint of clinically diagnosed dementia and mild cognitive impairment are 74% and 80% respectively in community samples (Callahan et al., 2002).

Word List Learning.

Word List Learning (WLL), from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery (J. C. Morris et al., 1989), were telephone administered in REGARDS. These measures were first incorporated into the REGARDS follow-up telephone interviews in Jan. 2006 during assessments occurring at 18-mo. intervals. The frequency of assessment was changed to 2-yr. intervals in Feb. 2008. The list learning portion consists of three learning trials of a list of 10 semantically-unrelated words which are presented in a fixed order that varies across the three trials, followed by a free recall trial after a 5-minute delay filled with non-cognitive interview questions. In REGARDS, this measure was administered according to the standard protocol, with two modifications for telephone administration: (1) no simultaneous visual presentation of the word list and (2) participants were instructed not to write anything down. In addition, a recognition trial was not administered in REGARDS. The instructions for each learning trial, including the oral presentations of the word list, were administered via a recording so that all participants were exposed to the same narration, thereby avoiding any differences in dialect, tone, gender, or volume

that might affect participants' performance. For list learning, the scores from the three trials were summed, yielding a score ranging from 0-30, after excluding repetitions (repeating the same word more than once) and intrusions (including a word not on the list).

Because telephone administration of these measures is associated with the opportunity for non-standard behavior among participants (such as writing down the lists despite the instruction not to do so), REGARDS developed a procedure for flagging performance patterns that were statistically and conceptually unlikely to occur by chance. Specifically, the score of any participant who responded to a learning trial with all 10 words, in the exact order presented on that trial or a prior trial, was flagged. In addition, the score of any participant whose score on the part of Delayed Recall trial was 3 or more points higher than their score on any learning trial was flagged (e.g., maximum of 7 on one of three learning trials, and score of 10 on the delayed recall trial). The REGARDS Cognitive Function Working Group consisting of selected REGARDS investigators and outside experts discussed and approved this procedure. In data analyses, participants with non-standard performance patterns may be excluded, or an indicator for suspect performance profiles may be used as a covariate in analyses. Of note, < 2% of REGARDS participants showed these non-standard response patterns.

Semantic and Phonemic Fluency.

The Semantic Fluency Test (Animal Fluency, AF) was first implemented into follow-up telephone interviews in Jan. 2006 and subsequently at 18-mo. intervals on a different follow-up schedule than WLL. The interval was changed to 2-yr. intervals and on the same follow-up schedule as WLL and WLD in Feb. 2008. Phonemic Fluency (Letter F, LF) was first implemented into follow-up interviews in Feb 2008 and currently was administered at 2-yr. intervals concurrently with WLL, WLD, AFT, and the remainder of the short battery. The fluency measures require participants to name as many words as they can beginning with the letter 'F', and subsequently, to name as many animals as they can. The time allotted for each measure is 1 minute. Raw scores on each consist of the total number of valid responses produced by each participant in 60 seconds, after subtracting repetition and intrusion errors.

With explicit verbal permission from the study participants, the assessments were recorded in WAV files at the time of survey and then played back later for scoring by trained college-educated scorers, following written scoring protocols, facilitated by computer-assisted scoring programs developed for REGARDS. These programs capture several variables beyond raw total scores that were used as secondary indices of processing speed and executive function (i.e., number of words produced in 15-sec. increments, order of responses for inspection of clustering strategies and switching frequency, number of intrusion errors, etc.). Ongoing quality control efforts consisted of evaluating scorers' agreement with an expert scorer.

Montreal Cognitive Assessment (MoCA)-Recall and Orientation Items.

The Recall and Orientation Items consists of selected subtests of the Montreal Cognitive Assessment (MoCA) : 5-word delayed memory recall, and 6-item orientation. The full MoCA instrument was designed to detect individuals with milder degrees of cognitive impairment, who may score within the normal range on other bedside cognitive tests (Nasreddine et al., 2005). The recall and orientation items from the MoCA were implemented into follow-up telephone assessments beginning in Mar. 2009 at 2-yr. intervals. For telephone administration in REGARDS, the spatial orientation items (place and city) were modified such that the participant was asked his or her street address and city (confirmed by the interviewer via a pre-populated field in the computer script).

Composite measures of two cognitive domains (memory and executive function) were created by converting each battery test into a z-score based on the mean and standard deviation for that specific test's results among all participants. The mean of the z-scores of memory and executive function was calculated as cognitive battery z-score presenting the average level of memory and executive domains. For participants only having results in one domain, the available records were considered as the cognitive battery z-score.

Study 1 Cross-sectional analysis

Participants.

This study included 7,339 participants of the 8,096 participants (out of the 20,076 participants who were invited to wear an accelerometer). Participants were excluded if they: 1. had self-reported stroke at baseline (n=264); 2. were identified as cognitively impaired >12 months prior to PA assessment (n=383); 3. had an incident stroke prior to wearing the accelerometer (n=6); 4. had no record of valid PA measurement associated with SIS assessment within ±12 months of PA assessment (n=104).

Independent and dependent variables.

The primary independent variables are the time spent in MVPA, LPA, and sedentary time, and the proportion of total wear time spent in MVPA (MVPA%), LPA (LPA%), sedentary time (SED%). Due to inherent variability in daily accelerometer wear time, we chose MVPA%, LPA% and SED% rather than the absolute time spent in PA as the main standard for quartiles of the independent variable to render results comparable among individuals.

Dependent variables were cognitive status (impairment or not) measured by SIS, and z-scores generated from WLL, AF, LF and MoCA-recall and orientation. We chose the most recent cognitive tests conducted closest to the time point of the PA measurement within a time range of ±12 months. Sensitivity analyses were conducted and it was decided to use tests conducted closest to the time point of the PA measurement within a time range of ±12 months to reach a larger sample size.

Statistical Analysis.

Differences in demographic variables, PA variables, and cognitive tests records across quartiles were tested by Analysis of Variance (continuous variables) or Chi-square tests (categorical variables). Differences in demographic variables, PA variables, and cognitive tests records across race/gender subgroups were also tested by Analysis of Variance (continuous variables) or Chi-square tests (categorical variables). Pearson product-moment correlation

coefficients were tested among different PA variables. Associations between PA (or sedentary time) and cognitive impairment were examined using multivariate logistic regression models. In the logistic models, Model 1 was unadjusted. Model 2 adjusted for age, sex, race, region of residence, and education. Model 3 adjusted for age, sex, race, region of residence, education, BMI, hypertension, smoking, and diabetes, each of which may be intermediate in the causal pathway between PA (or sedentary time) and cognitive function. Odds ratios (ORs) and 95% confidence intervals (CIs) were generated from logistic regression models. General Linear regression models with adjustment for potential confounders were used to assess the association between PA (or sedentary time) and standardized composite scores generated from WLL, AF, LF and MoCA-recall and orientation. Trend across quartiles was determined by entering quartile of PA variables into the regression models as continuous variables. We conducted similar analysis for quartiles of MVPA%, LPA%, and SED%. All probability values were based on 2-tailed tests; $P<0.05$ was taken to indicate statistical significance. Analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC).

Study 2 Longitudinal analysis

Participants.

The cohort in Study 1 were analyzed as the baseline cohort in this study. Participants were excluded if they:

1. had an incident stroke before the most recent follow-up SIS assessment within 24 months after the date of wearing the accelerometer (n=3);
2. had an incident cognitive impairment before the most recent follow-up SIS assessments within 24 months after the date of wearing the accelerometer (n=140);
3. No SIS assessment during the follow-up period of 24 months or more after the date of wearing the accelerometer (n=3811).

Independent and dependent variables.

The primary independent variables were MVPA%, LPA%, SED%.

We used the cognitive function tests for the cross-sectional analysis mentioned above as the baseline measurements of this longitudinal analysis. The main dependent variable was incident cognitive impairment defined as a shift from intact cognitive screening status (score of 5 or 6 correct on the SIS assessment) at the closest assessment to the baseline PA measurement to impaired cognitive screening status (score of 4 or fewer correct) at the latest follow-up assessment. The incidence derived from SIS served as the measure of global cognitive function among white and black older adults. The secondary dependent variables were the change of z-scores in the domains of memory or executive function.

Statistical Analysis.

For longitudinal analysis, cognitive function tests that were obtained, scored, and included in the REGARDS study dataset by December, 2014 were used. Similar analysis with the participants included was conducted for differences in demographic variables, PA variables, and cognitive tests records across quartiles or race/gender subgroups by Analysis of Variance (continuous variables) or Chi-square tests (categorical variables). Logistic regression analysis was selected to assess the probability of being impaired by SIS at the most recent available assessment. Differences in incident cognitive impairment across various quartiles of independent variables (MVPA%, LPA%, and SED%) were examined after multivariate adjustment for age, sex, race, region of residence, education, BMI, hypertension, smoking, and diabetes, as well as the time interval between each participant's baseline and most recent assessment, which varied depending upon the date of enrollment. Odds ratios (ORs) and 95% confidence intervals (CIs) were generated from the regression models.

Survival analyses using Cox proportional hazards regression models were also conducted to determine whether censoring cases following the first occurrence of an SIS score indicative of cognitive impairment would produce results different than the regression approach in which we considered only the most recent assessments for capturing incident cognitive impairment. Person-time for each participant was computed from the date of the baseline assessment to the date of cognitive impairment, or the date of the most recent assessment. Incidence rates were calculated

as the number of cases divided by person-time follow-up. Cox proportional hazards regression analysis was used to estimate hazard ratios (HRs) and the associated 95% CIs. The proportional hazards assumption was confirmed with log-cumulative survival plots. In multivariable analyses, adjustments were made for age, sex, race, region of residence, education, BMI, hypertension, smoking, and diabetes.

General Linear regression models with adjustment for potential confounders, baseline scores and time intervals were used to assess the association between PA (or sedentary time) and the changes of z-scores generated from WLL, AF, LF and MoCA-recall and orientation during follow-up.

All probability values were based on 2-tailed tests; $P<0.05$ was taken to indicate statistical significance. Analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC).

CHAPTER 4

RESULTS

Study 1

Demographics, PA and cognitive function status are displayed in Tables 5 and 6 according to quartiles of MVPA%. Among the 7,339 participants, 54.2% were women, 31.7% were black, 54.6% were living in the Stroke Belt, and 4.4% exhibited impaired cognitive status at the assessment within ± 12 months of the PA measurement. The mean (±SD) time between PA assessment and each cognitive assessment was 5.4 ± 3.8 months. The mean (±SD) age of all participants was 70.1 ± 8.6 years, and they wore the accelerometer for 6.6 ± 0.8 days. Participants spent most of their wear time in sedentary behavior (69.9% ± 8.1%) and LPA (26.6% ± 7.7%). MVPA% was extremely limited (1.4% ± 1.9%). There were significant differences across quartiles of MVPA% in all variables listed in Table 6 ($P<0.001$). Participants with higher MVPA% were more likely to be men, white, younger, well-educated, non-smoker, without diabetes, hypertension, and cognitive impairment, and lower in BMI and systolic and diastolic blood pressure. Participants in the higher MVPA% quartiles also spent more time in HLPA and LLPA. Participants with higher level of MVPA had higher raw scores in WLL, AF, LF, and MoCA-recall and orientation, and higher z-scores in executive function and memory. A higher level of MVPA% was associated with lower prevalence of cognitive impairment as measured by SIS. There were fewer individuals with cognitive impairment in the highest MVPA% quartile (2.2%) than in the lowest MVPA% quartile (6.7%).

Table 5

Baseline Characteristics of Participants by Level of Moderate to Vigorous Physical Activity (% or mean ± SD， N = 7,339)

Variable	Quartile[a] 1	Quartile 2	Quartile 3	Quartile 4	Total
Women, n (%)	1213 (65.8)	1043 (57.5)	943 (51.2)	779 (42.4)[b]	3978 (54.2)
African American, n (%)	779 (42.3)	632 (34.8)	521 (28.3)	391 (21.3)[b]	2323 (31.7)
Stroke-belt, n (%)	1028 (55.8)	1017 (56.0)	1025 (55.7)	938 (51.0)[b]	4008 (54.6)
Education, n (%)					
Less than high school	211 (11.4)	113 (6.2)	88 (4.8)	50 (2.7)	462 (6.3)
High school graduate	560 (30.4)	455 (25.1)	383 (20.8)	266 (14.5)	1664 (22.7)
Some college	505 (27.4)	572 (31.5)	480 (26.1)	399 (21.7)	1956 (26.7)
College graduate and above	568 (30.8)	675 (37.2)	890 (48.3)	1124 (61.1)[b]	3257 (44.4)
Smoking, n (%)	263 (14.3)	229 (12.6)	180 (9.8)	115 (6.3)[b]	787 (10.7)
Hypertension, n (%)	1271 (68.9)	1008 (55.5)	864 (46.9)	671 (36.5)[b]	3814 (52.0)
Diabetes, n (%)	473 (25.7)	317 (17.5)	221 (12.0)	166 (9.0)[b]	1177 (16.0)
Age (yr)	75.2±8.1	70.9±7.7	68.0±7.9	66.2±7.8[b]	70.1±8.6
Body Mass Index ($kg*m^{-2}$)	30.1±6.4	29.3±5.8	28.4±5.3	26.9±4.7[b]	28.7±5.7
Systolic blood pressure (mmHg)	130.1±16.3	126.5±15.5	124.5±14.9	121.4±14.3[b]	125.6±15.6
Diastolic blood pressure (mmHg)	76.4±9.6	76.4±9.4	76.4±9.2	75.7±8.7[b]	76.2±9.2

[a] Denotes the quartiles of the proportion of total time spent in moderate to vigorous physical activity.

[b] Denotes significant difference among quartiles (P<0.001), tested by Analysis of Variance (continuous variables) or Chi-square (categorical variables)

Table 6

Baseline Physical Activity and Cognitive Function by Level of Moderate to Vigorous Physical Activity (% or mean ± SD，N = 7,339 unless otherwise noted)

Variable	Quartile[a] 1	Quartile 2	Quartile 3	Quartile 4	Total
Compliance (days with valid wear)	6.5±0.9	6.6±0.8	6.6±0.8	6.7±0.7[l]	6.6±0.8
Total wear time (min/day)	869.7±117.8	885.8±104.7	897.7±99.9	910.7±93.2[l]	890.9±105.4
MVPA[b] (min/day)	0.4±0.4	3.3±1.5	11.1±3.9	37.0±19.4[l]	13.0±17.5
HLPA[c] (min/day)	5.9±5.2	17.0±8.9	28.6±14.4	41.2±21.1[l]	23.2±19.1
LLPA[d] (min/day)	111.7±55.0	165.1±55.5	185.1±58.1	194.0±55.3[l]	163.9±64.5
Sedentary time (min/day)	751.6±120.2	700.4±109.2	672.9±105.6	638.5±107.3[l]	690.9±118.2
MVPA%[e]	0.05±0.05	0.37±0.15	1.24±0.40	4.06±2.09[l]	1.43±1.91
HLPA%[f]	0.7±0.6	1.9±1.0	3.2±1.6	4.6±2.3[l]	2.6±2.1
LLPA%[g]	12.9±6.2	18.8±6.3	20.8±6.3	21.5±6.1[l]	18.5±7.1
SED%[h]	86.3±6.7	78.9±6.9	74.8±7.5	69.9±8.1[l]	77.5±9.5
Cognitive impairment[i] , n (%)	124 (6.7)	96 (5.3)	60 (3.3)	40 (2.2)[l]	320 (4.4)
Letter fluency score (n=5,524)	10.6±4.4	11.4±4.5	12.1±4.5	12.7±4.9[l]	11.7±4.6
Animal fluency score (n=6,620)	15.8±5.2	17.7±5.4	18.7±5.8	20.3±6.0[l]	18.2±5.8
Word list learning score[j] (n=6,411)	16.5±5.2	17.8±4.7	18.6±4.7	19.2±4.3[l]	18.1±4.8
MoCA[k] recall and orientation (n=6,568)	9.7±1.5	10.0±1.3	10.1±1.3	10.1±1.3[l]	10.0±1.4
Average cognitive z-score[m] (n=6,669)	-0.32±0.80	-0.05±0.76	0.09±0.76	0.25±0.76	0±0.80
Executive function z-score[n] (n=6,565)	-0.41±0.89	-0.07±0.93	0.08±0.98	0.36±1.03	0±1.00
Memory z-score[o] (n=6,635)	-0.28±1.16	0±1.05	0.12±1.04	0.22±0.98	0.02±1.07

[a] Denotes the quartiles of the proportion of total time spent in moderate to vigorous physical activity.
[b] MVPA refers to moderate to vigorous physical activity.
[c] HLPA refers to high light physical activity.
[d] LLPA refers to low light physical activity.
[e] Denotes the proportion of total wear time spent in moderate to vigorous physical activity.
[f] Denotes the proportion of total wear time spent in high light physical activity.
[g] Denotes the proportion of total wear time spent in low light physical activity.
[h] Denotes the proportion of total wear time spent in sedentary behavior.
[i] Cognitive impairment is defined as a score of 4 or fewer correct responses in six-item screener. The score ranges from 1 to 6, consisting of a 3-item recall and 3-item temporal orientation.
[j] Word List Learning Score (WLL) is from the Consortium to Establish a Registry for Alzheimer's Disease battery (0-30).
[k] MoCA refers to Montreal Cognitive Assessment, including a 5-word delayed memory recall test (0-5), and 6-item orientation test (0-6).
[l] Denotes significant difference among quartiles (P<0.001), tested by Analysis of Variance (continuous variables) or Chi-square tests (categorical variables).
[m] Average cognitive z-score refers to the average of mean executive score and mean memory score.
[n] Executive z-score refers to the average of standardized scores of letter fluency and animal fluency tests. For participants with only one executive test, the mean score would be the result of that test.
[o] Memory z-score refers to the average of standardized scores of word list learning and MoCA recall and orientation tests. For participants with only one executive test, the mean score would be the result of that test.

Differences in PA and cognitive function variables across race/gender subgroups are displayed in Table 7. There were significant differences across race/gender groups in all variables listed in Table 7 ($P<0.001$). Most participants, either white or black, male or female, were quite compliant to the accelerometer procedure. White males accumulated the most MVPA and HLPA, while black females had the least MVPA. Black male were the most sedentary group, and had the highest prevalence of cognitive impairment. White female older adults accumulated more LLPA than any other groups. They had the best performance in the domains of executive function and memory, and lowest rate of cognitive impairment among these four groups.

Table 7

Baseline Physical Activity and Cognitive Function by Race/Sex (% or mean ± SD，N = 7,339 unless otherwise noted)

Variable	Black female (n=1,458)	Black male (n=865)	White female (n=2,520)	White male (n=2,496)
Compliance (days with valid wear)	6.4±0.9	6.5±0.8	6.7±0.7	6.7±0.7[l]
Total wear time (min/day)	885.4±125.6	900.6±130.1	885.7±91.8	896.2±94.9[l]
MVPA[a] (min/day)	7.8±12.5	11.8±16.0	11.9±16.0	17.5±20.7[l]
HLPA[b] (min/day)	16.5±14.8	23.1±19.0	21.7±17.3	28.8±21.3[l]
LLPA[c] (min/day)	157.1±69.7	155.5±68.4	171.9±62.8	163.0±60.6[l]
Sedentary time (min/day)	704.1±133.1	710.3±136.1	680.3±108.9	686.9±110.1[l]
MVPA%[d]	0.9±1.4	1.3±1.7	1.3±1.7	1.9±2.3[l]
HLPA%[e]	1.9±1.6	2.6±2.1	2.4±1.9	3.2±2.3[l]
LLPA%[f]	17.9±7.7	17.4±7.4	19.5±7.0	18.2±6.6[l]
SED%[g]	79.4±9.5	78.8±9.9	76.7±9.1	76.6±9.4[l]
Cognitive impairment[h] , n (%)	83 (5.7)	72 (8.3)	52 (2.1)	113 (4.5)[l]
Letter fluency score[i] (n=5,524)	11.1±4.7	11.0±4.4	12.4±4.6	11.7±4.7[l]
Animal fluency score[j] (n=6,620)	15.5±5.1	16.5±5.1	19.2±5.8	19.1±5.8[l]
Word list learning score[k] (n=6,411)	17.7±5.0	15.9±4.6	19.7±4.5	17.2±4.6[l]
MoCA[m] recall and orientation (n=6,568)	10.0±1.3	9.6±1.5	10.3±1.2	9.8±1.5[l]
Average cognitive z-score[m] (n=6,669)	-0.16±0.77	-0.32±0.80	0.24±0.72	-0.05±0.81[l]
Executive function z-score[n] (n=6,565)	-0.46±0.88	-0.28±0.88	0.18±0.99	0.17±1.00[l]
Memory z-score[o] (n=6,635)	0±1.05	-0.36±1.07	0.33±0.95	-0.15±1.13[l]

[a] MVPA refers to moderate to vigorous physical activity.
[b] HLPA refers to high light physical activity.
[c] LLPA refers to low light physical activity.
[d] Denotes the proportion of total wear time spent in moderate to vigorous physical activity.
[e] Denotes the proportion of total wear time spent in high light physical activity.
[f] Denotes the proportion of total wear time spent in low light physical activity.
[g] Denotes the proportion of total wear time spent in sedentary behavior.
[h] Cognitive impairment is defined as a score of 4 or fewer correct responses in six-item screener. The score ranges from 1 to 6, consisting of a 3-item recall and 3-item temporal orientation.
[i] Sample sizes for each race/sex category were: 1,034 (black female), 585 (black male), 2,001 (white female), 1,857 (white male), respectively.
[j] Sample sizes for each race/sex category were: 1,283 (black female), 717 (black male), 2,341 (white female), 2,224 (white male), respectively.
[k] Word List Learning Score is from the Consortium to Establish a Registry for Alzheimer's Disease battery (0-30). Sample sizes for each race/sex category were: 1,230 (black female), 702 (black male), 2,264 (white female), 2,166 (white male), respectively.
[m] MoCA refers to Montreal Cognitive Assessment, including a 5-word delayed memory recall test (0-5), and 6-item orientation test (0-6). Sample sizes for each race/sex category were: 1,267 (black female), 707 (black male), 2,217(white female), 1,857 (white male), respectively.
[l] Denotes significant difference among quartiles (P<0.001), tested by Analysis of Variance (continuous variables) or Chi-square tests (categorical variables).
[m] Average cognitive z-score refers to the average of mean executive score and mean memory score.
[n] Executive z-score refers to the average of standardized scores of letter fluency and animal fluency tests. For participants with only one executive test, the mean score would be the result of that test.
[o] Memory z-score refers to the average of standardized scores of word list learning and MoCA recall and orientation tests. For participants with only one executive test, the mean score would be the result of that test.

Correlation between measures of PA are listed in Table 8 and Table 9. All the PA variables were significantly associated with each other ($P<0.001$). Sedentary time was negatively associated with all the other PA variables. Higher correlation coefficients were found between sedentary time and LLPA, LLPA and HLPA, and HLPA and MVPA.

Table 8

Pearson Correlation Coefficients between Measures of Physical Activity (min)

	SED[a]	LLPA[b]	HLPA[c]	MVPA[d]
SED[a]	1	-0.48	-0.46	-0.27
LLPA[b]	-0.48	1	0.66	0.32
HLPA[c]	-0.46	0.66	1	0.63
MVPA[d]	-0.27	0.32	0.63	1

[a] SED refers to sedentary time.
[b] LLPA refers to low light physical activity.
[c] HLPA refers to high light physical activity.
[d] MVPA refers to moderate to vigorous physical activity.

Table 9

Pearson Correlation Coefficients between Measures of Physical Activity (%)

	SED%[a]	LLPA%[b]	HLPA%[c]	MVPA%[d]
SED%[a]	1	-0.95	-0.82	-0.55
LLPA%[b]	-0.95	1	0.64	0.28
HLPA%[c]	-0.82	0.64	1	0.61
MVPA%[d]	-0.55	0.28	0.61	1

[a] Denotes the proportion of total wear time spent in sedentary behavior.
[b] Denotes the proportion of total wear time spent in low light physical activity.
[c] Denotes the proportion of total wear time spent in high light physical activity.
[d] Denotes the proportion of total wear time spent in moderate to vigorous physical activity.

Results of logistic regression analyses are displayed in Table 10. In the unadjusted model (Model 1), those participants in the highest MVPA% quartile were 69% less likely to have cognitive impairment compared with those in the lowest quartile (OR [95% CI] =0.31 [0.22-0.44]). After adjustment for age, sex, race, region of residence, and education (Model 2), significance remained. Participants in the highest quartile were 42% less likely to have cognitive impairment (OR [95% CI] =0.58 [0.39-0.87]). In the fully adjusted model (Model 3), results were consistent with Model 2, with participants in the highest MVPA% quartile 39% less likely to have cognitive impairment (OR [95% CI] =0.61 [0.39-0.95]). There was a significant trend of difference across quartiles ($P<0.05$). Similar analyses with HLPA%, LLPA% and SED% did not reveal any significant associations ($P>0.05$) with the odds of cognitive impairment. Additionally, logistic regression analysis categorizing participants as accumulating more or less than 150 min/wk of MVPA indicated older adults were 38% less likely to have cognitive impairment if they accumulated ≥150 min/wk of MVPA (OR [95% CI] =0.62 [0.42-0.92]) after full adjustment. Subgroup logistic analyses were conducted for each race/sex group, but significance was not maintained. When using MVPA% as a continuous variable, there was no significant association between MVPA% and the prevalence of cognitive impairment when adjusted for confounders in Models 2 and 3 ($P>0.05$).

Table 10

Baseline Prevalence of Cognitive Impairment by Quartiles of Moderate to Vigorous Physical Activity (MVPA)

		Model 1[a]		Model 2[b]		Model 3[c]	
		O.R.	95.0% C.I.	O.R.	95.0% C.I.	O.R.	95.0% C.I.
MVPA%[d]	Q1(low)[e]	Ref.		Ref.		Ref.	
	Q2	0.78	0.59-1.02	1.05	0.78-1.40	1.05	0.77-1.45
	Q3	**0.47**	**0.34-0.64**	0.75	0.53-1.05	0.78	0.54-1.13
	Q4(high)	**0.31**	**0.22-0.44**	**0.58**	**0.39-0.87**	**0.61**	**0.39-0.95**
Weekly MVPA[f] (min)	<150min	Ref.		Ref.		Ref.	
	≥150min	**0.39**	**0.27-0.57**	**0.61**	**0.42-0.90**	**0.62**	**0.42-0.92**

[a] Unadjusted regression model.
[b] Adjusted by age, sex, race, region of residence, and education.
[c] Adjusted by age, sex, race, region of residence, education, body mass index, hypertension, smoking and diabetes.
[d] Denotes the proportion of total time spent in moderate to vigorous physical activity.
[e] Denotes the quartiles of the proportions of total time spent in moderate to vigorous physical activity. Q1 refers the lowest quartile, and Q4 refers the highest quartile.
[f] The U.S. Physical Activity Guidelines recommended older adults perform ≥150 minutes of moderate to vigorous physical activity per week.[24]

Results of race/sex subgroup analyses of the association between PA and the prevalence of cognitive impairment are displayed in Tables 11 and 12. The association between PA and cognitive function were not significant within each race/sex groups ($P>0.05$), except Quartile 4 in black female ($P<0.05$). Race and sex were significant moderator in the relationship between PA and cognitive function in this population.

Table 11

Baseline Prevalence of Cognitive Impairment by Race/Sex and Quartiles of Moderate to Vigorous Physical Activity (MVPA%[a])

		O.R.[b]	95.0% C.I.
Black Female	Q1(low)[c]	Ref.	
	Q2	1.00	0.58-1.74
	Q3	0.51	0.24-1.09
	Q4(high)	**0.29**	**0.10-0.89**
Black Male	Q1(low)	Ref.	
	Q2	1.43	0.76-2.69
	Q3	0.85	0.39-1.86
	Q4(high)	0.74	0.29-1.87
White Female	Q1(low)	Ref.	
	Q2	0.98	0.48-2.01
	Q3	0.73	0.30-1.75
	Q4(high)	0.85	0.32-2.26
White Male	Q1(low)	Ref.	
	Q2	0.93	0.54-1.58
	Q3	0.96	0.54-1.69
	Q4(high)	0.67	0.35-1.29

[a] Denotes the proportion of total time spent in moderate to vigorous physical activity.
[b] Adjusted by age, sex, race, region of residence, education, body mass index, hypertension, smoking and diabetes.
[c] Denotes the quartiles of the proportions of total time spent in moderate to vigorous physical activity. Q1 refers the lowest quartile, and Q4 refers to the highest quartile.

Table 12

Baseline Prevalence of Cognitive Impairment by Race/Sex and Whether Meet the Physical Activity Guideline or Not[a]

		O.R.[b]	95.0% C.I.
Black Female	<150 min	Ref.	
	>=150 min	**0.20**	**0.05-0.86**
Black Male	<150 min	Ref.	
	>=150 min	0.87	0.39-1.95
White Female	<150 min	Ref.	
	>=150 min	1.02	0.43-2.42
White Male	<150 min	Ref.	
	>=150 min	0.63	0.35-1.13

[a] The U.S. Physical Activity Guidelines recommends older adults perform ≥150 minutes of moderate to vigorous physical activity per week.[24]

[b] Adjusted by age, sex, race, region of residence, education, body mass index, hypertension, smoking and diabetes.

[c] Denotes the total time spent in moderate to vigorous physical activity per week.

Table 13 has shown there were 6,565 participants with at least one test of AF or LF in the domain of executive function (with 77% of those having both tests). Additionally, 6,669 participants had at least one z-score of memory or executive function (with 85% of those having both tests). Linear regression models revealed a significant association (P<0.001) between MVPA% and both cognitive function domains in the unadjusted model. These relationships remained significant when controlling for age, sex, race, region of residence, and education. When analyses were further adjusted for BMI, hypertension, smoking and diabetes, MVPA% remained significantly associated with z-scores of executive function, memory, and their average combined score. There was a significant trend of difference across quartiles in z-scores of executive function, memory, and their average combined score (P<0.001).

Table 13

*Association of Quartiles of **Moderate to Vigorous Physical Activity** with Z-scores of Expanded Cognitive Battery Tests at Baseline*

		Model 1[a]			Model 2[b]			Model 3[c]		
		Beta	SE	P	Beta	SE	P	Beta	SE	P
Average cognitive z-score[e] (N=6,669)	Q1(low)[d]									
	Q2	0.27	0.03	**<0.001**	0.12	0.03	**<0.001**	0.10	0.03	**<0.001**
	Q3	0.40	0.03	**<0.001**	0.15	0.03	**<0.001**	0.12	0.03	**<0.001**
	Q4(high)	0.57	0.03	**<0.001**	0.22	0.03	**<0.001**	0.18	0.03	**<0.001**
Executive function z-score[f] (N=6,565)	Q1(low)[d]									
	Q2	0.35	0.04	**<0.001**	0.13	0.03	**<0.001**	0.12	0.03	**<0.001**
	Q3	0.49	0.04	**<0.001**	0.11	0.03	**<0.001**	0.09	0.04	**0.009**
	Q4(high)	0.79	0.04	**<0.001**	0.26	0.04	**<0.001**	0.23	0.04	**<0.001**
Memory z-score[g] (N=6,635)	Q1(low)[d]									
	Q2	0.26	0.04	**<0.001**	0.13	0.04	**<0.001**	0.11	0.04	**0.006**
	Q3	0.37	0.04	**<0.001**	0.15	0.04	**<0.001**	0.12	0.04	**0.003**
	Q4(high)	0.50	0.04	**<0.001**	0.21	0.04	**<0.001**	0.16	0.04	**<0.001**

[a] Unadjusted regression model.
[b] Adjusted by age, sex, race, region of residence and education.
[c] Adjusted by age, sex, race, region of residence, education, body mass index, hypertension, smoking and diabetes.
[d] Denotes the quartiles of the proportion of total time spent in moderate to vigorous physical activity. Q1 refers the lowest quartile, and Q4 refers to the highest quartile.
[e] Average cognitive z-score refers to the average of mean executive score and mean memory score.
[f] Executive z-score refers to the average of standardized scores of letter fluency and animal fluency tests. For participants with only one executive test, the mean score would be the result of that test.
[g] Memory z-score refers to the average of standardized scores of word list learning and MoCA recall and orientation tests. For participants with only one executive test, the mean score would be the result of that test. MoCA refers to Montreal Cognitive Assessment, including a 5-word delayed memory recall test, and a 6-item orientation test.

Linear regression models (Table 14) revealed a significant association (P<0.001) between HLPA% and both cognitive function domains in the unadjusted model. These relationships remained significant when controlling for age, sex, race, region of residence, and education, except for HLPA% Quartile 2 for executive function z-score. When analyses were further adjusted for BMI, hypertension, smoking and diabetes, HLPA% remained significantly associated with z-scores of memory, executive function (highest HLPA% quartile only), and their average combined score (P<0.05). There was a significant trend of difference across quartiles in z-scores of executive function, memory, and their average combined score (P<0.001). Similar analyses with LLPA% and SED% did not reveal any significant associations (P>0.05) with the odds of cognitive impairment.

Table 14

*Association of Quartiles of **High Light Physical Activity** with Z-scores of Expanded Cognitive Battery Tests at Baseline*

		Model 1[a]			Model 2[b]			Model 3[c]		
		Beta	SE	P	Beta	SE	P	Beta	SE	P
Average cognitive z-score[e] (N=6,669)	Q1(low)[d]									
	Q2	0.26	0.03	**<0.001**	0.08	0.03	**0.003**	0.06	0.03	**0.012**
	Q3	0.42	0.03	**<0.001**	0.13	0.03	**<0.001**	0.10	0.03	**<0.001**
	Q4(high)	0.52	0.03	**<0.001**	0.15	0.03	**<0.001**	0.11	0.03	**<0.001**
Executive function z-score[f] (N=6,565)	Q1(low)[d]									
	Q2	0.27	0.04	**<0.001**	0.02	0.03	0.610	0.004	0.03	0.901
	Q3	0.48	0.04	**<0.001**	0.08	0.04	**0.029**	0.06	0.04	0.112
	Q4(high)	0.74	0.04	**<0.001**	0.19	0.04	**<0.001**	0.16	0.04	**<0.001**
Memory z-score[g] (N=6,635)	Q1(low)[d]									
	Q2	0.29	0.04	**<0.001**	0.12	0.04	**<0.001**	0.11	0.04	**0.004**
	Q3	0.42	0.04	**<0.001**	0.15	0.04	**<0.001**	0.13	0.04	**0.002**
	Q4(high)	0.46	0.04	**<0.001**	0.14	0.04	**<0.001**	0.10	0.04	**0.019**

[a] Unadjusted regression model.
[b] Adjusted by age, sex, race, region of residence and education.
[c] Adjusted by age, sex, race, region of residence, education, body mass index, hypertension, smoking and diabetes.
[d] Denotes the quartiles of the proportion of total time spent in high light physical activity. Q1 refers the lowest quartile, and Q4 refers to the highest quartile.
[e] Average cognitive z-score refers to the average of mean executive score and mean memory score.
[f] Executive z-score refers to the average of standardized scores of letter fluency and animal fluency tests. For participants with only one executive test, the mean score would be the result of that test.
[g] Memory z-score refers to the average of standardized scores of word list learning and MoCA recall and orientation tests. For participants with only one executive test, the mean score would be the result of that test. MoCA refers to Montreal Cognitive Assessment, including a 5-word delayed memory recall test, and a 6-item orientation test.

Table 15 displays the results for sensitivity analysis of choosing different time intervals between cognitive tests and PA assessments. The most recent cognitive tests conducted closest to the time point of the PA measurement within a time range of ±12 months was selected. This chosen window of time allowed for inclusion of as many participants as possible to provide robust and stable estimates of the relationships between MVPA% and cognitive function in this cohort. Sensitivity analyses were conducted with 1) a narrower window of ±6 months, and 2) restriction to the first cognitive assessment after PA assessment. The associations between PA and cognitive function in these analyses did not differ in direction from the primary analysis of ±12 months. As an example, please see the result of the sensitivity analysis of the association between MVPA% quartiles and the odds of cognitive impairment using different approaches below. The results show the sample size was largest in the second approach with the time range of ±12 months. In the first approach of ± 6 months, the time interval between PA assessment and cognitive tests was shortest. However, the sample size was the smallest, and the association between quartiles of MVPA% and odds of cognitive impairments was similar to the second approach with significance only in the highest quartile. In the third approach using the first cognitive test after PA assessment, the sample size was second largest, and there was a significant reduction of the odds of cognitive impairment as MVPA% increased across all quartiles. However, the average time interval between PA assessments and cognitive tests was 318.49 ± 159.60 days, which was three times longer than in the second approach. Due to the cross-sectional nature of the analyses, the third approach did not adequately fit.

Table 15

Sensitivity analysis of using different approaches to evaluate the association between MVPA% quartiles and the odds of cognitive impairment

	N	Time interval [a] (days; mean ± SD)	Quartiles [b]	O.R.[c]	95.0% C.I.
± 6 months	5728	23.25 ± 103.76	Q1(low)	Ref.	
			Q2	0.99	0.71-1.39
			Q3	0.83	0.57-1.23
			Q4(high)	**0.64**	**0.40-0.98**
± 12 months	7098	102.90 ± 100.73	Q1(low)	Ref.	
			Q2	0.97	0.71-1.31
			Q3	0.74	0.51-1.07
			Q4(high)	**0.63**	**0.43-0.93**
First test after PA measurement	6669	318.49 ± 159.60	Q1(low)	Ref.	
			Q2	**0.76**	**0.62-0.94**
			Q3	**0.75**	**0.60-0.94**
			Q4(high)	**0.58**	**0.45-0.76**

[a] Denotes the time intervals between PA assessment and cognitive tests.
[b] Denotes the quartiles of the proportions of total time spent in moderate to vigorous physical activity. Q1 refers the lowest quartile, and Q4 refers the highest quartile.
[c] Adjusted by age, sex, race, region of residence, education, proportion of time spent in sedentary behavior, body mass index, hypertension, smoking and diabetes.

Study 2

During an average follow-up of 2.7 ± 0.5 years (range: 2.0 - 4.1 years), 3,385 older adults were included in Study 2 with 157 incident cases of cognitive impairment according to SIS. Demographics, PA and cognitive function status are displayed in Tables 16 and 17 according to quartiles of MVPA%. The results were similar to those in Table 5 and 6 with 7,339 participants.

Table 16

Characteristics of Participants included in longitudinal analysis by Level of Moderate to Vigorous Physical Activity (% or mean ± SD， N = 3,385)

Variable	Quartile[a] 1	Quartile 2	Quartile 3	Quartile 4	Total
Women, n (%)	518 (69.6)	501 (58.6)	458 (50.8)	357 (40.4)[b]	1834 (54.2)
African American, n (%)	298 (40.1)	276 (32.3)	233 (25.8)	164 (18.6)[b]	971 (28.7)
Stroke-belt, n (%)	420 (56.5)	474 (55.4)	512 (56.8)	475 (53.7)[b]	1881 (55.6)
Education, n (%)					
Less than high school	77 (10.4)	41 (4.8)	38 (4.2)	19 (2.2)	175 (5.2)
High school graduate	225 (30.2)	223 (26.1)	193 (21.4)	139 (15.7)	780 (23.0)
Some college	202 (27.2)	257 (30.1)	222 (24.6)	188 (21.3)	869 (25.7)
College graduate and above	240 (32.3)	334 (39.1)	449 (49.8)	538 (60.9)[b]	1561 (46.1)
Smoking, n (%)	108 (14.5)	101 (11.8)	81 (9.0)	47 (5.3)[b]	337 (10.0)
Hypertension, n (%)	494 (66.4)	472 (55.2)	429 (47.6)	329 (37.2)[b]	1724 (50.9)
Diabetes, n (%)	172 (23.1)	134 (15.7)	114 (12.6)	80 (9.1)[b]	500 (14.8)
Age (yr)	74.7±7.8	70.8±7.4	68.7±7.4	67.0±7.4[b]	70.1±8.0
Body Mass Index ($kg*m^{-2}$)	30.1±6.4	29.3±5.7	28.0±5.1	26.7±4.3[b]	28.5±5.5
Systolic blood pressure (mmHg)	129.9±16.3	126.4±15.0	125.0±14.9	121.8±14.3[b]	125.6±15.4
Diastolic blood pressure (mmHg)	76.5±9.6	76.3±9.1	76.3±8.9	75.7±8.5[b]	76.2±9.0

[a] Denotes the quartiles of the proportion of total time spent in moderate to vigorous physical activity.

[b] Denotes significant difference among quartiles (P<0.001), tested by Analysis of Variance (continuous variables) or Chi-square (categorical variables)

Table 17

Baseline Physical Activity and Cognitive Function by Level of Moderate to Vigorous Physical Activity (% or mean ± SD，N = 3,385 unless otherwise noted)

Variable	Quartile[a] 1	Quartile 2	Quartile 3	Quartile 4	Total
Compliance (days with valid wear)	6.5±0.8	6.6±0.8	6.7±0.7	6.8±0.6[l]	6.6±0.7
Total wear time (min/day)	864.7±107.9	890.7±104.0	901.5±98.1	908.3±91.9[l]	892.5±101.5
MVPA[b] (min/day)	0.4±0.4	3.3±1.4	11.2±3.8	37.4±20.2[l]	13.7±18.0
HLPA[c] (min/day)	6.5±5.5	16.9±8.5	28.4±14.9	40.9±21.9[l]	24.0±19.2
LLPA[d] (min/day)	118.3±54.0	165.9±53.2	184.7±56.5	192.7±53.6[l]	167.4±61.1
Sedentary time (min/day)	739.5±112.2	704.6±109.6	677.2±104.7	637.3±108.8[l]	687.4±114.5
MVPA%[e]	0.05±0.05	0.37±0.15	1.24±0.39	4.12±2.20[l]	1.51±1.97
HLPA%[f]	0.7±0.6	1.9±1.0	3.2±1.6	4.5±2.4[l]	2.7±2.1
LLPA%[g]	13.7±6.2	18.8±6.1	20.6±6.2	21.4±5.9[l]	18.8±6.7
SED%[h]	85.5±6.6	78.9±6.7	75.0±7.3	69.9±8.2[l]	77.0±9.1
Cognitive impairment[i], n (%)	124 (6.7)	96 (5.3)	60 (3.3)	40 (2.2)[l]	320 (4.4)
Letter fluency score (n=2,846)	10.6±4.3	11.4±4.4	12.0±4.6	12.6±5.0[l]	11.7±4.6
Animal fluency score (n=3,342)	15.9±5.1	17.8±5.4	18.6±5.7	20.1±6.0[l]	18.2±5.8
Word list learning score[j] (n=3,260)	16.6±5.1	17.6±4.8	18.5±4.8	19.0±4.3[l]	18.0±4.8
MoCA[k] recall and orientation (n=3,350)	9.8±1.4	9.9±1.3	10.0±1.2	10.1±1.4[l]	10.0±1.3
Average cognitive z-score[m] (n=3,368)	-0.37±0.82	-0.09±0.77	0.10±0.75	0.23±0.76[l]	-0.02±0.80
Executive function z-score[n] (n=3,342)	-0.42±0.91	-0.11±0.92	0.10±0.99	0.32±1.01[l]	-0.01±1.00
Memory z-score[o] (n=3,363)	-0.39±1.19	-0.06±1.09	0.12±0.97	0.20±0.98[l]	-0.02±1.08

[a] Denotes the quartiles of the proportion of total time spent in moderate to vigorous physical activity.
[b] MVPA refers to moderate to vigorous physical activity.
[c] HLPA refers to high light physical activity.
[d] LLPA refers to low light physical activity.
[e] Denotes the proportion of total wear time spent in moderate to vigorous physical activity.
[f] Denotes the proportion of total wear time spent in high light physical activity.
[g] Denotes the proportion of total wear time spent in low light physical activity.
[h] Denotes the proportion of total wear time spent in sedentary behavior.
[i] Cognitive impairment is defined as a score of 4 or fewer correct responses in six-item screener. The score ranges from 1 to 6, consisting of a 3-item recall and 3-item temporal orientation.
[j] Word List Learning Score (WLL) is from the Consortium to Establish a Registry for Alzheimer's Disease battery (0-30).
[k] MoCA refers to Montreal Cognitive Assessment, including a 5-word delayed memory recall test (0-5), and 6-item orientation test (0-6).
[l] Denotes significant difference among quartiles (P<0.001), tested by Analysis of Variance (continuous variables) or Chi-square tests (categorical variables)
[m] Average cognitive z-score refers to the average of mean executive score and mean memory score.
[n] Executive z-score refers to the average of standardized scores of letter fluency and animal fluency tests. For participants with only one executive test, the mean score would be the result of that test.
[o] Memory z-score refers to the average of standardized scores of word list learning and MoCA recall and orientation tests. For participants with only one executive test, the mean score would be the result of that test.

Table 18 presents the association between MVPA% and cognitive function in older adults in the Cox proportional hazards models. The number of cases of cognitive impairment, and the rate and hazard ratio of cognitive impairment decreased across quartiles representing increasing MVPA% in the unadjusted model (Model 1) ($P<0.05$). After adjustment for age, sex, race, region of residence, and education (Model 2), significance remained in the highest quartile of MVPA% ($P<0.05$). Participants in the highest quartile were 49% less likely to experience cognitive impairment (OR [95% CI] =0.51 [0.30-0.87]). In the fully adjusted model (Model 3), results were consistent with Model 2, with participants in the highest MVPA% quartile 51% less likely to exhibit cognitive impairment (OR [95% CI] =0.49 [0.28-0.86]). There was a significant trend of difference across quartiles in hazards of cognitive impairment ($P<0.05$).

Table 18

Hazard Ratio for Cognitive Impairment by Levels of Moderate to Vigorous Physical Activity in Follow-up (N=3,385)

Variable	Quartile[d] 1	Quartile 2	Quartile 3	Quartile 4
No. of Cases	65	40	31	21
No. of Person-years	2019.7	2325.1	2434.4	2413.8
Rate (Per 100 person-years)	3.22	1.72	1.27	0.87
Model 1[a] HR (95% C.I.)	Ref.	**0.53 (0.36-0.79)**	**0.40 (0.26-0.61)**	**0.27 (0.16-0.44)**
Model 2[b] HR (95% C.I.)	Ref.	0.74 (0.49-1.12)	0.69 (0.44-1.09)	**0.51 (0.30-0.87)**
Model 3[c] HR (95% C.I.)	Ref.	0.73 (0.48-1.11)	0.67 (0.42-1.08)	**0.49 (0.28-0.86)**

[a] Unadjusted model.

[b] Adjusted by age, sex, race, region of residence and education.

[c] Adjusted by age, sex, race, region of residence, education, body mass index, hypertension, smoking and diabetes.

[d] Denotes the quartiles of the proportion of total time spent in moderate to vigorous physical activity. Q1 refers to the lowest quartile, and Q4 refers to the highest quartile.

Results of logistic regression analyses are displayed in Table 19. In the unadjusted model (Model 1), participants in the highest MVPA% quartile were 75% less likely to have cognitive impairment compared with those in the lowest quartile (OR [95% CI] =0.25 [0.15-0.42]). After adjustment for age, sex, race, region of residence, and education (Model 2), significance remained with participants in the highest quartile 50% less likely to have cognitive impairment (OR [95% CI] =0.50 [0.28-0.87]). In the fully adjusted model (Model 3), results were consistent with Model 2, with participants in the highest MVPA% quartile 48% less likely to have cognitive impairment (OR [95% CI] =0.52 [0.28-0.96]). There was a significant trend of difference across quartiles (P<0.001). Similar analyses with HLPA%, LLPA% and SED% did not reveal any significant associations (P>0.05) with the odds of cognitive impairment. Additionally, logistic regression analysis categorizing participants as accumulating more or less than 150 min/wk of MVPA indicated no significant differences after full adjustment (P>0.05). When using MVPA% as a continuous variable, there was also no significant association between MVPA% and the prevalence of cognitive impairment when adjusted for confounders in Models 2 and 3 (P>0.05).

Table 19

Multivariate Odds Ratios of Cognitive Impairment by Level of ***Moderate to Vigorous Physical Activity (MVPA)*** *during Follow-up (N=3,385)*

		Model 1[a]		Model 2[b]		Model 3[c]	
		O.R.	95.0% C.I.	O.R.	95.0% C.I.	O.R.	95.0% C.I.
MVPA%[d]	Q1(low)[e]	Ref.		Ref.		Ref.	
	Q2	**0.51**	**0.34-0.77**	0.72	0.47-1.10	0.69	0.43-1.11
	Q3	**0.37**	**0.24-0.58**	0.62	0.39-1.00	0.66	0.39-1.10
	Q4(high)	**0.25**	**0.15-0.42**	0.50	**0.28-0.87**	**0.52**	**0.28-0.96**
Weekly MVPA[f] (min)	<150min	Ref.		Ref.		Ref.	
	≥150min	**0.47**	**0.29-0.77**	0.78	0.47-1.31	0.82	0.47-1.43

[a] Unadjusted regression model.
[b] Adjusted by age, sex, race, region of residence, education, and periods of follow-up.
[c] Adjusted by age, sex, race, region of residence, education, body mass index, hypertension, smoking, diabetes, and periods of follow-up.
[d] Denotes the proportion of total time spent in moderate to vigorous physical activity.
[e] Denotes the quartiles of the proportions of total time spent in moderate to vigorous physical activity. Q1 refers to the lowest quartile, and Q4 refers to the highest quartile.
[f] The U.S. Physical Activity Guidelines recommended older adults perform ≥150 minutes of moderate to vigorous physical activity per week.[24]

Results of race/sex subgroup analyses of the association between PA and the prevalence of cognitive impairment are displayed in Tables 20 and 21. The association between PA and cognitive function were not significant within each race/sex groups (P>0.05). Race and sex were significant moderator in the relationship between PA and cognitive function in this population.

Table 20

Incidence of Cognitive Impairment by Race/Gender and Quartiles of Moderate to Vigorous Physical Activity (MVPA%[a]) during Follow-up

		O.R.[b]	95.0% C.I.
Black Female	Q1(low)[c]	Ref.	
	Q2	0.37	0.14-1.00
	Q3	0.36	0.11-1.17
	Q4(high)	0.34	0.07-1.57
Black Male	Q1(low)	Ref.	
	Q2	1.63	0.54-4.95
	Q3	0.67	0.19-2.45
	Q4(high)	0.24	0.04-1.38
White Female	Q1(low)	Ref.	
	Q2	0.66	0.28-1.56
	Q3	0.76	0.30-1.94
	Q4(high)	0.74	0.23-2.44
White Male	Q1(low)	Ref.	
	Q2	0.62	0.28-1.35
	Q3	0.57	0.25-1.29
	Q4(high)	0.54	0.23-1.30

[a] Denotes the proportion of total time spent in moderate to vigorous physical activity.
[b] Adjusted by age, sex, race, region of residence, education, body mass index, hypertension, smoking and diabetes.
[c] Denotes the quartiles of the proportions of total time spent in moderate to vigorous physical activity. Q1 refers the lowest quartile, and Q4 refers to the highest quartile.

Table 21

Incidence of Cognitive Impairment by Race/Gender and Whether Meet the Physical Activity Guideline or Not[a]

		O.R.[b]	95.0% C.I.
Black Female	<150 min[c]	Ref.	
	>=150 min	0.39	0.05-2.99
Black Male	<150 min	Ref.	
	>=150 min	0.27	0.06-1.29
White Female	<150 min	Ref.	
	>=150 min	1.21	0.43-3.44
White Male	<150 min	Ref.	
	>=150 min	1.03	0.49-2.14

[a] The U.S. Physical Activity Guidelines recommends older adults perform ≥150 minutes of moderate to vigorous physical activity per week.[24]

[b] Adjusted by age, sex, race, region of residence, education, body mass index, hypertension, smoking and diabetes.

[c] Denotes the total time spent in moderate to vigorous physical activity per week.

Follow-up periods of cognitive tests are shown in Table 22, and changes of cognitive function according to quartiles of MVPA% are in Table 23. The periods of follow-up were similar across quartiles within all cognitive tests. Participants with higher MVPA% were more likely to experience less change in cognitive scores in WLL, AF, LF, and MoCA-recall and orientation and successfully maintain cognitive function ($P<0.05$). A higher level of MVPA% was associated with less change in z-scores of executive function and memory ($P<0.05$).

Table 22

Follow-up Periods of Cognitive Tests by Level of Moderate to Vigorous Physical Activity (days [d]; mean ± SD)

	Quartile[a] 1	Quartile 2	Quartile 3	Quartile 4	Total
Follow-up for Letter Fluency Score (d)	199.1±457.4	168.2±476.7	155.2±476.6	188.7±478.1	176.9±472.9
Follow-up for Animal Fluency Score (d)	631.0±439.2	645.2±443.5	651.9±398.0	663.4±437.4	648.6±429.2
Follow-up for Word List Learning Score (d)	500.1±602.1	491.0±597.4	502.7±601.8	539.2±605.4	508.7±601.7
Follow-up for MoCA Recall and Orientation (d)	743.3±337.4	740.6±356.7	752.9±325.2	767.6±344.2	751.5±341.0
Follow-up for Average Cognitive Z-score[b] (d)	536.0±357.1	530.3±366.0	532.8±347.8	555.0±365.4	538.7±359.1
Follow-up for Executive Function Z-score[c] (d)	447.2±403.5	441.0±420.3	442.9±384.1	459.4±405.2	447.7±403.1
Follow-up for Memory Z-score[d] (d)	623.9±426.2	618.2±427.0	628.7±414.1	654.1±428.9	631.6±424.0

[a] Denotes the quartiles of the proportion of total time spent in moderate to vigorous physical activity. Q1 refers to the lowest quartile, and Q4 refers to the highest quartile.

[b] Average cognitive z-score refers to the average of mean executive score and mean memory score.

[c] Executive z-score refers to the average of standardized scores of letter fluency and animal fluency tests. For participants with only one executive test, the mean score would be the result of that test.

[d] Memory z-score refers to the average of standardized scores of word list learning and MoCA recall and orientation tests. For participants with only one executive test, the mean score would be the result of that test. MoCA refers to Montreal Cognitive Assessment, including a 5-word delayed memory recall test, and a 6-item orientation test.

Table 23

Changes of Cognitive Function by Level of Moderate to Vigorous Physical Activity (mean ± SD)

	Quartile[a] 1	Quartile 2	Quartile 3	Quartile 4	Total
Change of Letter Fluency Score (N=2,846)	-0.09±2.50	-0.19±2.56	-0.25±2.59	-0.08±2.58	-0.15±2.56
Change of Animal Fluency Score (N=3,342)	-0.95±4.27	-1.10±4.35	-0.74±4.42	-0.98±4.63	-0.94±4.43
Change of Word List Learning Score (N=3,260)	0.04±4.29	0.48±4.38	0.55±4.24	0.63±3.97	0.44±4.22
Change of MoCA Recall and Orientation (N=3,350)	-0.09±1.52	0.01±1.42	0.09±1.37	0.05±1.43	0.02±1.43
Change of Average Cogntive Z-score[b] (N=3,368)	-0.08±0.61	-0.03±0.61	0.01±0.59	0.01±0.59	-0.02±0.60
Change of Executive Function Z-score[c] (N=3,350)	-0.03±0.74	-0.04±0.76	0.03±0.77	-0.01±0.81	-0.01±0.77
Change of Memory Z-score[d] (N=3,363)	-0.15±1.04	-0.03±1.04	0.01±0.98	0.01±1.02	-0.03±1.02

[a] Denotes the quartiles of the proportion of total time spent in moderate to vigorous physical activity. Q1 refers to the lowest quartile, and Q4 refers to the highest quartile.

[b] Average cognitive z-score refers to the average of mean executive score and mean memory score.

[c] Executive z-score refers to the average of standardized scores of letter fluency and animal fluency tests. For participants with only one executive test, the mean score would be the result of that test.

[d] Memory z-score refers to the average of standardized scores of word list learning and MoCA recall and orientation tests. For participants with only one executive test, the mean score would be the result of that test. MoCA refers to Montreal Cognitive Assessment, including a 5-word delayed memory recall test, and a 6-item orientation test.

Linear regression models in Table 24 revealed a significant association (P<0.05) between MVPA% and change in z-scores of memory in the unadjusted model. The relationship remained significant (P<0.05) when controlling for age, sex, race, region of residence, and education. When analyses were further adjusted for BMI, hypertension, smoking and diabetes, MVPA% remained significantly associated with change in z-scores of memory (P<0.05). The similar pattern of significant associations existed between MVPA% and change in average cognitive z-scores. There was a significant trend of difference across the quartiles of MVPA% in change in z-scores of memory, and the change in average combined score for cognitive function (P<0.001). However, no significant association was found between MVPA% and change in z-scores of executive function in any of the three models (P>0.05).

Table 24

*Association of **Moderate to Vigorous Physical Activity** with the Change of Expanded Cognitive Battery Test Z-scores during Follow-up*

		Model 1[a]			Model 2[b]			Model 3[c]		
		Beta	SE	P	Beta	SE	P	Beta	SE	P
Change of average cognitive z-score[e] (N=3,368)	Q1(low)[d]									
	Q2	0.06	0.03	0.082	0.05	0.03	0.066	0.05	0.03	0.116
	Q3	**0.08**	**0.03**	**0.007**	**0.09**	**0.03**	**0.004**	**0.08**	**0.03**	**0.010**
	Q4(high)	**0.09**	**0.03**	**0.004**	**0.10**	**0.03**	**0.002**	**0.09**	**0.03**	**0.008**
Change of executive function z-score[f] (N=3,342)	Q1(low)[d]									
	Q2	-0.02	0.04	0.615	0.003	0.04	0.932	-0.01	0.04	0.894
	Q3	0.05	0.04	0.184	0.06	0.04	0.125	0.05	0.04	0.214
	Q4(high)	0.01	0.04	0.864	0.06	0.04	0.151	0.04	0.04	0.318
Change of memory z-score[g] (N=3,363)	Q1(low)[d]									
	Q2	**0.13**	**0.05**	**0.016**	**0.12**	**0.05**	**0.008**	**0.11**	**0.05**	**0.018**
	Q3	**0.15**	**0.05**	**0.005**	**0.16**	**0.05**	**0.001**	**0.15**	**0.05**	**0.003**
	Q4(high)	**0.18**	**0.05**	**<0.001**	**0.17**	**0.05**	**<0.001**	**0.16**	**0.05**	**0.003**

[a] Unadjusted regression model.

[b] Adjusted by age, sex, race, region of residence, education, scores at baseline, and periods of follow-up.

[c] Adjusted by age, sex, race, region of residence, education, body mass index, hypertension, smoking, diabetes, scores at baseline, and periods of follow-up.

[d] Denotes the quartiles of the proportion of total time spent in high light physical activity. Q1 refers to the lowest quartile, and Q4 refers to the highest quartile.

[e] Average cognitive z-score refers to the average of mean executive score and mean memory score.

[f] Executive z-score refers to the average of standardized scores of letter fluency and animal fluency tests. For participants with only one executive test, the mean score would be the result of that test.

[g] Memory z-score refers to the average of standardized scores of word list learning and MoCA recall and orientation tests. For participants with only one executive test, the mean score would be the result of that test. MoCA refers to Montreal Cognitive Assessment, including a 5-word delayed memory recall test, and a 6-item orientation test.

Linear regression models (Table 25) revealed a significant association (P<0.001) between the highest quartiles of HLPA% and change in z-score of both cognitive function domains in the unadjusted model. These relationships remained significant when controlling for age, sex, race, region of residence, and education. When analyses were further adjusted for BMI, hypertension, smoking and diabetes, the highest HLPA% quartiles remained significantly associated with change in z-score of executive function, memory and their average combined score of cognitive function (P<0.05). There was a significant trend of difference across the quartiles of HLPA% in z-scores of executive function, memory, and their average combined score (P<0.001). Similar analyses with LLPA% and SED% did not reveal any significant associations (P>0.05) with the odds of cognitive impairment.

Table 25

*Association of Quartiles of **High Light Physical Activity** with the Change of Expanded Cognitive Battery Tests Z-scores during Follow-up*

		Model 1[a]			Model 2[b]			Model 3[c]		
		Beta	SE	P	Beta	SE	P	Beta	SE	P
Change of average cognitive z-score[e] (N=3,368)	Q1(low)[d]									
	Q2	0.03	0.03	0.314	0.03	0.03	0.305	0.03	0.03	0.388
	Q3	0.04	0.03	0.163	0.03	0.03	0.247	0.03	0.03	0.356
	Q4(high)	**0.13**	**0.03**	**<0.001**	**0.11**	**0.03**	**0.001**	**0.09**	**0.03**	**0.005**
Change of executive function z-score[f] (N=3,342)	Q1(low)[d]									
	Q2	0.03	0.04	0.424	0.04	0.04	0.304	0.03	0.04	0.363
	Q3	0.05	0.04	0.226	0.04	0.04	0.282	0.04	0.04	0.368
	Q4(high)	**0.09**	**0.04**	**0.024**	**0.14**	**0.04**	**0.001**	**0.13**	**0.04**	**0.004**
Change of memory z-score[g] (N=3,363)	Q1(low)[d]									
	Q2	0.05	0.05	0.357	0.06	0.05	0.237	0.05	0.05	0.293
	Q3	0.06	0.05	0.257	0.06	0.05	0.233	0.05	0.05	0.324
	Q4(high)	**0.20**	**0.05**	**<0.001**	**0.15**	**0.05**	**0.005**	**0.13**	**0.05**	**0.014**

[a] Unadjusted regression model.
[b] Adjusted by age, sex, race, region of residence, education, and scores at baseline.
[c] Adjusted by age, sex, race, region of residence, education, body mass index, hypertension, smoking, diabetes, scores at baseline, and periods of follow-up.
[d] Denotes the quartiles of the proportion of total time spent in high light physical activity. Q1 refers to the lowest quartile, and Q4 refers to the highest quartile.
[e] Average cognitive z-score refers to the average of mean executive score and mean memory score.
[f] Executive z-score refers to the average of standardized scores of letter fluency and animal fluency tests. For participants with only one executive test, the mean score would be the result of that test.
[g] Memory z-score refers to the average of standardized scores of word list learning and MoCA recall and orientation tests. For participants with only one executive test, the mean score would be the result of that test. MoCA refers to Montreal Cognitive Assessment, including a 5-word delayed memory recall test, and a 6-item orientation test.

Figure 2 exhibits significant differences in the changes between baseline and the most recent z-scores of memory during the follow-up across quartiles of MVPA% ($P<0.05$), after adjustments of all the covariates. There is no significant difference across quartiles of MVPA% for executive function ($P>0.05$). Pairwise comparisons shows significances existing between Quartile 1 and Quartile 3, and Quartile 1 and Quartile 4 in z-score of memory, respectively ($P<0.05$). The decrease of the z-score of memory is less among those adults with higher level of MVPA% when compared with the lowest quartile.

The data in Figure 3 indicate significant differences in the changes between baseline and the most recent z-scores of memory and executive function existed across quartiles of HLPA% ($P<0.05$), after adjustments of all the covariates. Pairwise comparisons shows significances existing between Quartile 1 and Quartile 4 in z-score of executive function, and Quartile 1 and Quartile 4 in z-score of memory, respectively ($P<0.05$). The decreases of the z-scores of executive function and memory are less among participants with a higher level of HLPA% when compared with the lowest quartile.

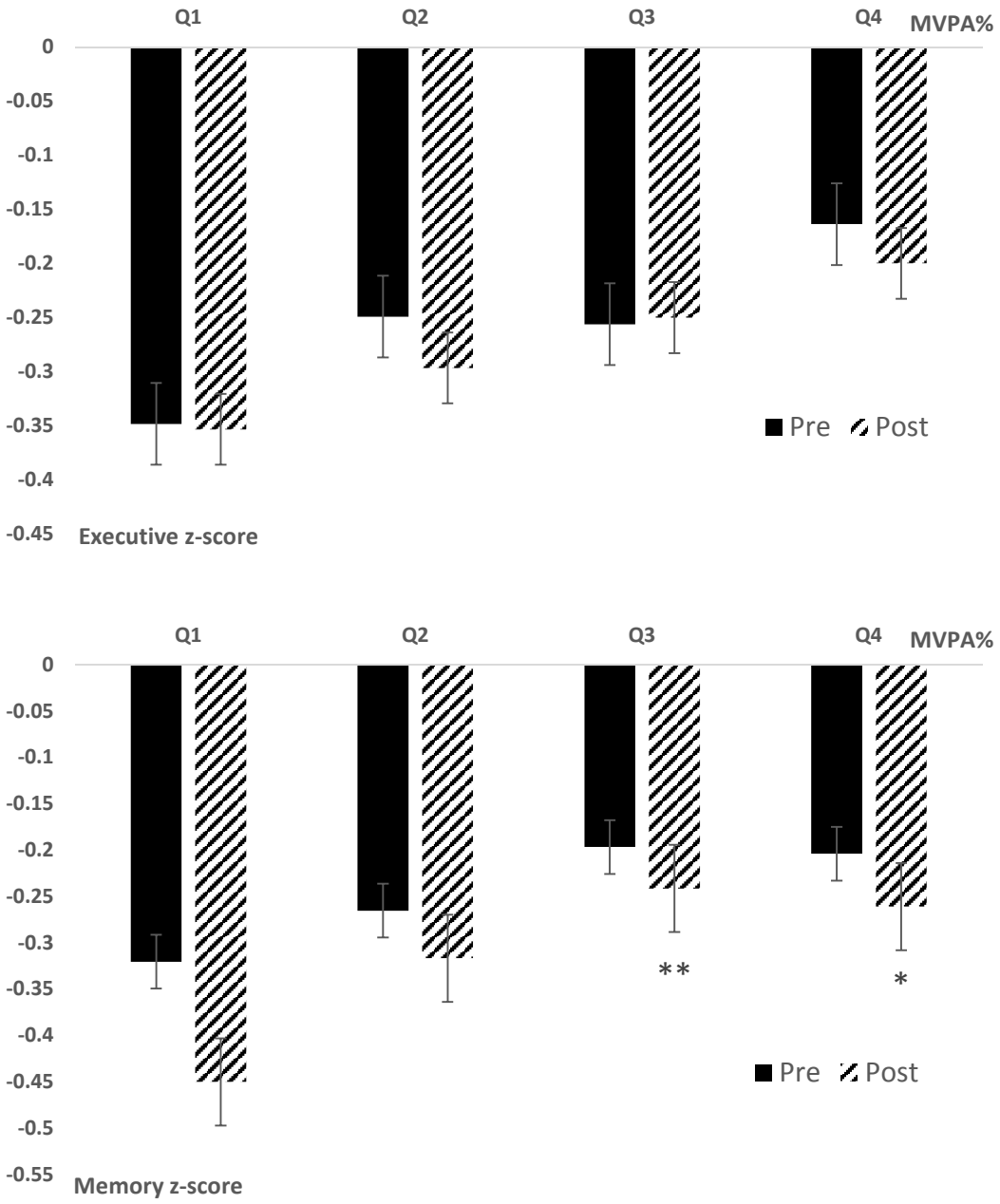


Figure 2. Association between MVPA% and cognitive scores by quartiles of MVPA%. Q1-Q4 denotes the quartiles of MVPA%. * denotes P<0.05, ** denotes P<0.01, compared to Q1. Z-scores have been adjusted by age, sex, race, region of residence, education, body mass index, hypertension, smoking, diabetes, scores at baseline, and periods of follow-up.

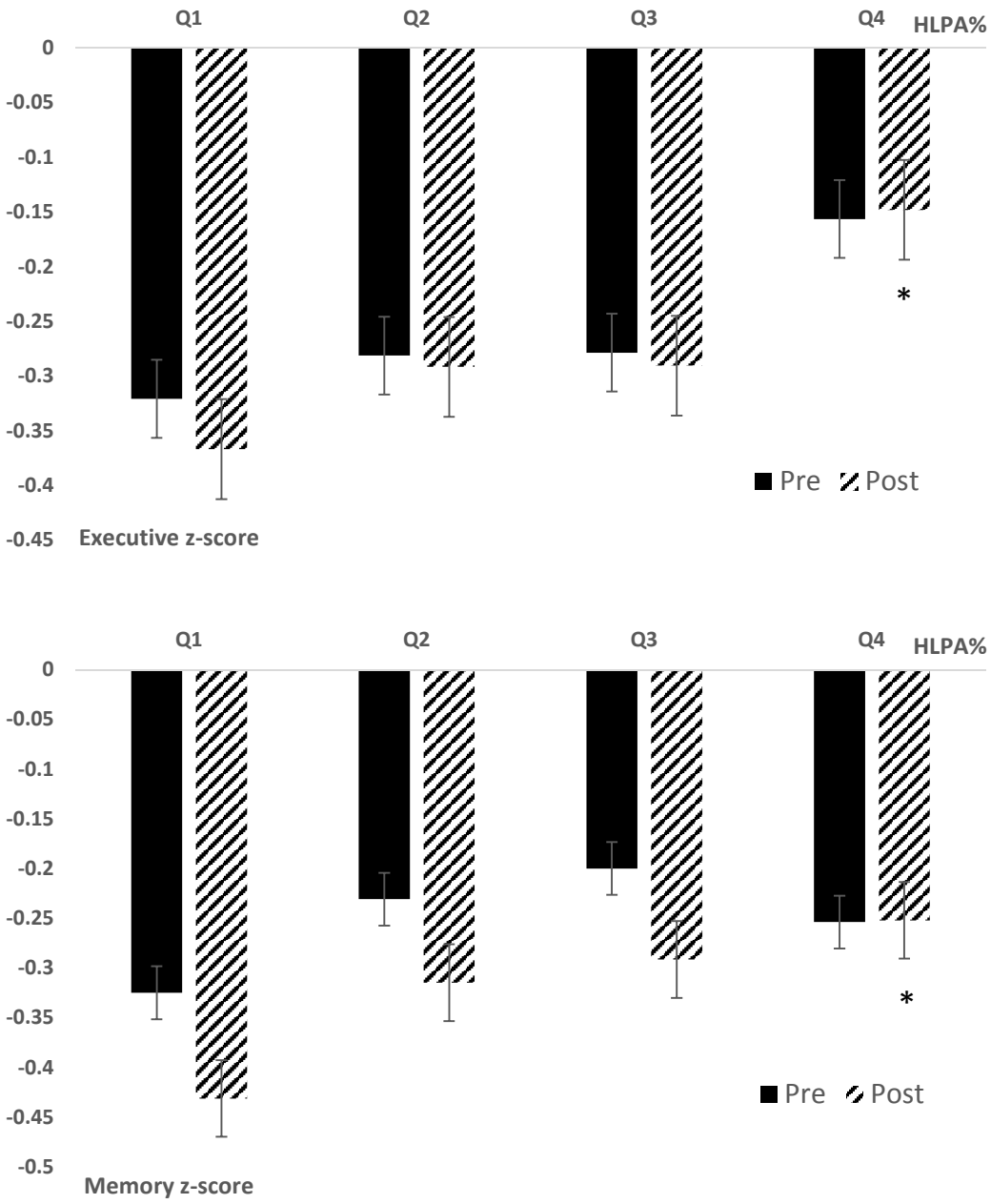


Figure 3. Association between HLPA% and cognitive scores by quartiles of HLPA%. Q1-Q4 denotes the quartiles of HLPA%. * denotes P<0.05, ** denotes P<0.01, compared to Q1. Z-scores have been adjusted by age, sex, race, region of residence, education, body mass index, hypertension, smoking, diabetes, scores at baseline, and periods of follow-up.

CHAPTER 5

DISCUSSION

Objectively-measured PA in older adults

In this study, objective measurements of time spent in sedentary behavior and varying intensities of PA were obtained in a very large sample of community-dwelling midlife and older adults in the U.S. Overall, the results indicated older adults rarely undertook MVPA and accumulated very high levels of sedentary behavior (approximately 11-13 hr/day). The subgroups most affiliated with this pattern were those participants who were women, black, older, less-educated, a current smoker, with diabetes and hypertension, and higher BMI and systolic and diastolic blood pressure. The proportion of wear time spent in sedentary behavior (78-87%) is higher than formerly reported for comparably-aged U.S. (Buman et al., 2010; Hagstromer, Troiano, Sjostrom, & Berrigan, 2010; Shiroma, Freedson, Trost, & Lee, 2013), Swedish (Hagstromer et al., 2010) and Norwegian adults (Hansen, Kolle, Dyrstad, Holme, & Anderssen, 2012), and similar to Icelandic (Arnardottir et al., 2013) and UK midlife and older adults (Davis et al., 2011; Golubic et al., 2014; Harris et al., 2009) who wore accelerometers. Differences in mean age, race/ethnicity, health status, living conditions, other social or environmental factors, or devices and data management methodology may account for inconsistent results between studies. Regardless, the amount of time in sedentary behavior was alarmingly high in the current study and supports proposals for interventions to specifically reduce this behavior (Dunstan, Howard, Healy, & Owen, 2012; C. E. Matthews, Moore, George, Sampson, & Bowles, 2012; Thorp et al., 2011).

Equally concerning was the miniscule amount of MVPA accumulated. Across subgroups, mean daily minutes of MVPA ranged from 0-30 minutes accounting for only 0-3.5% of total wear time. These data align with previous results indicating minimal exposure to daily MVPA in adult populations. Investigators from various counties have revealed midlife and older adults devote 1-11% of total wear time to MVPA (Arnardottir et al., 2013; Dyrstad, Hansen, Holme, & Anderssen, 2014; Hansen et al., 2012; Harris et al., 2009; Troiano et al., 2008) and accumulate 4-41 minutes

of MVPA per day (Arnardottir et al., 2013; Buman et al., 2010; Davis & Fox, 2007; Davis et al., 2011; Dyrstad et al., 2014; Golubic et al., 2014; Hagstromer et al., 2010; Hansen et al., 2012).

Significant differences in baseline characteristics across quartiles of MVPA% corroborate previous findings with population-based samples demonstrating PA declines with age (Colley et al., 2011; Dyrstad et al., 2014; Troiano et al., 2008; Tucker, Welk, & Beyler, 2011), is less among those with obesity (Golubic et al., 2014; Hagstromer et al., 2010; Hawkins et al., 2009; Lakoski & Kozlitina, 2014), and is lowest in the Southeastern U.S. (Lakoski & Kozlitina, 2014; C. E. Matthews et al., 2008; Troiano et al., 2008; Tucker et al., 2011; Whitt-Glover, Taylor, Heath, & Macera, 2007). Comparisons of race and sex disclosed white and black women at highest risk for exceptionally low levels of health-enhancing PA. White and black women accumulated merely 3-4 min/day of MVPA (0.3-0.4% of total wear time) which is similar to a previous study reporting 6-9 min/day of MVPA (<1% of total wear time) of objectively measured PA for older white and black women. As with previous studies employing accelerometers (Colley et al., 2011; Davis et al., 2011; Dyrstad et al., 2014; Golubic et al., 2014; Troiano et al., 2008), within a given race/ethnic group, men and white participants in the current study were more active than their peers.

Cross-sectional relationship between PA and cognitive function

To our knowledge, this is also one of the first studies to examine the dose-response association between objectively measured PA and cognitive function in a large and diverse older population. Objectively measured MVPA (both absolute min/wk and MVPA%) was independently associated with cognitive impairment and continuous measures of cognitive function among a population of 7,339 older white and black adults. The odds of cognitive impairment was significantly lower in those with the highest level of PA (36.9 min/day, 258.3 min/wk), which is above that recommended in U.S. national guidelines (i.e., accumulating $\geq$150 min/wk). Older adults with a greater proportion of accelerometer wear time spent in MVPA had higher levels of memory and executive function than their less active peers. Additionally, objectively measured HLPA was independently associated with continuous measures of cognitive function in this cohort, suggesting

the potential association between HLPA and cognitive function in older adults. This denotes the possibility of reconsidering the potential impact of LPA, especially in older adults.

Previous cross-sectional studies using self-reported PA measurements suggest more active individuals may be less likely to develop cognitive impairment and dementia. For example, women who self-reported being physically active at any point over the life course, especially as teenagers, had a lower likelihood of cognitive impairment in late life. Interventions should promote PA early in life and throughout the life course (Middleton et al., 2010). A history of high PA is associated with better cognitive performance among old adults living in the community (Landi et al., 2007). Compared to a controlled cohort, active elderly marathon runners or bicyclists older than 60 years had better performance in cognitive tests. Extensive endurance exercise training may be beneficial for maintaining cognitive function in older adults (Winker et al., 2010). While moderate activity may be protective, long-term strenuous activity may lower cognitive performance later in life (Tierney et al., 2010).

A few studies with objectively measured data in humans have also reported active older adults may have lower risks of cognitive impairment and dementia. However, to our knowledge, there are no national-level data to examine the association between objectively measured PA and cognitive function among a racially diverse population of older adults. One cross-sectional study (Barnes et al., 2008) of 2,735 older women (83±4 yr old) showed participants in the highest PA quartiles had better mean cognitive test scores than those in the lowest quartile, and were less likely to be cognitively impaired. One cross-sectional study (Burzynska et al., 2014) used MRI to examine the association of both accelerometer-measured PA and cardiorespiratory fitness with measures of white matter integrity in 88 healthy low-fit adults (age 60-78 years). The results showed that greater MVPA was related to lower volume of white matter lesions, with no significant relationship found between LPA or sedentary behavior and white matter volume. The association between PA and white matter microstructural integrity was region-specific: LPA was positively related to temporal white matter, while sedentary behavior was negatively associated with integrity in the parahippocampal white matter. Those findings highlight that engaging in PA of various

intensity in parallel with avoiding sedentariness are important in maintaining white matter health in older age.

Our results regarding LLPA% and SED% revealed no relationships to cognitive function. MVPA% displayed a significant dose-response relationship with the odds of cognitive impairment in this population, while both MVPA% and HLPA% were associated with the cognitive domains of executive function and memory. These findings suggested PA intensity and volume may be an important factor influencing the relationship between PA and cognitive function in older adults. The association between MVPA and cognitive function in older adults has been confirmed in previous research. One study of 1,927 healthy men and women aged 45-70 years in the Netherlands showed higher intensity (tertiles of weighted average intensity) of self-reported PA was significantly positively associated with executive function, memory, and overall cognitive function (Angevaren et al., 2007). The results showed no significant associations between the total time spent in PA and the cognitive parameters. Another study (Tierney et al., 2010) in older women demonstrated self-reported MVPA may be marginally related to cognitive function, while long-term strenuous activity can lower cognitive performance in older women.

Studies applying accelerometers as the main measurements of PA also reported that intensity of PA is important in the association between PA and cognitive function in older adults. For example, participants in the highest tertile of PA intensity were shown to perform better than those in the lowest tertile in cognitive tasks related to memory and executive function (Brown et al., 2012). Another study (Kerr et al., 2013) with 217 older adults indicated a dose response relationship between objectively measured PA intensity and cognitive function with a stronger association existing between MVPA and cognitive function. Three cut points were used to assess LLPA, HLPA, and MVPA. LLPA was not related to cognitive function, and HLPA was significantly related to cognition only in unadjusted models. MVPA was related to the domains of executive function, memory and visuoperceptual abilities after adjusting for demographic variables. However, the sample size was relatively small in this study, and they used the absolute time spent in PA as the

independent variable. To our knowledge, our study was the first one indicating the significant relationship of both MVPA and HLPA with cognitive function in older adults.

Previous research also indicated diverse types of sedentary behaviors may be differently associated with cognitive function. Computer using time was positively associated with memory and executive function, while television viewing time was negatively associated with cognitive function in older adults (Hamer & Stamatakis, 2013; Kesse-Guyot et al., 2012). Unfortunately, we were not able to record the type of sedentary behavior in our study. Additional investigations are necessary to more fully explore the impact of sedentary behavior and LPA on cognitive function in older adults as this is how they spend the vast majority of their time.

Longitudinal relationship between PA and cognitive function

We also examined the longitudinal relationship between objectively measured PA and cognitive function among 3,385 older adults with at least two-year follow-up (2.7 ± 0.5 yr, range: 2.0-4.1 yr) in the same cohort. We found that MVPA was independently associated with cognitive impairment and continuous measures of cognitive function in older adults. The hazards of developing cognitive impairment was significantly lower in those with the highest level of PA (37 min/day, 259 min/wk), which is above that recommended in U.S. national guidelines. Older adults with a greater proportion of accelerometer wear time spent in MVPA at baseline had higher levels of memory than their less active peers in their most recent cognitive measurements. Older adults who accumulated the highest level of HLPA (41 min/day, 287 min/wk) at baseline also had significantly higher levels of executive function and memory during follow-up. These findings were consistent with the cross-sectional analysis, and confirmed the relationship between PA and cognitive function from a prospective aspect.

Some previous longitudinal studies using self-reported PA as a predictor have reported a similar relationship between PA and cognitive function (Etgen et al., 2010; Middleton et al., 2008; Weuve et al., 2004; K. Yaffe et al., 2001). A meta-analysis (Hamer & Chida, 2009) of 16 prospective studies using self-reported PA indicated the relative risks of incident dementia and Alzheimer's disease in the highest PA category compared with the lowest were reduced by 28% and 45%,

respectively. However, most previous studies on the relationship between PA and cognitive function have been limited by the bias of self-report measures of PA, and also have difficulties identifying effects of LPA and sedentary time on cognitive function.

The long-term association between objectively-measured PA and cognitive function in older adults has also been explored in a few recent studies. Barnes et al. (Barnes et al., 2003) demonstrated higher levels of aerobic fitness at baseline predicted better performance on measures of attention and executive function, whereas self-reported PA was not predictive of cognition six years later. Middleton et al. (Middleton et al., 2011) used activity energy expenditure in 197 men and women (mean age, 74.8 years) who were free of mobility and cognitive impairments at baseline. Cognitive function was assessed at baseline and 2 or 5 years later using the Modified Mini-Mental State Examination. After adjustments, older adults in the highest sex-specific tertile of activity energy expenditure had lower odds of incident cognitive impairment than those in the lowest tertile. There was a significant dose response between activity energy expenditure and incidence of cognitive impairment. In the Rush Memory and Aging Project, total daily PA was objectively measured continuously for up to 10 days with Actigraph from 716 older individuals without dementia participating, (Buchman et al., 2012). After an average follow-up of about 4 years, the Cox proportional hazards model adjusting for age, sex, and education indicated that total daily PA was substantially associated with incident AD. The association remained after adjusting for self-report physical, social, and cognitive activities, as well as current level of motor function, depressive symptoms, chronic health conditions, and APOE allele status. The level of total daily PA was significantly associated with the rate of global cognitive decline. However, the sample sizes of these longitudinal studies are relatively small, and they are mostly focused on white Americans. Our study confirms the association between objectively measured PA and cognitive function in a large and diverse older population.

Moreover, the influence of LPA and sedentary behavior on cognitive function is still not fully understood. A longitudinal study in Japan determined self-reported LPA and sedentary time were associated with cognitive impairment after 8 years of follow-up (Lee et al., 2013). However, another

study reported LPA measured by accelerometer was not significantly associated with memory and executive function after adjustments by confounders (Kerr et al., 2013). In our analysis, the highest quartile of HLPA% presented a significant association with cognitive scores in the domains of executive function and memory. To our knowledge, this is the first study indicating the relationship between objectively measured HLPA and cognitive function in such a diverse older population. It may due to the relatively large volume of HLPA accumulated each day in addition to MVPA, and the amount of HLPA may also indicate biologic processes related to more social interactions and mental activities which could stimulate cognitive health. There have been some studies (Buman et al., 2010; Buman et al., 2014; Healy et al., 2007) demonstrating the positive association of LPA (especially HLPA) with type 2 diabetes, cardiovascular disease, and general health and well-being. Specifically, replacing sedentary time with equal amounts of LLPA or HLPA was associated with better physical health (Buman et al., 2010; Buman et al., 2014). More prospective or intervention studies are needed to understand the exact relationship between LPA and cognitive function.

We did not observe a significant association between MVPA and executive function in this cohort, which was inconsistent with some previous studies (Barnes et al., 2003; Kerr et al., 2013). This may due to the low level of MVPA in this cohort, or the period of the test of letter fluency under the domain of executive function is shorter than the other tests (0.5 ± 1.3 yr). The annual cognitive function tests in REGARDS are still ongoing, and new analysis with longer follow-up periods will be available in the future.

The association between PA and cognitive function remains robust in older adults when adjusted for race, sex, education, and age (Landi et al., 2007; Middleton et al., 2010; Winker et al., 2010). In this analysis, race/sex subgroup analysis showed white males accumulated the most MVPA and HLPA, while black females had the least MVPA. Black male were the most sedentary group, and the prevalence of cognitive impairment was highest among them. The White female older adults accumulated more LLPA than any other groups, and had the best performance in most of the cognitive tests and lowest rate of cognitive impairment among these four groups. However, the relationship between MVPA and cognitive function was no longer significant within each

race/sex group. Race and sex may be two important moderators in the relationship between PA and cognitive function in this population. More studies need to be conducted to explore the potential pattern and mechanism for the differences among varied race/sex groups.

PA may be related to cognitive function through different mechanisms. Research suggests PA is associated with greater brain volume in specific areas related to executive function and memory (e.g., hippocampus volume) (Ho et al., 2010; Honea et al., 2009), increased levels of brain-derived neurotrophic factor (Yau, Lau, & So, 2011), improved cerebrovascular function (Davenport, Hogan, Eskes, Longman, & Poulin, 2012), and reduced vascular risk associated with hypertension, type 2 diabetes and obesity (Gregory et al., 2012). Moreover, studies suggest improved cognitive function and reduced risk of dementia may be mediated by significant changes in cardiorespiratory fitness (S. J. Colcombe et al., 2006; Erickson et al., 2012; Gregory et al., 2012).

Strengths and limitations

This study has several strengths. First and most important, an objective measure of PA was used to examine the association of PA with cognitive function in a large population of older adults. This allowed for analyses with both absolute amount and proportion of time spent in PA of varying intensity. Also, the sample was recruited from a well-characterized cohort of midlife and older black and white adults living in the U.S. The participants were also extremely compliant with the 7-day protocol providing a large pool of quality accelerometer-derived data. Secondly, this is one of the first studies to examine both cross-sectional and longitudinal association between objectively measured PA (i.e. MVPA, HLPA, LLPA) and cognitive function in a diverse population, providing more detailed analysis for older white and black women and men. Finally, the relationship of accelerometer-derived PA, especially MVPA and HLPA, with specific domains of memory and executive function were able to be explored in addition to odds of impairment in global cognitive status.

The findings of this study were also subject to limitations. Despite the advantage of obtaining an objective measure of sedentary behavior and PA, there are limitations to using accelerometers, including not being able to identify types and domains of PA or capture upper-

body or non-ambulatory movement, potentially resulting in an under-estimation of total PA. Concerns may arise from participants making changes to their behavior while wearing the device or one week of data not accurately reflecting the person's typical pattern of behavior. However, the protocol employed has been widely used and reflects currently accepted practice (Tudor-Locke et al., 2012).

In addition, the application of standard cut-points to differentiate time spent being sedentary and physically active at varying intensities does not account for potential differences in fitness levels, especially among older adults. It is possible that some PA classified as LPA by the accelerometer may have been of sufficient relative intensity to be considered MVPA (or HLPA). The cut-points used were derived from a lab-based validation study with adults with similar demographic characteristics (Hooker et al., 2011), and the non-wear algorithm was developed with a subgroup of adults from REGARDS (Hutto et al., 2013). However, accelerometers calibrated and validated on structured activities performed in a laboratory rather than on free-living activities have been shown to underestimate MVPA (Crouter, DellaValle, Haas, Frongillo, & Bassett, 2013). Thus, the measured time in MVPA in this REGARDS cohort may be underestimated. Accelerometer counts from a hip worn device can be similar for sitting and standing with negligible movement leading to overestimation of time in sedentary behavior and underestimation of LPA (Lyden, Keadle, Staudenmayer, & Freedson, 2014). On the other hand, the absolute Actical™ cut-points for sedentary behavior (<50 cpm) and MVPA (>1065 cpm) applied in this study are lower than used by others (Colley et al., 2011; Glazer et al., 2013), thus offsetting to some degree any potential overestimation of sedentary time and underestimation of MVPA.

The cohort was quite sedentary and there was a significant skewness of the main independent variable of MVPA%. The range of MVPA% was also narrow. Also, this was a cohort without stroke and cognitive impairment at baseline with the prevalence of cognitive impairment for this sample low (5.1%), and the average period of follow-up was relatively short (2.7 ± 0.5 yr). These factors may limit variability of the dependent variable and trend of the association, making it

hard to determine a precise threshold of MVPA for reducing risk of cognitive impairment in this study.

Our cognitive tests were limited to a simple screener test (SIS) and two main domains of cognitive function (executive function and memory), and the sensitivity and specificity may be the concern. However, previous findings from REGARDS have attested to the utility of these tests in detecting broad patterns of association with conditions affecting cognition, such as race, sex, and region of residence (Wadley et al., 2011).

Also, as an observational study, causality cannot be inferred. Because of the potential for other confounding factors and random errors or noise in the dataset, the results should be interpreted with caution. Future research is needed to explicitly address these issues.

CHAPTER 6

CONCLUSION

In summary, higher levels of objectively measured MVPA% were independently associated with lower prevalence and incidence of cognitive impairment for both white and black older adults. Higher levels of MVPA% were also independently associated with better performance in memory and executive function. There was a dose-response relationship between MVPA% and cognitive function in older adults, with the highest level of MVPA% associated with higher cognitive function. The amount of MVPA associated with less risk of cognitive impairment is higher than the minimal level recommended for adults in the U.S. PA guidelines. In addition, HLPA% was associated with executive function and memory of older adults. Neither LLPA% nor SED% was associated with any measures of cognitive function in this cohort warranting further investigation.

REFERENCES

Aarsland, D., Sardahaee, F. S., Anderssen, S., Ballard, C., & Alzheimer's Society Systematic Review group. (2010). Is physical activity a potential preventive factor for vascular dementia? A systematic review. *Aging & Mental Health, 14*(4), 386-395.

Aguiar, A. S.,Jr, Speck, A. E., Prediger, R. D., Kapczinski, F., & Pinho, R. A. (2008). Downhill training upregulates mice hippocampal and striatal brain-derived neurotrophic factor levels. *Journal of Neural Transmission (Vienna, Austria : 1996), 115*(9), 1251-1255.

Alexopoulos, G. S., Raue, P., & Arean, P. (2003). Problem-solving therapy versus supportive therapy in geriatric major depression with executive dysfunction. *The American Journal of Geriatric Psychiatry : Official Journal of the American Association for Geriatric Psychiatry, 11*(1), 46-52.

Alzheimer's Association. (2013). 2013 Alzheimer's disease facts and figures. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association, 9*(2), 208-245.

Angevaren, M., Vanhees, L., Nooyens, A. C., Wendel-Vos, C. G., & Verschuren, W. M. (2010). Physical activity and 5-year cognitive decline in the doetinchem cohort study. *Annals of Epidemiology, 20*(6), 473-479.

Angevaren, M., Vanhees, L., Wendel-Vos, W., Verhaar, H. J., Aufdemkampe, G., Aleman, A., & Verschuren, W. M. (2007). Intensity, but not duration, of physical activities is related to cognitive function. *European Journal of Cardiovascular Prevention and Rehabilitation: Official Journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology, 14*(6), 825-830.

Arnardottir, N. Y., Koster, A., Van Domelen, D. R., Brychta, R. J., Caserotti, P., Eiriksdottir, G., . . . Sveinsson, T. (2013). Objective measurements of daily physical activity patterns and sedentary behaviour in older adults: Age, Gene/Environment susceptibility-reykjavik study. *Age and Ageing, 42*(2), 222-229.

Baker, L. D., Frank, L. L., Foster-Schubert, K., Green, P. S., Wilkinson, C. W., McTiernan, A., . . . Cholerton, B. A. (2010a). Effects of aerobic exercise on mild cognitive impairment: A controlled trial. *Archives of Neurology, 67*(1), 71.

Baker, L. D., Frank, L. L., Foster-Schubert, K., Green, P. S., Wilkinson, C. W., McTiernan, A., . . . Craft, S. (2010b). Aerobic exercise improves cognition for older adults with glucose intolerance, a risk factor for alzheimer's disease. *Journal of Alzheimer's Disease : JAD, 22*(2), 569-579.

Ball, K., Berch, D. B., Helmers, K. F., Jobe, J. B., Leveck, M. D., Marsiske, M., . . . Advanced Cognitive Training for Independent and Vital Elderly Study Group. (2002). Effects of cognitive training interventions with older adults: A randomized controlled trial. *Jama, 288*(18), 2271-2281.

Barnes, D. E., Blackwell, T., Stone, K. L., Goldman, S. E., Hillier, T., Yaffe, K., & Study of Osteoporotic Fractures. (2008). Cognition in older women: The importance of daytime movement. *Journal of the American Geriatrics Society, 56*(9), 1658-1664.

Barnes, D. E., Yaffe, K., Satariano, W. A., & Tager, I. B. (2003). A longitudinal study of cardiorespiratory fitness and cognitive function in healthy older adults. *Journal of the American Geriatrics Society, 51*(4), 459-465.

in the human olfactory bulb. *Brain Research.Developmental Brain Research, 151*(1-2), 159-168.

Bopp, M., Wilcox, S., Laken, M., Butler, K., Carter, R. E., McClorin, L., & Yancey, A. (2006). Factors associated with physical activity among african-american men and women. *American Journal of Preventive Medicine, 30*(4), 340-346.

Borhani, N. O. (1965). Changes and geographic distribution of mortality from cerebrovascular disease. *American Journal of Public Health and the Nation's Health, 55*, 673-681.

Bowen, M. E. (2012). A prospective examination of the relationship between physical activity and dementia risk in later life. *American Journal of Health Promotion : AJHP, 26*(6), 333-340.

Brosse, A. L., Sheets, E. S., Lett, H. S., & Blumenthal, J. A. (2002). Exercise and the treatment of clinical depression in adults: Recent findings and future directions. *Sports Medicine (Auckland, N.Z.), 32*(12), 741-760.

Brown, B. M., Peiffer, J. J., Sohrabi, H. R., Mondal, A., Gupta, V. B., Rainey-Smith, S. R., . . . AIBL research group. (2012). Intense physical activity is associated with cognitive performance in the elderly. *Translational Psychiatry, 2*, e191.

Buchman, A. S., Boyle, P. A., Yu, L., Shah, R. C., Wilson, R. S., & Bennett, D. A. (2012). Total daily physical activity and the risk of AD and cognitive decline in older adults. *Neurology, 78*(17), 1323-1329.

Buman, M. P., Hekler, E. B., Haskell, W. L., Pruitt, L., Conway, T. L., Cain, K. L., . . . King, A. C. (2010). Objective light-intensity physical activity associations with rated health in older adults. *American Journal of Epidemiology, 172*(10), 1155-1165.

Buman, M. P., Winkler, E. A., Kurka, J. M., Hekler, E. B., Baldwin, C. M., Owen, N., . . . Gardiner, P. A. (2014). Reallocating time to sleep, sedentary behaviors, or active behaviors: Associations with cardiovascular disease risk biomarkers, NHANES 2005-2006. *American Journal of Epidemiology, 179*(3), 323-334.

Burke, D., Hickie, I., Breakspear, M., & Gotz, J. (2007). Possibilities for the prevention and treatment of cognitive impairment and dementia. *The British Journal of Psychiatry : The Journal of Mental Science, 190*, 371-372.

Burzynska, A. Z., Chaddock-Heyman, L., Voss, M. W., Wong, C. N., Gothe, N. P., Olson, E. A., . . . Kramer, A. F. (2014). Physical activity and cardiorespiratory fitness are beneficial for white matter in low-fit older adults. *PloS One, 9*(9), e107413.

Callahan, C. M., Unverzagt, F. W., Hui, S. L., Perkins, A. J., & Hendrie, H. C. (2002). Six-item screener to identify cognitive impairment among potential subjects for clinical research. *Medical Care, 40*(9), 771-781.

Cassilhas, R. C., Viana, V. A., Grassmann, V., Santos, R. T., Santos, R. F., Tufik, S., & Mello, M. T. (2007). The impact of resistance exercise on the cognitive function of the elderly. *Medicine and Science in Sports and Exercise, 39*(8), 1401-1407.

Catellier, D. J., Hannan, P. J., Murray, D. M., Addy, C. L., Conway, T. L., Yang, S., & Rice, J. C. (2005). Imputation of missing data when measuring physical activity by accelerometry. *Medicine and Science in Sports and Exercise, 37*(11 Suppl), S555-62.

Centers for Disease Control and Prevention (CDC). (2005). Adult participation in recommended levels of physical activity--united states, 2001 and 2003. *MMWR.Morbidity and Mortality Weekly Report, 54*(47), 1208-1212.

Chan, R. C., Shum, D., Toulopoulou, T., & Chen, E. Y. (2008). Assessment of executive functions: Review of instruments and identification of critical issues. *Archives of Clinical Neuropsychology : The Official Journal of the National Academy of Neuropsychologists, 23*(2), 201-216.

Choi, L., Ward, S. C., Schnelle, J. F., & Buchowski, M. S. (2012). Assessment of wear/nonwear time classification algorithms for triaxial accelerometer. *Medicine and Science in Sports and Exercise, 44*(10), 2009-2016.

Cohen, S., Kamarck, T., & Mermelstein, R. (1983). A global measure of perceived stress. *Journal of Health and Social Behavior, 24*(4), 385-396.

Colcombe, S. J., Erickson, K. I., Scalf, P. E., Kim, J. S., Prakash, R., McAuley, E., . . . Kramer, A. F. (2006). Aerobic exercise training increases brain volume in aging humans. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 61*(11), 1166-1170.

Colcombe, S. J., Kramer, A. F., Erickson, K. I., Scalf, P., McAuley, E., Cohen, N. J., . . . Elavsky, S. (2004). Cardiovascular fitness, cortical plasticity, and aging. *Proceedings of the National Academy of Sciences of the United States of America, 101*(9), 3316-3321.

Colley, R. C., Garriguet, D., Janssen, I., Craig, C. L., Clarke, J., & Tremblay, M. S. (2011). *Physical activity of canadian adults: Accelerometer results from the 2007 to 2009 canadian health measures survey* Statistics Canada Ottawa.

Copeland, J. L., & Esliger, D. W. (2009). Accelerometer assessment of physical activity in active, healthy older adults. *Journal of Aging and Physical Activity, 17*(1), 17-30.

Crichton, G. E., Bryan, J., & Murphy, K. J. (2013). Dietary antioxidants, cognitive function and dementia--a systematic review. *Plant Foods for Human Nutrition (Dordrecht, Netherlands), 68*(3), 279-292.

Crouter, S. E., DellaValle, D. M., Haas, J. D., Frongillo, E. A., & Bassett, D. R. (2013). Validity of ActiGraph 2-regression model, matthews cut-points, and NHANES cut-points for assessing free-living physical activity. *Journal of Physical Activity & Health, 10*(4), 504-514.

Cushman, M., Cornell, E. S., Howard, P. R., Bovill, E. G., & Tracy, R. P. (1995). Laboratory methods and quality assurance in the cardiovascular health study. *Clinical Chemistry, 41*(2), 264-270.

Dartigues, J. F., Commenges, D., Letenneur, D., Barberger-Gateau, P., Gilleron, V., Fabrigoule, C., . . . Salamon, R. (1997). Cognitive predictors of dementia in elderly community residents. *Neuroepidemiology, 16*(1), 29-39.

Davenport, M. H., Hogan, D. B., Eskes, G. A., Longman, R. S., & Poulin, M. J. (2012). Cerebrovascular reserve: The link between fitness and cognitive function? *Exercise and Sport Sciences Reviews, 40*(3), 153-158.

Daviglus, M. L., Plassman, B. L., Pirzada, A., Bell, C. C., Bowen, P. E., Burke, J. R., . . . Williams, J. W.,Jr. (2011). Risk factors and preventive interventions for alzheimer disease: State of the science. *Archives of Neurology, 68*(9), 1185-1190.

Davis, M. G., & Fox, K. R. (2007). Physical activity patterns assessed by accelerometry in older people. *European Journal of Applied Physiology, 100*(5), 581-589.

Davis, M. G., Fox, K. R., Hillsdon, M., Sharp, D. J., Coulson, J. C., & Thompson, J. L. (2011). Objectively measured physical activity in a diverse sample of older urban UK adults. *Medicine and Science in Sports and Exercise, 43*(4), 647-654.

Dogra, S., & Stathokostas, L. (2012). Sedentary behavior and physical activity are independent predictors of successful aging in middle-aged and older adults. *Journal of Aging Research, 2012*, 190654.

Draganski, B., Gaser, C., Busch, V., Schuierer, G., Bogdahn, U., & May, A. (2004). Neuroplasticity: Changes in grey matter induced by training. *Nature, 427*(6972), 311-312.

Driscoll, I., Davatzikos, C., An, Y., Wu, X., Shen, D., Kraut, M., & Resnick, S. M. (2009). Longitudinal pattern of regional brain volume change differentiates normal aging from MCI. *Neurology, 72*(22), 1906-1913.

Driscoll, I., Hamilton, D. A., Petropoulos, H., Yeo, R. A., Brooks, W. M., Baumgartner, R. N., & Sutherland, R. J. (2003). The aging hippocampus: Cognitive, biochemical and structural findings. *Cerebral Cortex (New York, N.Y.: 1991), 13*(12), 1344-1351.

Dunstan, D. W., Howard, B., Healy, G. N., & Owen, N. (2012). Too much sitting–a health hazard. *Diabetes Research and Clinical Practice, 97*(3), 368-376.

Dyrstad, S. M., Hansen, B. H., Holme, I. M., & Anderssen, S. A. (2014). Comparison of self-reported versus accelerometer-measured physical activity. *Medicine and Science in Sports and Exercise, 46*(1), 99-106.

Eckerstrom, C., Olsson, E., Borga, M., Ekholm, S., Ribbelin, S., Rolstad, S., . . . Malmgren, H. (2008). Small baseline volume of left hippocampus is associated with subsequent conversion of MCI into dementia: The goteborg MCI study. *Journal of the Neurological Sciences, 272*(1-2), 48-59.

Erickson, K. I., Prakash, R. S., Voss, M. W., Chaddock, L., Hu, L., Morris, K. S., . . . Kramer, A. F. (2009). Aerobic fitness is associated with hippocampal volume in elderly humans. *Hippocampus, 19*(10), 1030-1039.

Erickson, K. I., Raji, C. A., Lopez, O. L., Becker, J. T., Rosano, C., Newman, A. B., . . . Kuller, L. H. (2010). Physical activity predicts gray matter volume in late adulthood: The cardiovascular health study. *Neurology, 75*(16), 1415-1422.

Erickson, K. I., Voss, M. W., Prakash, R. S., Basak, C., Szabo, A., Chaddock, L., . . . Kramer, A. F. (2011). Exercise training increases size of hippocampus and improves memory.

Proceedings of the National Academy of Sciences of the United States of America, 108(7), 3017-3022.

Erickson, K. I., Weinstein, A. M., & Lopez, O. L. (2012). Physical activity, brain plasticity, and alzheimer's disease. *Archives of Medical Research, 43*(8), 615-621.

Etgen, T., Sander, D., Huntgeburth, U., Poppert, H., Forstl, H., & Bickel, H. (2010). Physical activity and incident cognitive impairment in elderly persons: The INVADE study. *Archives of Internal Medicine, 170*(2), 186-193.

Fam, N. P., Verma, S., Kutryk, M., & Stewart, D. J. (2003). Clinician guide to angiogenesis. *Circulation, 108*(21), 2613-2618.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research, 12*(3), 189-198.

Fratiglioni, L., Paillard-Borg, S., & Winblad, B. (2004). An active and socially integrated lifestyle in late life might protect against dementia. *The Lancet.Neurology, 3*(6), 343-353.

Freedson, P. S., Melanson, E., & Sirard, J. (1998). Calibration of the computer science and applications, inc. accelerometer. *Medicine and Science in Sports and Exercise, 30*(5), 777-781.

Geda, Y. E., Roberts, R. O., Knopman, D. S., Christianson, T. J., Pankratz, V. S., Ivnik, R. J., . . . Rocca, W. A. (2010). Physical exercise, aging, and mild cognitive impairment: A population-based study. *Archives of Neurology, 67*(1), 80-86.

Gillette-Guyonnet, S., & Vellas, B. (2008). Caloric restriction and brain function. *Current Opinion in Clinical Nutrition and Metabolic Care, 11*(6), 686-692.

Glazer, N. L., Lyass, A., Esliger, D. W., Blease, S. J., Freedson, P. S., Massaro, J. M., . . . Vasan, R. S. (2013). Sustained and shorter bouts of physical activity are related to cardiovascular health. *Medicine and Science in Sports and Exercise, 45*(1), 109-115.

Golubic, R., Martin, K. R., Ekelund, U., Hardy, R., Kuh, D., Wareham, N., . . . NSHD scientific and data collection teams. (2014). Levels of physical activity among a nationally representative sample of people in early old age: Results of objective and self-reported assessments. *The International Journal of Behavioral Nutrition and Physical Activity, 11*, 58-5868-11-58.

Gorman, E., Hanson, H. M., Yang, P. H., Khan, K. M., Liu-Ambrose, T., & Ashe, M. C. (2014). Accelerometry analysis of physical activity and sedentary behavior in older adults: A systematic review and data analysis. *European Review of Aging and Physical Activity : Official Journal of the European Group for Research into Elderly and Physical Activity, 11*, 35-49.

Grady, C. L., McIntosh, A. R., Beig, S., Keightley, M. L., Burian, H., & Black, S. E. (2003). Evidence from functional neuroimaging of a compensatory prefrontal network in alzheimer's disease. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 23*(3), 986-993.

Gregory, S. M., Parker, B., & Thompson, P. D. (2012). Physical activity, cognitive function, and brain health: What is the role of exercise training in the prevention of dementia? *Brain Sciences, 2*(4), 684-708.

Gretebeck, R. J., & Montoye, H. J. (1992). Variability of some objective measures of physical activity. *Medicine and Science in Sports and Exercise, 24*(10), 1167-1172.

Hachinski, V. (2006). NINDS-CSN vascular cognitive impairment harmonization standards. *Stroke (1970), 37*, 2220.

Hagstromer, M., Troiano, R. P., Sjostrom, M., & Berrigan, D. (2010). Levels and patterns of objectively assessed physical activity--a comparison between sweden and the united states. *American Journal of Epidemiology, 171*(10), 1055-1064.

Hamer, M., & Chida, Y. (2009). Physical activity and risk of neurodegenerative disease: A systematic review of prospective evidence. *Psychological Medicine, 39*(1), 3-11.

Hamer, M., & Stamatakis, E. (2013). Screen-based sedentary behavior, physical activity, and muscle strength in the english longitudinal study of ageing. *PloS One, 8*(6), e66222.

Hamilton, M. T., Hamilton, D. G., & Zderic, T. W. (2004). Exercise physiology versus inactivity physiology: An essential concept for understanding lipoprotein lipase regulation. *Exercise and Sport Sciences Reviews, 32*(4), 161-166.

Hansen, B. H., Kolle, E., Dyrstad, S. M., Holme, I., & Anderssen, S. A. (2012). Accelerometer-determined physical activity in adults and older people. *Medicine and Science in Sports and Exercise, 44*(2), 266-272.

Harris, T. J., Owen, C. G., Victor, C. R., Adams, R., Ekelund, U., & Cook, D. G. (2009). A comparison of questionnaire, accelerometer, and pedometer: Measures in older people. *Medicine and Science in Sports and Exercise, 41*(7), 1392-1402.

Haskell, W. L., Lee, I. M., Pate, R. R., Powell, K. E., Blair, S. N., Franklin, B. A., . . . American Heart Association. (2007). Physical activity and public health: Updated recommendation for adults from the american college of sports medicine and the american heart association. *Circulation, 116*(9), 1081-1093.

Hawkins, M. S., Storti, K. L., Richardson, C. R., King, W. C., Strath, S. J., Holleman, R. G., & Kriska, A. M. (2009). Objectively measured physical activity of USA adults by sex, age, and racial/ethnic groups: A cross-sectional study. *The International Journal of Behavioral Nutrition and Physical Activity, 6*, 31-31.

Healy, G. N., Dunstan, D. W., Salmon, J., Cerin, E., Shaw, J. E., Zimmet, P. Z., & Owen, N. (2007). Objectively measured light-intensity physical activity is independently associated with 2-h plasma glucose. *Diabetes Care, 30*(6), 1384-1389.

Healy, G. N., Dunstan, D. W., Salmon, J., Cerin, E., Shaw, J. E., Zimmet, P. Z., & Owen, N. (2008). Breaks in sedentary time: Beneficial associations with metabolic risk. *Diabetes Care, 31*(4), 661-666.

Healy, G. N., Dunstan, D. W., Salmon, J., Shaw, J. E., Zimmet, P. Z., & Owen, N. (2008). Television time and continuous metabolic risk in physically active adults. *Medicine and Science in Sports and Exercise, 40*(4), 639-645.

Hickie, I., Naismith, S., Ward, P. B., Scott, E., Mitchell, P., Wilhelm, K., & Parker, G. (2005). Vascular risk and low serum B12 predict white matter lesions in patients with major depression. *Journal of Affective Disorders, 85*(3), 327-332.

Ho, A. J., Raji, C. A., Becker, J. T., Lopez, O. L., Kuller, L. H., Hua, X., . . . Toga, A. W. (2010). The effects of physical activity, education, and body mass index on the aging brain. *Human Brain Mapping, 32*(9), 1371-1382.

Holzschneider, K., Wolbers, T., Roder, B., & Hotting, K. (2012). Cardiovascular fitness modulates brain activation associated with spatial learning. *Neuroimage, 59*(3), 3003-3014.

Honea, R. A., Thomas, G. P., Harsha, A., Anderson, H. S., Donnelly, J. E., Brooks, W. M., & Burns, J. M. (2009). Cardiorespiratory fitness and preserved medial temporal lobe volume in alzheimer disease. *Alzheimer Disease and Associated Disorders, 23*(3), 188-197.

Hooker, S. P., Feeney, A., Hutto, B., Pfeiffer, K. A., McIver, K., Heil, D. P., . . . Blair, S. N. (2011). Validation of the actical activity monitor in middle-aged and older adults. *Journal of Physical Activity & Health, 8*(3), 372-381.

Howard, V. J., Cushman, M., Pulley, L., Gomez, C. R., Go, R. C., Prineas, R. J., . . . Howard, G. (2005). The reasons for geographic and racial differences in stroke study: Objectives and design. *Neuroepidemiology, 25*(3), 135-143.

Hurd, M. D., Martorell, P., & Langa, K. M. (2013). Monetary costs of dementia in the united states. *The New England Journal of Medicine, 369*(5), 489-490.

Hutto, B., Howard, V. J., Blair, S. N., Colabianchi, N., Vena, J. E., Rhodes, D., & Hooker, S. P. (2013). Identifying accelerometer nonwear and wear time in older adults. *The International Journal of Behavioral Nutrition and Physical Activity, 10*, 120-5868-10-120.

Jack, C. R.,Jr, Petersen, R. C., Xu, Y., O'Brien, P. C., Smith, G. E., Ivnik, R. J., . . . Kokmen, E. (2000). Rates of hippocampal atrophy correlate with change in clinical status in aging and AD. *Neurology, 55*(4), 484-489.

Jack, C. R.,Jr, Petersen, R. C., Xu, Y. C., O'Brien, P. C., Smith, G. E., Ivnik, R. J., . . . Kokmen, E. (1999). Prediction of AD with MRI-based hippocampal volume in mild cognitive impairment. *Neurology, 52*(7), 1397-1403.

Jack, C. R.,Jr, Petersen, R. C., Xu, Y. C., Waring, S. C., O'Brien, P. C., Tangalos, E. G., . . . Kokmen, E. (1997). Medial temporal atrophy on MRI in normal aging and very mild alzheimer's disease. *Neurology, 49*(3), 786-794.

Jernigan, T. L., Archibald, S. L., Fennema-Notestine, C., Gamst, A. C., Stout, J. C., Bonner, J., & Hesselink, J. R. (2001). Effects of age on tissues and regions of the cerebrum and cerebellum. *Neurobiology of Aging, 22*(4), 581-594.

Jones, W. J., Williams, L. S., & Meschia, J. F. (2001). Validating the questionnaire for verifying stroke-free status (QVSFS) by neurological history and examination. *Stroke; a Journal of Cerebral Circulation, 32*(10), 2232-2236.

Kalmijn, S., van Boxtel, M. P., Ocke, M., Verschuren, W. M., Kromhout, D., & Launer, L. J. (2004). Dietary intake of fatty acids and fish in relation to cognitive performance at middle age. *Neurology, 62*(2), 275-280.

Kerr, J., Marshall, S. J., Patterson, R. E., Marinac, C. R., Natarajan, L., Rosenberg, D., . . . Crist, K. (2013). Objectively measured physical activity is related to cognitive function in older adults. *Journal of the American Geriatrics Society, 61*(11), 1927-1931.

Kesaniemi, Y. K., Danforth, E.,Jr, Jensen, M. D., Kopelman, P. G., Lefebvre, P., & Reeder, B. A. (2001). Dose-response issues concerning physical activity and health: An evidence-based symposium. *Medicine and Science in Sports and Exercise, 33*(6 Suppl), S351-8.

Kesse-Guyot, E., Charreire, H., Andreeva, V. A., Touvier, M., Hercberg, S., Galan, P., & Oppert, J. M. (2012). Cross-sectional and longitudinal associations of different sedentary behaviors with cognitive performance in older adults. *PloS One, 7*(10), e47831.

Keysor, J. J. (2003). Does late-life physical activity or exercise prevent or minimize disablement? A critical review of the scientific evidence. *American Journal of Preventive Medicine, 25*(3 Suppl 2), 129-136.

Lakoski, S. G., & Kozlitina, J. (2014). Ethnic differences in physical activity and metabolic risk: The Dallas heart study. *Medicine and Science in Sports and Exercise, 46*(6), 1124-1132.

Landi, F., Russo, A., Barillaro, C., Cesari, M., Pahor, M., Danese, P., . . . Onder, G. (2007). Physical activity and risk of cognitive impairment among older persons living in the community. *Aging Clinical and Experimental Research, 19*(5), 410-416.

Larson, E. B., Wang, L., Bowen, J. D., McCormick, W. C., Teri, L., Crane, P., & Kukull, W. (2006). Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. *Annals of Internal Medicine, 144*(2), 73-81.

Latimer, C. S., Searcy, J. L., Bridges, M. T., Brewer, L. D., Popovic, J., Blalock, E. M., . . . Porter, N. M. (2011). Reversal of glial and neurovascular markers of unhealthy brain aging by exercise in middle-aged female mice. *PloS One, 6*(10), e26812.

Lautenschlager, N. T., Cox, K. L., Flicker, L., Foster, J. K., van Bockxmeer, F. M., Xiao, J., . . . Almeida, O. P. (2008). Effect of physical activity on cognitive function in older adults at risk for alzheimer disease: A randomized trial. *Jama, 300*(9), 1027-1037.

Lee, S., Yuki, A., Nishita, Y., Tange, C., Kim, H., Kozakai, R., . . . Shimokata, H. (2013). Research relationship between light-intensity physical activity and cognitive function in a community-dwelling elderly population-an 8-year longitudinal study. *Journal of the American Geriatrics Society, 61*(3), 452-453.

Liu, R., Sui, X., Laditka, J. N., Church, T. S., Colabianchi, N., Hussey, J., & Blair, S. N. (2012). Cardiorespiratory fitness as a predictor of dementia mortality in men and women. *Medicine and Science in Sports and Exercise, 44*(2), 253-259.

Liu-Ambrose, T., Nagamatsu, L. S., Graf, P., Beattie, B. L., Ashe, M. C., & Handy, T. C. (2010). Resistance training and executive functions: A 12-month randomized controlled trial. *Archives of Internal Medicine, 170*(2), 170-178.

Lou, S. J., Liu, J. Y., Chang, H., & Chen, P. J. (2008). Hippocampal neurogenesis and gene expression depend on exercise intensity in juvenile rats. *Brain Research, 1210*, 48-55.

Lyden, K., Keadle, S. K., Staudenmayer, J., & Freedson, P. S. (2014). A method to estimate free-living active and sedentary behavior from an accelerometer. *Medicine and Science in Sports and Exercise, 46*(2), 386-397.

Malmstrom, T. K., Wolinsky, F. D., Andresen, E. M., Miller, J. P., & Miller, D. K. (2005). Cognitive ability and physical performance in middle-aged african americans. *Journal of the American Geriatrics Society, 53*(6), 997-1001.

Masel, M. C., Raji, M., & Peek, M. K. (2010). Education and physical activity mediate the relationship between ethnicity and cognitive function in late middle-aged adults. *Ethnicity & Health, 15*(3), 283-302.

Masur, D. M., Sliwinski, M., Lipton, R. B., Blau, A. D., & Crystal, H. A. (1994). Neuropsychological prediction of dementia and the absence of dementia in healthy elderly persons. *Neurology, 44*(8), 1427-1432.

Matthews, C. E., Jurj, A. L., Shu, X. O., Li, H. L., Yang, G., Li, Q., . . . Zheng, W. (2007). Influence of exercise, walking, cycling, and overall nonexercise physical activity on mortality in chinese women. *American Journal of Epidemiology, 165*(12), 1343-1350.

Matthews, C. E., Moore, S. C., George, S. M., Sampson, J., & Bowles, H. R. (2012). Improving self-reports of active and sedentary behaviors in large epidemiologic studies. *Exercise and Sport Sciences Reviews, 40*(3), 118-126.

Matthews, C. E., Chen, K. Y., Freedson, P. S., Buchowski, M. S., Beech, B. M., Pate, R. R., & Troiano, R. P. (2008). Amount of time spent in sedentary behaviors in the united states, 2003-2004. *Am. J. Epidemiol., 167*(7), 875-881.

McEwen, B. S. (2002). Sex, stress and the hippocampus: Allostasis, allostatic load and the aging process. *Neurobiology of Aging, 23*(5), 921-939.

Middleton, L. E., Barnes, D. E., Lui, L. Y., & Yaffe, K. (2010). Physical activity over the life course and its association with cognitive performance and impairment in old age. *Journal of the American Geriatrics Society, 58*(7), 1322-1326.

Middleton, L. E., Manini, T. M., Simonsick, E. M., Harris, T. B., Barnes, D. E., Tylavsky, F., . . . Yaffe, K. (2011). Activity energy expenditure and incident cognitive impairment in older adults. *Archives of Internal Medicine, 171*(14), 1251-1257.

Middleton, L. E., Mitnitski, A., Fallah, N., Kirkland, S. A., & Rockwood, K. (2008). Changes in cognition and mortality in relation to exercise in late life: A population based study. *PloS One, 3*(9), e3124.

Morgenthaler, T. I., Lee-Chiong, T., Alessi, C., Friedman, L., Aurora, R. N., Boehlecke, B., . . . Standards of Practice Committee of the American Academy of Sleep Medicine. (2007). Practice parameters for the clinical evaluation and treatment of circadian rhythm sleep disorders. an american academy of sleep medicine report. *Sleep, 30*(11), 1445-1459.

Morris, J. C., Heyman, A., Mohs, R. C., Hughes, J. P., van Belle, G., Fillenbaum, G., . . . Clark, C. (1989). The consortium to establish a registry for alzheimer's disease (CERAD). part I. clinical and neuropsychological assessment of alzheimer's disease. *Neurology, 39*(9), 1159-1165.

Morris, J. C., Storandt, M., Miller, J. P., McKeel, D. W., Price, J. L., Rubin, E. H., & Berg, L. (2001). Mild cognitive impairment represents early-stage alzheimer disease. *Archives of Neurology, 58*(3), 397-405.

Morris, M. C. (2012). Nutritional determinants of cognitive aging and dementia. *The Proceedings of the Nutrition Society, 71*(1), 1-13.

Murphy, S. L. (2009). Review of physical activity measurement using accelerometers in older adults: Considerations for research design and conduct. *Preventive Medicine, 48*(2), 108-114.

Nakajima, S., Ohsawa, I., Ohta, S., Ohno, M., & Mikami, T. (2010). Regular voluntary exercise cures stress-induced impairment of cognitive function and cell proliferation accompanied by increases in cerebral IGF-1 and GST activity in mice. *Behavioural Brain Research, 211*(2), 178-184.

Nasreddine, Z. S., Phillips, N. A., Bedirian, V., Charbonneau, S., Whitehead, V., Collin, I., . . . Chertkow, H. (2005). The montreal cognitive assessment, MoCA: A brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society, 53*(4), 695-699.

Nelson, M. E., Rejeski, W. J., Blair, S. N., Duncan, P. W., Judge, J. O., King, A. C., . . . Castaneda-Sceppa, C. (2007). Physical activity and public health in older adults: Recommendation from the american college of sports medicine and the american heart association. *Medicine and Science in Sports and Exercise, 39*(8), 1435-1445.

Obisesan, T. O., Umar, N., Paluvoi, N., & Gillum, R. F. (2012). Association of leisure-time physical activity with cognition by apolipoprotein-E genotype in persons aged 60 years and over: The national health and nutrition examination survey (NHANES-III). *Clinical Interventions in Aging, 7*, 35-43.

O'Brien, J. T. (2006). Vascular cognitive impairment. *The American Journal of Geriatric Psychiatry : Official Journal of the American Association for Geriatric Psychiatry, 14*(9), 724-733.

Orme, J. G., Reis, J., & Herz, E. J. (1986). Factorial and discriminant validity of the center for epidemiological studies depression (CES-D) scale. *Journal of Clinical Psychology, 42*(1), 28-33.

Owen, N., Healy, G. N., Matthews, C. E., & Dunstan, D. W. (2010). Too much sitting: The population-health science of sedentary behavior. *Exercise and Sport Sciences Reviews, 38*(3), 105.

Pa, J., Goodson, W., Bloch, A., King, A. C., Yaffe, K., & Barnes, D. E. (2014). Effect of exercise and cognitive activity on self-reported sleep quality in community-dwelling older adults with cognitive complaints: A randomized controlled trial. *Journal of the American Geriatrics Society, 62*(12), 2319-2326.

Panel on Prevention of Falls in Older Persons, American Geriatrics Society and British Geriatrics Society. (2011). Summary of the updated american geriatrics Society/British geriatrics society clinical practice guideline for prevention of falls in older persons. *Journal of the American Geriatrics Society, 59*(1), 148-157.

Panza, F., D'Introno, A., Colacicco, A. M., Capurso, C., Del Parigi, A., Caselli, R. J., . . . Solfrizzi, V. (2005). Current epidemiology of mild cognitive impairment and other predementia syndromes. *The American Journal of Geriatric Psychiatry : Official Journal of the American Association for Geriatric Psychiatry, 13*(8), 633-644.

Parker, B. A., Thompson, P. D., Jordan, K. C., Grimaldi, A. S., Assaf, M., Jagannathan, K., & Pearlson, G. D. (2011). Effect of exercise training on hippocampal volume in humans: A pilot study. *Research Quarterly for Exercise and Sport, 82*(3), 585-591.

Pasquier, F. (1999). Early diagnosis of dementia: Neuropsychology. *Journal of Neurology, 246*(1), 6-15.

Penedo, F. J., & Dahn, J. R. (2005). Exercise and well-being: A review of mental and physical health benefits associated with physical activity. *Current Opinion in Psychiatry, 18*(2), 189-193.

Perrig-Chiello, P., Perrig, W. J., Ehrsam, R., Staehelin, H. B., & Krings, F. (1998). The effects of resistance training on well-being and memory in elderly volunteers. *Age and Ageing, 27*(4), 469-475.

Petersen, R. C., Doody, R., Kurz, A., Mohs, R. C., Morris, J. C., Rabins, P. V., . . . Winblad, B. (2001). Current concepts in mild cognitive impairment. *Archives of Neurology, 58*(12), 1985-1992.

Petersen, R. C., Jack, C. R.,Jr, Xu, Y. C., Waring, S. C., O'Brien, P. C., Smith, G. E., . . . Kokmen, E. (2000). Memory and MRI-based hippocampal volumes in aging and AD. *Neurology, 54*(3), 581-587.

Pietrelli, A., Lopez-Costa, J., Goni, R., Brusco, A., & Basso, N. (2012). Aerobic exercise prevents age-dependent cognitive decline and reduces anxiety-related behaviors in middle-aged and old rats. *Neuroscience, 202*, 252-266.

Piolino, P., Desgranges, B., Hubert, V., Bernard, F. A., Matuszewski, V., Chetelat, G., . . . Eustache, F. (2008). Reliving lifelong episodic autobiographical memories via the hippocampus: A correlative resting PET study in healthy middle-aged subjects. *Hippocampus, 18*(5), 445-459.

Plasqui, G., & Westerterp, K. R. (2007). Physical activity assessment with accelerometers: An evaluation against doubly labeled water. *Obesity (Silver Spring, Md.), 15*(10), 2371-2379.

Plassman, B. L., Langa, K. M., Fisher, G. G., Heeringa, S. G., Weir, D. R., Ofstedal, M. B., . . . Wallace, R. B. (2008). Prevalence of cognitive impairment without dementia in the united states. *Annals of Internal Medicine, 148*(6), 427-434.

Pober, D. M., Staudenmayer, J., Raphael, C., & Freedson, P. S. (2006). Development of novel techniques to classify physical activity mode using accelerometers. *Medicine and Science in Sports and Exercise, 38*(9), 1626-1634.

Prakash, R. S., Snook, E. M., Motl, R. W., & Kramer, A. F. (2010). Aerobic fitness is associated with gray matter volume and white matter integrity in multiple sclerosis. *Brain Research, 1341*, 41-51.

Proper, K. I., Singh, A. S., van Mechelen, W., & Chinapaw, M. J. (2011). Sedentary behaviors and health outcomes among adults: A systematic review of prospective studies. *American Journal of Preventive Medicine, 40*(2), 174-182.

Rikli, R. E. (2000). Reliability, validity, and methodological issues in assessing physical activity in older adults. *Research Quarterly for Exercise and Sport, 71*(2 Suppl), S89-96.

Scarmeas, N., Luchsinger, J. A., Schupf, N., Brickman, A. M., Cosentino, S., Tang, M. X., & Stern, Y. (2009). Physical activity, diet, and risk of alzheimer disease. *Jama, 302*(6), 627-637.

Shiroma, E. J., Freedson, P. S., Trost, S. G., & Lee, I. (2013). Patterns of accelerometer-assessed sedentary behavior in older women. *JAMA, 310*(23), 2562-2563.

Smith, P. J., Blumenthal, J. A., Hoffman, B. M., Cooper, H., Strauman, T. A., Welsh-Bohmer, K., . . . Sherwood, A. (2010). Aerobic exercise and neurocognitive performance: A meta-analytic review of randomized controlled trials. *Psychosomatic Medicine, 72*(3), 239-252.

Sofi, F., Valecchi, D., Bacci, D., Abbate, R., Gensini, G. F., Casini, A., & Macchi, C. (2011). Physical activity and risk of cognitive decline: A meta-analysis of prospective studies. *Journal of Internal Medicine, 269*(1), 107-117.

Stewart, A. L., Mills, K. M., King, A. C., Haskell, W. L., Gillis, D., & Ritter, P. L. (2001). CHAMPS physical activity questionnaire for older adults: Outcomes for interventions. *Medicine and Science in Sports and Exercise, 33*(7), 1126-1141.

Stopford, C. L., Thompson, J. C., Neary, D., Richardson, A. M., & Snowden, J. S. (2012). Working memory, attention, and executive function in alzheimer's disease and frontotemporal dementia. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior, 48*(4), 429-446.

Studholme, C., Cardenas, V., Maudsley, A., & Weiner, M. (2003). An intensity consistent filtering approach to the analysis of deformation tensor derived maps of brain shape. *Neuroimage, 19*(4), 1638-1649.

Thies, W., Bleiler, L., & Alzheimer's Association. (2013). 2013 alzheimer's disease facts and figures. *Alzheimer's & Dementia : The Journal of the Alzheimer's Association, 9*(2), 208-245.

Thorp, A. A., Owen, N., Neuhaus, M., & Dunstan, D. W. (2011). Sedentary behaviors and subsequent health outcomes in adults a systematic review of longitudinal studies, 1996-2011. *American Journal of Preventive Medicine, 41*(2), 207-215.

Tierney, M. C., Moineddin, R., Morra, A., Manson, J., & Blake, J. (2010). Intensity of recreational physical activity throughout life and later life cognitive functioning in women. *Journal of Alzheimer's Disease : JAD, 22*(4), 1331-1338.

Tombaugh, T. N., & McIntyre, N. J. (1992). The mini-mental state examination: A comprehensive review. *Journal of the American Geriatrics Society, 40*(9), 922-935.

Troiano, R. P., Berrigan, D., Dodd, K. W., Masse, L. C., Tilert, T., & McDowell, M. (2008). Physical activity in the united states measured by accelerometer. *Medicine and Science in Sports and Exercise, 40*(1), 181-188.

Trost, S. G., McIver, K. L., & Pate, R. R. (2005). Conducting accelerometer-based activity assessments in field-based research. *Medicine and Science in Sports and Exercise, 37*(11 Suppl), S531-43.

Tucker, J. M., Welk, G. J., & Beyler, N. K. (2011). Physical activity in U.S.: Adults compliance with the physical activity guidelines for americans. *American Journal of Preventive Medicine, 40*(4), 454-461.

Tudor-Locke, C., Camhi, S. M., & Troiano, R. P. (2012). A catalog of rules, variables, and definitions applied to accelerometer data in the national health and nutrition examination survey, 2003-2006. *Preventing Chronic Disease, 9*, E113.

Van der Borght, K., Havekes, R., Bos, T., Eggen, B. J., & Van der Zee, E. A. (2007). Exercise improves memory acquisition and retrieval in the Y-maze task: Relationship with hippocampal neurogenesis. *Behavioral Neuroscience, 121*(2), 324-334.

Wadley, V. G., Unverzagt, F. W., McGuire, L. C., Moy, C. S., Go, R., Kissela, B., . . . Howard, G. (2011). Incident cognitive impairment is elevated in the stroke belt: The REGARDS study. *Annals of Neurology, 70*(2), 229-236.

Warburton, D. E., Nicol, C. W., & Bredin, S. S. (2006). Health benefits of physical activity: The evidence. *CMAJ : Canadian Medical Association Journal = Journal De l'Association Medicale Canadienne, 174*(6), 801-809.

Washburn, R. A. (2000). Assessment of physical activity in older adults. *Research Quarterly for Exercise and Sport, 71*(2 Suppl), S79-88.

Washburn, R. A., Heath, G. W., & Jackson, A. W. (2000). Reliability and validity issues concerning large-scale surveillance of physical activity. *Research Quarterly for Exercise and Sport, 71*(2 Suppl), S104-13.

Westerterp, K. R. (2008). Physical activity as determinant of daily energy expenditure. *Physiology & Behavior, 93*(4-5), 1039-1043.

Weuve, J., Kang, J. H., Manson, J. E., Breteler, M. M., Ware, J. H., & Grodstein, F. (2004). Physical activity, including walking, and cognitive function in older women. *JAMA: The Journal of the American Medical Association, 292*(12), 1454-1461.

Whitt-Glover, M. C., Taylor, W. C., Heath, G. W., & Macera, C. A. (2007). Self-reported physical activity among blacks: Estimates from national surveys. *American Journal of Preventive Medicine, 33*(5), 412-417.

Williamson, J. D., Espeland, M., Kritchevsky, S. B., Newman, A. B., King, A. C., Pahor, M., . . . LIFE Study Investigators. (2009). Changes in cognitive function in a randomized trial of physical activity: Results of the lifestyle interventions and independence for elders pilot study. *The Journals of Gerontology.Series A, Biological Sciences and Medical Sciences, 64*(6), 688-694.

Wilson, R. S., Beckett, L. A., Bennett, D. A., Albert, M. S., & Evans, D. A. (1999). Change in cognitive function in older persons from a community population: Relation to age and alzheimer disease. *Archives of Neurology, 56*(10), 1274-1279.

Winker, R., Lukas, I., Perkmann, T., Haslacher, H., Ponocny, E., Lehrner, J., . . . Dal-Bianco, P. (2010). Cognitive function in elderly marathon runners: Cross-sectional data from the marathon trial (APSOEM). *Wiener Klinische Wochenschrift, 122*(23-24), 704-716.

Winkler, E. A., Gardiner, P. A., Clark, B. K., Matthews, C. E., Owen, N., & Healy, G. N. (2012). Identifying sedentary time using automated estimates of accelerometer wear time. *British Journal of Sports Medicine, 46*(6), 436-442.

Yaffe, K., Barnes, D., Nevitt, M., Lui, L., & Covinsky, K. (2001). A prospective study of physical activity and cognitive decline in elderly womenwomen who walk. *Archives of Internal Medicine, 161*(14), 1703-1708.

Yaffe, K., Kanaya, A., Lindquist, K., Simonsick, E. M., Harris, T., Shorr, R. I., . . . Newman, A. B. (2004). The metabolic syndrome, inflammation, and risk of cognitive decline. *Jama, 292*(18), 2237-2242.

Yau, S. Y., Lau, B. W., & So, K. F. (2011). Adult hippocampal neurogenesis: A possible way how physical exercise counteracts stress. *Cell Transplantation, 20*(1), 99-111.

Yau, S. Y., Lau, B. W., Tong, J. B., Wong, R., Ching, Y. P., Qiu, G., . . . So, K. F. (2011). Hippocampal neurogenesis and dendritic plasticity support running-improved spatial learning and depression-like behaviour in stressed rats. *PloS One, 6*(9), e24263.

APPENDIX A

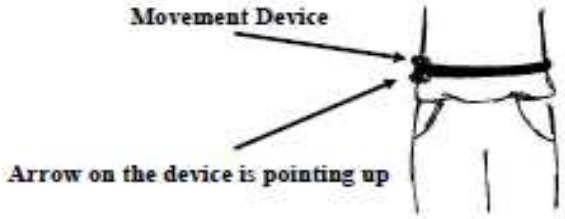
INSTRUCTION FOR WEARING THE MOVEMENT DEVICE

Instructions for Wearing the Movement Device

HOW TO WEAR THE MOVEMENT DEVICE

It is very important that you wear the movement device properly. Please follow these instructions carefully:

- Start wearing the device after you wake up on the day after you receive it in the mail. RECORD THE START DATE ON THE YELLOW LOG SHEET.
- Please wear the device for 7 days in a row.
- If you miss a day, put the device on the next day and finish the 7 day period that you had already started.
- Wear the belt snugly around your waist, either underneath or on top of your clothing. It should be worn just above your right hipbone. **Please see the picture below.**



*****PLEASE DO NOT CUT OR PERMANENTLY ALTER THE LENGTH OF BELT*****
If the belt is too large, you may tie the belt or use safety pins to secure it to your waist.

- When wearing the device, the arrow should point toward your head.
- The belt can be adjusted by simply pulling apart sides and adjusting to desired position.
- Do not remove the device from the belt.
- Put the belt on in the morning, just after getting out of bed or just after you shower/bathe. **Take it off just before you go to bed at night.**
- The device can be worn while showering, bathing, or swimming. If it gets wet, dry it off and it should be fine.
- During the next 7 days, please do not change anything about your usual activities. Simply do what you usually do each day.
- When you have completed wearing the device, please send it back as soon as possible in the addressed and stamped envelope you were given.
- Please put the *Daily Activity Log* (yellow sheet) in the envelope with the device when you mail it back.

Please call the REGARDS Operations Center at 1-888-734-2738 if you have any questions or concerns about wearing the device.

APPENDIX B

CHECKLIST FOR PHYSICAL ACTIVITY PROJECT

CHECKLIST FOR PHYSICAL ACTIVITY PROJECT

- ❑ Begin wearing the belt and device the very next day after you receive it
- ❑ Wear the belt so that the arrow on the device points up 
- ❑ Enter the date you started wearing the movement device on the ***Daily Activity Log*** **(yellow sheet)** in the **"Date Started" box.**
  ******This date is very important in determining your results******
- ❑ Wear the movement device for **7** days in a row
- ❑ On the ***Daily Activity Log*** **(yellow sheet),** write down:
  1) The time you put the device on and take it off each day
  2) If you took it off anytime during the day
- ❑ Mark on the ***Daily Activity Log*** **(yellow sheet)** whether you did any exercise or worked while you wore the device.
- ❑ After wearing the movement device for **7** days, immediately return the **device** and ***Daily Activity Log*** **(yellow sheet)** in the pre-addressed stamped envelope.

APPENDIX C

DAILY ACTIVITY LOG

Circle the day of the week that you first begin wearing the device, then **fill in the date**. In the table below, note the times, including "am" and "pm" that you put the device on and take it off during each day. Please wear the movement device for *7 consecutive days*.

Day Started

M T W Th F S Su

IMPORTANT → / / Date Started (MM/DD/YY) ← IMPORTANT

	Time On	Time Off	Did you participate in any exercise while wearing the device?	Did you remove the device for any reason?	If yes, during what times was the device off?	What was the reason you took off the device?	Did you work during the time you wore the device?	What times did you work?
SAMPLE	7:30 AM	10:15 PM	(Y) N	Y (N)			(Y) N	9AM - 1 PM
Day 1			Y N	Y N			Y N	
Day 2			Y N	Y N			Y N	
Day 3			Y N	Y N			Y N	
Day 4			Y N	Y N			Y N	
Day 5			Y N	Y N			Y N	
Day 6			Y N	Y N			Y N	
Day 7			Y N	Y N			Y N	

Write down anything else you would like to tell us about wearing the device:_____

_____

_____

APPENDIX D

SIX ITEM SCREENER

1. I would like to ask you some questions that ask you to use your memory. I am going to name three objects. Please wait until I say all three words, then repeat them. Remember what they are because I am going to ask you to name them again in a few minutes. Please repeat these words for me: APPLE—TABLE—PENNY. (Interviewer may repeat names 3 times if necessary but repetition not scored.)

Did patient correctly repeat all three words?	*Yes*	*No*
	Incorrect	Correct
1. What year is this?	0	1
2. What month is this?	0	1
3. What is the day of the week?	0	1
What were the three objects I asked you to remember?		
4. *Apple* =	0	1
5. *Table* =	0	1
6. *Penny* =	0	1

APPENDIX E

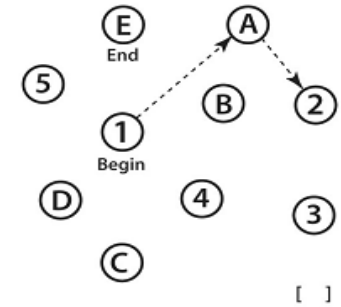
MONTREAL COGNITIVE ASSESSMENT (MOCA, memory and orientation were included)

MONTREAL COGNITIVE ASSESSMENT (MOCA)

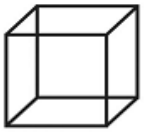
Version 7.1 Original Version

NAME :
Education :
Sex :
Date of birth :
DATE :

VISUOSPATIAL / EXECUTIVE



[ ]



Copy cube

[ ]

Draw CLOCK (Ten past eleven)
(3 points)

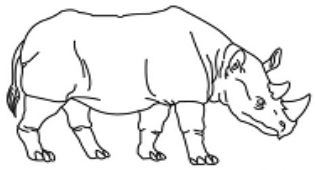
[ ] Contour [ ] Numbers [ ] Hands

POINTS

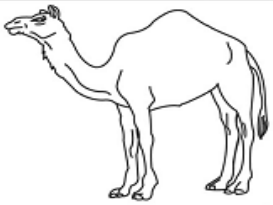
__/5

NAMING

[ ]



[ ]



[ ]

__/3

MEMORY

Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION

Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2

__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

__/3

LANGUAGE

Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ]

__/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words)

__/1

ABSTRACTION

Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler

__/2

DELAYED RECALL

	FACE	VELVET	CHURCH	DAISY	RED	
Has to recall words **WITH NO CUE**	[ ]	[ ]	[ ]	[ ]	[ ]	Points for UNCUED recall only
Optional Category cue						
Optional Multiple choice cue						

__/5

ORIENTATION

[ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

__/6

www.mocatest.org

Normal ≥ 26 / 30

TOTAL __/30