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Relationship between Cognitive Performance, Physical Activity, and Socio-Demographic/ Individual Characteristics among Aging Americans

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RELATIONSHIP BETWEEN COGNITIVE PERFORMANCE, PHYSICAL ACTIVITY, AND SOCIO-DEMOGRAPHIC/INDIVIDUAL CHARACTERISTICS AMONG AGING AMERICANS

A Thesis

by

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ABSTRACT

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Despite the attenuation of association following adjustments for covariates, participants who engaged in 3-6 hr/wk of vigorous- and > 1 hr/wk of moderate-intensity PA scored significantly higher in tests that assessed executive function and processing speed domains of cognition compared to inactive peers ($\eta 2 = 0.005$ & 0.007 respectively, $p < 0.05$). Also, after adjustment, the effects of 1-3 hr/wk of vigorous-intensity PA became trivial for the delayed recall memory domain test scores ($\beta = 0.33$; 95% CI: -0.01, 0.67; $\eta 2 = 0.002$; $p = 0.56$). There was no clear dose-response relationship between the cognitive test scores and weekly moderate-intensity PA. Interestingly, higher handgrip strength and higher late-life body-mass-index were associated with a higher performance across all cognitive domains. Observed associations provide evidence linking habitual PA with superior cognition health among older adults. Furthermore, increased muscle strength and higher late-life adiposity may also impact cognition and require further investigation.

KEYWORDS: Cognitive function, Alzheimer's disease, Handgrip strength, Executive function, Memory, Physical activity.

DEDICATION

I would like to dedicate this thesis to the two most important women in my life, my mother and my wife. I take this chance to express my gratitude for their unwavering love, support, and motivation.

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CHAPTER I

INTRODUCTION

Age-related decline in fluid cognition (the ability to learn and process new information, critical thinking, and manipulate the surrounding) has been well documented in the scientific literature (Hedden & Gabrieli, 2004; T. Salthouse, 2012). Research has also noticed individual domains of fluid cognition, such as executive function, processing speed, language ability, and memory, undergo age-related decline (Harada, Love, & Triebel, 2013; Hayden & Welsh-Bohmer, 2011; T. A. Salthouse, 2010). Aging is also associated with an increased risk of severe cognitive impairment like dementia and Alzheimer's disease (AD) (Brayne, Gill, Paykel, Huppert, & O'Connor, 1995; Seeley & Miller, 2018b), which is a major cause of disability and dependency among older adults (Association, 2021). More than 6 million aging Americans are suffering from AD in 2021 and are projected to grow 13.8 million by 2060 (Association, 2021). This dramatic increase in AD cases will generate a more than threefold increase in government and individual spending on healthcare and long-term care, costing the nation more than 1.1 trillion US dollars (Association, 2021). Furthermore, none of the pharmacological interventions available today slow or stop neuropathological changes associated with AD (Association, 2021). Thus, the role of non-pharmacological interventions such as physical activity (PA) in connection to cognitive performance has attracted attention among researchers.

PA has shown promise as a non-pharmacological preventive intervention maintaining cognitive function by slowing cognitive decline (Muscari et al., 2010) and reducing AD-risk by exerting neuroprotection and slowing neuropathological changes associated with AD and other dementias (Müller et al., 2018). Furthermore, PA modifies the lifestyle risk factors (obesity, hypertension, diabetes, late-life depression, social isolation, etc.) associated with a higher risk of dementia and AD (Kirk-Sanchez & McGough, 2014). However, controversies remain regarding the effectiveness of PA across all domains of cognition. Several studies have linked PA to enhanced cognitive function across all domains (Aarsland, Sardahaee, Anderssen, Ballard, & the Alzheimer's Society Systematic Review, 2010; Kivipelto et al., 2008). Contrastingly, others failed to notice the beneficial effect of PA across all domains and illustrated a selective beneficial effect of PA for cognitive ability in older adults (Frederiksen et al., 2015; Netz, Dwolatzky, Zinker, Argov, & Agmon, 2011; Wilbur et al., 2012). In addition, Angevaren et al. (2007) reported no significant associations between the time spent weekly on PA and the various cognitive domains as well as overall cognition. Therefore, research investigating the relationship between individual domains of fluid cognition and PA is warranted for clarification.

Extensive research is also being performed to explore various PA dosages (duration, intensity) to prescribe optimal doses to improve cognitive health in older adults. However, despite these advances, according to many researches the optimal intensity and duration of PA to improve cognitive health remain unknown (Kovacevic, Fenesi, Paolucci, & Heisz, 2020; Panza et al., 2018). Although several studies reported a positive dose-response effect of PA on cognition (Weuve et al., 2004; L. Xu et al., 2011), several others reported selective (Vidoni et al., 2015) or no dose-response relationship (Etnier, Nowell, Landers, & Sibley, 2006). Researchers

suggested that these mixed results may be due to several methodological inconsistencies and confounders like socio-demographic and individual characteristics (Panza et al., 2018).

Problem Statement and Study Purposes

The relationship between individual domains of fluid cognition (executive function, processing speed, language ability, and memory) and PA remains elusive. Additionally, investigations exploring the relationship between different durations and intensities of PA and domains of cognitive function to determine optimal PA dosage are warranted. Therefore, epidemiological research involving a large national sample of older adults to investigate the potential relationship between various doses of PA and cognitive performance across different domains would contribute to current understanding and aid the development of generalizable recommendations.

Hence, the purposes of the study were three folds: 1) to examine possible associations between different durations and intensities of PA and cognitive performance across different domains (executive function, processing speed, verbal fluency, and memory), 2) to investigate dose-response association between PA and cognitive domains, and 3) to determine the association (if any) between other socio-demographics and cognitive domains among aging Americans by using a national database, the National Health and Nutrition Examination Survey (NHANES) 2011-2014.

Significance of the Study

AD is also the sixth leading cause of death in the United States (J. Xu, Kochanek, Murphy, & Tejada-Vera, 2010) and the fifth leading cause of death among aging Americans 65

years or older (Heron & Smith, 2013). Furthermore, it is one of the leading causes of long-term illness needing healthcare and caregiving support (Brodaty, Seeher, & Gibson, 2012; Tom et al., 2015). Millions of Americans are currently suffering or are at high risk of developing AD or other dementias. Epidemiological studies have also projected an increase of at least 12% cases from 2019 to 2025 (Association, 2019). This increase would have a significant burden on national healthcare and financial assistance programs, which pay for long-term care and support for dementia patients.

While there are no current disease-modifying therapeutic measures for AD or associated dementias, PA has shown promise as a non-pharmacological preventive intervention. PA appears to show beneficial effects on maintaining cognitive function and slow neuropathological changes associated with AD and other dementias (Müller et al., 2018). Hence, it is necessary to explore the implications of PA on cognitive performance in older adults. By investigating the association between PA and cognitive performance across different domains, this study will provide a better understanding of the domain-specific role of PA. Furthermore, by examining different intensities and duration of PA among a national sample of older adults, this study will help outline the optimal intensity and duration necessary for the maintenance of cognitive health in the elderly.

Assumptions, Limitations, and Delimitations

No assumptions were made as this study used a national data source for this study. The variables selected are each identified in the files and discussed further in Chapter III.

The limitations of using NHANES data include the self- or proxy reports, thereby increasing data error and placing limits on data interpretation and conclusions and they are well documented and accounted for in its Analytic and Reporting Guidelines (CDC, 2018a).

Research Questions

In order to test the hypotheses, the following research questions were addressed:

1) Will there be any effect of PA on the cognitive performance assessment test scores across different domains in aging Americans?

2) Will there be any effect of different intensities of PA on the cognitive performance assessment test scores across different domains in aging Americans?

3) Will there be any dose-response effect of PA on the cognitive performance assessment test scores across different domains in aging Americans?

4) Are there any other socio-demographic and individual variables associated with cognitive domains?

Hypotheses

1) Aging Americans engaging in weekly PA would perform better in all the cognitive performance assessment tests across all domains compared to inactive counterparts.
2) Aging Americans engaging in higher intensity PA would perform better on the cognitive performance tests across all domains.
3) There will be a linear dose-response effect of PA on the cognitive performance assessment test scores across different domains.

4) There will be several socio-demographic and individual variables associated with cognitive domains.

Operational Definitions

To aid the reader, the following terms are defined as used in this study:

1) **Fluid cognition:** The ability to learn and process new information, critical thinking, and manipulate the surrounding (Stawski, Almeida, Lachman, Tun, & Rosnick, 2010).
2) **Executive function:** Capabilities that enable an individual to engage in complex purposefully independent self-serving mental actions and subsequent response (Hobson & Leeds, 2001).
3) **Processing speed:** The ability to process information rapidly, is closely related to the ability to perform higher-order cognitive tasks (Lichtenberger & Kaufman, 2012).
4) **Verbal fluency:** Cognitive ability that facilitates information retrieval from memory in a certain amount of time (Patterson, 2011).
5) **Declarative or explicit memory:** Conscious recollection of experiences, events, and information used in everyday living (Grote-Garcia & McDowell, 2011).
6) **Episodic or autobiographical memory:** Ability to recall and mentally re-experience specific episodes from one's personal past (Hudson, Mayhew, & Prabhakar, 2011).
7) **Semantic memory:** Long-term memory for meaning, understanding, and conceptual facts about the world (Schendan, 2012).
8) **Dementia:** An acquired impairment of cognition abilities that commonly involves memory and at least one other cognitive domain (language, visuospatial, executive function) (Eric B Larson, 2016).

9) **Mild cognitive impairment (MCI):** Transitional phase of cognitive impairment where cognitive decline is greater than expected but have not reached clinical dementia (Emily Frith & Loprinzi, 2020; Jack Jr, 2012).
10) **Alzheimer's disease:** The most prevalent and devastating form of dementia (Seeley & Miller, 2018b).
11) **Cognitive reserve:** The ability of the brain to utilize neuronal network connections in a versatile manner (Association, 2019).
12) **Arousal:** The state of being activated, either physiologically or psychologically to a point of perception (Niven & Miles, 2013).
13) **Physical activity:** Bodily movement that increased heart rate and made an individual to breathe hard some of the time.
14) **Vigorous-intensity physical activity:** Activities that require hard physical effort and cause large increases in breathing or heart rate.
15) **Moderate-intensity physical activity:** Activities that require moderate physical effort and cause small increases in breathing or heart rate.

Summary

This chapter is an introduction to the concerns surrounding the relationship between individual domains of fluid cognition (executive function, processing speed, verbal fluency, and memory) and PA. Chapter 2 contains a review of relevant literature providing additional evidence validating the research study. Chapter 3 contains the description of methodology that occurred in this study. Chapter 4 contains the results and analyses of this study. Chapter 5

includes the discussion of interpretation of findings and conclusion of this study, as well as future recommendations.

CHAPTER II

REVIEW OF THE LITERATURE

The purposes of the study were three folds: 1) to examine possible associations between different durations and intensities of PA and cognitive performance across different domains (executive function, processing speed, verbal fluency, and memory), 2) to investigate dose-response association between PA and cognitive domains, and 3) to determine the association (if any) between other socio-demographics and cognitive domains among aging Americans by using a national database, the NHANES 2011-2014.

Cognitive Aging

The developmental process of aging is accompanied by several physical and mental changes. Age-related cognitive changes are some of the most prominent of these changes and have been well documented in the scientific literature. Previous research has demonstrated that some cognitive abilities such as processing speed, memory, and vocabulary show remarkable preservation across most of the adult lifespan (Harada et al., 2013). However, non-pathological aging is associated with the gradual decline in some cognitive abilities (Harada et al., 2013; Hedden & Gabrieli, 2004). Both cross-sectional and longitudinal studies suggest that fluid cognition (the ability to learning and processing new information, critical thinking and manipulate the surrounding) tend to show a decline with age at an estimated rate of -0.02 standard deviations per year (Hedden & Gabrieli, 2004; T. Salthouse, 2012).

Executive function, processing speed, language ability, and memory are components of fluid cognitive domains (Harada et al., 2013). Capabilities that enable an individual to engage in complex purposefully independent self-serving mental actions and subsequent response are referred to as executive function (Hobson & Leeds, 2001). It includes a wide range of cognitive abilities such as, critical thinking, behavioral flexibility, problem-solving, and self-awareness (Lezak, Howieson, Loring, & Fischer, 2012). Previous research has suggested that as the primarily responsible area of executive functioning (the prefrontal cortex) undergoes the largest age-related volumetric decline, these are particularly susceptible to age effects (Hayden & Welsh-Bohmer, 2011; Raz et al., 2004). Several studies have demonstrated that older adults lack mental flexibility, concept formation ability, and the ability to produce novel responses especially after the age of 70 years (Harada et al., 2013; Lezak et al., 2012; T. A. Salthouse, 2010; Singh-Manoux et al., 2012). Previous research also reported that executive controls demanding speeded motor performance are particularly influenced by age (Hayden & Welsh-Bohmer, 2011). The speed at which cognitive processes and motor responses are conducted is referred to as processing speed (Harada et al., 2013). Studies by Salthouse and colleagues have reported that slowed processing speed substantially reduces the performance of older adults in a wide variety of cognitive and neuropsychological tests designed to measure other cognitive domains (e.g. verbal fluency) (T. A. Salthouse, 2010). Verbal fluency, a cognitive ability that facilitates information retrieval from memory in a certain amount of time (Patterson, 2011), is the fluid cognitive ability of the language domain (Harada et al., 2013). The age-related decline is also noticeable in verbal fluency (T. A. Salthouse, 2010; Singh-Manoux et al., 2012).

Memory is highly sensitive to the normal aging continuum (Harada et al., 2013; T. A. Salthouse, 2010). As the decline in grey matter volume, white matter integrity, and changes in dendritic spines may disrupt the connection between brain areas, they have been linked with declines in many domains of cognitive function, especially memory (Buckner, 2004; Burke & Barnes, 2006; He et al., 2012). Declarative or explicit memory [conscious recollection of experiences, events, and information used in everyday living (Grote-Garcia & McDowell, 2011)], one of two major types of memory, have shown a decline with normal aging (Harada et al., 2013; Rönnlund, Nyberg, Bäckman, & Nilsson, 2005). Furthermore, studies have also revealed that the two types of declarative memory, semantic memory and episodic memory, are also sensitive to age-related decline (Davis, Eacott, Easton, & Gigg, 2013; Lövdén et al., 2004). However, these reductions occur at various times of life (Harada et al., 2013). Research has observed episodic or autobiographical memory [ability to recall and mentally re-experience specific episodes from one's personal past (Hudson et al., 2011)] deteriorates gradually from the age of 20 and onward, whereas semantic memory [long-term memory for meaning, understanding, and conceptual facts about the world (Schendan, 2012)] shows a decline in late-life (Harada et al., 2013; Lövdén et al., 2004; Park et al., 2002; Rönnlund et al., 2005; St. Jacques & Levine, 2007).

Even the healthiest aged brain undergoes decrements in different domains of cognitive functioning due to structural and functional changes in the brain. The developmental trajectory of cognitive aging is of primary concern to investigators to distinguish normal aging from “pathological cognitive aging” (e.g., dementia).

Pathological Cognitive Decline

Pathological cognitive decline is described as a progressive neurodegenerative disorder called dementia. The severity and global nature of cognitive impairment distinguish dementia from the mild and variable cognitive decline that occurs with normal aging (Health, 2014). Eric B Larson (2016) defined dementia as an acquired impairment of cognition abilities that commonly involves memory and at least one other cognitive domain (language, visuospatial, executive function). The clinical course is usually progressive from the preclinical disease [disease-associated biomarkers are present but patient have not yet developed symptoms (Association, 2019)] to mild cognitive impairment (MCI) [transitional phase, cognitive decline greater than expected but have not reached clinical dementia (Emily Frith & Loprinzi, 2020; Jack Jr, 2012)] to clinical dementia due to Alzheimer's disease, the most prevalent and devastating form (Seeley & Miller, 2018b).

Clinical dementia due to Alzheimer's disease hampers an individual's ability to perform the daily activity and is characterized by noticeable cognitive dysfunction (Association, 2019). Individuals with Alzheimer's dementia experience multiple symptoms that change over a period of years based on affected anatomical areas of the brain (Association, 2019; Seeley & Miller, 2018a). Alzheimer's disease usually starts in the medial temporal lobe's entorhinal region and spreads to the hippocampus. Then gradually spreads to the posterior temporal lobes and the parietal neocortex, resulting in generalized degeneration (Seeley & Miller, 2018b). Therefore, the characteristic cognitive changes associated with Alzheimer's disease appear to follow a predictable trend that starts with loss of memory followed by higher cortical functions such as vocabulary, visuospatial deficits, and finally executive dysfunction (Seeley & Miller, 2018a).

Episodic memory impairment occurs in the early stage of illness but often such symptoms are ignored (Seeley & Miller, 2018b). Researchers now believe that AD-related changes in the brain (discussed below) precede a decade or two before memory dysfunctions are noticeable (Association, 2019). Individuals gradually begin to experience behavioral disturbances and communicating difficulties as the disease progresses to the areas dealing with producing or comprehending language (Health, 2014). Furthermore, as the frontal lobe (prefrontal cortex) is frequently affected, executive dysfunction is a common symptom of Alzheimer's disease that occurs in any stage of the disease (Swanberg, Tractenberg, Mohs, Thal, & Cummings, 2004). Therefore, individuals have difficulties performing routine tasks and symptoms begin to interfere with activities of daily living such as following instructions, driving, shopping, and housekeeping (Seeley & Miller, 2018a). Therefore, individuals lose their functional independence and also the ability to maintain social relationships (Emily Frith & Loprinzi, 2020).

In short, dementia due to AD is a progressive cognitive dysfunction that detrimentally impacts an individual's quality of life. It gives rise to greater healthcare and caregiving demands, and financial challenges. However, it can be difficult to differentiate between AD-associated symptoms and normal cognitive aging in the early stages. Increasing evidence suggests that the trademark cellular pathology and cell loss in the brain associated with clinical AD precede symptoms. These cellular pathological changes in the brain are the focus of the next section.

Neuropathological changes in AD

At autopsy, a series of morphologic cellular abnormalities and molecular changes are usually found in the brain of a patient with AD. The earliest and most severe alterations are

mostly seen in the medial temporal lobe (entorhinal/perirhinal cortex and hippocampus) and inferolateral temporal cortex (Seeley & Miller, 2018a). The primary cardinal histopathological lesions associated with AD are the amyloid-β senile plaques and the neurofibrillary tangle (tau-tangles) (Perl, 2010; Seeley & Miller, 2018a).

Alzheimer's neurofibrillary tangles are still regarded as a major microscopic lesions associated with the condition (Perl, 2010). These are intracytoplasmic fibrillar aggregations composed of abnormally phosphorylated tau protein. In normal conditions, tau stabilizes microtubules, but these hyperphosphorylated tau proteins are unable to bind with microtubules and redistribute to induce misfolding of native (unfolded) tau into pathological conformations (Bachiller et al., 2018; Seeley & Miller, 2018a). Then they bind to each other to form threads that eventually form intraneuronal tangles. This results in compromising brain function by blocking the neuron's transport system and interneural communication (Perl, 2010; Seeley & Miller, 2018a). Furthermore, cellular death follows without cytoskeletal support of tau. Neuronal death is (Santiago, Bottero, & Potashkin, 2017).

Evidence suggests that Alzheimer's-related brain changes may result from a complex association among abnormal tau and amyloid-β proteins. Amyloid-β peptides are produced intra- and extracellularly and contribute to structural changes in the neocortex (Gouras, Tampellini, Takahashi, & Capetillo-Zarate, 2010). Amyloid-β polymerization and fibril formation lead to neuritic plaques. These plaques are the other cardinal pathological lesion encountered in patients suffering from Alzheimer's disease (Perl, 2010). The plaques are surrounded by several microglial cells and astrocytes which brings about a neuroinflammatory pathogenetic cascade

(Jack Jr, 2012; Perl, 2010). Recent research has proposed the role of microglial cells in the development of AD (Bachiller et al., 2018).

In a normal brain, microglial cells are considered immune sentinels and support brain protection by phagocytotic debris removal. The gene triggering receptor expressed on myeloid cells 2 (TREM2) promotes microglial phagocytosis, proliferation, and neuron survival (Bachiller et al., 2018). In AD neuropathology, amyloid-β species can trigger increased expression of TREM2, which has been linked to the recruitment of microglia to amyloid plaques resulting in chronic neuroinflammation. Recent research suggests that neuroinflammation exacerbates tau hyperphosphorylation (Gratuze, Leyns, & Holtzman, 2018). Furthermore, research has also proposed that AD-risk variants of TREM2 impair the proper function of microglial phagocytosis, inflammatory response, energy metabolism, plaque compaction, and activation, affecting disease progression (Bachiller et al., 2018; Gratuze et al., 2018). However, despite these suggestions, there are still important gaps in understanding the nature of the pathological processes and exact mechanism remains dubious.

The neuropathological changes discussed above are a result of a complex interplay between several non-modifiable (e.g. advancing age, family history and genetic factor) and modifiable (e.g. lifestyle factors). The following segment focuses on the lifestyle risk factors that contribute substantially to AD.

Lifestyle risk factors for AD

There is increasing evidence that some lifestyle factors are linked to the development of AD. According to the Lancet Commission, nearly 35% of AD-dementia cases are caused by a

combination of nine potentially modifiable risk factors (Livingston et al., 2017). These include several cardiovascular and metabolic risk factors (obesity, hypertension, diabetes, and smoking), physical inactivity, late-life depression, low educational attainment, social isolation, and hearing loss (Association, 2019; Livingston et al., 2017).

Obesity, one of the modifiable risk factors associated with cardiovascular disease (Van Gaal, Mertens, & De Block, 2006), has been linked with increased dementia risk (Gorospe & Dave, 2006; Gottesman et al., 2017). Although previous studies showed confusing evidence [null (D. R. Gustafson et al., 2009) or reduced risk (Qizilbash et al., 2015)] for the link between high body mass index (BMI) and dementia, there is increasing evidence suggesting that increased obesity are associated with a higher risk of dementia incidence (K. J. Anstey, N. Cherbuin, M. Budge, & J. Young, 2011; D. R. Gustafson et al., 2009; Ma, Ajnakina, Steptoe, & Cadar, 2020). A recent study by Ma et al. (2020) analyzed 6582 participants of ≥ 50 years from the English Longitudinal Study of Ageing (ELSA). Anthropometric measurements (BMI and waist circumference) of the participants were recorded and dementia assessment was determined using a triangulation method with three sources of information. The participants were followed up on average 11 years later to determine the development of dementia. Findings indicated that having a higher body weight or abdominal obesity is related to a higher risk of dementia. Furthermore, researchers also reported that this association is independent of other AD and dementia risk factors such as, history of hypertension, diabetes, smoking, and having a genetic risk factor (the APOE ε4 gene) (Ma et al., 2020).

Researchers have known about the link between cardiovascular and metabolic conditions and AD for years (Luchsinger, Tang, Stern, Shea, & Mayeux, 2001; Skoog et al., 1996). Recent

research has bolstered these claims by demonstrating a significant association between AD-dementia risk and cardiovascular-metabolic disease risk factors such as hypertension (Abell et al., 2018; Livingston et al., 2017), high cholesterol (Meng et al., 2014), diabetes (Gudala, Bansal, Schifano, & Bhansali, 2013; Strachan, Price, & Frier, 2008). Research has proposed that cardio-metabolic risk factors generate hemodynamic disruption leading to alteration of cerebral perfusion and ultimately cerebral injury (accumulation of amyloid-β and neuronal death) (Barnes, 2015). Researchers also suggested that the age at which certain risk factors begin to manifest may influence dementia risk. Whereas midlife-obesity (K. Anstey, N. Cherbuin, M. Budge, & J. Young, 2011; K. J. Anstey et al., 2011), hypertension (Ninomiya et al., 2011) has been associated with higher dementia risk, the onset of obesity (Annette L. Fitzpatrick et al., 2009), and hypertension (Corrada et al., 2017) after the age of 80 have been associated with decreased risk of dementia.

Individuals who have completed more years of formal education have a lower chance of AD and other dementias than people with fewer years of formal education (Stern, 2012). Researchers proposed that more years of formal schooling build greater "cognitive reserve", which is the ability of the brain to utilize neuronal network connections in a versatile manner (Association, 2019). Valenzuela and Sachdev (2006) conducted a meta-analysis of 22 longitudinal studies evaluating the incidence of dementia in relation to behavioral brain reserve (cognitive reserve). After incorporating data from over 29000 people over a median of 7.1 years of follow-up, they reported that a higher cognitive reserve is linked to a lower risk of dementia (odds ratio, 0.54; 95% confidence interval (CI): 0.49,0.59) (Valenzuela & Sachdev, 2006). Furthermore, higher formal education is usually followed by mentally stimulating jobs and

activities that also build cognitive reserve (Grzywacz, Segel-Karpas, & Lachman, 2016). Besides, having fewer years of formal education is associated with lower socioeconomic status (Association, 2019), which has been linked to cardiovascular risk factors associated with AD and other dementia (Menke, Casagrande, Geiss, & Cowie, 2015; Steptoe & Marmot, 2004).

Depression, a major mental health issue in the elderly (Luppa et al., 2012), has been associated with the cognitive deficit (Sheline et al., 2006; Wei et al., 2019). Studies have demonstrated depressive episodes deteriorate a range of cognitive functions, including memory (Burt, Zembar, & Niederehe, 1995; Nebes et al., 2000), processing speed (Nebes et al., 2000; Sheline et al., 2006), and executive function (Snyder, 2013). Furthermore, depression may prompt social isolation and loneliness (Taylor, Taylor, Nguyen, & Chatters, 2018), which are also linked to significant dementia risk (National Academies of Sciences & Medicine, 2020). However, Holwerda et.al (2014) emphasized loneliness (being alone) over social isolation as the major risk factor of clinical dementia (Holwerda et al., 2014). Nonetheless, both depression and social isolation/ loneliness have been linked to increased incidence of cardiovascular risk factors of dementia (Hare, Toukhsati, Johansson, & Jaarsma, 2014; Knox & Uvnäs-Moberg, 1998). Additionally, a synergistic effect of diabetes and depression on cognitive impairment is also evident in recent studies (Demakakos, Muniz-Terrera, & Nouwen, 2017; Downer, Vickers, Al Snih, Raji, & Markides, 2016).

Physically inactive lifestyle has been linked to higher risk of AD and other dementias. Longitudinal studies such as the Honolulu–Asia Aging Study in men reported that people who walked less than 1 mile per day during midlife and late-life have a higher risk for developing dementia compared to men who walked more than 2 miles per day, after following 2257 men

over three decades (Abbott et al., 2004). Furthermore, Bugg and Head reported that decrease in brain volume in several subcortical areas (including medial temporal lobe) correlated with age in the low-exercising group, but not with the high-exercise group (30 minutes 5 times per week) by observing 2 groups of older adults over a period of 10 years (Bugg & Head, 2011). As physical inactivity significantly increases cardiovascular and metabolic morbidities (Biolo et al., 2005; Prasad & Das, 2009) and depression (Achttien, van Lieshout, Wensing, van der Sanden, & Staal, 2019), which may initiate a series of interconnected phenomenon leading to dementia and AD (Barnes, 2015; Kirk-Sanchez & McGough, 2014).

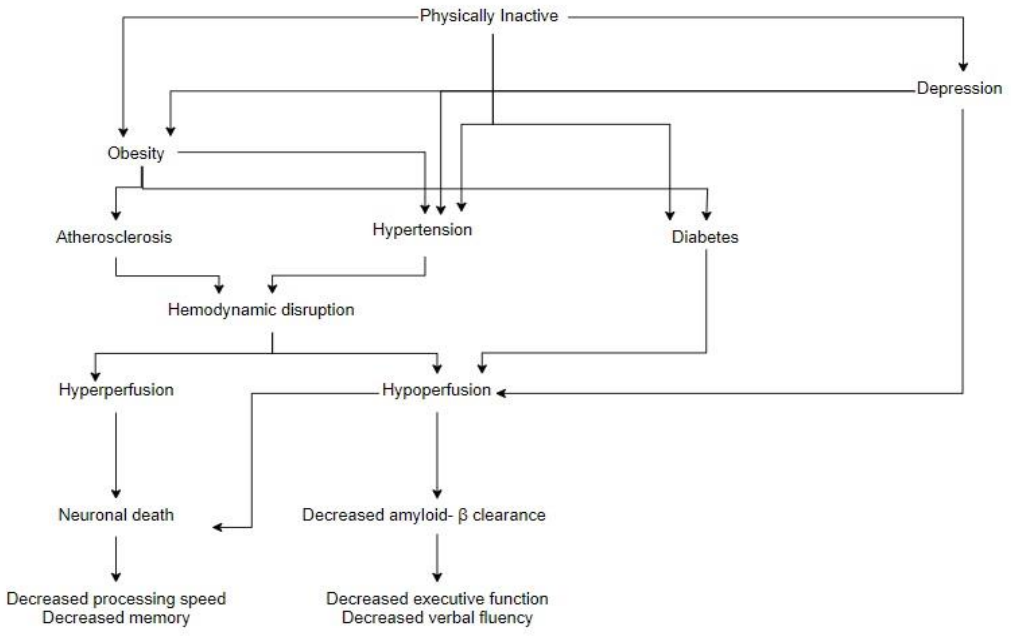


Figure 1. Relationship between lifestyle risk factors and cognitive dysfunction due to AD. Figure was adapted and modified from (Barnes, 2015).

Beneficial effects of PA in AD and dementia

As to date, no pharmacological cure is available for AD and related dementia, researchers have focused extensively on the role of non-pharmacological interventions such as PA in relation

to cognitive function. S. Colcombe and Kramer (2003) conducted a landmark meta-analysis of 18 exercise trials from 1966-2001 and reports improvement in all cognitive domains as a result of increased aerobic fitness due to PA (overall effect size= 0.48). However, they mentioned that PA benefits executive function more than memory (S. Colcombe & Kramer, 2003). This idea was bolstered by a couple of research by Baker and associates, which reported the cognitive enhancing effect of aerobic PA (Baker, Frank, Foster-Schubert, Green, Wilkinson, McTiernan, Cholerton, et al., 2010; Baker, Frank, Foster-Schubert, Green, Wilkinson, McTiernan, Plymate, et al., 2010). They also reported no change in memory function following exercise intervention (Baker, Frank, Foster-Schubert, Green, Wilkinson, McTiernan, Plymate, et al., 2010). In contrast, Ruscheweyh and colleagues assessed the influence of 6 months long PA regimes on the performance in a memory task (Ruscheweyh et al., 2011). Sixty-two healthy elderly individuals were assessed for aerobic fitness, PA level, and memory score at the baseline and after 6 months intervention of low- or moderate-intensity PA or control. They demonstrate that an increase in PA led to improved memory performance in healthy elderly individuals. They also implicated that PA may prevent cognitive decline (Ruscheweyh et al., 2011).

Other studies have also suggested that PA decreases the rate of cognitive decline. Muscari et al. (2010) recruited 120 healthy older adults and conducted a randomized controlled trial of a 12-month long exercise training intervention. They suggested that PA programs may reduce the progression of age-related cognitive decline in healthy older adults (Muscari et al., 2010). Several others reported a similar finding in the different populations such as individuals with mild cognitive impairment (Geda et al., 2010) and individuals at risk of AD (Lautenschlager et al., 2008).

In line with these findings, PA has been shown to lower the risk of AD and other dementias. E. B. Larson et al. (2006) follow-up 1740 healthy elders for about 6.2 years to determine the association between regular exercise and reduced dementia and AD risk. They reported that participants who exercised 3 or more times/ week had lower dementia incident compared to those who exercised less than 3 times/ week. They suggest a link between regular exercise and reduced risk for incidents of dementia and AD (E. B. Larson et al., 2006). Recently, the study by Buchman and associates also examined the link between daily PA and AD incidents. They continuously monitored PA and non-activity data from 716 older individuals for up to 10 days with actigraphy and performed a follow-up after 4 years for the incident of dementia and AD. They provided additional support for the link by reporting an association between reduced AD risk with a higher level of total daily PA (Buchman et al., 2012).

Although the exact mechanism is still undiscovered, researchers have proposed multiple physiologic processes that may be responsible for the neuroprotective and neuroplastic effects of exercise on brain structures.

Neuroprotective mechanism of PA in AD and other dementias

Researchers suggested that PA improves cardiorespiratory fitness in older adults (Petrella, Lattanzio, Shapiro, & Overend, 2010), which in turn provide several neuroprotective effects. Honea et al. (2009) reported that cardiorespiratory fitness is associated with regional brain volumes in the medial temporal and parietal cortices (most affected by AD) and maintaining cardiorespiratory fitness may modify AD-related brain atrophy. Relatedly, Burns et al. (2008) reported an increase in cardiorespiratory fitness is associated with reduced brain atrophy in AD by correlating cardiorespiratory fitness (measured by peak oxygen consumption)

and brain atrophy (measuring whole brain volume by MRI) in subjects with early AD versus no dementia. Additionally, research has also implied that an increase in cardiorespiratory fitness is associated with brain activation (S. J. Colcombe et al., 2004) and increased regional brain connectivity (Erickson, Gildengers, & Butters, 2013; Voss et al., 2010). Therefore, it is evident that PA level modulates the relationship between brain structure, function, and cognition by regulating cardiovascular fitness.

In line with maintaining brain volume, recent research increasingly recognized the role of PA in attenuating expression of AD-associated biomarkers in cerebrospinal fluid of cognitively normal older adults (Liang et al., 2010) and reduce the deleterious influence of age-related biomarkers alterations in preclinical AD (Okonkwo et al., 2014). Furthermore, the Australian Imaging, Biomarkers and Lifestyle Study of Ageing reported that lower levels of key AD pathogenic factors (amyloid-β load in plasma and brain) have been detected in 546 older adults with higher levels of PA (Belinda M Brown et al., 2013).

PA also modifies all the lifestyle risk factors associated with a higher risk of dementia and AD (Kirk-Sanchez & McGough, 2014). E. Frith and Loprinzi (2017) evaluated the association between PA and cognitive function among a hypertensive older adult in the national sample. They reported that a higher PA level is associated with higher cognitive function in hypertensives. Therefore, PA reduces the risk of cognitive dysfunction due to hypertension (E. Frith & Loprinzi, 2017). PA has also proven beneficial in the management of diabetes, obesity, and hypercholesterolemia (Kirk-Sanchez & McGough, 2014). Recently, Hu, Smith, Imm, Jackson, and Yang (2019) found that PA preserved cognitive function by altering the depression-cognition relationship in older adults.

As noted above, PA exerts a variety of neuroprotective and neuroplastic effects through interconnected physiological processes. Numerous advantages of PA provide a strong foundation for its prescription as a cost-effective preventive, and therapeutic alternative to enhance cognitive function. Therefore, extensive research is being performed to explore various PA dosages (duration, intensity) to prescribe optimal dose to improve brain health and cognition in older adults.

PA intensity and cognitive performance

As PA provides a cost-effective therapeutic option for improving brain and cognitive health in older adults, optimal dosage prescriptions to maximize health outcomes are of great pursuit. Recently, the World Health Organization (WHO) and the Center for Disease Control and Prevention (CDC) recommended at least 150 minutes to 300 minutes (2 hr and 30 minutes to 5 hr) a week of moderate-intensity, or 75 minutes to 150 minutes (1 hr and 15 minutes to 2 hr and 30 minutes) a week of vigorous-intensity aerobic PA, or an equivalent combination of PA for older adults (CDC, 2018b; WHO). These recommended guidelines of PA are claimed to be beneficial for overall health of aging Americans. However, these guidelines are facing criticism as they are based on expert opinion of very few meta-analyses available at that time that explored the scope of PA in prevention and treatment of AD (Panza et al., 2018). Furthermore, the analyses used produced mixed results due to several methodological inconsistencies (lack of adherence to methodological standards) and socio-demographic and individual confounders (age and sex, etc.) (Panza et al., 2018). Therefore, according to many researches the optimal intensity of PA to improve cognitive health still remains unknown (Kovacevic et al., 2020; Panza et al., 2018).

Conclusion

In conclusion, the literature presented provides strong evidence delineating the association between PA and cognition. However, despite such advances, the relationship between individual domains of fluid cognition and PA remains elusive. Furthermore, the optimal duration and intensity of PA needed to improve cognitive health is currently unknown. Nonetheless, there is dearth of information on the relationship between different duration and intensity of PA and various domains of cognitive function among free living national sample of older adults. Hence, the present study specifically aimed to test how different duration and intensity of PA relate to performance on cognitive tests.

CHAPTER III

METHODS

The purposes of the study were three folds: 1) to examine possible associations between different durations and intensities of PA and cognitive performance across different domains (executive function, processing speed, verbal fluency, and memory), 2) to investigate dose-response association between PA and cognitive domains, and 3) to determine the association (if any) between other socio-demographics and cognitive domains among aging Americans by using a national database, the NHANES 2011-2014.

Data source

The study objectives were evaluated through a cross-sectional analysis of participants who participated in the NHANES. NHANES is a serial ongoing cross-sectional survey conducted by the National Center of Health Statistics (NCHS) of the CDC. It is designed to evaluate the health status of nationally representative sample of community dwelling population (non-institutionalized U.S. civilians) through a complex, multistage, stratified, clustered probability design. It intentionally oversamples Hispanics, non-Hispanic blacks, low-income whites/ other ethnicities, non-Hispanic Asians, and older adults of all ethnicity (> 60 years). The survey consists of in-home interview utilizing computer-assisted personal interviewing (CAPI), followed by a standardized health examination in specially equipped mobile examination centers (MECs). About 5000 people are surveyed each year in 15 counties across the country (Johnson,

Dohrmann, Burt, & Mohadjer, 2014). The data is made publicly available in two-year cycles. This study is restricted to data from two NHANES cycles (2011-2012, 2013-2014) as cognitive tests were administered during these survey waves.

The NHANES sample represents the total noninstitutionalized civilian U.S. population residing in the 50 states and District of Columbia. The multi-stage sample design used in NHANES 2011–2014 consisted of 4 stages.

1st stage – Selection of primary sampling unit (PSU) from a list of every county in the US. PSUs (mainly counties) were selected with the probabilities proportionate to a measure of size, with neighboring counties being combined in a few instances to hold PSUs above a certain minimum size.

2nd stage – Sampled PSUs were divided up into area segments, comprising census blocks or combinations of blocks.

3rd stage - Consisted of dwelling units (DUs) such as households or dormitories. Following segment selection, a list of all DUs in the sampled segments was generated in each PSU, and a subset of these was allocated for screening to classify possible sampled participants.

4th stage – Consisted of individuals within occupied DUs. A subsample of individuals was chosen randomly based on sex-age-race screening subdomain from all eligible members of a household.

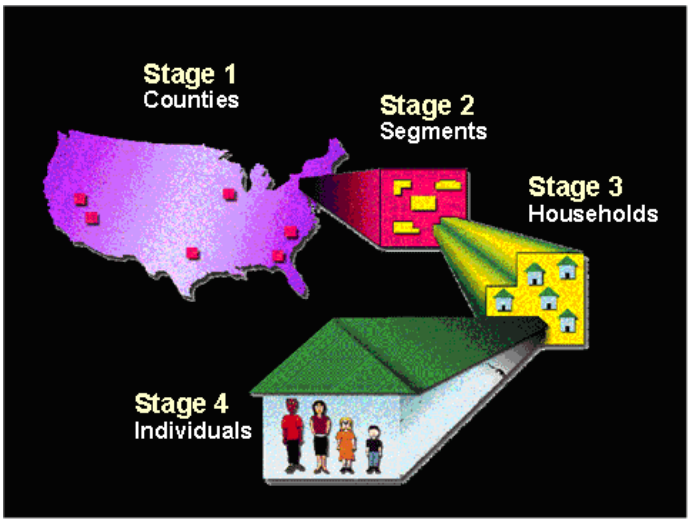


Figure 2. Four Stages of NHANES Sampling Procedure.

Adapted from CDC .

Sample weights used in NHANES accounts for the survey's intricate design (including oversampling), non-response, and post-stratification adjustment to match the Census Bureau's total population counts. A weighted sample is representative of the civilian noninstitutionalized resident population in the United States. Each sampled individual is assigned a sample weight. It is a measure of the number of people in the population represented by that sample person. Additional details regarding study design, sample weighting, data collection and laboratory procedures is available on the NHANES website (https://wwwn.cdc.gov/nchs/nhanes.htm).

The protocol was approved by the NCHS Research Ethics Review Board. All the data collection procedures performed in NHANES were carried out in accordance with the recommendations of the Health Statistics Research Ethics Review Board. The participants were informed about all the procedures and associated risk and provided written consent in accordance with the Declaration of Helsinki (Johnson et al., 2014).

Analytic sample

A total of 19, 931 people of all ages were enrolled in NHANES surveys from 2011-2014. Among them study participants were selected based on following inclusion criteria:

1. Older adults aged 60 years and older who were living in the US and participated in the NHANES survey.
2. Completed all assessments evaluating cognitive performance.
3. Completed PA questionnaire.
4. Completed information on all other demographic and physical attributes covariates included in the analysis (discussed below).

The following participants were excluded from the sample

1. Individuals who are < 60 years old.
2. Any respondents who answered “Refused” or “Don’t know” to any questions.

After accounting for all inclusion and exclusion criteria, 2377 elderly participants were included in the current analyses (Fig 3).

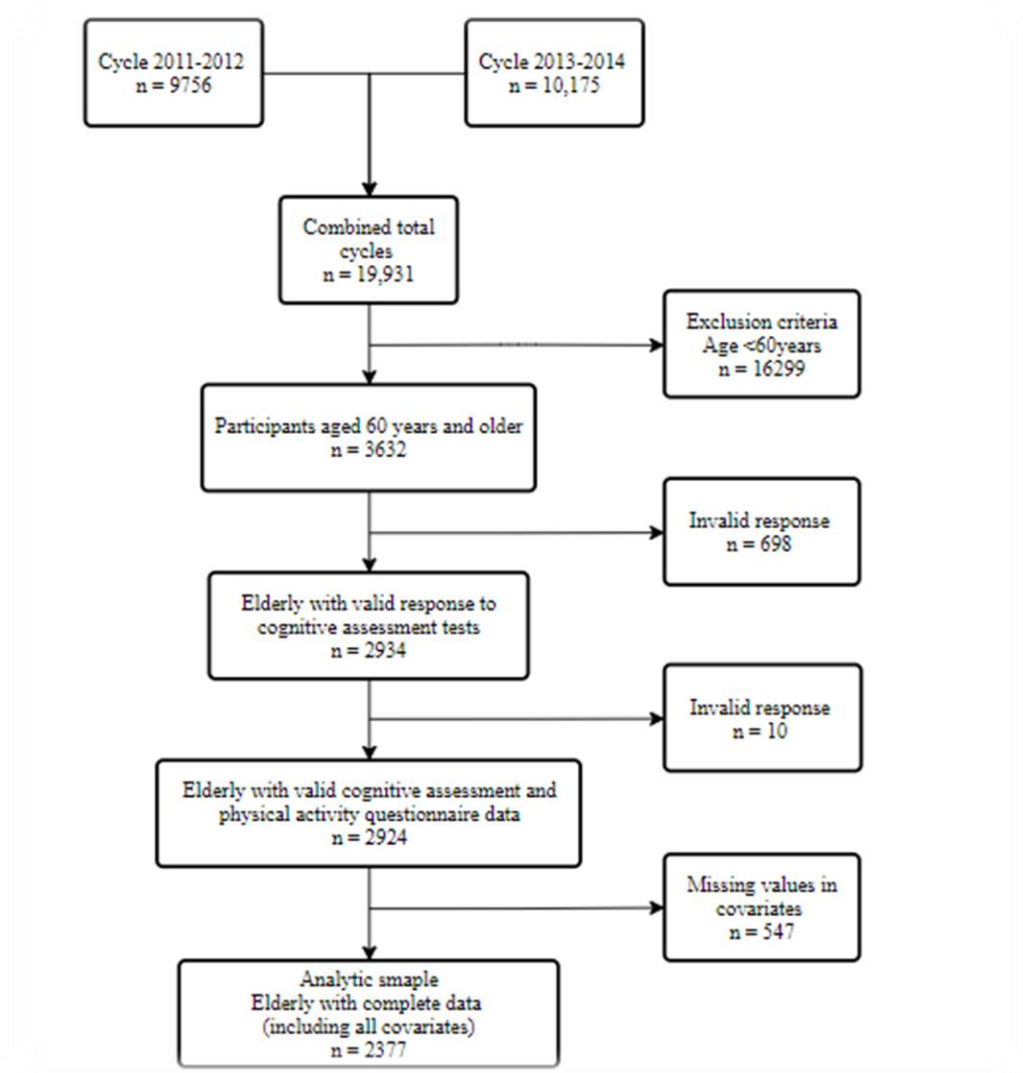


Figure 3. Flow diagram of analytic sample selection from NHANES 2011-2014 dataset based on inclusion and exclusion criteria.

Assessment of Cognitive Performance

Three separate cognitive performance assessments were employed in NHANES 2011-2014 to evaluate the cognitive performance of the participants aged 60 years or older. The assessments were conducted by trained interviewers during the MEC visit. The assessments evaluated the

following domains: (1) verbal learning and memory, (2) verbal fluency, and (3) processing speed and attention (CDC). However, none of these assessments conducted by NHANES provide a clinical diagnosis of dementia (Brody, Kramarow, Taylor, & McGuire, 2019).

The 1st test, Consortium to Establish a Registry for AD (CERAD) word learning subtest, assesses immediate and delayed learning ability for new verbal information (memory sub-domain) (Morris et al., 1989). It has been widely used in major epidemiological studies (Fillenbaum et al., 2008; Gao et al., 2009). The test includes three consecutive immediate learning trials (CERAD.IR), and a single delayed recall trial (CERAD.DR). For the learning trials, participants read aloud a list of ten unrelated words from a computer screen and upon completion, were immediately asked to recall as many words as possible. One point was earned for each correct word recalled. The maximum score for each trial was 10. The order of the ten words was switched for the three trials. We used the sum of three rounds of CERAD.IR for a maximal score of 30 to assess immediate recall memory. Following the three CERAD.IR trials the CERAD.DR occurred approximately 10 minutes after the 1st trial of CERAD.IR. The maximum score for CERAD.DR was also 10 which measured delayed recall memory.

The second test was the Animal Fluency test (AFT) that examines categorical verbal fluency (a measure of executive function) (Strauss, Sherman, & Spreen, 2006), and language ability (Whiteside et al., 2016). This too has been employed in various epidemiological cohorts (Clark et al., 2009; Ramirez-Gomez et al., 2017). The participants were asked to name as many animals as possible in one minute, scoring one point for each named animal.

The final cognitive performance assessment test was the Digit Symbol Substitution (DSS) test that assesses processing speed, sustained attention, and working memory. It is a component of the Wechsler Adult Intelligence Scale III (Wechsler, 1997). It has been used in large epidemiological and clinical studies (Bienias, Beckett, Bennett, Wilson, & Evans, 2003; Plassman et al., 2007; Proust-Lima, Amieva, Dartigues, & Jacqmin-Gadda, 2007). The test was conducted using paper-and-pencil format and the paper form contained a key code table of number 1-9, each paired with a distinct symbol. Following a practice trial, participants were instructed to copy the corresponding symbols in 133 boxes that adjoin the numbers within 2 minutes. A score was given for each correct match. Total number summarized as the test score.

Self-reported PA

Participants self-reported their PA pattern by completing the Global PA Questionnaire (GPAQ) (Hallal et al., 2012). GPAQ is a valid tool to assess moderate-to-vigorous PA and the data obtained by GPAQ has correlated with accelerometer- derived moderate-to- vigorous PA (r=0.48) (Cleland et al., 2014). Recreational engagement in moderate- intensity PA (MPA) and vigorous- intensity PA (VPA) was assessed. Participants reported the frequency and duration of MPA and VPA in a typical week. Weekly PA was calculated from the product of the number of days by minutes per day and reported as minutes per week.

For current analyses participants were categorized based on their total minutes of activity per week. VPA was categorized as less than 1 hour of activity (VPA <1 hr), 1-3 hours of activity (VPA 1-3 hr), 3-6 hours of activity (VPA 3-6 hr) and more than 6 hours (VPA 6+ hr) of activity per week.

MPA was categorized as no activity (MPA No activity), less than 1 hour of activity (MPA <1 hr), 1-3 hours of activity (MPA 1-3 hr), 3-6 hours of activity (MPA 3-6 hr), 6-9 hours of activity (MPA 6-9 hr), 9-12 hours of activity (MPA 9-12 hr), and more than 12 hours of activity (MPA 12+ hr).

Covariates

The following covariates were selected based on *a priori* knowledge:

Socio - demographic information –

Age (years, continuous), gender (male or female),

Self-reported race (Hispanic [Mexican American and other Hispanic], Non-Hispanic white, Non-Hispanic black, or Other [Non-Hispanic Asian and Other race-including multi-racial]),

Education status [<9^{th} grade, 9-11^{th} grade (Includes 12th grade with no diploma), High school graduate/ GED or equivalent, some college or AA degree, College graduate or above],

Marital status (lives alone or living with someone).

Physical attributes and disease conditions -

BMI was calculated as kilogram/$meter^2$ (kg/m^2) using weight and height measurement taken during the MEC visit. Weight measurements were obtained using a digital scale. Weight was recorded in both pounds and kg. Participants with amputations or prosthetic limbs were assigned a body weight variable as missing. A vertical stadiometer was used to determine height. The examiner instructed the participants to stand up straight on a platform with their feet flat on

the ground, knees and heels touching, and toes pointing at a 60-degree angle. Participants were instructed to look straight ahead, with their shoulders, shoulder blades, buttocks, and heels touching the stadiometer's back surface. A head piece was adjusted to touch the top of the participant's head. Two consecutive measurements were taken.

An indicator for hypertension was included. Participants were categorized based on physician-diagnosed hypertension status (Yes or No). An indicator of diabetes, physician-diagnosed diabetes status (categorized as Yes, No, or Borderline), was also included in the analysis.

As recent evidence suggests a link between high-density lipoprotein-cholesterol (HDL) with lower risk of AD (Marsillach et al., 2020), serum HDL level (mg/dl, continuous) was included in the analysis as well.

Patient Health Questionnaire (PHQ-9), a validated 9-item depression screener (Kroenke, Spitzer, & Williams, 2001), assessed depressive symptoms were included. As each item scored on a 0-3 scale, the total score ranged from 0-27. Severity of symptoms was categorized based on PHQ-9 scores (0-4 "none or minimum", 5-9 "mild", 10-14 "moderate", 15-19 "moderately severe", and 20-27 "severe") (Hu et al., 2019).

As choric comorbid conditions can affect the level of PA (Peng et al., 2019) and also cognitive ability (Cai, Li, Hua, Liu, & Chen, 2017), we included a total of seven chronic conditions in the analysis by using a scoring system. The comorbid conditions included chronic cardiovascular diseases such as coronary artery disease, stroke, congestive heart failure, heart attack, chronic musculoskeletal disease (arthritis), and chronic lung disease such as emphysema

and chronic bronchitis. One point was added for each comorbidity. Therefore, the total score ranged from 0-7.

In older adults, muscular strength is also highly associated with performing PA (Liu, Shiroy, Jones, & Clark, 2014). Therefore, muscular strength (handgrip strength) was included in the analysis as well. The force exerted on the environment by the hand and forearm is known as handgrip strength (Bohannon, 2015). Handgrip strength in kg was measured with a digital handgrip dynamometer (Takei Dynamometer Model T.K.K.5401; Akiha-Ku, Japan) over three trials separated by 60 seconds and alternating hands. After a submaximal trial of familiarization and adjustment of grip size, participants completed the test using randomly assigned hand. To complete the test, participants had to squeeze the dynamometer as hard as they could with one hand, then switch to the other hand for a total of three alternating times. For this study combined grip strength (calculated as the sum of the largest reading from each hand) was used.

Statistical Analyses

Descriptive statistics were computed on participants' characteristics according to the gender of participants. The contrast between genders was computed using a t-test for continuous variables and Fisher's exact test for categorical variables. Hierarchical linear regression analyses were computed to examine the associations of levels of PA (VPA and MPA) and cognitive performance test scores. Models were computed separately for each cognitive performance test. In each model, VPA or MPA was the main independent variable. For all models, the most physically inactive group was considered as the reference group. The β-coefficient and 95% CI were estimated and presented. The associations were considered statistically significant if the CI of the β-coefficient did not include 0. Size of effect (η^2) was analyzed as well. The unadjusted

model represents the bivariate relationship between the cognitive performance test scores and PA (VPA/MPA) that did not control for covariates. In the minimally adjusted models, the greatest change in the β-coefficients was observed. The fully adjusted model included all the covariates discussed above. Finally, surface analysis plots were computed to explore the relationship between cognitive performance, education status, and VPA. They were computed by the weighted inverse of the variance of each data point. The analyses were conducted using R version 4.0.3. All analyses were two-tailed and statistical significance was established as a nominal alpha of 0.05.

CHAPTER IV

RESULTS

The purposes of the study were three folds: 1) to examine possible associations between different durations and intensities of PA and cognitive performance across different domains (executive function, processing speed, verbal fluency, and memory), 2) to investigate dose-response association between PA and cognitive domains, and 3) to determine the association (if any) between other socio-demographics and cognitive domains among aging Americans by using a national database, the NHANES 2011-2014.

Descriptive Characteristics

Among the analytic sample of 2377 older adults, 1209 (50.86%) were female and 1168 (49.14%) were male. Characteristics of study participants are shown in Table 1. Participants, on average, were 69.3 years old; the majority (50.0%) of the analytic sample were non-Hispanic Whites. The majority of participants were physically inactive. 82.71% of participants (n=1966) engaged in VPA for less than an hr and 35.59% of participants (n=846) did not engage in any weekly MPA.

Both highest [college graduate and above ($p < 0.001$)] and lowest level [$<9^{th}$ grade ($p < 0.001$)] of education showed male predominance. Males were also more likely to be physically active [significantly higher amount of time participating in both VPA ($p < 0.001$, $\eta^2=0.016$) and MPA ($p < 0.001$, $\eta^2=0.006$)], had higher handgrip strength ($p < 0.001$, $\eta^2=0.502$), and had

someone to live with ($p < 0.001$) compared to females. Whereas, females had higher BMI ($p < 0.001$, $\eta^2=0.007$), higher serum HDL level ($p < 0.001$, $\eta^2=0.088$), higher prevalence of hypertension ($p=0.009$) and comorbid illnesses ($p=0.015$, $\eta^2=0.003$) compared to males. However, these are trivial differences, and they are not significantly different from each other.

Table 1. Demographic, lifestyle, and health characteristics of participants included in analyses from NHANES (2011-2014), by Gender.

Variable	Male (n=1168)	Female (n=1209)	Total (n=2377)
AGE (mean (SD))	69.32 (6.78)	69.28 (6.69)	69.30 (6.73)
RACE (%)			
Non- Hispanic White	562 (48.1)	627 (51.9)	1189 (50.0)
Hispanic	216 (18.5)	225 (18.6)	441 (18.6)
Non- Hispanic Black	275 (23.5)	259 (21.4)	534 (22.5)
Other	115 (9.8)	98 (8.1)	213 (9.0)
Education**			
<9th grade	135 (11.6)	110 (9.1)	245 (10.3)
9-11th grade	149 (12.8)	165 (13.6)	314 (13.2)
High school grad/ GED	261 (22.3)	302 (25.0)	563 (23.7)
College	301 (25.8)	383 (31.7)	684 (28.8)
College Grad and above	322 (27.6)	249 (20.6)	571 (24.0)
Marital status *=Live with someone (%)	838 (71.7)	561 (46.4)	1399 (58.9)
BMI (mean (SD))*	28.56 (5.48)	29.58 (6.92)	29.08 (6.28)
Grip Strength (mean (SD))*	75.52 (16.38)	48.15 (10.32)	61.60 (19.32)
HDL (mean (SD))*	49.55 (14.67)	59.28 (16.5)	54.50 (16.36)
Cognitive performance assessment			
CERAD.IR (mean (SD))*	18.30 (4.36)	19.98 (4.52)	19.16 (4.52)
CERAD.DR (mean (SD))*	5.65 (2.23)	6.44 (2.21)	6.05 (2.25)
AFT (mean (SD))	17.07 (5.55)	16.84 (5.40)	16.95 (5.47)
DSS (mean (SD))*	44.31 (16.00)	49.82 (17.44)	47.11 (16.97)
Physical activity			
Total minutes of vigorous- intensity activity/ week (mean (SD))*	122.48 (367.60)	47.00 (217.58)	84.08 (303.09)
Vigorous- intensity activity **			
<1 hr	903 (77.3)	1063 (87.9)	1966 (82.7)
1-3 hr	86 (7.4)	73 (6.0)	159 (6.7)
3-6 hr	78 (6.7)	28 (2.3)	106 (4.5)
6+ hr	101 (8.6)	45 (3.7)	146 (6.1)

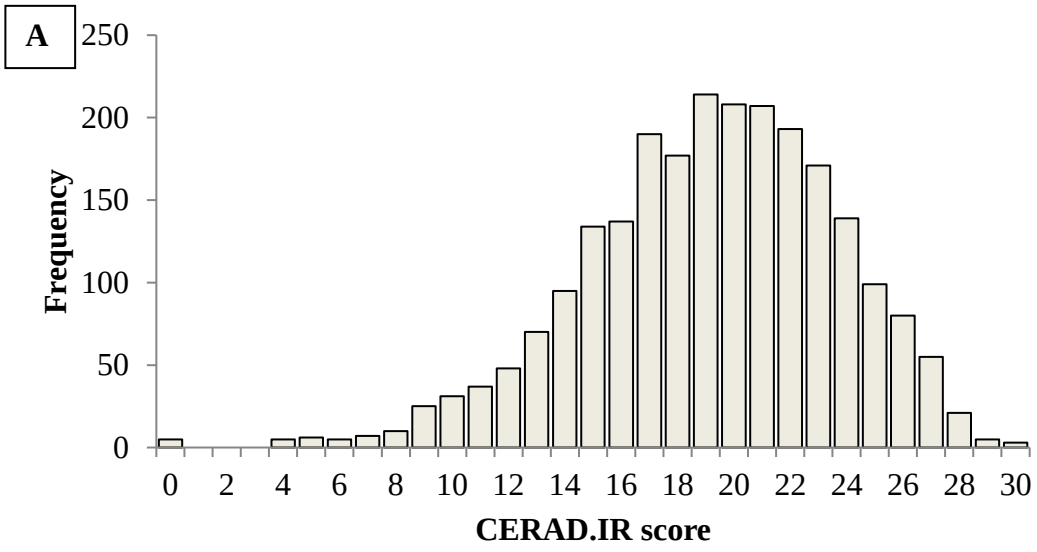
Variable	Male (n=1168)	Female (n=1209)	Total (n=2377)
Total minutes of moderate- intensity activity/ week (mean (SD))*	353.18 (578.87)	268.68 (497.11)	310.20 (540.38)
Moderate-intensity activity**			
No activity	379 (32.4)	467 (38.6)	846 (35.6)
<1 hr	75 (6.4)	67 (5.5)	142 (6.0)
1-3 hr	207 (17.7)	241 (19.9)	448 (18.8)
3-6 hr	184 (15.8)	182 (15.1)	366 (15.4)
6-9 hr	84 (7.2)	81 (6.7)	165 (6.9)
9-12 hr	66 (5.7)	52 (4.3)	118 (5.0)
12+ hr	173 (14.8)	119 (9.8)	292 (12.3)
Depression status (%)**			
Minimum	949 (81.2)	832 (68.8)	1781 (74.9)
Mild	143 (12.2)	233 (19.3)	376 (15.8)
Moderate	44 (3.8)	86 (7.1)	130 (5.5)
Moderate Severe	18 (1.5)	42 (3.5)	60 (2.5)
Severe	14 (1.2)	16 (1.3)	30 (1.3)
Physician-diagnosed Hypertension= Yes(%)*	682 (58.4)	770 (63.7)	1452 (61.1)
Physician-diagnosed Diabetes			
No	838 (71.7)	902 (74.6)	1740 (73.2)
Borderline	54 (4.6)	57 (4.7)	111 (4.7)
Yes	276 (23.6)	250 (20.7)	526 (22.1)
Comorbidity score (mean (SD))*	0.85 (1.03)	0.95 (0.97)	0.90 (1.00)

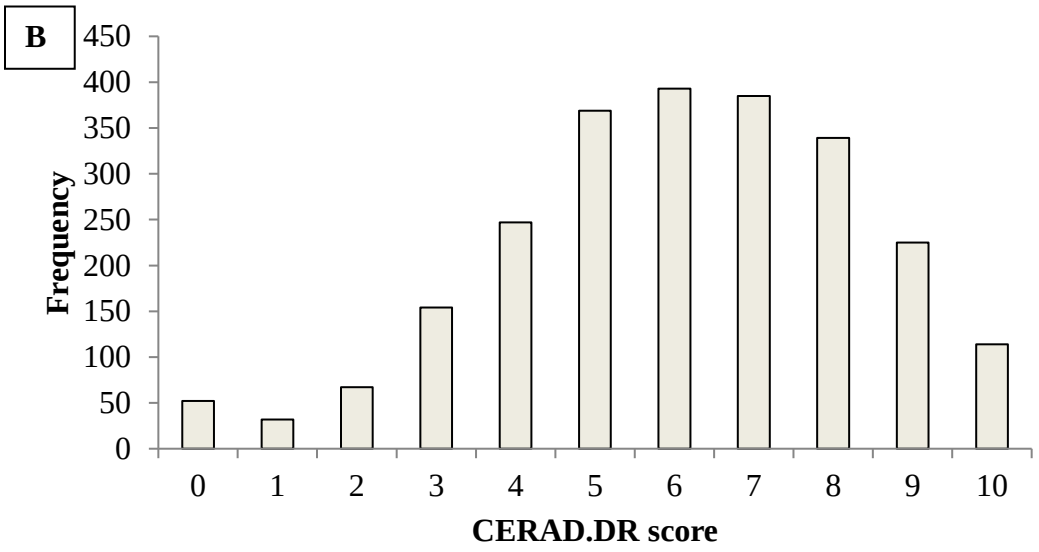
Unweighted sample size
* Student t test, $p < 0.05$, **Fisher's exact test, $p < 0.05$.
CERAD.IR immediate recall memory test, *CERAD.DR* delayed recall memory test, *AFT* animal fluency test, *DSS* Digit symbol substitution test

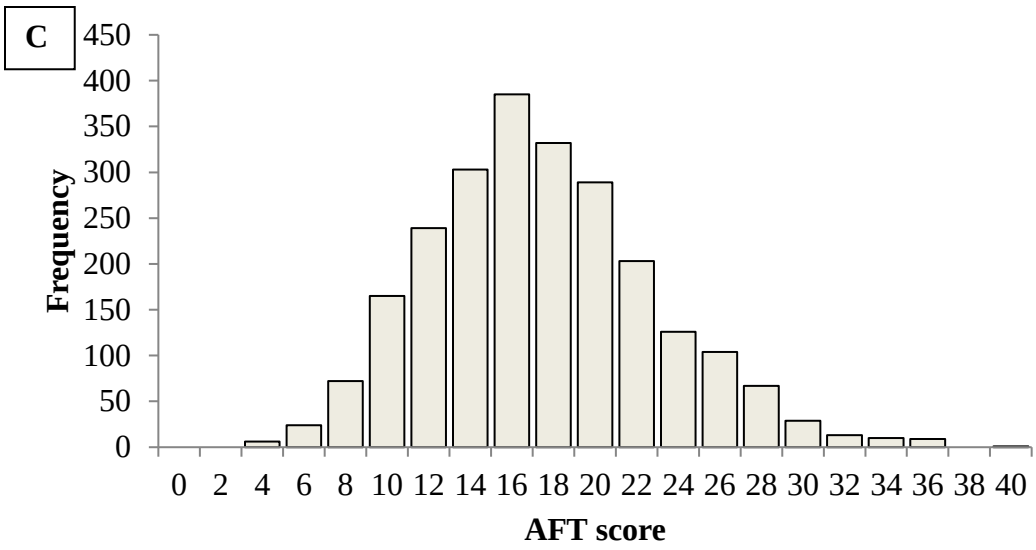
CERAD.IR scores ranged from 0 to 30 with mean ± SD of 19.16 ± 4.52; CERAD.DR scores ranged from 0 to 10 with a mean ± SD of 6.05 ± 2.25. Both memory assessment test scores were distributed in a right-skewed manner (Fig 4 A, B). AFT scores ranged from 3 to 40 with a mean ± SD of 16.95 ± 5.47 and were distributed in a left- skewed manner with a median of 16 (Fig 4 C). DSS scores ranged from 0 to 105 with a mean ± SD of 47.11 ± 16.97 and

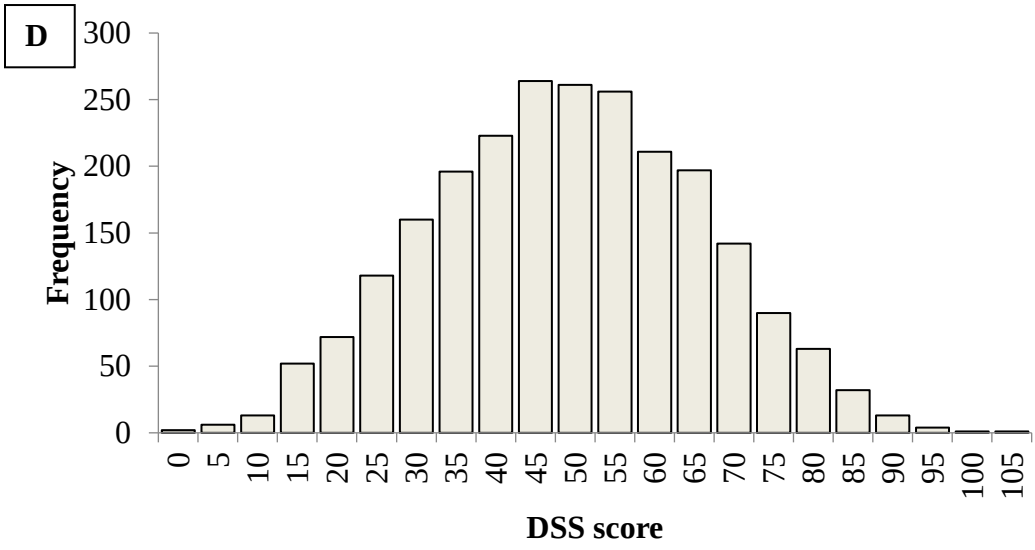
median of 47 and were normally distributed (Fig 4 D). Except for AFT, females scored significantly higher in all the cognitive performance assessment tests (all $p < 0.01$) (Table 1).

Figure 4. Cognitive performance assessment scores.









VPA and Cognitive Performance

Cognitive performance assessment scores across different categories of VPA is shown in Table 2.

Table 2. Cognitive performance assessment scores across different categories vigorous-intensity physical activity (n=2377). Mean ± SD.

	VPA			
	<1 hr (n=1966)	1-3 hr (n=159)	3-6 hr (n=106)	6+ hr (n=146)
Age in years	69.8 ± 6.81	67.01 ± 5.91	67.17 ± 5.84	66.55 ± 5.53
CERAD.IR	18.95 ± 4.58	20.53 ± 3.95	20.22 ± 3.77	19.64 ± 4.45
CERAD.DR	5.96 ± 2.28	6.80 ± 2.15	6.56 ± 1.96	6.20 ± 2.08
AFT	16.51 ± 5.33	19.20 ± 5.86	19.75 ± 5.93	18.38 ± 5.26
DSS	45.79 ± 16.79	55.22 ± 16.62	55.27 ± 16.05	50.08 ± 16.03

The hierarchical regression analyses evaluating the association between the cognitive performance assessment scores and VPA is shown in Table 3.

Table 3. Regression analyses examining the association between cognitive performance assessment scores and vigorous-intensity physical activity (n=2377)

	β (95% CI)		
Model	Unadjusted	Minimally adjusted	Fully adjusted
CERAD.IR			
VPA <1 hr	Ref	Ref	Ref
VPA 1-3 hr	1.58 (0.86, 2.31) ***	0.56(-0.12, 1.23) ^	0.41 (-0.26, 1.08)
VPA 3-6 hr	1.26 (0.39, 2.14) **	0.55 (-0.26, 1.36)	0.42 (-0.39, 1.23)
VPA 6+ hr	0.69 (-0.06, 1.45) ^	0.42 (-0.27, 1.12)	0.30 (-0.40, 0.99)
R-squared	0.01	0.188	0.197
Partial Eta-squared	VPA 0.011	VPA 0.002	VPA 0.001
		Gender 0.041	Gender 0.033
		Age 0.068	Age 0.044
		Race 0.009	Race 0.007
		Education 0.066	Education 0.056
			BMI 0.001
			Handgrip 0.004
			Depression 0.005
CERAD.DR			
VPA <1 hr	Ref	Ref	Ref
VPA 1-3 hr	0.84 (0.48, 1.20) ***	0.37 (0.03, 0.71) *	0.33 (-0.01, 0.67) ^
VPA 3-6 hr	0.60 (0.16, 1.04) **	0.28 (-0.13, 0.69)	0.23 (-0.18, 0.64)

VPA 6+ hr	0.24 (-0.13, 0.62)	0.07 (-0.28, 0.42)	0.04 (-0.31, 0.39)
R-squared	0.01	0.172	0.18
Partial Eta-squared	VPA 0.011	VPA 0.003	VPA 0.002
		Gender 0.036	Gender 0.025
		Age 0.079	Age 0.051
		Race 0.013	Race 0.014
		Education 0.039	Education 0.034
			BMI 0.005
			Handgrip 0.002

AFT

VPA <1 hr	Ref	Ref	Ref
VPA 1-3 hr	2.69 (1.82, 3.56) ***	1.01 (0.21, 1.82) *	0.76 (-0.04, 1.56) ^
VPA 3-6 hr	3.23 (2.18, 4.28) ***	1.57 (0.60, 2.53) **	1.27 (0.31, 2.24) **
VPA 6+ hr	1.86 (0.96, 2.77) ***	1.03 (0.20, 1.86) *	0.83 (0.00, 1.66) ^
R-squared	0.031	0.208	0.226
Partial Eta-squared	VPA 0.032	VPA 0.008	VPA 0.005
		Age 0.067	Age 0.043
		Race 0.070	Race 0.069
		Education 0.074	Education 0.061
			BMI 0.003
			Handgrip 0.007
			Hypertension 0.002
			Depression 0.008
			HDL 0.004

DSS

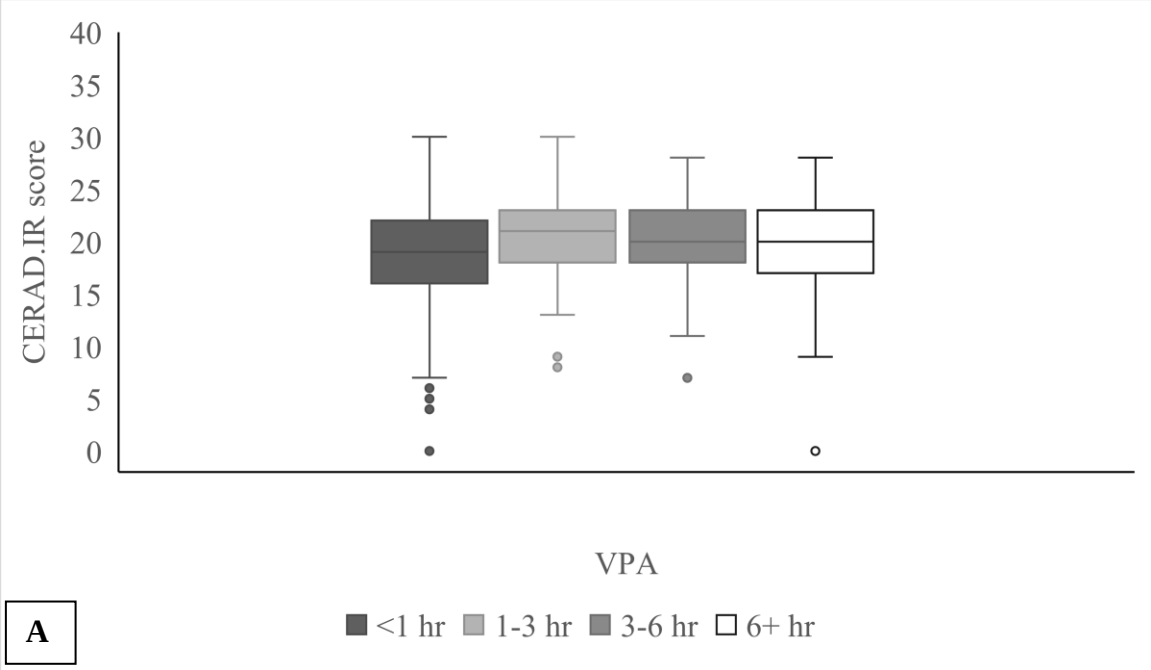
VPA <1 hr	Ref	Ref	Ref
VPA 1-3 hr	9.43(6.73,12.13) ***	2.75 (0.72, 4.78) **	1.81 (-0.18, 3.80) ^
VPA 3-6 hr	9.48(6.22,12.74) ***	3.68 (1.22, 6.13) **	2.81 (0.41, 5.22) *
VPA 6+ hr	4.28 (1.47, 7.09) **	2.03 (-0.07, 4.13) ^	1.16 (-0.90, 3.22)
R-squared	0.031	0.473	0.499
Partial Eta-squared	VPA 0.033	VPA 0.007	VPA 0.003
		Gender 0.047	Gender 0.055
		Age 0.129	Age 0.113
		Race 0.116	Race 0.120
		Education 0.246	Education 0.224
			BMI 0.001
			Handgrip 0.015

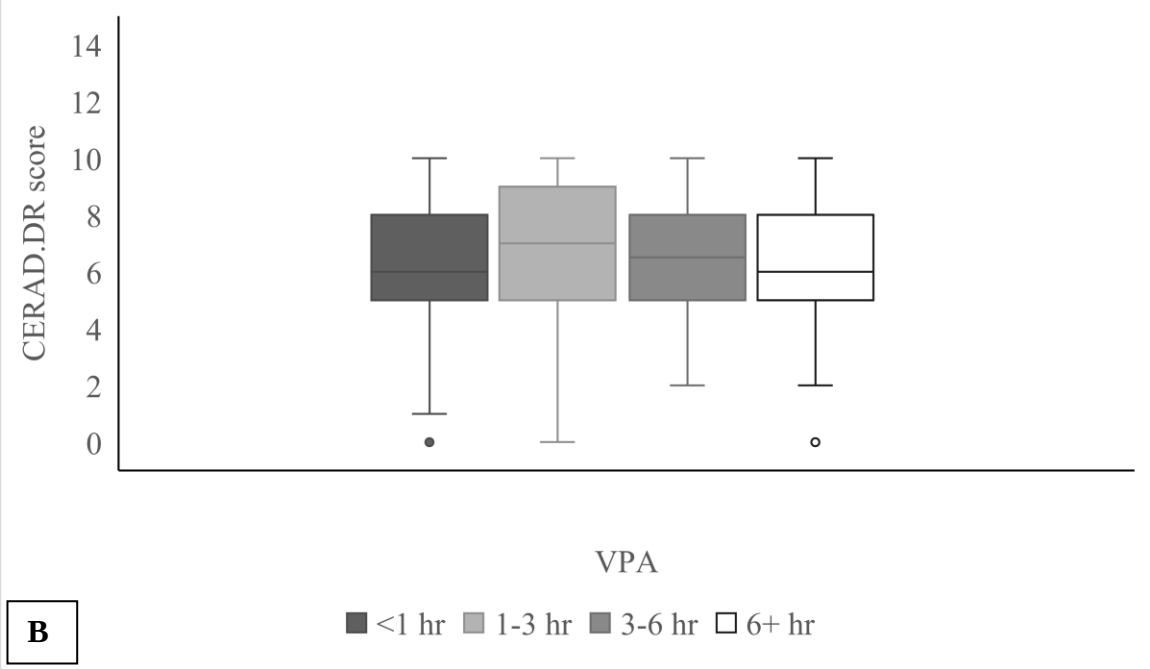
	Diabetes	0.003
	Depression	0.019
	Comorbidity	0.001

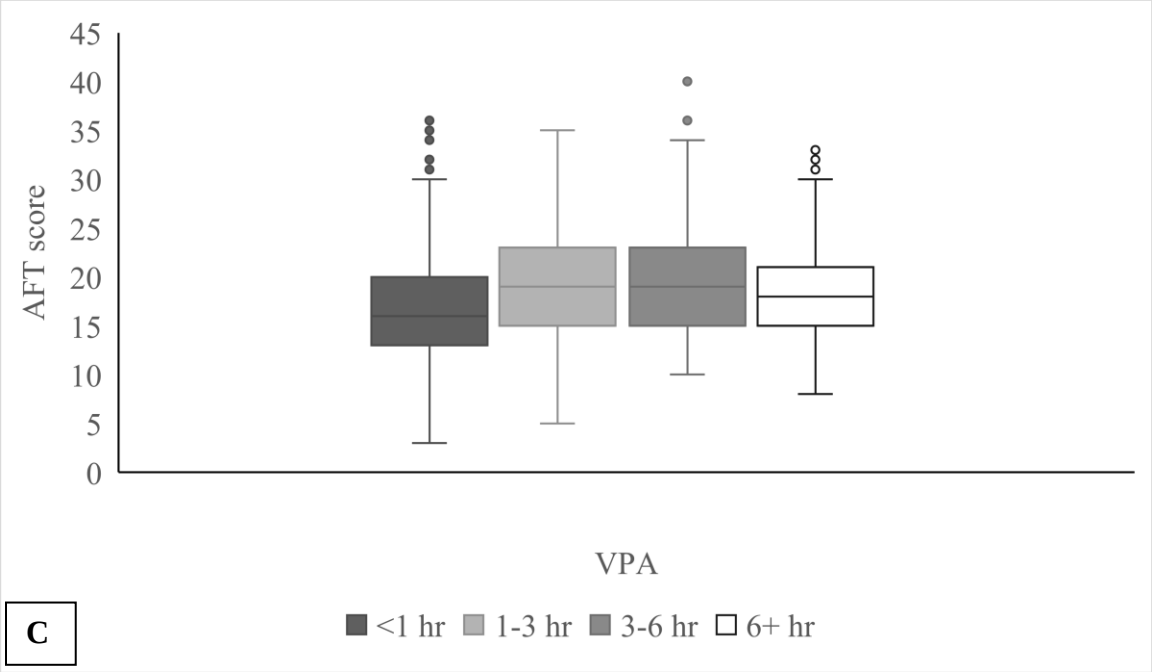
Minimally adjusted model included the covariates age, gender, race, and education
Fully adjusted model included the covariates age, gender, race, education, marital status, BMI, handgrip strength, hypertension status, diabetes status, depression status, comorbid score, and serum HDL level.
'***' $p < 0.001$, '**' $p < 0.01$, '*' $p < 0.05$. '^' $p < 0.1$
Ref reference category, *CERAD.IR* immediate recall memory test, *CERAD.DR* delayed recall memory test, *AFT* animal fluency test, *DSS* Digit symbol substitution test.
Effect size is represented by Partial Eta-squared.

The unadjusted linear regression models showed that those who engaged in weekly VPA 1-3 hr had higher memory test scores, CERAD.IR (β=1.58; 95% CI: 0.86, 2.31; η^2=0.011) and CERAD.DR (β=0.84; 95% CI: 0.48, 1.20; η^2=0.011), compared to those engaging in weekly VPA <1 hr (Fig 5 A and B show dispersion of the data). Whereas, those who engaged in weekly VPA 3-6 hr showed higher verbal fluency and processing speed, AFT (β=2.69; 95% CI: 1.82, 3.56; η^2=0.032) and DSS (β=9.48; 95% CI: 6.22, 12.74; η^2=0.032), compared to those who engaged in weekly VPA <1 hr (Fig 5 C and D show dispersion of the data).

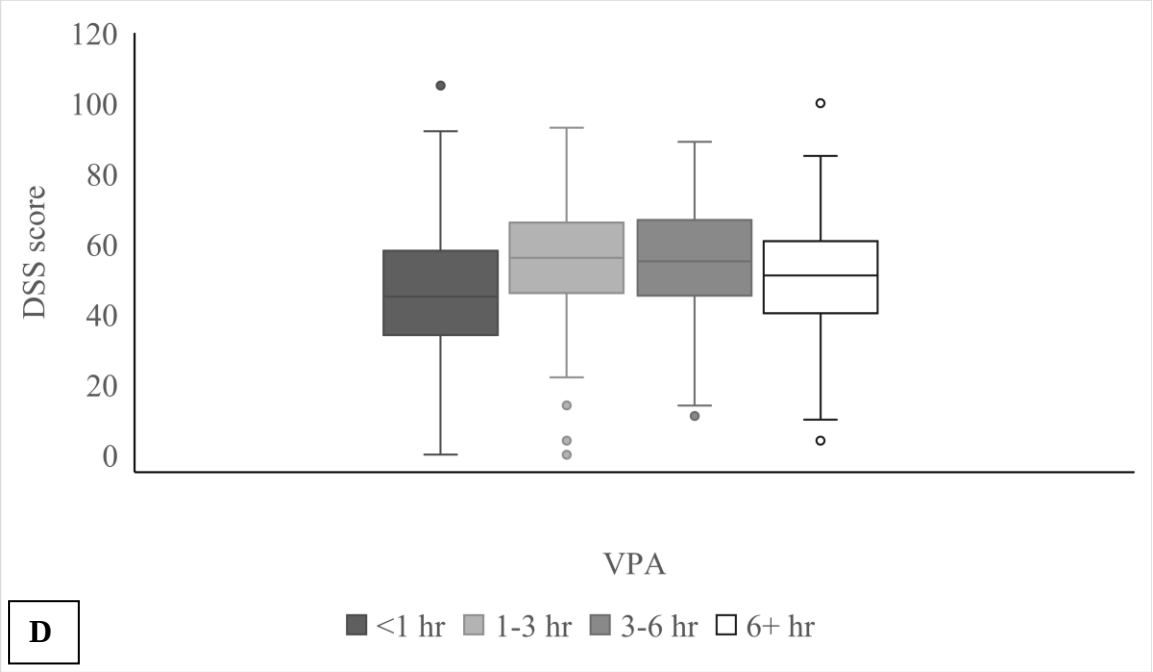
Figure 5. Cognitive performance assessment scores by vigorous-intensity physical activity category.






45
40
35
30
25
20
15
10
5
0
AFT score
VPA
<1 hr
1-3 hr
3-6 hr
6+ hr

C


120
100
80
60
40
20
0
DSS score
VPA
<1 hr
1-3 hr
3-6 hr
6+ hr

D

Interestingly, after fully adjusting for all potential confounders (socio-demographic, lifestyle, and health characteristics), the association between VPA and CERAD.IR test scores attenuates (Table 2). However, despite attenuation, older adults engaging in weekly VPA 1-3 hr showed a trend to score slightly higher in CERAD.DR test (β=0.33; 95% CI: -0.01, 0.67; η^2=0.002; p=0.56), compared to those engaging in weekly VPA <1 hr. Additionally, participants engaging in weekly VPA 3-6 hr still showed significantly higher language ability and processing speed, AFT (β=1.27; 95% CI: 0.31, 2.24; η^2=0.005; p < 0.01) and DSS (β=2.81; 95% CI: 0.41, 5.22; η^2=0.003; p < 0.05), compared to those who engaged in weekly VPA <1 hr. Interestingly, across all models, the most active older adults (weekly VPA 6+ hr) tend to score lower in all the cognitive performance tests relative to the ones who performed weekly VPA 1-3 hr and VPA 3-6 hr. Therefore, a linear dose-response association was not evident.

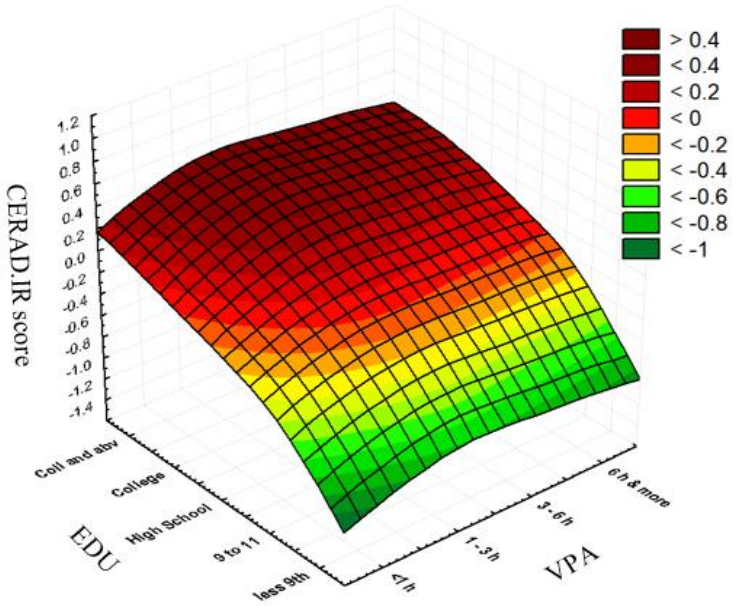
The covariates with significant negative associations with all the cognitive tests scores included increasing age, some racial Hispanic and Non-Hispanic Black ethnicity, lower education level, increasing severity of depression (all p < 0.05). Additionally, hypertension demonstrated significant negative association with AFT scores (p < 0.05). Diabetes (p < 0.01) and chronic comorbidities (p < 0.05) were negatively associated with DSS test scores. Whereas, female gender, higher educational attainment, higher handgrip strength demonstrated significant positive association with cognitive test scores. Interestingly, a higher BMI and HDL level was positively associated with higher AFT score. A higher BMI was also associated with higher CERAD.DR score.

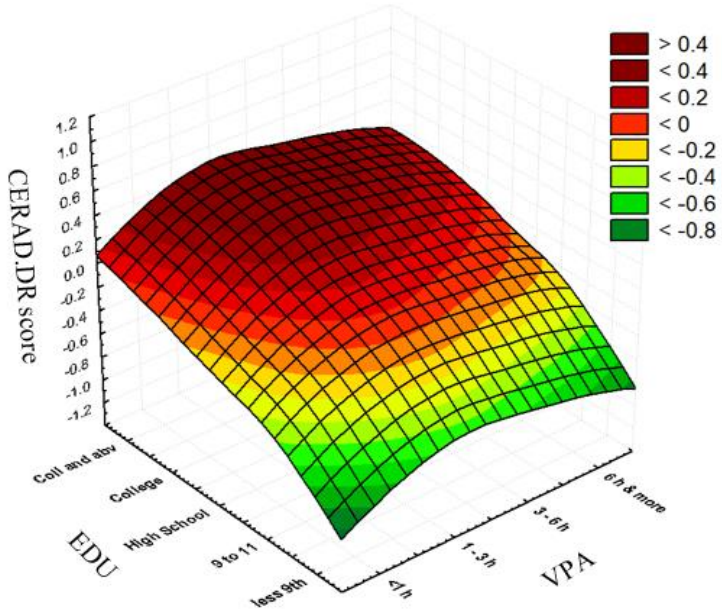
Notably, after adjusting for socio-demographic characteristics (age, gender, race, education status), the greatest change in the β-coefficients was observed (Table 2). This is

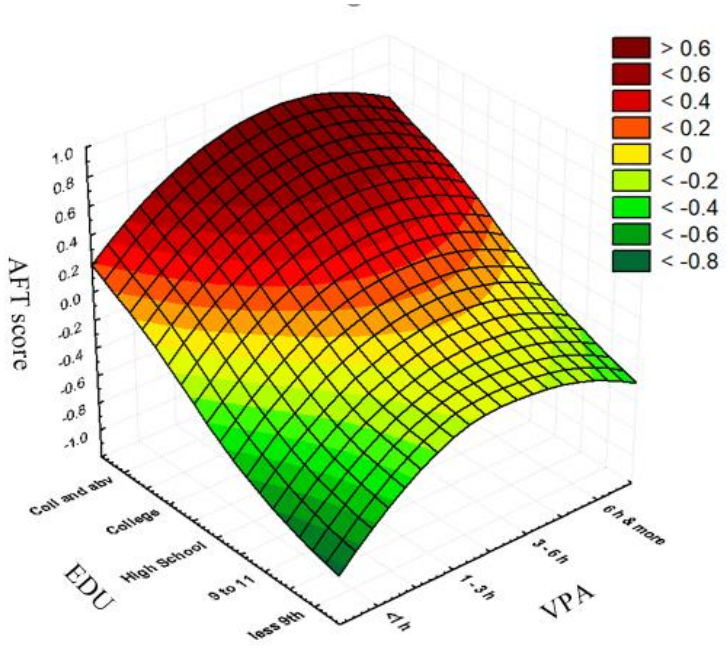
suggestive that these covariates may play a major role regarding the determination of cognitive performance. Among them, education status showed highest influence on cognition (η^2=0.056).

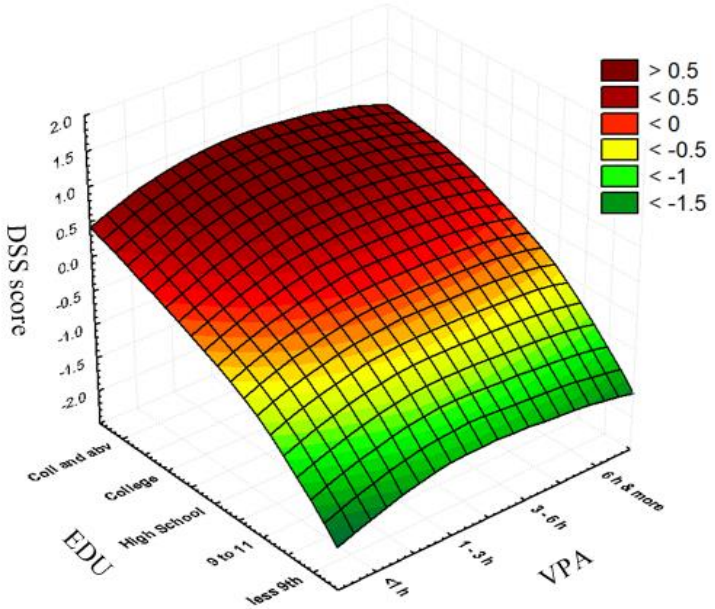
Therefore, the relationship between cognitive performance, VPA, and education status was further explored by surface analyses. The surface plots demonstrating the relationship between education status and VPA and the cognitive performance assessment test scores of the older adults participating in NHANES 2011-2014 are shown in Fig 6. As expected, the highest values of all the assessment scores correspond with higher education status. Interestingly, an increase in weekly VPA, from VPA <1 hr to VPA 1-3 hr, increased the AFT score, even in participants with lower education status. This increase in scores was also noticed in participants who engaged in VPA 3-6 hr. However, beyond this duration of weekly VPA, a decrease in the AFT score is noticed. This demonstrates that the most active older adults, who performed weekly VPA 6+ hr, scored lower in AFT scores relative to the ones who performed weekly VPA 1-3 hr and VPA 3-6 hr. Although not as profound as the changes observed in the AFT scores, a similar pattern was noticeable in other cognitive performance assessment tests as well.

Figure 6. Relationship between education status, vigorous-intensity physical activity and cognitive performance assessment scores.






> 0.6
< 0.6
< 0.4
< 0.2
< 0
< -0.2
< -0.4
< -0.6
< -0.8
AFT score
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
-0.4
-0.6
-0.8
-1.0
Coll and abv
College
High School
9 to 11
less 9th
EDU
<1 h
1-3 h
3-6 h
6 h & more
VPA


> 0.5
< 0.5
< 0
< -0.5
< -1
< -1.5
DSS score
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
Coll and abv
College
High School
9 to 11
less 9th
EDU
<1 h
1-3 h
3-6 h
6 h & more
VPA

MPA and Cognitive Performance

Table 4 demonstrates the mean cognitive test scores by category of MPA among US adults aged 60 years and older (n=2377) from NHANES 2011-2014.

Table 4. Cognitive performance assessment scores by moderate-intensity physical activity category (n=2377). Mean ± SD.

	MPA						
	No activity (n=846)	<1 hr (n=142)	1-3 hr (n=448)	3-6 hr (n=366)	6-9 hr (n=165)	9-12 hr (n=118)	12+ hr (n=292)
Age in years	70.02 ± 6.90	70.01 ± 6.74	69.29 ± 6.69	69.27 ± 6.90	68.84 ± 6.21	67.99 ± 6.10	67.72 ± 6.27
CERAD. IR	18.78 ± 4.72	18.92 ± 5.03	19.49 ± 4.50	19.31 ± 4.30	19.55 ± 3.82	19.27 ± 4.09	19.39 ± 4.46
CERAD. DR	5.82 ± 2.36	6.16 ± 2.21	6.23 ± 2.22	6.10 ± 2.25	6.38 ± 1.93	6.08 ± 2.32	6.16 ± 2.13
AFT	15.91 ± 5.35	16.61 ± 5.23	17.43 ± 5.45	17.47 ± 5.38	17.30 ± 5.59	17.20 ± 5.64	18.44 ± 5.45
DSS	43.89 ± 16.94	48.91 ± 16.38	49.16 ± 17.03	49.35 ± 16.37	48.62 ± 18.12	49.24 ± 16.00	47.90 ± 16.40

The hierarchical regression analyses evaluating the association between the cognitive performance assessment tests and MPA is shown in Table 5. The fully adjusted model shows no association between MPA and CERAD.IR and CERAD.DR assessment scores (Table 5). Whereas, MPA was inconsistently associated with AFT and DSS assessment scores. Older adults engaging in highest weekly MPA (MPA12+ hr) showed highest association to AFT test score (β=1.39; 95% CI: 0.73, 2.05; η^2=0.009; $p < 0.001$), compared to their inactive peers. However, participants performing MPA 1-3 hr (β=0.90; 95% CI: 0.34, 1.46; η^2=0.009; $p < 0.01$) and MPA 3-6 hr (β=0.79; 95% CI: 0.18, 1.39; η^2=0.009; $p < 0.05$) also scored significantly higher compared to the reference group. Participants engaging in weekly MPA <1 hr (β=3.36; 95% CI:

1.22, 5.50; η^2=0.007; p < 0.01) and MPA 1-3 hr (β=2.06, 95% CI: 0.67, 3.45; η^2=0.007; p < 0.01) showed significantly higher DSS score compared to those who did not engage in any MPA. Furthermore, older adults engaging in weekly MPA 3-6 hr showed a trend to score slightly higher in DSS test (β=1.38; 95% CI: -0.13, 2.88; η^2=0.007, p=0.73), compared to those engaging in weekly MPA No activity. Therefore, an inconsistent dose-response relationship was observed between the executive function and processing speed performance and duration of weekly MPA.

Table 5. Regression analyses examining the association between cognitive performance assessment scores and moderate- intensity physical activity (n=2377)

	β (95% CI)		
Model	Unadjusted	Minimally adjusted	Fully adjusted
CERAD.IR			
MPA No activity	Ref	Ref	Ref
MPA <1 hr	0.14 (-0.66, 0.94)	-0.07 (-0.80, 0.66)	-0.12(-0.85, 0.60)
MPA 1-3 hr	0.71 (0.19, 1.23) **	0.34 (-0.13, 0.81)	0.23 (-0.25, 0.70)
MPA 3-6 hr	0.53 (-0.03, 1.08) ^	0.06 (-0.44, 0.57)	-0.06 (-0.57, 0.45)
MPA 6-9 hr	0.76 (0.01, 1.52) *	0.37 (-0.32, 1.05)	0.22 (-0.47, 0.90)
MPA 9-12 hr	0.49 (-0.38, 1.36)	0.09 (-0.70, 0.88)	-0.06 (-0.85, 0.73)
MPA 12+ hr	0.61 (0.00, 1.21) *	0.25 (-0.30, 0.80)	0.04 (-0.51, 0.60)
R-squared	0.002	0.187	0.196
Partial Eta-squared	MPA 0.005	MPA 0.001	MPA 0.001
		Gender 0.039	Gender 0.032
		Age 0.072	Age 0.046
		Race 0.010	Race 0.007
		Education 0.068	Education 0.058
			Handgrip 0.004
			Depression 0.005
CERAD.DR			
MPA No activity	Ref	Ref	Ref
MPA <1 hr	0.34 (-0.06, 0.74) ^	0.28 (-0.08, 0.65)	0.25 (-0.11, 0.62)
MPA 1-3 hr	0.40 (0.15, 0.66) **	0.23 (-0.01, 0.46) *	0.20 (-0.04, 0.44)
MPA 3-6 hr	0.27 (0.00, 0.55) ^	0.06 (-0.19, 0.31)	0.05 (-0.21, 0.30)
MPA 6-9 hr	0.55 (0.18, 0.93) **	0.34 (0.00, 0.68) *	0.31 (-0.04, 0.66)

MPA 9-12 hr	0.25 (-0.18, 0.69)		0.03 (-0.37, 0.43)		0.00 (-0.40, 0.40)	
MPA 12+ hr	0.33 (0.03, 0.63) *		0.15 (-0.12, 0.43)		0.10 (-0.18, 0.38)	
R-squared	0.004		0.171		0.180	
Partial Eta-squared	MPA	0.007	MPA	0.003	MPA	0.003
			Gender	0.036	Gender	0.023
			Age	0.083	Age	0.054
			Race	0.013	Race	0.014
			Education	0.041	Education	0.034
					BMI	0.005
					Handgrip	0.003

AFT

MPA No activity	Ref		Ref		Ref	
MPA <1 hr	0.70 (-0.026, 1.66)		0.33 (-0.54, 1.19)		0.26 (-0.60, 1.12)	
MPA 1-3 hr	1.52 (0.90, 2.14) ***		1.05 (0.49, 1.60) ***		0.90 (0.34, 1.46) **	
MPA 3-6 hr	1.56 (0.90, 2.22) ***		0.95 (0.35, 1.55) **		0.79 (0.18, 1.39) *	
MPA 6-9 hr	1.38 (0.48, 2.29) **		0.83 (0.02, 1.64) *		0.61 (-0.20, 1.43)	
MPA 9-12 hr	1.29 (0.25, 2.33) *		0.78 (-0.17, 1.72) ^		0.62 (-0.32, 1.55)	
MPA 12+ hr	2.52 (1.80, 3.24) ***		1.66 (1.01, 2.32) ***		1.39 (0.73, 2.05) ***	
R-squared	0.023		0.212		0.228	
Partial Eta-squared	MPA	0.025	MPA	0.013	MPA	0.009
			Age	0.071	Age	0.046
			Race	0.072	Race	0.071
			Education	0.076	Education	0.063
					BMI	0.004
					Handgrip	0.007
					Hypertension	0.002
					Depression	0.007
					HDL	0.004

DSS

MPA No activity	Ref		Ref		Ref	
MPA <1 hr	5.02 (2.03, 8.01) **		3.57 (1.37, 5.76) **		3.36 (1.22, 5.50) **	
MPA 1-3 hr	5.27 (3.34, 7.19) ***		2.82 (1.40, 4.23) ***		2.06 (0.67, 3.45) **	
MPA 3-6 hr	5.46 (3.40, 7.52) ***		2.23 (0.71, 3.75) **		1.38 (-0.13, 2.88) ^	
MPA 6-9 hr	4.73 (1.92, 7.53) ***		1.82 (-0.24, 3.88) ^		0.74 (-1.29, 2.77)	
MPA 9-12 hr	5.35 (2.11, 8.59) **		2.67 (0.29, 5.06) *		1.83 (-0.51, 4.16)	
MPA 12+ hr	4.01 (1.78, 6.25) ***		1.38 (-0.28, 3.04) ^		0.13 (-1.51, 1.77)	
R-squared	0.018		0.474		0.501	

Partial Eta-squared	MPA	0.021	MPA	0.009	MPA	0.007
			Gender	0.044	Gender	0.053
			Age	0.173	Age	0.119
			Race	0.120	Race	0.124
			Education	0.247	Education	0.225
					BMI	0.001
					Handgrip	0.015
					Diabetes	0.003
					Depression	0.019
					Comorbidity	0.002

Minimally adjusted model included the covariates age, gender, race, and education

Fully adjusted model included the covariates age, gender, race, education, marital status, BMI, handgrip strength, hypertension status, diabetes status, depression status, comorbid score, and serum HDL level.

'***' $p < 0.001$, '**' $p < 0.01$, '*' $p < 0.05$. '^' $p < 0.1$

Ref reference category, *CERAD.IR* immediate recall memory test, *CERAD.DR* delayed recall memory test, *AFT* animal fluency test, *DSS* Digit symbol substitution test

Effect size is represented by Partial Eta-squared.

CHAPTER V

DISCUSSION

The findings of this study provide suggestive evidence of the following:

Firstly, PA (both VPA and MPA) is associated with better performance in measures of executive function, and processing speed but not memory.

Secondly, VPA (not MPA) is associated with enhancing memory-specific cognitive ability (delayed recall memory), suggesting an intensity-specific cognitive health-related outcome.

Thirdly, PA may be effective in promoting cognitive function in a non-linear dose-response manner.

Fourthly, higher handgrip strength was associated with a higher cognitive performance across all domains (memory, executive function, and processing speed).

Lastly, a higher BMI at late-life may provide protective benefits against cognitive dysfunction.

In this cross-sectional analysis of a nationally representative sample of community-dwelling older adults in the US, bivariate analysis suggested robust association between PA

(both VPA and MPA) with cognitive function, including memory, verbal fluency, and executive function and processing speed. This suggested that cognitive function was preserved among older adults who engaged in regular PA compared to their less-active counterparts. However, the magnitude of the association was diminished for delayed memory, verbal fluency, executive function/ processing speed, and was completely absent for immediate memory when we controlled for confounding factors (socio-demographic and physical attributes).

PA (both VPA and MPA) Benefits Executive Function and Processing Speed

In the present study, PA (both VPA and MPA) correlated with significantly better performance on the measures of executive function and processing speed but not memory. This suggests a differential effect of PA on these cognitive domains. This finding is analogous to a study conducted by Frederiksen et al. (2015). They used the data from the Leukoaraiosis And DISability (LADIS) study to examine how PA affects processing speed, executive function, and memory in non-demented elderly subjects. PA was assessed by interview at baseline. Cognitive performance across different domains (processing speed, executive function, and memory) was assessed by compounding scores from the different tests conducted at baseline and 3-year follow-up. They found that PA positively affects executive function and processing speed test scores but not memory in older subjects (Frederiksen et al., 2015). Additionally, a similar finding was also reported by S. Colcombe and Kramer (2003), who conducted a meta-analysis by including 18 interventional studies to examine the relationship between PA and cognitive vitality in healthy sedentary older adults. They illustrated a selective beneficial effect of PA for the cognitive ability of elderly non-demented individuals and suggested that PA benefits executive function more than memory (S. Colcombe & Kramer, 2003). Furthermore, several observational

studies suggest that processing speed and executive function are more susceptible to PA compared to other cognitive domains (Netz et al., 2011; Wilbur et al., 2012). This selective beneficial effect of PA may be due to augmented activity of key nodes in the executive control network (S. J. Colcombe et al., 2004; Rosano et al., 2010) resulting from neurogenesis (an increase in grey and white matter volume) of the prefrontal cortex of older adults (S. J. Colcombe et al., 2006).

Several other mechanisms mediated by vascular factors [such as increase cerebral blood flow, reduction in amyloid-β accumulation, increase production, and release of brain-derived neurotrophic factor (BDNF)] have also been suggested (Erickson et al., 2011; Frederiksen et al., 2015). As anticipated, due to an increase in cardiac output during exercise, blood flow to the brain rises (Ide, Schmalbruch, Quistorff, Horn, & Secher, 2000; Rooks, Thom, McCully, & Dishman, 2010). This increase in blood flow may facilitate cerebral amyloid clearance and reduce the cerebral accumulation of amyloid-β. Logically, this hyper-perfusion may result in higher executive function, as hypoperfusion in specific brain regions leading to an increasing cerebral amyloid level has been associated with the decreased performance of the executive function (McDade et al., 2014). Furthermore, it has been hypothesized that the release of BDNF, a protein that promotes neuroplasticity, is best explained by shear stress from increased cerebral blood flow (Borror, 2017).

In contrast to these findings, several studies demonstrated that PA is linked to better cognitive function across all domains (Aarsland et al., 2010; Kivipelto et al., 2008). Furthermore, PA has also been linked to improved memory performance independently in several cross-sectional studies (Sabia, Kivimaki, Kumari, Shipley, & Singh-Manoux, 2010; Vercambre,

Grodstein, Manson, Stampfer, & Kang, 2011). These claims are supported by research that demonstrated the association between higher brain volume in both prefrontal and hippocampal areas and PA by monitoring 299 older adults after a 9-year follow-up (Erickson et al., 2010). Increased hippocampal blood flow (Burdette et al., 2010) and increased hippocampal and medial temporal lobe volume were also noticed in physically active older adults (Erickson et al., 2009; Honea et al., 2009). Therefore, it remains dubious if PA affects individual cognitive domains differently and affords an opportunity for future experimental studies to test this and related hypotheses.

VPA (not MPA) is beneficial for delayed memory

The results suggest that VPA may provide delayed memory-enhancing benefits in older adults. However, MPA does not provide such a beneficial effect. This is in line with findings of an interventional study involving young adult participants (Winter et al., 2007). They performed immediate (1 week) and delayed (> 8 months) memory assessments after VPA (high impact anaerobic sprints), MPA (low impact aerobic running), or a period of rest in 27 healthy young adults and reported a superior delayed memory performance following VPA compared to other intensities (Winter et al., 2007). Such finding is further supported by other observational studies (Angevaren et al., 2007; B. M. Brown et al., 2012). Furthermore, a recent meta-analysis by Chang, Labban, Gapin, and Etnier (2012) also proposed that VPA may provide favorable effects on memory test performance after a delay following PA compared to MPA.

Researchers have suggested that VPA-induced heightened physical arousal facilitates learning and information consolidation in long-term memory stores (Winter et al., 2007). This claim is based on the evidence from animal (McGaugh, 2004) and human (Cahill & Alkire,

2003) studies that imply physical exertion promotes arousal level during learning, in turn, modulates the memory storage process. Furthermore, post-exercise increase in catecholamines (especially plasma epinephrine) has also been linked to long-term information retention (Cahill & Alkire, 2003; Winter et al., 2007). A similar findings are also evident in animal research where increased peripheral epinephrine levels were correlated with enhanced memory performance (Costa-Miserachs, Portell-Cortés, Aldavert-Vera, Torras-García, & Morgado-Bernal, 1994). However, a problem is represented by the experimental context as the intensity of VPA performed in the discussed studies greatly varied between the maximum (90% or more) vs. the submaximal (70-89%). Previous research has demonstrated that there can be differences between the physiological effects among these intensities as well (Deuster et al., 1989). Thus, it is crucial to use accepted guideline definitions to collect data regarding intensity of PA/exercise. Furthermore, the majority of the studies discussed above involved younger participants who performed limited bouts of PA. Thus, it may be worthwhile to examine how long-term VPA impacts memory function in older participants.

Memory creation and consolidation require energy especially during arousal (Proia, Di Liegro, Schiera, Fricano, & Di Liegro, 2016). To meet the energy requirements, lactate, an important substrate for neuronal metabolism, is supplied to the neurons mostly by astrocytic glycogenolysis (Skriver et al., 2014). Current research indicates that astrocyte-neuronal lactate transport plays a critical role for the induction of changes necessary for long-term memory formation (Newman, Korol, & Gold, 2011; Suzuki et al., 2011). Suzuki et al. (2011) have also demonstrated that PA causes a surge of extracellular lactate in the hippocampal region of the brain. Additionally, lactate uptake in the brain is increased to 20% during PA (van Hall et al.,

2009). Lactate produced during muscle activity can cross the blood-brain barrier and interact with astrocytes to reach neurons (Proia et al., 2016).

Recent research further indicated that VPA elevates BDNF levels more than MPA (Jiménez-Maldonado, Rentería, García-Suárez, Moncada-Jiménez, & Freire-Royes, 2018; Saucedo Marquez, Vanaudenaerde, Troosters, & Wenderoth, 2015). BDNF is a key molecule related to learning and memory, as it modulates the neural structure and activity of the hippocampus and parahippocampal regions of the brain (Miranda, Morici, Zanoni, & Bekinschtein, 2019). This could be attributed to a higher concentration of lactate, which is also associated with higher BDNF plasma and/or serum levels (Ferris, Williams, & Shen, 2007; Rojas Vega et al., 2006). However, the interaction between lactate and BDNF levels remains unclear and requires further clarification.

Dose-Response Relationship Between PA and Cognitive Performance

The multivariable analyses suggest that older adults who engaged in the highest duration weekly VPA tend to perform lower in all the cognitive performance assessments relative to the ones who performed moderate-duration weekly VPA. This finding is in alignment with a meta-analysis that evaluated 18 interventional studies and reported that cognitive function among older adults improved more effectively with moderate-duration PA than long-duration PA sessions (S. Colcombe & Kramer, 2003). The evidence is further supported by a cross sectional study that observed no significant associations between the time spent weekly on PA and the various cognitive domains as well as overall cognition (Angevaren et al., 2007).

Contrary to these findings epidemiological studies suggest that individuals who engage in a greater level of PA tend to perform better in cognitive assessments (Weuve et al., 2004; L. Xu et al., 2011) and are at lower risk of AD and related dementias (Laurin, Verreault, Lindsay, MacPherson, & Rockwood, 2001). However, Etnier et al. (2006) performed a meta-regression method to assess the statistical association between aerobic fitness and cognitive performance and reported no significant linear or curvilinear relationship. In parallel literature, Sofi et al. (2011) conducted a meta-analysis of 15 prospective trials and observed no dose-response impact. They concluded by stating that all PA levels are protective against cognitive impairment. Furthermore, in a recent experimental trial, Vidoni et al. (2015) examined the relationship of PA dose (duration) on cognition by dividing older adults into four groups who performed aerobic PA 0 minutes/wk, 75 minutes/wk, 150 minutes/wk, 225 minutes/wk. They reported that only visuospatial processing speed improved in a dose-response manner. All the other cognitive domains improved in all exercising groups equivalently. They reported that cognitive benefits in older adults may be achieved at the low duration of PA (Vidoni et al., 2015).

Furthermore, there was no clear dose-response relationship between the executive function and processing speed test scores and duration of weekly MPA. In case of executive function, a significant improvement in performance is noticeable in participants performing MPA 1-3 hr and MPA 3-6 hr per week, followed by a decline in those who engaged in 6-12 hr of weekly MPA. This is again accompanied by a significant increase in the executive function in older adults who participated in 12+ hr of weekly MPA. For processing speed, the ones who performed MPA <1 hr performed superiorly among others and similar increase is noticeable up to 3hr of MPA. This is followed by a decline except an improvement at MPA 9-12 hr. Although

it is difficult to explain such spurious results in the data suggesting lower scores on executive function and processing speed in some duration of MPA, it can be due to higher variance of scores among the participants and relatively low participants among these groups and difference in degree of MPA performed.

The findings of this study recommend a minimum of 3 hr of VPA per week is necessary to significantly improve cognitive health in older individuals. Performing more than 3 hr of VPA up to 6 hr per week may result in a similar benefit. The highest gain is noticeable in the executive function domain. Similar improvement may also be noticed in other domains however in a lower magnitude. Furthermore, performing more than 6 hr of weekly VPA may result in some negative impact on cognition. However, it should be noted that this recommendation is exclusive to cognitive health and PA duration above and below this recommendation can be beneficial for other physiological systems.

Handgrip Strength and Cognitive Performance

The results of this investigation revealed that higher handgrip strength was related to higher cognitive performance across all domains in aging Americans. This finding is similar to a cross-sectional study conducted by Ramnath, Rauch, Lambert, and Kolbe-Alexander (2018). This observational study also reported that increased handgrip strength was significantly correlated with cognitive function tasks ($r=0.42$; $p < 0.01$) in elderly participants ($n=70$) (Ramnath et al., 2018). Furthermore, a large-scale study conducted by McGrath et al. (2019) demonstrated the associations between lower handgrip strength and poorer cognitive functioning for aging Americans. They evaluated handgrip strength and cognitive performance of 13,828 older participants and followed biennially for 8 years. They reported that every 5-kg decrease in

handgrip strength was associated with 10% increased odds for poor cognitive function and any cognitive impairment and 18% increased odds for severe cognitive dysfunction (AD and related-dementia) (McGrath et al., 2019). Additional evidence is provided by several other studies that indicated an association between poorer handgrip strength and cognitive dysfunction (Heward et al., 2018; S. Jeong & Kim, 2018; S. M. Jeong et al., 2018). However, in a prospective study of 4086 community-dwelling older adults, Doi et al. (2019) explored the association between several physical performance tests including handgrip strength and dementia risk and reported no association between them. A similar finding is also reported by several other studies (Gray et al., 2013; Sattler, Erickson, Toro, & Schröder, 2011; Sibbett, Russ, Allerhand, Deary, & Starr, 2018; Veronese et al., 2016). Hence, more investigations for the association of handgrip strength and cognitive function in older adults are warranted. Such investigation should be directed towards unraveling the direction of causation and potential mediators for this association in different populations.

The finding also implies that interventions augmenting muscle strength may improve cognitive health-related outcomes. This adds to the evidence that has illustrated that muscle strengthening activities have the potential to prevent and treat cognitive impairment (Gheysen et al., 2018). Previous research has identified reduced muscle strength as a potential risk factor for cognitive deficits (Carson, 2018) and linked the age-related decrease in the motor system functioning to the onset of cognitive impairment (Bishop, Lu, & Yankner, 2010; Seidler et al., 2010). Therefore, resistance exercise, which has proven beneficial effect on muscle mass, strength, and power particularly in the older population (Haskell et al., 2007; Hunter, McCarthy, & Bamman, 2004) and reduce the risk factors associated with age-related muscle loss or

sarcopenia (Johnston, De Lisio, & Parise, 2008; Visvanathan & Chapman, 2010) has been found to enhance cognitive outcomes (Cassilhas et al., 2007; Liu-Ambrose et al., 2010; Nagamatsu, Handy, Hsu, Voss, & Liu-Ambrose, 2012). Several underlying mechanisms have been proposed connecting resistance exercise and cognition. Among them, insulin-like growth factor-1 (IGF-1) was identified as a potential link between resistance exercise and cognition (Chang, Pan, Chen, Tsai, & Huang, 2012). In both animal (Carro, Trejo, Busiguina, & Torres-Aleman, 2001) and human models (Borst et al., 2001), significantly elevated levels of IGF-1 were detected following resistance exercise. In the aging brain, IGF-1 has been shown to maintain brain volume by neurogenesis mediated by increasing concentration of BDNF and vascular endothelial growth factor and preventing brain tissue loss (Cotman & Berchtold, 2002; Lopez-Lopez, LeRoith, & Torres-Aleman, 2004). Studies have also identified that IGF-1 promotes synaptic plasticity and neuronal survival (Cotman & Berchtold, 2002; Vaynman, Ying, Yin, & Gomez-Pinilla, 2006). These collectively improve cognitive performance. Others have postulated that older adults need to recruit more brain regions (especially the prefrontal cortex) as the strength training dose (intensity or load) increases (Herold, Törpel, Schega, & Müller, 2019; Reuter-Lorenz & Park, 2010).

Assessment of handgrip strength is an inexpensive, non-invasive procedure that is widely available (Ferlay et al., 2019). It is also a viable screening tool for determining sarcopenia (Shaughnessy et al., 2020). Furthermore, growing evidence suggests that measures of handgrip strength may serve as an important measure for the detection of poor cognitive performance. Future investigations should focus on examining measurements of muscle strength including

handgrip strength to aid healthcare providers to detect the onset and progression of cognitive impairment in clinical and epidemiological settings.

BMI And Cognitive Performance

The findings of this study suggested that elderly participants with higher BMI demonstrated higher cognitive ability. This indicates higher late-life adiposity plays a protective role in maintaining cognitive function. This finding is consistent with a previous cross-sectional study which analyzed data of 2,684 older adults taken from multicenter randomized controlled trials to assess the relationship between BMI and cognitive function and reported that individuals with higher BMI demonstrated better cognitive performance than normal-weight participants (Kuo et al., 2006). The finding is also in alignment with multiple epidemiological studies which illustrates late-life increased adiposity (overweight and obesity) is associated with decreased dementia risk (Atti et al., 2008; Hughes, Borenstein, Schofield, Wu, & Larson, 2009) and may provide protection against AD (the obesity paradox) (Alosco et al., 2017; Aslan, Starr, Pattie, & Deary, 2015; Bell et al., 2017; Sun et al., 2020). Furthermore, research has also implied that higher lase-life adiposity may also slow the progression of AD (Besser et al., 2014).

In contrast to the present finding, various research studies support the idea of a negative correlation between adiposity and cognitive function. In a longitudinal study, Deborah Gustafson, Rothenberg, Blennow, Steen, and Skoog (2003) examined the relationship between BMI and dementia risk by analyzing data of 392 non-demented older adults. They followed up neuropsychiatric and anthropometric measurements for 18 years. They reported that older women who developed dementia and AD had a higher average BMI compared to their non-demented counterparts. They concluded by stating late-life increased adiposity (overweight) is

associated with the development of dementia and AD (Deborah Gustafson et al., 2003). A similar finding is also reported in older men in the Framingham Heart Study (Elias, Elias, Sullivan, Wolf, & D'Agostino, 2003). Furthermore, higher BMI over the life course has been linked to impairment of cognitive performance (Droogsma, van Asselt, Bieze, Veeger, & De Deyn, 2015; Elias, Goodell, & Waldstein, 2012).

Data from other studies imply that adiposity has a “bimodal” influence on cognitive performance (Naderali, Ratcliffe, & Dale, 2009). Most cross-sectional and longitudinal studies report a higher BMI in midlife appears to increase the risk of AD and dementia (D Gustafson et al., 2012; D. R. Gustafson & Luchsinger, 2013; Stewart et al., 2005). Whereas, a positive effect is noticed in individuals with higher BMI in later life (Atti et al., 2008). Fitzpatrick et al. (2009) evaluated associations between midlife and late-life obesity and risk of dementia by analyzing data of 2798 non-demented adults over an average follow-up period of 5.4 years. They reported a higher risk of development of dementia with midlife obesity (~ 50 years) and reversal of risk estimates with higher BMI at late-life (> 65 years) (Fitzpatrick et al., 2009). Another large-scale population-based study of 1,836 non-demented older Asian-Americans, who were followed up for 7 years, reported that the higher baseline BMI was significantly associated with a reduced risk of AD (hazard ratio=0.56; 95% CI: 0.33,0.97) and slower declining BMI in late-life are associated with a reduced risk of dementia (hazard ratio=0.37; 95% CI: 0.14,0.98) (Hughes et al., 2009).This indicates the protective effect of higher late-life adiposity in retaining cognitive function.

The hormone leptin (mainly secreted by adipose tissue) has been proposed as a possible mechanism for the protective relationship between obesity and cognition (Anjum, Fayyaz,

Wajid, Sohail, & Ali, 2018). Increased leptin level modulates hippocampal synaptic plasticity and amyloid-β processing (Anjum et al., 2018). Furthermore, leptin has been associated with the survival and proliferation of neurons (Morrison, 2009). Thus, these leptin-dependent molecular and cellular effects on brain structures and neuroprotection promote cognition and decrease the risk of AD and related-dementia. It can be speculated that leptin receptors expressed in brain areas might become resistant and/or less sensitive to prolonged exposure to leptin due to midlife adiposity. Hence, mid-life adiposity is unable to provide neuroprotection in later life. However, increased nutritional status and adiposity in late-life may increase leptin signaling contributing to neuroprotection and improved cognition.

Limitations

This study is not without limitations. Firstly, the use of an analytic cross-sectional nature of the current study can be considered as a limitation as the directionality of the observed association cannot be determined. Older adults included in the analytic sample with various levels of existing cognitive impairment may also be less likely to engage in weekly PA. Experimental studies should be conducted to uncover the probable mechanism of reverse causation. Secondly, tests administered to assess cognitive function were chosen for ease of administration (Brody et al., 2019). However, they may not be as sensitive to variations in PA level. Thirdly, the subjective assessment of PA can also be considered as a limitation as participants tend to provide an inflated estimate of physical activity. However, self-reported PA measures are reliable and valid instruments frequently utilized in research and clinical settings (Cleland et al., 2014). Previously it has been demonstrated that self-recalled VPA has greater accuracy compared to self-reported MPA (Kim, Park, & Kang, 2013). Research also

demonstrated that self-reported PA tends to mitigate associations toward the null, resulting in underestimation of the true effect (Tooze, Troiano, Carroll, Moshfegh, & Freedman, 2013). Hence, it is likely that the findings of this study are an underestimation of the actual association between PA and cognition. Finally, there is a lack of information regarding the location of residency of the participants. Different environmental settings (i.e. climate, altitude) could be an additional source of variation, as PA in different environmental settings results in different outcomes (Rogerson, Gladwell, Gallagher, & Barton, 2016).

Conclusions

The purposes of the study were three folds: 1) to examine possible associations between different durations and intensities of PA and cognitive performance across different domains (executive function, processing speed, verbal fluency, and memory), 2) to investigate dose-response association between PA and cognitive domains, and 3) to determine the association (if any) between other socio-demographics and cognitive domains among aging Americans by using a national database, the NHANES 2011-2014.

The research questions asked were:

1) Will there be any effect of PA on the cognitive performance assessment test scores across different domains in aging Americans?

2) Will there be any effect of different intensities of PA on the cognitive performance assessment test scores across different domains in aging Americans?

3) Will there be any dose-response effect of PA on the cognitive performance assessment test scores across different domains in aging Americans?

4) Are there any other socio-demographic and individual variables associated with cognitive domains?

Research Hypothesis 1

Aging Americans engaging in weekly PA would perform better in all the cognitive performance assessment tests across all domains compared to inactive counterparts.

The results of this study only partially support this hypothesis. While aging Americans engaging in weekly PA performed significantly better on the measures of executive function and processing speed compared to their inactive counterparts, such a significant improvement in performance was not associated with the memory domain of cognition.

Research Hypothesis 2

Aging Americans engaging in higher intensity PA would perform better on the cognitive performance tests across all domains.

Findings from this study only partially supported this hypothesis. Both VPA and MPA resulted in higher assessment test scores in the executive function and processing speed domains of cognition. While only in the memory domain (delayed recall memory) VPA showed a trend to provide additional beneficial effect where MPA did not.

Research Hypothesis 3

There will be a linear dose-response effect of PA on the cognitive performance assessment test scores across different domains.

Results obtained from this study did not support this hypothesis. Although VPA demonstrated some positive dose-response effect on the cognitive performance up to weekly

VPA 3-6 hr, there was a drop in cognitive performance beyond that level. Whereas, MPA showed some positive effects for 1-6 hr of activity for executive function and processing speed. However, beyond that level, was inconsistently associated with cognitive performance. Therefore, no clear dose-response relationship was noticed.

Research Hypothesis 4

There will be several socio-demographic and individual variables associated with cognitive domains.

Findings from this study support this hypothesis. There were several socio-demographic variables and individual variables (age, gender, race, education status, BMI, handgrip strength,) that influenced cognitive performance assessment scores across all domains. In addition, disease conditions like hypertension, diabetes, and chronic comorbidities negatively influenced executive function and processing speed.

In conclusion, this study provides evidence delineating positive association between PA and cognitive performance across different domains in a national sample of aging Americans. This suggestion adds to the growing body of evidence suggesting beneficial effects of PA on cognitive health. It also indicates a non-linear dose-response association between PA and cognition, recommending 3-6 hr of weekly VPA as an optimal range of PA for improving cognitive health. Furthermore, it provides clues regarding how individual characteristics like (handgrip strength and late-life adiposity) may relate to cognitive performance. Therefore, higher intensities of aerobic and resistance PA in older adults should be investigated further utilizing

objective measures and adhering to the high-quality methodological standards to better understand the potential relationship between PA and cognitive health.

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APPENDIX A

APPENDIX A

DEFINITIONS

1) **Fluid cognition:** The ability to learn and process new information, critical thinking, and manipulate the surrounding (Stawski et al., 2010).
2) **Executive function:** Capabilities that enable an individual to engage in complex purposefully independent self-serving mental actions and subsequent response (Hobson & Leeds, 2001).
3) **Processing speed:** The ability to process information rapidly, is closely related to the ability to perform higher-order cognitive tasks (Lichtenberger & Kaufman, 2012).
4) **Verbal fluency:** Cognitive ability that facilitates information retrieval from memory in a certain amount of time (Patterson, 2011).
5) **Declarative or explicit memory:** Conscious recollection of experiences, events, and information used in everyday living (Grote-Garcia & McDowell, 2011).
6) **Episodic or autobiographical memory:** Ability to recall and mentally re-experience specific episodes from one's personal past (Hudson et al., 2011).
7) **Semantic memory:** Long-term memory for meaning, understanding, and conceptual facts about the world (Schendan, 2012).

8) **Dementia:** An acquired impairment of cognition abilities that commonly involves memory and at least one other cognitive domain (language, visuospatial, executive function) (Eric B Larson, 2016).
9) **Mild cognitive impairment (MCI):** Transitional phase of cognitive impairment where cognitive decline greater than expected but have not reached clinical dementia (Emily Frith & Loprinzi, 2020; Jack Jr, 2012).
10) **Alzheimer's disease:** The most prevalent and devastating form of dementia (Seeley & Miller, 2018b).
11) **Cognitive reserve:** The ability of the brain to utilize neuronal network connections in a versatile manner (Association, 2019).
12) **Arousal:** The state of being activated, either physiologically or psychologically to a point of perception (Niven & Miles, 2013).
13) **Physical activity:** Bodily movement that increased heart rate and made an individual to breathe hard some of the time.
14) **Vigorous-intensity physical activity:** Activities that require hard physical effort and cause large increases in breathing or heart rate.
15) **Moderate-intensity physical activity:** Activities that require moderate physical effort and cause small increases in breathing or heart rate.

APPENDIX A

LIST OF ABBREVIATIONS

AD	Alzheimer's disease
AFT	Animal fluency test
BMI	Body mass index
BDNF	Brain-derived neurotropic factor
CAPI	Computer assisted personal interviewing
CDC	Centers for Disease Control and Prevention
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CERAD.DR	Delayed recall memory test
CERAD.IR	Immediate recall memory test
DSS	Digit symbol substitution test
DU	Dwelling unit
GPAQ	Global physical activity questionnaire
HDL	High-density lipoprotein-cholesterol
IGF-1	Insulin-like growth factor 1
MCI	Mild cognitive impairment
MEC	Mobile examination center
MPA	Moderate-intensity physical activity
NCHS	National Center of Health Statistics
NHANES	National Health and Nutritional Examination Survey

PA	Physical activity
PHQ-9	Patient Health Questionnaire
PSU	Primary sampling unit
TREM2	Triggering receptor expressed on myeloid cells 2
VPA	Vigorous-intensity physical activity
WHO	World Health Organization

BIOGRAPHICAL SKETCH

Imtiaz Masfique Dowllah earned his Bachelor of Medicine and Bachelor of Surgery at the Bangladesh University of Professionals at Dhaka, Bangladesh in March 2014. He previously served as a licensed physician in Bangladesh. He then earned his Master of Science degree in Exercise Science at the University of Texas Rio Grande Valley in July 2021. Imtiaz has also been accepted into the University of Florida's Health and Human Performance doctoral program. His email address is imtiaz.d.masfique@gmail.com and his mailing address is 3070 Holiday Springs Blvd Apt 103 Bldg. 16, Margate, FL 33063.