

University of Nevada, Reno

**Public Health Approaches to Promoting Physical Activity and a Healthy Diet to Reduce
Risk of Cognitive Decline Among Older Adults**

A thesis submitted in partial fulfillment
of the requirements for the degree of

Bachelor of Science in Community Health Sciences, Kinesiology Specialization and the Honors
Program

by

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May 2019

**UNIVERSITY OF
NEVADA, RENO**

THE HONORS PROGRAM

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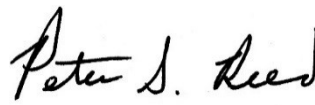
J'NAEY A. SOULE

entitled

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be accepted in partial fulfillment of the
requirements for the degree of

**BACHELOR OF SCIENCE IN COMMUNITY HEALTH SCIENCES (KINESIOLOGY
SPECIALIZATION) AND THE HONORS PROGRAM**



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May, 2019

Abstract

As the aging population continues to grow worldwide, the prevalence of physical and cognitive impairments (for example, chronic conditions) is rising. The trajectory of cognitive decline varies widely due to factors such as genetics, physiological changes, as well as environmental and behavioral factors. This fact increases the importance of reliable diagnostic techniques, widespread education, and reflective early intervention. Without any known disease-altering treatments, non-pharmacologic therapeutic approaches such as modifying unhealthy lifestyle factors should be promoted through specific public health campaigns. This should be done to reduce the prevalence and burden of cognitive impairments. **The goal of this thesis is to emphasize prevention as a key element to counteract the epidemic of cognitive impairment and consider ways that public health surveillance can facilitate this process.**

Acknowledgements

This thesis was possible because of the guidance, support, and encouragement from several individuals that I would like to express my utmost gratitude towards. First and foremost, I would like to thank Dr. Peter Reed for being my thesis advisor. Thank you for taking time out of your busy schedule to mentor me. I am thankful for the guidance and feedback on my work. Thank you for always being willing to answer any questions and provide clarification on topics and strategies.

Secondly, I would like to thank the Honors Department as a whole for providing me with this opportunity to write a senior thesis and their guidance throughout my undergraduate career at the University of Nevada, Reno. I have grown tremendously as a student and as a person. Specifically, I would like to thank Dr. Erin Edgington, Dr. Tamara Valentine, and Dr. Alison Johnson. Dr. Edgington and Dr. Valentine, you have been extremely helpful throughout this project. Thank you for outlining the writing process and for giving me the necessary tools that I needed to succeed. I would not have been able to complete this project without your support and direction. Dr. Johnson, thank you so much for working with me every week to revise, reorganize, and reconstruct my thesis. I cannot express how truly thankful I am for your support and guidance. Thank you for being invested in me and my project and for cheering for me day in and day out.

Lastly, I would like to thank my parents, Randy and Kami Soule, for teaching me from a young age the importance of lifelong health. They instilled in me a passion for maintaining an active lifestyle, eating a well-balanced diet, and a fervor for health and wellness. They have encouraged me to participate in activities that I enjoy and have supported me in anything and everything that I have wanted to try. Thank you for pushing me to be a well-rounded person who

can achieve anything that I set my mind do. I am infinitely grateful not only for the support throughout this project but also throughout my entire collegiate career. I wouldn't be where I am today without such loving and supportive parents. Mom, thank you for being as invested in my work as I am. Thank you for intricately revising my work.

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Chapter 1: Introduction

Today, as people are living longer due to advancements in medicine, sanitation, and education, the older population is growing rapidly. Considering the aging baby boomer generation, by the year 2030 over 20% of the population within the United States will be 65 years and older (Chapman et al., 2006; Gallaway et al., 2017; Harvey et al., 2013). As the population continues to age, it is predicted that 16% to 25% of older adults will experience some degree of cognitive impairment (Anderson & McConnell, 2007; Gallaway et al., 2017). From now until the year 2050, the number of people living with Alzheimer's disease (AD) is projected to increase from 5 million to approximately 16 million people within the U.S. (Gallaway et al., 2017; Lee et al., 2017; Wilcox et al., 2009).

Dementia and AD have become prominent health issues due to the the alarming number of surfacing cases, the lack of curative treatments, and the implications they have for personal well-being (Chertkow, Jacova & Massoud, 2013; Gallaway et al., 2017; Gillette-Guyonnet et al., 2013; Yuede et al., 2018). While there is no curative treatment, ongoing research suggests that modifiable lifestyle factors such as diet and exercise may reduce one's risk of developing abnormal cognitive decline (Anderson & Egge, 2014; T. Jackson et al., 2016; Nijholt et al., 2016). This thesis serves three roles. The first is to define and explain mild cognitive decline (MCI), dementia, vascular dementia (VaD), and AD as well as the research-based diagnostic tools for each. The second is to present evidence that reveals the mechanisms by which specifically-regimented physical activity and a heart-healthy diet can reduce the risk of cognitive decline. Finally, the third is to consider previously implemented public health strategies in order

to discuss how to implement successful campaigns and promote cognitive health more effectively in the future.

Definitions

Mild Cognitive Impairments (MCI). On the spectrum of cognitive impairment, mild cognitive impairment (MCI) that lies in between normal physiological changes in brain function, that occur with healthy aging and abnormal changes in brain function, such as those that lead to dementia (Petersen, 2011). MCI is a syndrome that involves an accumulation of negative cognitive symptoms that are potentially attributable to an underlying cause such as AD or a vitamin deficiency. The changes in cognition occur gradually and are minor, yet noticeable (Gallaway et al., 2017; Petersen, 2011). Inhibited thinking skills and an affected memory are both symptoms of a MCI; however, this level of impairment typically does not impact one's ability to perform activities of daily living (ADLs) (Gallaway et al., 2017; Petersen, 2011). Depending on the underlying etiology of one's MCI, symptoms will either improve, stay the same, or worsen rapidly. If one's MCI has a less serious reversible cause, such as a vitamin B deficiency, then symptoms will disappear with proper treatment. However, if there is an underlying neurodegenerative cause, the MCI may progress rapidly to a form of dementia. Unfortunately, more often than not, MCI progresses to AD or some other form of dementia (Gallaway et al., 2017).

MCI is very hard to diagnose because there are no assigned diagnostic tests to accurately identify the disorder. The diagnosis is made at the discretion of the practitioner (Gallaway et al., 2017; Petersen, 2011). MCI is commonly diagnosed based on a patient's self-reported symptoms. Unfortunately, self-reported assessments may complicate the objectivity and

accuracy of the diagnosis because they are unreliable and lead to bias (Gallaway et al., 2017). For this reason, the concept of MCI is still somewhat controversial. However, the Montreal Cognitive Assessment (MoCA) has recently been shown to be an effective tool in diagnosing MCI due to its sensitivity and specificity in identifying cognitive impairment (Gallaway et al., 2017)

MCI is a critical link between normal aging and dementia and can provide useful information regarding the effects on cognition of modifying lifestyle factors such as diet and regular physical activity may help to reduce its effects. Intervention is especially important before irreversible brain damage occurs, especially in cases with reversible etiologies. Further understanding of the relationship between intervention methods and cognitive decline will be a significant step towards reducing the impact of dementia (Gallaway et al., 2017).

Dementia. Dementia is not a specific disease. Dementia is the general umbrella term used to describe the collection of neuropsychiatric symptoms and physiological changes in the brain that result from a variety of different neurodegenerative diseases or abnormalities (AA¹, 2018; Chapman et al., 2006; Gallaway et al. 2017; Guure, Ibrahim, Adam, & Said, 2017; Ngandu et al., 2015; Prevention, 2011). Dementia is characterized by a number of behavioral, psychological, and cognitive changes that alter memory and thinking processes enough to interfere with daily life. Symptoms most commonly include memory loss, personality changes, such as aggression, anxiety, depression, and the inability to perform basic ADLs (AA, 2018; Chapman et al., 2006; Gallaway et al. 2017; Guure et al., 2017). The severity of dementia

¹ Alzheimer's Association

symptoms can range dramatically from mild to very severe and can be affected by compounding factors such as other chronic diseases (Chapman et al., 2006).

Dementia is diagnosed by a health care provider through a careful collection of the patient's medical history, a physical examination, and a report of characteristic changes in everyday thinking or functional behavior (AA, 2018; Gallaway et al., 2017). Physicians use the Diagnostic and Statistical Manual of Mental Disorders (DSM) standards to diagnose dementia as a major neurocognitive disorder (Ngandu et al., 2015). Dementia is often misdiagnosed because of the slow progression of symptoms and the lack of accurate systematic diagnostic tests. Issues related to diagnostic testing methods will be discussed further below.

There are several different causes of dementia, and each is associated with brain cell damage within a specific region or regions. Because each region of the brain is responsible for particular functions, damage to cells in that area will inhibit activity (AA, 2018). The most common causes of dementia include AD, vascular dementia (VaD), dementia with Lewy bodies (DLB), and mixed dementia (AA, 2018; Gallaway et al., 2017; Kennelly, Lawlor, & Kenny, 2009). AD accounts for 60 to 80% of dementia cases, making it the most common cause of dementia (Gillette-Guyonnet et al., 2013; Guure et al., 2017). Vascular dementia, which often occurs after a stroke, is the second most common cause of dementia. While minor cognitive decline is considered a normal part of the aging process, symptoms of dementia are not a normal part of aging (AA, 2018; Gallaway et al., 2017).

Alzheimer's Disease (AD). Alzheimer's Disease is currently the most common type of dementia-causing disease (Tangney, 2014; Gallaway et al., 2017; Lee et al., 2017). AD is a progressive yet fatal neurodegenerative brain disorder that damages brain cells. As a result, AD has an extensive list of adverse symptoms and effects. AD is generally described as having three

stages, early-stage, middle-stage, and late-stage, which are classified based on the general collection and severity of symptoms. However, the symptoms of AD vary from person to person, as does the rate at which they are exacerbated. Therefore, it is very difficult to assign a specific stage of AD at any given point in time for an individual person (AA, 2018).

According to the Alzheimer's Association (2018), the hippocampus and the brain cells surrounding this brain region are the first to be damaged by AD. The hippocampus is the brain's center for learning and memory, which explains why memory loss is one of the earliest signs of AD. As the disease progresses, AD affects cognition, behavior, mood, and psychological well-being. Cognitive symptoms include difficulty thinking or understanding, disorientation, forgetfulness, making things up, difficulty concentrating, and the inability to maintain good judgment. Behavioral expressions may include agitation, personality changes, and irritability among others. Physically, AD can inhibit one's ability to walk due to its limiting effect on the capability of combining muscle movements.

Two features that distinguish AD from other types of dementia are large numbers of extraneuronal amyloid plaques and intraneuronal neurofibrillary tangles (Hardy & Higgins, 1992; Kennelly et al., 2009; Tangney, 2014). These extraneuronal sticky plaques are deposits of protein fragments from the buildup of insoluble deposits of Beta-amyloid ($A\beta$) proteins. $A\beta$ proteins, which are cleaved fragments from a larger precursor polypeptide called amyloid precursor protein (APP), build up around the outside and in between brain neurons (AA, 2018; Gallaway et al., 2017; Kennelly et al., 2009). This accumulation of $A\beta$ proteins initiates a cascade of neurotoxic effects and leads to the formation of neurofibrillary structural abnormalities known as tangles (Gallaway et al., 2017, Hardy & Higgins, 1992; Kennelly et al., 2009; Selkoe, 2001). Neurofibrillary tangles are twisted fibers of hyperphosphorylated tau

protein. As these proteins build up inside the cells, they affect cellular structure and cells' ability to provide proper cell framework (AA, 2018; Gallaway et al., 2017; Kennelly et al., 2009). Although plaques and tangles develop in the aging brain, they do not always cause symptoms of cognitive decline. However, in AD an extensive network of plaques and tangles form in a predictable pattern. Typically patterns of development start in the areas of the brain that are most important for memory and spread to other regions, causing a block in cellular communication of nerve cells. As a result, cells do not survive, which causes memory failure, personality changes, and symptoms of AD to persist (AA, 2018).

A general hypothesis is that the accumulation of A β plaques, causing the cascade of neurotoxic effects, is the causative agent of AD pathology. This hypothesis is well accepted because it can explain almost all features of the disease (Selkoe, 2001). These cytotoxic effects include neuronal dysfunction, neurotransmitter deficits as a result of synaptic alterations, vascular damage, and neuronal cell death, which all lead to impaired cognitive function (Hardy & Higgins, 1992; Selkoe 2001). The cerebral cortex is generally the most affected region of the brain, and it is increasingly evident that the pathological changes are active long before the appearance of clinical dysfunction related to dementia symptoms (Gillette-Guyonnet et al., 2013). However, the pathophysiological mechanisms of the disease require further research (Gillette-Guyonnet et al., 2013; Yuede et al., 2018).

Vascular Dementia (VaD). The second most common form of dementia, VaD, falls under the subcategory of vascular cognitive impairment (VCI) (Gorelick et al., 2011). This form accounts for nearly 10% of dementia cases (AA, 2018; Gallaway et al., 2017). The VCI spectrum can range from a mild cognitive impairment to severe dementia symptoms depending on the amount of damage to the specific brain region affected (Gorelick et al., 2011). Symptoms of VaD

vary, but the most common symptoms involve an inability to make decisions, plan or organize, and memory loss (AA, 2018; Guure et al., 2017).

VaD, previously known as post-stroke or multi infarct dementia, is a direct result of damage caused by impeded cerebral vasculature to tissues in the cortical and subcortical regions in the brain. Hindered blood flow deprives the brain of vital nutrients and oxygen and causes many adverse symptoms (Gallaway et al., 2017; Gorelick et al., 2011; Kennelly et al., 2009). Vascular damage to these areas of the brain cause impairment to working memory and executive function (Kennelly et al., 2009).

VaD typically presents evidence of nerve cell damage and death in the brain. This type of dementia is very complicated because of the numerous pathologies that can reduce the brain's blood supply. One of the most common causes is the aggregation of harmful lesions from a number of small strokes that have gone unnoticed. If the damage is severe enough, it can destroy small areas of the brain and cause serious dementia symptoms. To complicate matters further, VaD can coexist with other forms of dementia, which result in more severe and exasperated dementia symptoms. VaD most commonly coexists with AD because A β plaques and tangles are trademark abnormalities of this type of dementia (AA, 2018; Gallaway et al., 2017). Lastly, diagnostic methods for VaD are ineffective due to the lack of validated testing measures and assessment tools (Gallaway et al., 2017).

Chapter 2: Methodology

I conducted an in-depth literature review of scholarly, peer-reviewed research in order to present an evidence-based argument that risk of cognitive decline can be reduced via the modifiable lifestyle factors of diet and exercise. The CDC Healthy Brain Initiative (2007) was the foundational source behind conceptualizing cognitive health, different lifestyle modifications, and the constituencies that directly and indirectly contribute to public health. This roadmap served as a rudimentary research guide and provided key goals and strategies for addressing the four traditional domains for public health: evaluation, empowerment of the nation, mobilization of partnerships, and assurance of a competent workforce. Studies that focused on maintaining cognitive function through physical activity and a healthy diet were my predominant concentration. An investigation regarding public health initiatives – what efforts have been set in place to prevent cognitive decline and promote healthy behaviors – was also conducted in order to understand how to effectively target different groups within public health. A thorough study of the science and systems designed to improve public health at the community and population level was conducted in order to better understand the approaches that can be taken to implement cognitive health promotional programs.

In order to gain a complete understanding of the data, I started by researching and defining MCI, dementia, AD, and VaD. I also considered diagnostic tools used and the challenges that arise with current diagnostic methods. Once a foundational understanding of basic terms was built, I transitioned to smaller, more refined searches. The CDC Healthy Brain Initiative reference list was used as a foundational research guide in conjunction with UNR Knowledge Center databases to find peer-reviewed articles. The analysis of each study included relevance, generalizability, and overall validity.

I chose public health as the perspective of my project because it can reach a much larger audience as compared to a specifically targeted population. The scope of public health includes the general public, healthcare practitioners, caregivers, public health officials, and experts within the field. With cognitive decline being so prevalent, there is a need to educate as many people as possible about cognitive decline and the protective factors available. This topic is important to me on a personal level as I will be pursuing a career within the healthcare field.

Chapter 3: Literature Review

Diagnostic Tools

Accurately testing for and diagnosing abnormal cognitive decline early on has important personal and clinical impacts. Further neurological damage can be prevented if a reversible or treatable condition is caught in its early stages. If the condition is not treatable, the patient is still able to be proactive and participate in legal, financial, and long-term care decisions. Lastly, an early diagnosis allows the patient to prioritize as well as utilize available clinical and community resources. In addition, many implications exist for clinical diagnostic methods for cognitive decline. Early detection may have the benefit of more accurately assessing the patient due to a more in-depth history from the patient, as well as acquiring a list of concerns. Additionally, early detection may provide additional opportunities for participation in clinical trials or other research.

Despite a large amount of research and new data regarding the clinical manifestations of dementia and AD, there is still no one diagnostic tool or method that can be used with certainty (AA, 2018; Arevalo-Rodriguez, 2014; Gallaway et al., 2017). However, there are confirmed procedures and tests that can help healthcare providers to diagnose these cases. Nearly 30 years ago, the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) determined that some of the most important diagnostic tools include a thorough medical history, extensive clinical examination of a person's vital signs, laboratory blood work, and neuroimaging tests (AA, 2018; Mckhann, 2011). In recent years, the National Institute on Aging and Alzheimer's Association reviewed to NINCDS-ADRDA criteria and have incorporated modern innovations including clinical, imaging, and laboratory assessments. These innovations were based on the evolving

study of the microscopic structure of brain tissue, a developed understanding of distinguishing features of other dementing conditions that were not recognized 10 years ago, inclusion of imaging tests, genetic testing, and rejection of the idea that dementia only occurs in older adults (McKhann et al., 2011).

Physical Examinations. First, a provider is responsible for collecting a medical history and performing a physical examination. The medical history gives the provider a clear understanding of the patient's family history while also providing insight into the patient's past cognitive abilities. This assessment, in conjunction with a description of the severity and duration of symptoms, allows the physician to rule out any other neurologic diseases before performing further tests (Diagnosing Dementia, 2017; Gallaway et al., 2017). After the medical history is collected, a physical examination is performed. Blood pressure and vital sign measurements may reveal other conditions that could mistakenly present as dementia or AD.

Following the medical history and physical examination, providers rely on the initial criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM) to diagnose dementia. In order to be properly recognized as a form of dementia, symptoms must be present over a period of at least six months and not be attributable to any other brain disease, delirium, or other major psychiatric disorder (Arevalo-Rodriguez, 2014). These neuropsychiatric symptoms include the development of multiple cognitive deficits, such as memory impairment, which are sufficiently severe enough to inhibit occupational or social functions. In addition to symptoms lasting more than six months, two of the core mental functions, as described by the DSM, must be notably compromised. The core mental functions include memory loss, difficulty with communication and language, reduced ability to focus and pay attention, poor reasoning and judgment, and lack of visual perception (AA, 2018).

Basic Cognitive Testing. After completing the basic family history and physical examination neuropsychological and cognitive tests can be used to analyze other mental abilities. Cognitive tests evaluate basic brain function, such as problem solving, general math skills, and rudimentary memory recall. (Diagnosing Dementia, 2017). One of the most commonly used cognitive tests is the mini-mental state examination (MMSE). The MMSE provides a measurement for overall cognitive functioning, such as attention, orientation, memory, registration, recall and is scored from zero (severe dementia) to thirty (lack of cognitive impairment) (Gallaway et al., 2017). Neurological tests assess balance, reflexes, and sensory responses to stimuli (Diagnosing Dementia, 2017).

Differential Diagnosis

The complexity of diagnosing MCI, dementia, or AD is exacerbated by the fact that physicians must first rule out any other possible conditions through a process of elimination. This process is known as a differential diagnosis. Additionally, growing research on dementia and AD has made the diagnostic process more complicated because physicians are expected to make judgments to determine the characterization, severity, and specificity of the symptoms as part of standard diagnostic procedures (Gallaway et al., 2017; Mckhann, 2011). Differentiating between normal age-related cognitive decline, (MCI), different variations dementia, and AD can be extremely challenging given the lack of specific diagnostic tests. This is very difficult because symptoms often vary significantly from person to person, conditions are usually progressive, and brain changes of different dementias can overlap (AA 2018; Gallaway et al., 2017; Mckhann, 2011). Research intended to find ways to facilitate the diagnostic process is ongoing. Existing imaging techniques are being used to view the structure of the brain and new methods, such as biomarker evidence, are being incorporated into the field.

Neurological Imaging on Biomarkers. The National Institute on Aging and Alzheimer's Association concur that imaging techniques such as such as magnetic resonance imaging (MRI) and positron emission tomography (PET) imaging, should be coupled with evolving histological pathology to have a more comprehensive diagnostic approach (McKhann et al., 2011). This neurological technology has become one of the most effective advancements in the diagnostic process for determining the specific course of dementia symptoms. These imaging methods enable providers to examine the brain's physical condition as well as observe the changes in structure and function (Diagnosing Dementia, 2017; Gallaway et al., 2017; Mckhann, 2011). The most commonly used imaging test is the PET scan (Gallaway et al., 2017). A drawback to this method is its high cost, which deters patients of limited means who may then be misdiagnosed (Gallaway et al., 2017; McKhann et al., 2011).

Biomarker evidence-based tests are the newest tools for diagnosing dementia. These tests should be used in conjunction with other methods (McKhann et al., 2011), as they provide added information about the etiology of cognitive impairment, such as neuronal injury, A β plaque buildup, synaptic dysfunction, and neuronal degeneration (Arevalo-Rodriguez, 2014). Specifically, the cerebrospinal fluid (CSF) assay reveals A β and tau protein accumulation. This is especially helpful because A β and tau protein accumulation is directly correlated to AD (Gallaway et al., 2017). Genetic information, as well as gene mutation identification, are evolving methods that may facilitate the diagnosis of AD (Arevalo-Rodriguez, 2014). Drawbacks to this test include availability of biomarker imaging tests, individuals who can interpret results, and inconclusive research on the design of these tests (McKhann et al., 2011).

Diagnostic Challenges. Dementia often coexists with other clinical disorders, such as delirium (Jackson et al., 2016), Parkinson's disease, and Huntington's disease (Gallaway et al.,

2017). During hospital visits, dementia is under-recognized and often misdiagnosed in older adults. According to T. Jackson et al. (2016), nearly half of hospitalized patients with dementia are not properly diagnosed. This is because dementia is often mistaken for delirium due to the resemblance of symptoms. Both delirium and dementia are characterized by attention deficits and recognizable changes in cognition. However, delirium is an acute syndrome that typically subsides, whereas dementia is a progressive neurodegenerative disease. Age and cognitive impairments are the biggest risk factors for delirium, making it especially important for patients with delirium to be properly assessed for dementia (T. Jackson et al., 2016).

Unfortunately, the DSM is not able to distinguish between dementia and delirium and, therefore, the cognitive testing may be inaccurate in the presence of delirium. T. Jackson et al. (2016) assessed the diagnostic accuracy of two tests that are able to distinguish between dementia and delirium. The first test, the Informant Questionnaire of Cognitive Decline in the Elderly (IQCODE-SF), is a scale-based questionnaire. The 16-item questionnaire takes approximately ten minutes to complete and asks the informant to rate, on a scale of one-to-five (with one meaning no change and five meaning the most extreme change) deviations in cognition, memory, and behavior over the last 10-year period. A higher overall score indicates a larger degree of cognitive impairment. The second test, the eight-item Interview to Differentiate Aging and Dementia (AD8), is also known as the Washington University Dementia Screening Test. It is an interview-based test that takes 5 minutes to complete. The test includes rating eight items of memory and thinking changes as “yes,” “no,” or “I don’t know.” Once again, a higher score indicates a larger degree of cognitive impairment (T. Jackson et al., 2016). T. Jackson et al. (2016) concluded that both tests have excellent diagnostic test accuracy in diagnosing dementia in older adults who present with delirium.

Despite a growing body of research and new diagnostic methods, the challenge of properly diagnosing patients persists. The accuracy, especially within special cases, of most diagnostic testing is still being determined in terms of sensitivity and specificity (Arevalo-Rodriguez, 2014). Despite these diagnostic challenges, a proper diagnosis is imperative in order to prescribe the right treatment, care, and proactively slow future cognitive decline.

Chapter 4: Risk Factors

There is a consensus among experts that the majority of cases involving cognitive decline develop as a result of interactions among multiple risk factors (AA, 2018). There are two types of risk factors that are associated with cognitive decline, MCI, and dementia, modifiable and nonmodifiable. Nonmodifiable risk factors include age, family history, and genetics (AA, 2018; Baumgart et al., 2015; Gurre et al., 2017). Modifiable risk factors are behaviors that can be changed in order to reduce one's risk of developing a disease. Modifiable risk factors include cardiovascular disease and its risk factors (obesity in midlife, hypertension, diabetes and smoking), depression, education, social and cognitive engagement, physical activity level, and diet (AA, 2018; Baumgart et al., 2015; Chapman et al., 2006; Gurre et al., 2017; P. Jackson et al., 2016; Lee et al., 2017; Yuede et al., 2018). It is estimated that nearly 33% of AD cases worldwide are attributable to modifiable lifestyle factors (Ngandu et al., 2015). This means that there are opportunities for prevention. The large Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) is a pivotal study in terms of understanding which approaches need to be taken to prevent cognitive decline in at-risk older adults. This randomized controlled trial concluded that a multi-domain approach targeting multiple modifiable risk factors should be taken when looking at intervention strategies to maintain cognitive decline. The comprehensive outcome of FINGER was that, if simultaneous risk factors are eliminated, then overall cognition, executive functioning, and processing speed will benefit (Gillette-Guyonnet et al., 2013; Ngandu et al., 2015). Furthermore, many additional studies have looked at the impact that physical activity and diet have on modifiable risk factors (AA, 2018; Baumgart et al., 2015; Lee et al., 2016; Ngandu et al., 2016; Nijholt et al., 2015).

Cardiovascular Health

The cardiovascular system - arteries, veins, capillaries, and heart - plays a critical role in cognitive health by delivering vital nutrients and oxygen to the brain. Therefore, it is necessary to reduce the risk of diseases that affect heart and vascular health such as coronary artery disease, cardiovascular disease, and hypertension (AA, 2018; Gallaway et al., 2017). Autopsies have revealed that nearly 80% of individuals with AD also have cardiovascular disease (AA, 2018). This finding can be attributed to the fact that health factors that increase one's risk of developing cardiovascular disease such as diabetes, obesity, smoking, high cholesterol, and hypertension also increase one's risk of developing AD (AA, 2018; Baumgart et al., 2015).

The brain is one of the most vulnerable organs in the body because of its rich blood vessel supply. Problems with the cardiovascular system may result in a disruption of blood flow to the brain, and without the proper nutrients, neurological cells die. Following a series of minor strokes or blocks in a major blood vessel, changes in thinking can appear. For this reason, cardiovascular problems are directly linked to VaD (AA, 2018; Gorelick et al., 2011). Depending on the severity of damage to blood vessels, the amount of cell death, and the part of the brain affected, symptoms of VaD can vary widely. Vascular brain changes often coexist with changes linked to other types of dementia because of the shared risk factors (AA, 2018; Gorelick et al., 2011). Vascular contributions to cognitive impairment and dementia are significant and should be detected as early as possible to prevent any further damage. MRIs and neuroimaging techniques are essential for VCI detection (Gorelick et al., 2011).

BMI and Obesity

Neuroimaging evidence suggests that obesity has a profound impact on age-related brain structure changes and may accelerate neurodegeneration (Gillette-Guyonnet et al., 2013; Ronan

et al., 2016). Mid-life obesity, especially, has a strong correlation to cognitive decline, dementia, AD, and VaD (Dauncey, 2014; Gallaway et al. 2017; Guure et al., 2017) in both men and women (Baumgart et al., 2015; Hong & Kim, 2010). It is unclear whether obesity directly alters brain structure or if it is caused by associated comorbidities such as cardiovascular disease. It is understood, however, that obesity has a widespread impact throughout the brain.

Individuals who are obese have an excessive amount of body fat, as well as an increased risk for many health problems. Additionally, obesity is a risk factor for neurovascular and neurodegenerative diseases because of its direct influence on oxidative stress,² inflammation, and insulin resistance (Gillette-Guyonnet et al., 2013; P. Jackson et al., 2016; Ronan et al., 2016). There is strong evidence that inflammatory processes in the brain underlie the development of AD (Chapman et al., 2006; Ronan et al., 2016). The aging brain is highly susceptible to oxidative stress. This susceptibility is increased in people who are obese due to the accelerated rate of oxidative metabolism. Antioxidant enzymes cannot remove the reactive oxygen species (ROS) fast enough, leading to induced damage to the brain (P. Jackson et al., 2016). They are a part of a self-sustaining feedback loop that is associated with increased brain atrophy and white matter changes (Ronan et al., 2016). Additionally, proinflammatory cytokines and leptin are both produced by adipose tissue. Proinflammatory cytokines³ and associated hormones, such as leptin, evoke an intense inflammatory response that is capable of changing gene expression. Altered genetic expression can cause adverse changes in overall health (Dauncey, 2014; Lee et al., 2016). For example, insulin-like growth factor-1 (IGF-I) is an important protein that sequences for

² Oxidative stress is a risk factor for the pathogenesis of cognitive decline due to the imbalance of reactive oxygen in the body. If the body is unable to detoxify the reactive intermediates fast enough, then the toxic substances build up and activate pathways that cause lesion formations in the brain. (Gillette-Guyonnet et al., 2013).

³ Cytokines regulate responses within the body. Proinflammatory cytokines increase the body's inflammatory response and produce adverse effects.

regulation of normal physiology. IGF-I levels elicit a hypoglycemic response similar to insulin and studies have revealed that high levels of IGF-I are related to glucose intolerance and insulin resistance (Dauncey, 2014; Friedrich et al., 2012).

The influence that obesity has on cognitive function may be directly related to the effects of adiposity (Baumgart et al., 2015; Gillette-Guyonnet et al., 2013). Adiposity prescribes a significant risk of neurodegeneration and cognitive decline because of its impact on brain structure, specifically white-matter volume. Ronan et al. (2016) assessed the impact of obesity and BMI on brain structure, looking specifically at the effects of obesity on gray⁴ and white⁵ matter in order to determine if obesity affects tissue types differently. They compared the cortical thickness and surface area of both gray and white matter based on the knowledge that different areas of the brain age at different rates. They found a statistically significant BMI interaction with white matter volume, but no statistical significance for BMI related differences in total cortical surface area (Ronan et al., 2016).

Data supports the notion that excessive adiposity increases brain age by nearly 10 years and is also one of the most significant risk factors for MCI (Gallaway et al., 2017; Ronan et al., 2016). Excessive adiposity is a significant risk factor for dementia and AD because it contributes to disrupted vascular function, neuronal abnormalities in the frontal lobe, and inhibited cerebral autoregulation (Gillette-Guyonnet et al., 2013; Gallaway et al., 2017; Ronan et al., 2016). Neuronal abnormalities in particular lead to accelerated aging in the frontal lobe (Gillette-Guyonnet et al., 2013). Impaired cerebral autoregulation perpetrates A β plaque accumulation and neurofibrillary tangles contributing to AD (Gallaway et al., 2017).

⁴ Gray matter contains all synapses, cell bodies, dendrites and axon terminals of neurons.

⁵ White matter consists of axons connecting the different parts of grey matter to each other,

Hypertension

Hypertension⁶ is a major risk factor for AD, VaD, and dementia (Gallaway et al., 2017; Kennelly et al., 2009; Wilcox et al., 2009). Baumgart et al. (2015) stated that individuals with hypertension are at a larger risk for cognitive decline when compared to healthy counterparts. However, the effects of hypertension on brain health may not be evident for many years. Kennelly et al. (2009) stated that there may be a prominent lag phase between the presence of hypertension and onset of dementia because of the direct correlation of elevated blood pressure in midlife, classified as ages 40-64, and the onset of dementia and AD in later life. Autopsies on patients with elevated systolic blood pressure in midlife revealed cerebrovascular changes, a lower brain weight, and much larger numbers of A β plaques. High diastolic blood pressure was associated with greater tau protein tangles in the hippocampus. Additionally, hippocampal atrophy is linked to untreated midlife hypertension (Kennelly et al., 2009).

Midlife hypertension increases the risk for VaD because chronically elevated blood pressure causes larger cerebral blood vessels to thicken, dramatically reducing their diameter, and plaques to accumulate in smaller vessels. If blood clots are present in the brain, they may get lodged in vessels that have a reduced diameter due to plaque buildup. Blockage results in infarction of the surrounding cerebral tissue. Various regions in the hippocampus, such as the cornu ammonis (CAI), are especially vulnerable to infarction relative to other areas of the brain. If neuronal death occurs in the CAI region due to reduced blood flow, cognitive processes and memory are severely impaired (Kennelly et al., 2009).

⁶ Hypertension is classified as a systolic blood pressure over 140 mmHg and a diastolic blood pressure over 90 mmHg (Kennelly et al., 2009).

The treatment of hypertension and reduction of vascular risk factors have demonstrated neuroprotective effects by re-establishing proper cerebral regulation (Baumgart et al., 2015; Gallway et al., 2017). This result emphasizes the importance of being regularly checked for hypertension and taking an active approach to lowering blood pressure. Additionally, improving cardiovascular fitness will positively impact brain health as well. This can be accomplished through individual behaviors including increasing physical activity and eating a well-balanced, heart-healthy diet.

Diabetes

Individuals with diabetes, both type one and two, are at risk for lower cognitive performance (Baumgart et al., 2015; Gallaway et al., 2017) and their risk nearly doubles for acquiring dementia, VaD, or AD when diagnosed with diabetes in midlife (Guure et al., 2017). Diabetes is a significant risk factor for many types of dementia, especially VaD, because elevated blood glucose levels impact vascular pathways (Baumgart et al., 2015; Gallaway et al., 2017; Wilcox et al., 2009). Excessive blood glucose levels cause systemic inflammation, microvascular disease, and tissue damage. If left untreated, high blood glucose levels may lead to brain cell death or stroke (Baumgart et al., 2015; Gallaway et al., 2017; Rodgers, 2018). Additionally, studies have shown that in individuals who have both MCI and diabetes, MCI is much more likely to progress to dementia (Baumgart et al., 2015).

Sedentary Behavior

Sedentary behavior has emerged as a serious risk factor for overall health and cognition independent of an active lifestyle (Biddle et al., 2016; Genuso, 2013; Harvey et al., 2013; Renzende et al., 2014; Santos et al., 2012). Sitting for prolonged periods of time, despite meeting the minimum physical activity recommendations, can hinder overall health and overall cognitive

function according to recent research (Dogra & Stathokostas, 2012; Gallaway et al., 2016; Santos et al., 2012).

Sedentary behavior is defined as low energy expenditure (less than 1.0-1.5 basal metabolic rate) during wake hours (Harvey et al., 2015; Renzende et al., 2014). Typically, this kind of behavior is classified by both sitting and lying postures, such as watching TV, reading books, or sitting at the computer (Harvey et al., 2015). Sedentary behavior results in reduced functional fitness, poor cognitive function, unhealthy aging, declining strength and balance and the onset of chronic disease (Dogra & Stathokostas, 2012; Harvey et al., 2015; Santos et al., 2012).

Functional fitness is defined as the physiological capacity to perform everyday activities safely and independently without extreme fatigue (Dogra & Stathokostas, 2012; Santos et al., 2012). Older adults who are less sedentary show better functional fitness and are more likely to maintain independence compared to their low-energy expenditure counterparts (Dogra & Stathokostas, 2012). Greater functional fitness contributes to overall well-being, more social opportunities, and greater life satisfaction. More time spent participating in sedentary behavior is related to increased weight, BMI, and waist circumference (Genuso, 2013; Harvey et al., 2015). Furthermore, metabolic-syndrome, obesity, cardiovascular disease, increased blood pressure and glucose levels, and poor cognitive health are significantly linked to a sedentary lifestyle. All of these factors contribute to MCI, dementia, and AD (Biddle et al., 2016; Genuso et al. 2013; Harvey et al., 2015; Renzende et al., 2014).

Epidemiological studies have revealed that over two thirds of the population ages 60 and older are in a low-energy expenditure state for approximately 80% of their awake time (Renzende et al., 2014; Santos et al., 2012). As people grow older, there is a rise in low energy

activities. Increasing age is correlated with more sedentary behavior, which is why the prevalence of risk factors for abnormal cognitive decline also escalates. In the age group 75 years and older the occurrence of sitting eight or more hours is 76.2% (Harvey et al., 2015; Santos et al., 2012). Sedentary behavior is often compounded with other unhealthy lifestyle factors such as consumption of high-calorie foods (Harvey et al., 2015), little to no physical activity, and unhealthy eating. Similarly, Rezende et al. (2014) concluded that sitting more than four hours per day increases a person's risk of being overweight or obese. A sedentary lifestyle is highly influential on physical activity and a healthy diet; therefore, minimizing the amount of sedentary behavior will be an essential measure for maintaining health as one ages (Biddle et al., 2016; Santos et al., 2012).

Genetic Causes

While nonmodifiable, genetic factors need to be taken into consideration when determining one's risk of experiencing cognitive decline. First, genetic predisposition may play a role in one's susceptibility to cardiovascular disease, neurodegeneration, A β plaque build-up, or to the protective effects of physical activity and diet (Gallaway et al., 2017). Second, specific genes, such as apolipoprotein E e-4 (APOE), have been directly associated with AD. The APOE e-4 gene is the strongest and most indicative risk factor for the development of late-onset AD because it plays an important role in A β plaque and clearance mechanisms, tau protein tangle formations, oxidation, and neurotoxicity. This gene accounts for over 95% of all AD cases (Gallaway et al., 2017). The APOE e-4 gene frequency is 19% of the African American population, 13.6% in Caucasians, 11% in Hispanics, and 8.9% in the Japanese population (Gallaway et al., 2017).

However, modifiable lifestyle factors have been associated with the outcome of APOE e-4 allele carriers and their development of AD and dementia. The APOE e-4 allele carriers risk of dementia may be more affected by lifestyle factors such as cardiovascular risk factors and diet. Unfortunately, physical activity does not affect the risk of APOE genotype carriers (Gallaway et al., 2017). This is indicative that adopting a healthy lifestyle can be a preventative strategy to decrease the risk or postpone the onset of dementia among APOE e-4 allele carriers.

Chapter 5: Physical Activity (PA)

Physical activity (PA) is defined as movement of the body that results in an elevated total body energy expenditure, above rest, due to skeletal muscle contraction (Rodgers 2018; Santos et al., 2012; Yuede et al., 2018). PA is an influencing factor for healthy aging,⁷ a lack of PA can lead to various chronic diseases, cognitive decline, inhibited functional fitness, and disability (AA, 2018; Harvey et al., 2015; Renzende et al., 2014; Rodgers, 2018; Rolland et al., 2010; What is Healthy Ageing, 2018). The effects of PA on cognitive decline and dementia have been extensively studied in healthy older adults as well as those with MCI, dementia, and AD (Gallaway et al., 2017; Rolland et al., 2010). According to Guure et al. (2017), PA reduces the risk of developing dementia in people over the age of 65 by 26%.

With age, all older adults experience some degree of decline both physically and cognitively. However, PA can reduce the rate of this decline and help to maintain proper function. There are many other health benefits associated with regularly engaging in PA such as enhancing physical fitness, improving mental health, and altering risk factors that affect cognitive function later in life (AA, 2018; Chapman et al., Rodgers, 2018). More specifically, exercise is associated with improved spatial memory, executive functioning, and connectivity in critical areas of the brain (Chapman et al., 2006; Gallaway et al., 2017; Rolland et al., 2010). PA helps improve these mechanisms by increasing cardiovascular fitness, lowering BMI and obesity, reducing inflammation and reducing insulin resistance, as well as promoting brain growth and cognitive reserve through neurogenesis (Gallaway et al., 2017; Genuso et al., 2013;

⁷ WHO defines Healthy Aging “as the process of developing and maintaining the functional ability that enables wellbeing in older age” (What is Healthy Ageing, 2018).

Hong & Kim, 2010). Studies have found a correlation in older adults between regular exercise and a decreased number of AD biomarkers (Yuede et al., 2018).

Protective Effects of PA on Risk factors

Cardiovascular Fitness and Increased Blood Flow to the Brain. PA helps to improve overall cardiovascular⁸ and cardiorespiratory⁹ health thus reducing the risk of heart disease and hypertension which are prominent risk factors of MCI, AD, and VaD (Cotman et al., 2007; Gallaway et al., 2017; Rodgers, 2018). Improved cardiovascular health may help to maintain a normal blood pressure and to reduce one's risk of hypertension (Rodgers, 2018; Rolland et al., 2010). Extensive evidence has shown that people who already have hypertension can benefit from PA because it can lower systolic and diastolic blood pressure over time (Gallaway et al., 2017; Rodgers, 2018). According to Gallaway et al. (2017), older adults were able to lower their blood pressure by participating in PA for thirty minutes three times per week. For people with cardiovascular disease or hypertension, the U.S. Department of Health and Human Services recommends a minimum of 150 minutes per week of aerobic and muscle-strength training (Rodgers, 2018).

Not only does PA have effects on the body, but it also directly affects the brain. PA helps to maintain cerebrovascular integrity, or the ability of the brain and its blood vessels to maintain full function (Gallaway et al., 2017; Guure et al., 2017). Blood is able to flow to the brain more quickly and efficiently to meet its oxygen and nutrient demands (Gallaway et al., 2017; Guure et al., 2017; Rolland et. al, 2010). Increased blood flow reduces the risks of MCI, AD, and VaD by

⁸ Cardiovascular health refers to the body's ability to pump blood throughout the body more efficiently with each beat.

⁹ Cardiorespiratory health refers to the overall health of the heart, lungs, and blood vessels.

nourishing brain cells. Damage and cell death are limited by helping to remove plaque-causing proteins and by creating alternate routes of blood flow to areas that may be blocked (Gallaway et al., 2017; Rolland et al., 2010). The effects of increased blood flow from PA can be seen during and directly after PA (Rodgers, 2018).

Improving Metabolic Health. Improving metabolic health may be a secondary mechanism by which PA decreases MCI, AD, and VaD and optimizes brain health. Strong evidence shows that PA can reduce the risk of metabolic syndrome and abnormal cognitive decline by preventing type 2 diabetes, controlling blood glucose levels, controlling cholesterol levels and helping to maintain a healthy BMI (Baumgart et al., 2015; Cotman et al., 2007; Gallaway et al., 2017; Rodgers, 2018). In addition to hypertension, glucose intolerance is one of the most crucial components related to cognitive function (Cotman et al., 2007). PA helps to manage blood glucose levels by reducing proinflammatory conditions that promote insulin resistance (Cotman et al., 2007; Rodgers, 2018). For people who already have type 2 diabetes, PA may reduce the progression of the disease. Insulin sensitivity can be improved with a single episode of PA (Cotman et al., 2007; Rodgers, 2018). Exercise also improves cardio-metabolic health (Cotman et al., 2007). Specifically, PA helps to reduce one's risk of being overweight or obese by lowering triglyceride (lipid) levels and controlling blood glucose (Rodgers, 2018).

Mechanisms of PA Effects on Brain Health

Growth Factor Cascade. The benefits of exercise are seen primarily via the cascade of growth factor signaling. This cascade increases synaptic plasticity, promotes structural and functional changes and stimulating neurogenesis. Other benefits of PA include reduction of peripheral risk factors and inflammation. The three main growth factors that mediate the effects of exercise on the brain are brain-derived neurotrophic factor (BDNF), insulin growth factor

(IGF-1), and vascular endothelial derived growth factor (VEGF). BDNF is essential for hippocampal function, synaptic plasticity, learning, and modulating depression.

Increased Synaptic Plasticity. The brain retains the capacity to regenerate new connections and new neurons throughout life (Rolland et al., 2010). PA facilitates this process by stimulating neurogenesis in response to neuronal stress caused by increased physical demands of exercise. These responses boost production of a neurotrophic factor within the brain. This neurotrophic factor is involved in multiple cell signaling systems and is considered to be one of the most critical factors in cell genesis, growth, and neurologic processes (Cotman et al., 2017; Dauncey, 2014; P. Jackson et al., 2016; Rolland et al., 2010). Neurogenesis enhances brain structure and integrity through increasing synaptic plasticity, which prevents deterioration of cognitive and brain function (P. Jackson et al., 2016; Rolland et al., 2010). Several studies have demonstrated greater grey matter in the prefrontal, parietal, and temporal regions in older adults who were more physically active. They also had a higher volume of white matter in the genu of the corpus callosum than their nonactive counterparts (P. Jackson et al., 2016; Rolland et al., 2010).

Additional studies have shown that exercise primarily facilitates synaptic plasticity in the hippocampus, which is essential for learning and memory. PA increases the level of synaptic proteins and glutamate receptors, which contributes to greater intrinsic brain connectivity (Cotman et al., 2007). It also increases the number of growth factors present. Growth factors, such as IGF-1, can enhance plasticity. The benefits of PA are primarily achieved through modulating vascular function and reducing inflammation (Cotman et al., 2017; P. Jackson et al., 2016), which will be discussed later.

Structural Change. Studies have found a link between exercise and fitness in later life and connectivity in the hippocampus and prefrontal cortex. This connection is evidenced by higher volumes of grey matter. Greater amounts of PA have long-term effects of maintaining grey matter volume later into adulthood. One study, in particular, revealed that participants who partook in higher levels of PA had higher grey matter volume in several regions, including the hippocampus, compared to non-active counterparts up to nine years after the study was concluded (Jackson et al., 2016). Maintaining hippocampal volume is vital because atrophy in the hippocampus is linked to AD (P. Jackson et al., 2016). In addition, memory task performance improves as hippocampal volume increases. Engaging in regular amounts of PA of moderate intensity is sufficient to increase the size of the hippocampus throughout one's life (P. Jackson et al., 2016). Similarly, higher cardiorespiratory fitness in cognitively normal adults is associated with greater volume in the hippocampus (P. Jackson et al., 2016).

Increasing Cognitive Reserve. Additionally, participation in PA may lower the risk or impact of cognitive decline and improve brain health by improving cognitive reserve (P. Jackson et al., 2015; Rolland et al., 2010). Reserve refers to the capacity of the brain to maintain function in the presence of damage (for example, neurodegeneration or acute injury) or obstructions by finding alternative ways for the brain to accomplish tasks (Groot et al., 2018; P. Jackson et al., 2015). There are three types of reserve: biological reserve, cerebrovascular reserve, and cognitive reserve. Biological reserve is measured by brain volumes and refers to the structural integrity of the brain. Cerebrovascular reserve refers to the blood vessels of the brain and their ability to maintain proper blood flow in response to stimuli. Lastly, cognitive reserve is the capacity of the brain to operate properly in order to maintain cognitive function by activating alternate neural networks (Groot et al., 2018; P. Jackson et al., 2015). Higher cognitive reserve

may delay the onset of the symptoms associated with clinical manifestations of the dementia; therefore, it is especially important to partake in behaviors such as physical activity to increase reserve and cognitive function. If a person is able to maintain a large cognitive reserve they may not experience the full effects of VaD or AD because the reserve would be large enough to offset the damage (Rolland et al., 2010). Particularly in AD cases, cognitive reserve and biological reserve lessen cognitive symptoms (Groot et al., 2018).

Reduced Inflammation. A common feature of the previously mentioned metabolic syndrome factors is systemic inflammation. Pro-inflammatory cytokines have a deleterious effect on growth factor signaling (Cotman et al., 2007; Rolland et al., 2010). Inflammation especially inhibits IGF-1, which is essential for glucose metabolism, maintaining tissue, cerebrovascular function, angiogenesis, and learning. Low levels of IGF-1 are also directly linked to cognitive impairment (Cotman et al., 2007). PA may counteract the inflammatory pathway and improve growth factor signaling transduction of IGF-1, VEGF, BDNF, and endorphins by reducing pro-inflammatory cytokines (Cotman et al., 2007; Rolland et al., 2010). Overall reduction of inflammation in the brain through exercise can reduce the risk of diabetes, cognitive decline, or further neurodegeneration (Cotman et al., 2007).

Increased Cognitive and Social Engagement. PA additionally provides opportunities to engage in cognitive and social interaction. Studies have shown that people engaging in more cognitively-stimulating social activities reduces the risk of cognitive decline. Physical and social engagement helps to prevent depression, reduces stress, and creates a better perceived quality of life (Gallaway et al., 2016; P. Jackson et al., 2015; Lee et al., 2017; Rodgers, 2018). Depression and stress are known risk factors for dementia and AD. Depression in late life is mainly linked to

AD in APOE carriers (Cotman et al., 2007; Gallaway et al., 2016). Lastly, encouraging social interaction is important in order to prevent isolation and detachment.

Effects of PA on Persons without Cognitive Impairments

For the sake of this study, PA will be broken into two categories: Chronic PA and acute PA. Chronic PA will refer to structured, regimented, and repetitive exercises ranging from high-to-moderate intensity, whereas acute PA will entail leisurely everyday activities that require additional energy expenditure above that of a sedentary level (Yuede et al., 2018). For older adults, 150 to 300 minutes of moderate-intensity PA per week is recommended (Rodgers, 2018).

Chronic Physical Activity. As previously mentioned, chronic PA refers to a structured, repetitive regime of high-to-moderate intensity that is intended to improve physical health over the course of weeks or months (Yuede et al., 2018). For further clarification, chronic PA can be broken down into two groups based upon variables such as intensity,¹⁰ duration,¹¹ and frequency.¹² The first group includes high-to-moderate physical exercise that is designed to improve physiological function through cardiovascular and muscle endurance, increase maximum oxygen consumption, and improve muscle strength. Examples of this type of PA include aerobic activities, weight training, or high-intensity interval training. The second group entails moderate to light exercise that is not enough to change physical fitness such as a daily walk (Yuede et al., 2017). The problem with drawing conclusions this early is that more research is needed to understand by what mechanism these PA-related variables affect cognition (Yuede et al., 2017).

¹⁰ Exercise intensity is referred to how hard the activity feels to an individual person.

¹¹ Exercise duration is the amount of time a person spends participating in one session of physical activity.

¹² Frequency is the number of times per week one participates in exercise.

Aerobic Training. Aerobic activities, as defined by the U.S. Department of Health and Human Services, are those in which people move large muscle groups in a rhythmic manner for a sustained period of time, typically resulting in an increased heart and respiratory rates (Rodgers, 2018). Such activities include brisk walking, jogging, biking, dancing, some yard work, and swimming. Two of the most well-known benefits of aerobic exercise include improving physical and mental health (Gallaway et al., 2016). Physiological benefits of aerobic training include increasing gray matter volume in the hippocampus (Lee et al., 2016), as well as stimulating brain perfusion, cerebral vascular functioning, and angiogenesis (Rolland et al., 2010). Aerobic exercise increases plasticity in the prefrontal and parietal areas of the brain. Both of these regions are involved in executive control (Rolland et al., 2010). Additionally, an active lifestyle contributes to the reduction of stress and cortisol levels (Guure et al., 2017).

According to Guure et al. (2017), older adults over the age of 65 can reduce their risk of developing cognitive decline by 36% if they participate in vigorous PA. Additional studies have shown that when compared to sedentary counterparts, people with higher reported levels of PA throughout their lives show better working memory, vocabulary, and reaction time (Rolland et al., 2010). As demonstrated by Rolland et al. (2010), improved cardiorespiratory fitness, achieved through aerobic exercise, is directly related to an improvement in cognitive capacity, increased brain volume, attention, executive functions, and enhance neural plasticity (Dauncey, 2014; Rolland et al., 2010).

Similarly, a study by Guure et al. (2016) investigated the association between high and moderate PA and the risk of cognitive decline, VaD, and AD. They concluded that high to moderate PA is inversely related to dementia. This corresponds with the overall consensus that cognitive functioning can be sustained by aerobic exercise interventions (Baumgart et al., 2015;

Nijholt et al., 2016; Rolland et al., 2010). Aerobic activity programs may be more beneficial for cognitive health than other types of PA, however, further research is needed.

Resistance Training. Resistance exercise refers to weight lifting and strength training. Examples may include use of resisted exercise bands, hand weights, body weight exercises, carrying groceries, as well as some forms of yoga and t'ai chi. Adults are highly encouraged to do this type of PA at least twice a week in order to achieve health benefits (Rodgers, 2018). A year-long randomized clinical trial found that resistance training programs promoted memory, reduced atrophy in white matter, and increased muscle strength. A two-year follow up suggested that weight training has long-term effects (Gallaway et al., 2016). Reducing the amount of atrophy in white matter volume can promote healthy cognitive function help to prevent cognitive decline and dementia. Cortical white matter volume is especially important for maintaining cognitive function in older adults because dementia is associated with a loss of white matter volume (Gallaway et al., 2016). Further research is needed to understand the underlying mechanisms by which resistance training promotes cognitive function. Variables of interest include both intensity and frequency.

Acute (Light-to-Moderate) Physical Activity. Even light exercise is considered beneficial. There is substantial evidence suggesting that light-to-moderate physical activity shows significant cognitive benefits, especially for MCI (Gallaway et al., 2016; Hong & Kim, 2010). This kind of physical activity can include leisure activities such as walking, gardening, yoga, or doing yard work (Hong & Kim, 2010). Hong & Kim (2010) also state that light walking for 1.5 hours per week provides cognitive benefit.

Reflective Exercise. Yoga and t'ai chi are two reflective exercise therapies that have been studied extensively (Gallaway et al., 2016; Lee et al., 2017; Rodgers, 2018). Many different

practices of yoga exist and they range in physical demand from meditative to power yoga (Rodgers, 2018). T'ai chi is a practice that focuses on simple stretching and toning exercises (Gallaway et al., 2016). This form of exercise can strengthen muscles, improve balance, and physical function (Rodgers, 2018). Both yoga and t'ai chi have been shown to increase global cognition through improved logical memory, working memory, verbal fluency, recall, attention, mood, and increase cerebral blood flow. They have both demonstrated the ability to maintain and enhance cognitive function in people with dementia. When compared to aerobic training they share similar benefits, but more research is needed to determine the extent of their benefits on cognition (Gallaway et al., 2017).

The reason these therapies are so beneficial is that they use the interaction between psychological processes and the nervous and immune systems of the body (Lee et al., 2017; Azar, 2001). These activities promote relaxation and stress reduction, which, in turn decreases the levels cytokines, which are a known cause of cognitive decline (Azar, 2001). Cytokines are substances, such as interleukin proteins and growth factors that are secreted by the cells in the immune system that affect other cells. Interleukins are proteins that regulate immune and inflammatory responses. This inflammatory response can change the expression of genes and alter the course of aging and cognition (Azar, 2001). The immune system is also responsible for sending signals to the brain that may inhibit neural activity, thus altering behavior, thought, and mood (Azar, 2001).

Little-to-no Physical Activity. On the other hand, lack of physical activity nearly doubles the risk for dementia or AD (Gallaway et al., 2016; Hong & Kim, 2010; Lee et al., 2017). Poor scores on fitness tests are a direct indication of poor cognitive functioning. Low physical performance such as walking speed, poor standing balance, and poor grip-strength are

associated with higher rates of cognitive decline and dementia (Rolland et al., 2010). Individuals should remain physically active throughout their life in order to achieve optimal cognitive health as an older adult.

PA Effects for People with MCI, Dementia, VaD, and AD

The Cardiovascular Health Cognition Study states that individuals should participate in PA four times per week to reduce their risk of developing dementia by up to 50% (Gallaway et al., 2016). PA can improve physical and mental status among people with MCI, dementia, and VaD as well as reducing the incidence of cognitive decline (Chapman et al., 2006; Gallaway et al., 2017; Guure et al., 2017). Physical activity has been shown to reduce depressive symptoms among people with AD, to improve behavioral problem, and to improve cognitive status (Chapman et al., 2006; Lee et al. 2016). When compared to their sedentary counterparts, individuals with existing neurodegenerative disorders who participate in PA have much better cognitive scores (Gallaway et al., 2017).

It remains unclear how much physical activity, what type, frequency, and duration is optimally effective in reducing risk of cognitive decline and dementia. However, research has shown the most individuals benefit when a multicomponent approach, that is engaging in different types of PA throughout the week, is taken (Rodgers, 2018; Rolland et al., 2010). Some studies suggest that walking is associated with a decreased risk of cognitive impairment, while other studies argue that vigorous activity is needed in order to produce benefits (Baumgart et al., 2015). The U.S. Department of Health and Human Services recommends aerobic and muscle strengthening exercises for older adults who have cognitive disabilities (Rodgers, 2018). A multicomponent analysis of PA and cognitive decline is necessary. The neuroprotective benefits

of PA such as flexibility training, strength training, endurance, and aerobic training need to be quantified to better show their effects (Rolland et al., 2010).

Fall Prevention. Other added benefits of PA for people who have dementia or AD is that it can facilitate ADLs, reduce the risk of falls, and prevent injuries and disabilities. Falls are a major concern for people with dementia. As cognitive function declines, the risk of falls doubles. Intervention strategies for reducing falls and improving ADLs will help people with cognitive impairments to maintain independence longer (Rodgers, 2018).

How Different Stress Responses Affects Results of Exercise

The circumstances of where, how, and when one participates in PA may determine its effect on cognitive impairment, and more specifically on AD pathology, as with some forms of PA may induce stress in some individuals. Psychological stress is associated with many disorders and may exacerbate symptoms and onset of AD. Mild stress is beneficial, whereas chronic stress can be detrimental to cognitive function. Acute, or mild, stress activates the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS). When these symptoms are targeted, glucocorticoids and catecholamines are released more rapidly. Glucocorticoids and catecholamines initiate the neuroendocrine response, which mobilizes lipids, glucose, and other resources to facilitate cognitive function and meet the physical demand. This may lead to metabolic dysfunction, cardiovascular disorders, and cognitive impairments. Yuede et al. (2018) examined the interaction between physical activity and stress on AD pathology. They compared responses in the context of forced versus voluntary PA. They wanted to know if PA promoted stress resistance or resilience in AD pathology and at what threshold these effects occurred (Yuede et al., 2018). They also wanted to know if factors such as intensity, duration, and type of exercise matter. Acute stress is not tied to an increased metabolic demand and these

neuroendocrine responses provide a healthy response. However, under chronic stress conditions the neuroendocrine system is activated for a prolonged period of time, which may cause resilience to cognitive decline (Yuede et al., 2018)

Chapter 6: Nutrition, the Brain and Cognition

Nutrition is especially important when it comes to maintaining brain health, normal physiological functioning, as well as neurological protection from cell injury and oxidative stress. Extensive research has concluded that there is a direct link between diet, nutritional status, and cognitive function. Dietary factors not only influence one's risk of developing dementia, but also the rate at which cognitive decline progresses clinically (Gillette-Guyonnet et al., 2013; Jackson et al., 2015; Marcason, 2015; Morris, 2016; Nijholt et al., 2016; Vandewoude et al., 2016). Some forms of dementia can be reversed through timely intervention, such as those caused by vitamin deficiencies (Chapman et al., 2006). Adopting a lifestyle that uses food to fuel the brain and body is essential in order to maintain neurological function, prevent degeneration, and slow the aging process (Dauncey, 2014; Vandewoude et al., 2016).

There is uncertainty within the research as to whether specific nutrients, a regimented dietary pattern, a healthy body mass index, or if a combination of all these factors has the greatest impact on cognition. There is a debate because of the multifaceted dynamics that occur across the lifespan that may influence brain function. Although the data are ambiguous, the existing research is extremely important due to the absence of curative treatments (Marcason, 2015; Nijholt et al., 2016; Vandewoude et al., 2016).

Micronutrients

Previous research has focused on the role that individual nutrients play in dementia and AD. It is, of course, important to avoid nutritional deficiencies throughout early, middle, and late life in order to maintain optimal cognitive health. Epidemiological data suggests that there are specific micronutrients that play a protective role in brain health (Wilcox et al., 2009). There are varying mechanisms by which these micronutrients may act as neuroprotective agents. For

example, they may stimulate the immune system, monitor cholesterol synthesis, hold antioxidant properties, or modulate detoxifying enzymes (Leof & Walach, 2012). Some of the researched micronutrients discussed here include antioxidants, B vitamins, vitamin C, polyphenols, carotenoids, and polyunsaturated omega-3 fatty acids such as fish (Gillette- Guyonnet et al., 2013; Leof & Walach, 2012; Morris, 2016; Wilcox et al., 2009).

Antioxidants. Oxidative stress causes an accumulation of intracellular damage, due to uncontrolled reactive oxygen. Aged tissues are especially vulnerable to oxidative stress and functional impairment is more likely to occur in older individuals. For this reason, oxidative stress is one proposed cause of the development of dementia and AD (Gillette- Guyonnet et al., 2013; Leof & Walach, 2012). Researchers have examined the ability of antioxidants to combat a variety of neurodegenerative disorders leading dementia. A balanced combination of several antioxidants may be able to reduce the risk of dementia or delay its onset (Chapman et al., 2006; Nijholt et al., 2016). Antioxidants have the ability to upregulate¹³ the levels of circulating brain derived neurotrophic factor (BDNF). BDNF plays a key role in synaptic plasticity. However, it is still not clear whether supplemental or dietary intake of these compounds is most beneficial and at what levels. The most common antioxidants include vitamin E, C, A and beta-carotene (Chapman et al., 2006; Gillette-Guyonnet et al., 2013).

Vitamin E. Vitamin E is essential for brain function and has demonstrated specific neuroprotective effects. Vitamin E is inversely related to the risk of AD and may slow the progression of the disease (Chapman et al., 2006; Gillette-Guyonnet et al., 2013; Leof & Walach,

¹³ Upregulation is the process by which a cell increases the quantity of a cellular component, such as a certain protein, in response to an external stimulus.

2012). Compounds within Vitamin E have both antioxidant and anti-inflammatory properties that help combat oxidative stress and inflammation, two proposed pathologies of AD (Chapman et al., 2016). Vitamin E is also a regulator of signal transduction and gene expression. The idea that vitamin E can be used as both therapy and prevention for AD is supported by clinical and epidemiological observations (Vandewoude et al., 2016). However, Gillette- Guyonnet et al. (2013) state that a combination of several antioxidant nutrients may be more beneficial in preventing cognitive decline or dementia than the consumption of one antioxidant.

Vitamin C. Vitamin C is primarily found in fruits and plays a vital role in combination with vitamin E. Vitamin C acts as a co-antioxidant for vitamin E, meaning that it helps to reduce vitamin E radicals and restore its full antioxidant capacity (Leof & Walach, 2012). Evidence from cross-sectional studies has demonstrated a positive outcome of increased vitamin C levels on cognition by measuring plasma concentrations in the brain (Vandewoude et al., 2016). However, the role of vitamin C in preventing cognitive decline is still in question and further studies are needed to confirm the benefits of supplementation concerning brain health.

Carotenoids and Flavonoids. Carotenoids and flavonoids are both antioxidants (Gillette-Guyonnet et al., 2013; P. Jackson et al., 2015). Carotenoids are natural fat pigments found in fruits, vegetables, and fish that have a beneficial impact on brain health (Gillette-Guyonnet et al., 2013; Leof & Walach, 2012). There is a large variety of carotenoids, however, only a limited number of them have been found to be clinically significant (Gillette-Guyonnet et

al., 2013). Flavonoids are one classification group of polyphenols.¹⁴ They are found in foods such as fruits, vegetables, chocolates, and in drinks such as wine and tea. Flavonoids are chemically diverse and can be divided into six subgroups. Carotenoids and flavonoids are diverse and have many neuroprotective benefits, such as reducing inflammation, combating oxidative stress, and promoting vascular function. They also improve functions such as cognitive performance, memory, and attention (Leof & Walach, 2012; P. Jackson et al., 2015; Vandewoude et al., 2016).

One naturally occurring antioxidant and flavonoid that has been extensively studied is Ginkgo biloba. The Ginkgo Evaluation of Memory (GEM) is a large study that has conducted randomized controlled trials and has conducted extensive research to analyze the accuracy of neuroprotective effects of naturally occurring flavonoids such as Ginkgo biloba. It is still inconclusive on the specific effects that Ginkgo biloba has on cognitive health and further research is needed to determine the clinical significance (Gillette-Guyonnet et al., 2013; Wilcox et al., 2009).

Vitamin B. B vitamins are chemical compounds that the body cannot synthesize naturally; therefore, a diet rich in vitamin B is beneficial. Vitamin B is an organic, water-soluble compound that plays a key role in cell metabolism and is essential for optimal growth and physiological function (Dauncey, 2014; Gillette-Guyonnet et al., 2013; Vandewoude et al.,

¹⁴ Polyphenols are a large class of chemical compounds that can be divided into several groups (one of which is represented by flavonoids). They have antioxidant, anti-inflammatory, anti-carcinogenic, and may protect from oxidative stress and some diseases (P. Jackson et al., 2015; Vandewoude et al., 2016).

2016). There are eight chemically distinct types of vitamin B. Vitamins B6, B9 (folate), and B12 have been linked with neuroprotective qualities. Vitamins B9 and B12 play essential roles in the metabolism of DNA and protein synthesis. A deficiency in these vitamins can be detrimental to cognitive function. A deficiency in folate and B12 causes homocysteine levels to rise. An increased level of homocysteine is inversely related to cognitive performance and is a known risk factor for dementia and cognitive impairment (Vandewoude et al., 2016). This is because increased homocysteine levels may contribute to neuronal death due to amyloid and tau protein accumulation and neurotoxicity (Gillette-Guyonnet et al., 2013; Vandewoude et al., 2016). Homocysteine also stimulates apoptosis, platelet activation, and proliferation of smooth muscle cells, which contributes to white matter lesions, vascular injury, and changes in the brain (Gillette-Guyonnet et al., 2013). Studies have shown that these changes are negatively correlated with neuropsychological test scores (Vandewoude et al., 2016).

Low concentrations of folate, B6, and B12 may be associated with impaired cognition and risk of dementia, whereas high levels of B6 are associated with better attention, executive function scores, and overall cognition scores. B vitamin deficiency is a reversible cause of dementia. If proper B vitamin supplementation is received, then cognitive function will be restored. When levels of B vitamins are stabilized, neuroprotective effects include reduced blood homocysteine levels, slowed shrinkage of total brain volume, and reduced cerebral atrophy in gray matter regions (Gillette-Guyonnet et al., 2013; Vandewoude et al., 2016). However, further research is needed to understand the effects of supplementation on individuals with and without mild to moderate cognitive decline.

Vitamin D. Vitamin D is important for brain development and function throughout the lifespan. Low levels of vitamin D are associated with increased odds of dementia and AD

(Dauncey, 2014; Vandewoude et al., 2016). Vitamin D has neuroprotective factors such as the production of nerve growth, neurotrophin, and nitric oxide synthase. Gillette-Guyonnet et al. (2013) suggested that low concentrations of Vitamin D are associated with cognitive decline and has been found to predict the onset of dementia within seven years (Gillette-Guyonnet et al., 2013). Not only is vitamin D necessary for the treatment and prevention of cognitive dysfunction, but it is also beneficial for muscle function, cardiovascular health, diabetes, and cancer prevention. Vitamin D deficiency plays a significant role in the development of many age-associated diseases aside from cognitive dysfunction. Vitamin D deficiency should be supplemented regardless of cognitive health because it can reduce one's risk of developing some types of cancer and helps to prevent heart disease, type 2 diabetes, and stroke (Vandewoude et al., 2016).

Omega-3 Fatty Acids. The brain accumulates omega-3 polyunsaturated fatty acids (PUFAs) in order to maintain the cellular membranes in various brain structures, which directly correlates to better global cognition and memory function. Omega-3 PUFAs allow these brain structures to conduct normal cell signaling, modulate transmembrane transport, manage inflammatory processes, and mediate oxidative stress (Gillette-Guyonnet et al., 2013; Jackson et al., 2015; Vandewoude et al., 2016). The primary fatty acids that are beneficial to the human body include eicosatetraenoic acid (EPA) and docosahexaenoic acid (DHA) (Vandewoude et al., 2016). Together, EPA and DHA attenuate the inflammatory response by suppressing pro-inflammatory pathways and reducing oxidative stress (Jackson et al., 2015). DHA is predominantly found in the central nervous system and is responsible for maintaining the integrity and neuronal function through neurogenesis. Increased neurogenesis impacts plasma membrane function, synaptic plasticity, and transmission, in addition to improved cellular

signaling. As a result, higher levels of DHA is associated with improved recognition memory and lower rates of incident dementia (Gillette-Guyonnet et al., 2013; Jackson et al., 2015). Fish is the main dietary source of both EPA and DHA.

Macronutrients

According to Vandewoude et al. (2016), there is insufficient evidence to recommend the use of a specific food for supplementation to reduce the effects of cognitive decline. This is because it is highly unlikely that a single macronutrient plays a major role in cognitive decline due to the complexity of nutrient consumption and cognitive decline (Gillette-Guyonnet et al., 2013). However, there are specific dietary components that hold nutritional value and may play a protective role. The assimilation of different chemical and nutrients in whole foods may cause synergistic health benefits (Leof & Walach, 2012; P. Jackson et al., 2015). Such foods include fish, fruits and vegetables, nuts, berries, beans, whole grains, poultry, extra virgin olive oil (EVOO) and wine (Hong & Kim, 2010; Marcason, 2015).

Fish. Fish has protective effects on cognition because it is high in vitamin D and omega-3 PUFAs (DHA and EPA), which is believed to exert beneficial effects against the pathology of AD (Hong & Kim, 2010; Leof & Walach, 2012; P. Jackson et al., 2015; Nijholt et al., 2016). A seven-year study revealed that older adults who consumed at least one fish meal per week had reduced cognitive decline (Vandewoude et al., 2016). This reduction may be a result of decreased white matter damage and grey matter atrophy associated with higher circulating levels of omega-3 PUFAs (P. Jackson et al., 2015).

Fruits and vegetables. Fruits and vegetables have high levels of antioxidants and polyphenols, which are believed to protect against neuronal damage (Hong & Kim, 2010; Jackson et al., 2015; Nijholt et al., 2016). Vegetable consumption, in particular, is associated

with significant protective effects against cognitive decline because of their high levels of vitamin E and C, carotenoids, polyphenols, and folate (Morris, 2016; Trichopoulou et al., 2015; Vandewoude et al., 2016). In their systematic review, Leof and Walach (2012) summarized their findings from nine different studies examining the effects of fruit and vegetable consumption on the risk of dementia and age-associated cognitive decline. Overall, frequent consumption of vegetables, especially cruciferous, legumes, and green leafy vegetables, showed the strongest protective effect. Consistently, the nine studies found that, with a high vegetable intake, the rate of cognitive decline was slower. There was a decreased risk of MCI, dementia, and AD, better ADL functioning, and a smaller decline in informational processing speed as well as global cognitive functioning (Leof & Walach, 2012). A 4.7-year study conducted at Rush University, called the Rush Memory and Aging Project, discovered that individuals, aged 58-98 who consumed 1-2 servings of leafy greens per day, as compared to individuals who rarely or never ate them, cognitively performed at a level that reflected an age eleven years younger than their actual age (Morris, 2016).

The protective properties of fruits on cognitive decline are still controversial and further research is needed. Leof and Walach (2012) were unable to associate fruits with cognitive decline. However, some data suggests that an equal ratio of fruits and vegetables is needed in order to maintain a balanced diet. Fruits help to enhance the beneficial effects of vitamin E, dietary fiber intake, vitamin C levels, B-carotenoid levels, and monosaccharide levels (Leof & Walach, 2012; Jackson et al., 2015; Morris, 2016). Some fruits, in particular, have added benefits that do correlate to memory performance. For example, berries such as strawberries, blueberries, and blackberries are high in polyphenols and have been shown to delay cognitive aging by over

two years. Blueberries in particular have specific properties that help to indirectly reduce oxidative stress and inflammation as well as maintain neuronal plasticity (P. Jackson et al., 2015)

Legumes, grains, and nuts. Legumes, cereal, and some nuts are foods that have a low glycemic index (GI).¹⁵ This means that these carbohydrates have a minimal impact on blood glucose levels. Foods with a low GI value (55 or less) are digested at a slower rate than foods with a higher GI. Because the foods are digested at a slower rate, they are absorbed and metabolized slower as well. This allows for a slower rise in blood glucose levels. Foods that are less likely to cause dramatic spikes in blood sugar levels are beneficial to overall health because they reduce one's risk of being overweight, experiencing insulin resistance, or developing type 2 diabetes. Additionally, nuts increase levels of vitamin C and E, carotenoids, polyphenols, long-chain polyunsaturated fatty acids (Vandewoude et al., 2016).

EVOO. EVOO and wine provide a surplus of polyphenols while EVOO also provides a rich source of monounsaturated fatty acids (Tangney, 2014; Vandewoude et al., 2016). Moderate alcohol consumption may protect against dementia and is associated with higher cognitive functioning in later life by enhancing insulin sensitivity, lowering the inflammatory response, reducing the risk of stroke, coronary heart disease, and type 2 diabetes, and preventing oxidative damages to the brain (Vandewoude et al., 2016).

Red wine. Red wine, specifically, has polyphenols that are thought to be responsible for its cognition preserving effects and brain health. The particular polyphenol found in red wine has antioxidant properties to protect against oxidative stress (Hong and Kim, 2010; Vandewoude et al., 2016) as well as anti-inflammatory and antiviral components (Jackson et al., 2015). These

¹⁵ The Glycemic Index refers to how carbohydrates are ranked relative to their effect on blood glucose levels.

effects are protective against the development of both cancer and cardiovascular disease and play a role in improving insulin sensitivity (P. Jackson et al., 2015). Not only do these effects increase longevity but they also show potential for preserving brain health. Additionally, polyphenols found in the skin of red grapes have the ability to increase perfusion¹⁶ of A β protein plaques that are related to AD. This increases the rate at which the A β proteins pass through the circulatory system which prevents them from clogging important vasculature. The term alcohol moderation varied significantly from one to two drinks per week to one to two drinks per month in the reviewed studies. There was, however, a consensus that positive effects of alcohol are not seen in heavy drinkers. Therefore, alcohol consumption in moderation is important because chronic alcohol consumption is closely associated with many neurodegenerative diseases (Hong and Kim, 2010; Vandewoude et al., 2016). Individuals who do not already drink should not start in order to delay cognitive decline because of the increased risk of falls among older adults.

As more research is done on nutrition and cognitive decline, the literature has moved from focusing on specific foods and towards examining whole dietary patterns and regimented diets (Lee et al., 2017; Marcason, 2015).

Regimented Diets

Dietary patterns have gained prominence because of accumulating evidence that combinations of beneficial nutrients can synergistically provide stronger benefits to cognition than individual nutrients can (Lee et al., 2017; Marcason, 2015; Nijholt et al., 2016; Trichopoulou et al., 2015). Proposed ways that diet can maintain age-appropriate cognition is

¹⁶ Perfusion is the passage of fluid through the circulatory or lymphatic system to an organ or a tissue. In this case,

through enhanced neurotransmitter¹⁷ activity and improved synaptic plasticity through consuming various combinations of folic acid, plant extracts, and antioxidants through regimented dietary patterns. Correspondingly, the Alzheimer's Association recommends a heart-healthy diet, for people who have dementia and to those who do not yet have any clinical symptoms, as a modifiable lifestyle factor that has a positive effect on cognition. A heart-healthy diet includes limiting intake of sugar and saturated fats and consuming fruits vegetables and whole grains (AA, 2018). The Dietary Approach to Stop Hypertension (DASH) diet, the Mediterranean diet, and the newly integrated Mediterranean-DASH diet intervention for neurodegenerative delay (MIND) diet have been studied with specific reference to brain health and are recommended by the Alzheimer's Association (AA, 2018; Lee et al., 2016; P. Jackson et al., 2015; Marcason, 2015; Morris, 2016; Tangney, 2014; Trichopoulou et al., 2015).

The Mediterranean Diet. The Mediterranean dietary pattern is characterized by high consumption of whole and minimally processed grains, fruits and vegetables, (EVOO), fish, and a regular but modest intake of wine or alcohol. Limited amounts of poultry, low-fat milk and dairy are also included (AA, 2018; Marcason, 2015; Morris, 2016; Nijholt et al., 2016; Tangney, 2014; Trichopoulou et al., 2015; Vandewoude et al., 2016;). Numerous studies have determined that the Mediterranean diet offers several positive effects to enhance cerebral function and provides neuroprotective effects, such as increasing reserve within the brain and cerebrovascular domain to maintain cognitive function (P. Jackson et al., 2015). Trichopoulou et al. (2015) monitored a cohort of 400 older men and women living in a Mediterranean country for a period of seven years and found that individuals who most closely follow the Mediterranean diet

¹⁷ Neurotransmitters are able to enhance of function of mature neurons and promote the production of new neurons (Hayden et al., 2017).

guidelines have improved performance on the mini-mental state examination (MMSE). They concluded that the Mediterranean diet is inversely related to cognitive decline. Moreover, evidence from epidemiological studies and clinical trials suggests that the diet also reduces the risk of developing cancer, cardiovascular disease and diabetes, stroke, vascular disease, and was associated with a lower incidence of all-cause mortality (P. Jackson et al., 2015; Tangney, 2014; Trichopoulou et al., 2015; Vandewoude et al., 2016). Adherence to the Mediterranean diet can reduce the risk of stroke by 46% according to the PREDIMED¹⁸ study (P. Jackson et al., 2015). The Mediterranean diet has other known benefits, such as anti-inflammatory effects, as noted by Hayden et al. (2016) in their research with inflammatory biomarkers in blood plasma. The anti-inflammatory effects may be facilitated by a high intake of omega-3 fatty acids and large antioxidant intake (P. Jackson et al., 2015; Vandewoude et al., 2016). Another benefit of the Mediterranean diet is better cognition and memory function in older adults. It is believed that specific components of the Mediterranean diet, fatty acids, in particular, are significant for brain health (P. Jackson et al., 2015).

The DASH Diet. The DASH diet emphasizes consumption of low-fat dairy products, fruits, vegetables, whole grains, fish, poultry, beans, seeds, and nuts. The diet limits sodium and added sugar as well as red meat (AA, 2018; Marcason, 2015). The DASH dietary guidelines restrict sodium intake, sweets and candy, and saturated fats (Morris, 2016). The DASH diet is most commonly known for lowering blood pressure through its protective effects lowering low-density lipoprotein (LDL) cholesterol levels, decreasing the risk of obesity, minimizing oxidative

¹⁸ Primary Prevention of Cardiovascular Disease with a Mediterranean Diet

stress and inflammation, and improving insulin sensitivity (Morris, 2016). The DASH diet has been proven to protect against hypertension and cardiovascular disease as well (Vandewoude et al., 2016). Many different trials have provided promising evidence that adherence to the DASH diet leads to better overall cognition, reduced risk of dementia, and improved psychomotor speed when compared to non-DASH diet participants (Morris, 2016).

The MIND Diet. Rush University created the MIND diet, a combination of the Mediterranean diet and the DASH diet, to address the gaps in the types and quantities of foods shown to protect against neurodegeneration in the other two diets. The DASH diet possesses modifications based on the most up-to-date scientific evidence on foods and nutrients that protect the brain. All three diets fundamentally emphasize natural, plant-based foods, limited animal products, and reduced intake of foods with high saturated fat content (Morris, 2016). Unique to the MIND diet is the promotion of berries and leafy green vegetables consumed in high quantities. In addition, there are the eight brain-healthy food groups: nuts, beans, whole grains, fish, poultry, other vegetables, EVOO, and wine (Marcason, 2015; Morris, 2016). Green leafy vegetables are emphasized because, as previously mentioned, they have demonstrated the most potent protective effects against cognitive decline. The guidelines for the diet are eating three servings of whole grains, a salad, one additional serving of vegetables, and one glass of wine each day. Nuts are encouraged as snacks. Poultry is recommended two times a week and fish is recommended once per week. The serving sizes are based on the evidence of other prospective studies. Lastly, the MIND diet discourages the consumption of red meats, butter, margarine, cheese, pastries, and sweets as well as fast or fried food (Marcason, 2015).

The MIND diet is associated with a slower decline in overall cognitive function when compared to the Mediterranean and DASH diet (Lee et al., 2017; Marcason, 2015; Morris,

2016). Research done at Rush University Medical Center found that the MIND diet lowered the risk of AD by 53% in participants who strictly followed the diet, and those who loosely adhered to the diet saw a 35% risk decrease (Marcason, 2015; Morris, 2016).

AD and Nutritional Status. The development of dementia and AD is a long-term process; therefore, both prevention and intervention are imperative. Intervention is crucial during the early stages of AD because the relationship between nutritional status and cognitive function grows increasingly complex as the disease progresses (Vandewoude et al., 2016). Levels of nutrients play a specific role in the pathophysiology of AD and malnutrition is an established feature of the disease in later stages. Several studies have determined that there is an association of low circulating levels of vitamin B, C, E, choline, and long chain omega-3 fatty acids nutrients in people who have AD as compared to their healthy counterparts (Vandewoude et al., 2016).

Various factors contribute to lower nutrient status in AD including inadequacies in food choices, an altered metabolism, and increased consumption of nutrients by the brain. This results in an inadequate intake of nutrients. When signs of malnutrition are indicated through weight loss and biomarker tests, intervention with oral nutritional supplements becomes instrumental for maintaining health and cognition (Vandewoude et al., 2016). Weight loss is typically associated with the later stages of AD. Weight loss and malnutrition affects 15% to 45% of patients with AD. Unfortunately, weight loss and undernutrition also accelerate the progression of AD (Vandewoude et al., 2016). Therefore, it is especially important to take the proper steps to make sure that people with AD do not become undernourished or malnourished. Malnutrition increases the severity of symptoms.

Chapter 6: Public Health and Surveillance

There is an increasing prevalence of people living with dementia and AD worldwide (Mrak, 2007). Despite the extensive research over the past decade, the cause of AD is still unclear. It is understood that AD is caused by a combination of factors, some of which may be modifiable (AA, 2018). While there currently is no cure, research has provided insight regarding early interventions and possible modifiable risk factors associated with cognitive decline (Dubois et al., 2016). As the prevalence of dementia and AD continues to grow, understanding the connection between cognitive risk and protective factors will become a major public health challenge (AA, 2018). Public health approaches need to be taken to promote an active physical lifestyle and heart-healthy diet in order to reduce the risk of cognitive decline.

Public health is defined as “the science and art of preventing disease, prolonging life and promoting health, and efficiency through organized community effort” (AA, 2018). In the past, public health efforts have produced notable health outcomes on many conditions. State and local health agencies can play a significant role in the implementation of cognitive health initiatives. Education is one of the most critical areas to focus on. Currently, an essential component of public health is The Healthy Brain Initiative: The Public Health Road Map for State and National Partnerships (2018-2023). This coalition was formed by the National Institute on Aging, the Administration on Aging, the Center for Disease Control and Prevention, and the Alzheimer’s Association as one of the most significant efforts to advance cognitive health (AA, 2018). The core areas of focus in the roadmap are to educate and empower the public, develop policies and mobilize partnerships, assure a competent workforce, and monitor and evaluate national and state data (AA, 2018).

Surveillance is the systematic collection, analysis, interpretation, and distribution of health-related data. In order to effectively implement changes and target vast populations

surveillance is one of the most beneficial tools used by public health professionals. This is because surveillance provides essential data to assess the prevalence and risk factors for health conditions and applies to a broad population while also identifying limitations in resources (AA, 2018).

Selecting appropriate surveillance methods for cognitive decline poses some unique challenges. One such challenge is defining the criteria for cognitive decline and which diagnostic tools will be used. Distinguishing between age-related changes in cognition, MCI, and dementia is a difficult process in itself because of the unconventional diagnostic process. The next challenge is how to accurately measure the severity of cognitive impairment. Knowing the severity of impairment is crucial in order to plan for future public health care needs, services, and family education.

Surveillance methods for cognitive health also differ from most other surveillance designs. They will require long-term follow up procedures to accurately appraise the effectiveness of interventions on the progression of cognitive decline. The reason for additional long-term follow up procedures is that self-reported data, in this case, may be inaccurate. When a person experiences a cognitive impairment of any kind their reality is altered, which may affect the way that they answer questions on self-reported tests. The most accurate data will be obtained through a physician's evaluation, neurological testing, or a report from a caretaker on perceived changes in cognition.

Additionally, the variety of risk factors associated with cognitive decline imposes a challenge in choosing surveillance criteria (AA, 2018). It is understood that an active lifestyle and a heart-healthy diet contribute to overall vascular health. However, there are many small components within those larger categories to evaluate. Dementia and AD are multifaceted

problems that will require careful planning and a thorough understanding of current research in order to choose which specific factors to survey.

The development of appropriate surveillance systems will be possible with the proper research and the development of clearly defined goals of public health professionals. Goals of the surveillance system should include defining the burden of cognitive decline in the population, as well as monitoring trends in risk factors, such as diet and exercise. The burden of dementia is caused by the progressive worsening of cognitive function that impacts memory, causes personality changes, and impedes basic activities of daily living (ADLs) Both mental and physical health can have profound implications on a person's ability to perform ADLs (AA, 2018).

One's ability to perform ADLs on their own is one of the most relevant determinants of independent living. Older adults with significantly impaired cognition may be unable to engage in necessary everyday tasks, ultimately leading to total dependency. As a society, we must anticipate the significant increase in health care demands that will result from the projected increase of dementia and AD within the next two generations. If appropriate action is not taken, the increased health care needs will place a burden on society as a whole with regard to long-term care needs, public health policy, and impact on caregivers (AA, 2014).

The second goal of the surveillance system should include addressing trends in protective factors, such as diet and exercise. According to the Alzheimer's Association, one of the biggest misconceptions is that cognitive decline is an inevitable and irreversible part of the aging process (2018). New research is determining that in a healthy brain, no matter one's age, there is nerve cell regeneration, as well as the new formation of synapses until death. While there is no treatment for dementia, there are recommendations regarding identified risk factors that, if

modified, may have a protective effect that prevents further cognitive decline. Some risk reduction methods that have been recommended by the Alzheimer's Association include improving cardiovascular function, increasing physical fitness, and eating a heart-healthy diet. Once a successful surveillance system is in place and the proper data is collected, then it will be possible to monitor progress and inform public health policymakers. Public health policymakers are the ones responsible for the implementation of improved healthcare systems, public education, new community programs, and behavioral programs.

Chapter 7: Conclusion

An important facet of public health and healthcare delivery is to determine the prevalence of, risk factors for, and potential interventions to prevent cognitive decline in order for individuals to maintain independence. By the year 2050, 22% of the world's population will be 65 years or older (Renzende et al., 2014). As the life expectancy of the worldwide population continues to rise, the prevalence of dementia cases will rise as well. The World Health Organization (WHO) estimates that every year 7.7 million new cases of dementia are diagnosed worldwide (Gallaway et al., 2017) and it is estimated that, by the year 2050, 131.5 million people will be living with dementia. Sixteen million of those cases will be in the United States (Lee et al., 2017).

Evidence from studies reveals that nearly a third of Alzheimer's disease cases may be attributable to lifestyle factors that are modifiable (Ngandu et al., 2015). Several modifiable risk factors for cognitive decline have been identified, such as low education, midlife hypertension, obesity, diabetes, physical inactivity, smoking, depression, and an unhealthy diet (Ngandu et al., 2015). In the absence of a disease-modifying cure and in the case of an increased prevalence of dementia, reducing risk factors associated with developing dementia will become more important. Doing so will minimize the burden of cognitive decline on our health, political, and economic systems (Baumgart et al., 2015; Marcason, 2015).

Potential interventions include early detection, treatment of underlying conditions, and providing needed services. It is essential that individuals recognize their symptoms in the earliest stages of the disease in order to optimize their health and possibly prevent further damage. Therefore, timely recognition and intervention are key to optimal care of older adults with dementia. Services are also a necessary intervention and because the symptoms of dementia are

distributed along a continuum, services offered need to be flexible. Services will help to maintain health and quality of life for both the patient and their caregiver. Examples of services include adult day care and respite services (Chapman et al., 2006). For these interventions to happen, public health officials need to take action with a delineated approach to emphasizing cognitive health among older adults (Anderson and Egge, 2014).

Moving forward, public health plans should adhere to the Healthy Brain Initiative Road Map (2018-2023). This map is an updated version of previous guides that have been instrumental to public health campaigns and public surveillance. Following the Healthy Brain Initiative Road Map, public health should focus on four domains. The first domain entails educating the public about brain health and cognitive aging with the most current information. It is important to educate not only the aging population but also the younger generations so that they can take the necessary steps to age well and prevent abnormal cognitive decline. Education should include the benefits of early detection of cognitive impairments, evolving diagnostic methods, associated risk factors to avoid, and lifestyle changes that can be made through diet and exercise to promote healthy cognitive aging. Public health can help to educate the public on what we already know about preventative measures such as PA and diet.

In summary, non-pharmacological interventions such as PA and a healthy diet hold promise as effective, low-cost, and adaptable strategies for people with neurodegenerative conditions. PA is important for the prevention of chronic diseases and maintaining functional fitness and may help to lower the risk of some types of dementias (AA, 2018; Rodgers, 2018). Moderate intensity aerobic exercise, resistance training, stretching, toning, and t'ai chi may yield cognitive benefits in older adults. However, the exact mechanism by which PA decreases the risk for dementia is unknown. The benefits of PA may be a direct result of the activities themselves,

or they may be due to the overall benefit of a healthy lifestyle. Proposed mechanisms by which PA improves cognition are improved cerebral blood flow, reduction of cerebrovascular disease, stimulation of neurologic activity, such as synaptic plasticity, secretion of trophic factors, neurotransmitter synthesis, and neurogenesis. PA also reduces toxic stress hormones, such as cortisol, which helps to reduce systemic inflammation.

Additionally, diet has a significant impact on cognition. Maintaining a good nutritional state is imperative for both prevention and intervention. Healthy eating starts with proper food choices. Adhering to a specific, regimented diet, such as the Mediterranean diet, DASH diet or MIND diet is recommended because they promote adequate intake of the proper macronutrients and micronutrients. Nutritional deficiencies should be avoided because they can increase one's risk of developing dementia as well as the rate at which it progresses (Vandewoude et al., 2016). Public health campaigns should focus on teaching the population what to look for at the grocery store, restaurants, or workplace.

Multiple studies conclude that while PA and a heart-healthy diet have health benefits on their own, a multidomain intervention strategy should be implemented because of the complex nature of neurodegeneration. Multiple factors can influence brain function throughout one's life and enhance neuroprotective effects (Gillette-Guyonnet et al., 2013). Public health campaigns need to consider the fact that risk factors can change over time and target current epidemics. For example, in our current generation we have seen many changes in our dietary patterns and activity levels. In the United States, the general population faces difficulty with diabetes and obesity due to the massive amounts of added sugar to our food as well as living a predominantly sedentary lifestyle. Sedentary behavior has created a new public health challenge. Along with the

promotion of PA, campaigns need to emphasize the importance of taking periodic breaks to stand up and move around (Renzende et al., 2014).

The second domain consists of developing policies and partnerships to promote brain health. With many new studies emerging, entities should be encouraged to use the best available data concerning brain health. Additionally, public health figures should highlight the areas that need more research to help direct future studies. By addressing the gaps, public health will guide new studies and clinical trials. Policymakers should be informed on the basics of cognitive health and understand the implications that cognitive decline will have on our society in the future if action is not taken.

As previously mentioned, the impact of dementia on our communities, nation, and the world as a whole will be tremendous. Small interventions will make a big difference in the amount of care needed, financial burden, and resources demanded. MCI, dementia, and AD are all progressive disorders that cause neurodegeneration. These changes result in a diminished quality of life, such that erodes functional abilities and eventually causes total dependence. Caregivers play a vital role in the well-being of people with dementia. They help them with nutrition, exercise, and ADLs. Unfortunately, most caregivers are family members that are untrained. Caregiving takes an enormous emotional and financial toll on them. Depression is very commonly associated with caregivers as they are challenged to handle problematic behaviors associated with dementia and AD. These problems cause caregivers to discontinue home care and increases the need for professional care (Chapman et al., 2006; Vandewoude et al., 2016). With this being said, the increased prevalence of dementia and AD will amplify the need for care and services. Not only will this burden put stress on public health policy, but it will be one of the biggest public health challenges within the next several decades. Public health can

diffuse the situation by encouraging care planning and training caregivers. Educating caregivers and helping them to understand the current research will allow them to give better care to their loved one or patient, and they may be inspired to implement the dietary and activity changes in their own lives. Such behavioral changes could lead to improved nutritional status and health for both the person with dementia and the caregiver. Public health officials and healthcare professionals need to educate the public on factors such as being physically active, eating a heart-healthy diet, and improving cardiovascular related health problems. This can be done through various health campaigns, promotional programs, and through media outlets are low cost, low risk, and could potentially be a highly successful intervention (Baumgart et al., 2015).

In order to successfully put this education platform into place, we must first understand what the public already knows. This can be done by looking at and replicating previous studies that have examined what the general population knows about cognitive decline and dementia. These studies highlight the areas that public health needs to target by revealing the disconnects, misconceptions, and misunderstandings. In other words, we can see where promotion and education are strong and where they are lacking.

A study by Cations, Radisic, Crotty and Laver (2018) aimed to compare the general consensus of the public's understanding in Europe, the U.S., Eastern Asia, and Australia of dementia as a condition that is treatable. They found that knowledge about potential risk reduction and treatment of symptoms was poor. One of the most commonly reported misconceptions was that dementia was not preventable and was a normal part of aging. Similarly, a study by Wilcox et al. (2009) also examined how older adults perceive cognitive decline and the associated risk factors. They found that most older adults know that dementia rates are on the rise and have a vague idea of how to maintain cognitive health. Specific

knowledge of interventions was not clear, however, participants from all ethnic groups agreed that physical activity keeps the brain healthy. A wide range of specific physical activities from walking to gardening were mentioned. Very generic terms were also used, such as “keep active.” Diet and nutrition themes that emerged included the role of diet on a healthy brain and specific characteristics of diet that promotes brain health, such as the way food is prepared. Diet was mentioned much less frequently than physical activity.

Data from these two studies suggest that specific interventions are necessary to inform people of specific methods of how to exercise and eat well. To improve awareness of the risk factors for dementia it is important to eliminate all stereotypes and target as broad an audience as possible. This includes targeting the aging population as well as middle-age and younger generations (Cations et al., 2018; Chapman et al., 2006).

Emphasizing that lifestyle modifications need to be implemented in middle-aged adults is imperative because studies have shown that the pathology of cognitive decline evolves before symptoms occur. Also, changing habits of older adults is much more difficult than influencing younger adults to adhere to a heart-healthy and brain-healthy lifestyle. Currently, public health is looking to reduce the existential problem of dementia and AD. Public health initiatives need to stress short-term goals for the older generations in order to maintain cognition and functional fitness and long-term goals for younger adults that focus on prevention. Goals should consist of adhering to a physically active lifestyle and heart-healthy diet. This will help to prevent the epidemic of dementia, AD, and MCIs from becoming a larger problem. Even if effective treatments do become available, risk reduction strategies should remain a necessary prevention approach in order to reduce the need for treatment (Baumgart et al., 2015).

MCI, dementia, and AD have become a serious social, economic, and health care burden (Ngandu et al., 2015). In 2015, dementia and AD costs within the U.S. alone totaled \$226 billion (Marcason, 2015). The financial burden had increased by \$10 billion just one year later (Lee et al., 2017). Dementia-related costs exceed the costs of heart disease and cancer and are typically paid out of pocket by families (Brassure). Dementia increases the mean annual healthcare costs by over \$4,000 for people with dementia. These costs are attributable to hospital visits due to inadequate care as well as skilled nursing facility costs (Chapman et al., 2006).

The second domain consists of developing policies and partnerships. Promotional strategies should increase public awareness of the severity of the problem at hand and educate the general public about potentially modifiable risks factors of dementia. Public health campaigns that promote strategies for non-communicable diseases are one method. Public health officials will need to be involved in order to have a sustained and productive impact. Education on the complexity of cognitive decline will be relevant because focusing on a single risk factor is insufficient to reduce the risk of developing cognitive decline. Multiple risk factors should be addressed simultaneously with a broad approach being taken by a collection of agencies.

In addition to educating individuals, the third domain includes educating the healthcare workforce. It is necessary to introduce sources of reliable and up-to-date information on cognitive impairment. As research continues to evolve, health care professionals should be informed on the current science, research and innovations. Another significant aspect is encouraging health promotion and treatment of chronic conditions because, as previously mentioned, chronic conditions play a deleterious role in brain health. Healthcare professionals should be familiar with diet and exercise recommendations and should work with their patients to develop a complete health regimen. Healthcare professionals should be encouraged to

communicate with their patients, their caregivers, and public health officials about the implications of dementia in addition to advocating for needed services. In order for this to be achieved, public health representatives need to plan and implement the necessary counseling, create information packets, provide caregiving services, and have continued care management for the population in place.

The fourth and final domain is including surveillance systems. By monitoring and evaluating data that is collected, new programs can be advocated for and implemented in communities. In this phase it will be critical for patients, caregivers, health care providers, and public health officials to collaborate.

Several problems exist that need to be addressed and changed in future studies. A major challenge is that people are not educated enough about cognitive impairments, therefore, they do not believe that they are an abnormal part of aging. Research is limited even further by this lack of knowledge because it limits the number of participants and the amount of funding that studies may receive. Challenges also exist in the validity of current research. Although remarkable advancements have been made in defining and classifying categories of cognitive decline, obstacles still exist. Some of the problems that exist are within the diagnostic procedures, reporting biases, limited resources, poor classification, definitions within studies, and poor correspondent follow-ups. New diagnostic procedures are still being developed and studied to mitigate these problems. Challenges also occur in diagnosing and classifying the kinds of cognitive impairments that patient have. In relation to studies that examined diet and PA, most variables were not quantified. For example, most authors do not quantify energy expenditure; instead, they record types of physical activity. This may result in inaccuracies and biases, which drastically change the dynamic of the studies. Additionally, serving sizes in diet studies are not

recorded and broad generalizations are made. Complications also arise from the complexity of associated factors and the convolution of cognitive decline. For this reason, it may not be valid to say that one risk factor, in particular, may have an effect on cognitive decline. The lack of longitudinal studies and challenges with follow-ups is a concern for the validity of the studies as well because neurodegeneration does over a long period of time.

When moving forward with the public health approaches, it is critical to integrate what has worked in the past into new data. An analysis of past public surveillance systems will reveal what is relevant in the future. In order to see the most profound impact, a multicomponent approach must be taken. On the one hand, the promotion of risk reduction based on current evidence should be used, and on the other hand, research needs to proceed and address problems with the reliability and validity of existing evidence. Future research is needed to understand the complete pathologies of dementia and AD, diagnostic criteria, and the exact mechanisms by which PA, diet, and cardiovascular risk factors affect cognitive decline. In addition, research is needed to examine which specific exercise programs reduce the risk of dementia, improve cognitive function in older adults, slow the progression of the disease, and promote successful aging.

Future research should include diverse ethnic and gender populations as well as reaching underserved and rural populations. A new study by the Alzheimer's Association is advancing research in innovative and necessary ways. The study is called the U.S. Study to Protect Brain Health Through Lifestyle Intervention to Reduce Risk (U.S. POINTER). It will be a two-year clinical trial, beginning in 2018 with 2,500 volunteers, aged 60-79, who are at increased risk for cognitive decline. The study will examine whether lifestyle interventions that target the risk factors can protect cognitive function.

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