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Risk of Alzheimer's Disease Among Older Hispanic/Latinos with Diabetes

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Abstract

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MSPAS, Western University of Health Sciences, 2003

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Dissertation Submitted in Partial Fulfillment

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Public Health

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Abstract

Alzheimer's disease (AD) is the 6th leading cause of death in older Americans. Currently there is no cure for AD, and even though the specific cause is unknown, diabetes mellitus type 2 (DM2) is regarded as a risk factor. Hispanics have a higher incidence of DM2 and possibly AD. I chose a life course theoretical model for this quantitative cross-sectional study to illuminate the variables most pertinent to a pathway from good health to poor health. The variables chosen were hypertension (HTN), obesity, smoking, stroke, dyslipidemia, and lower educational attainment. The research questions were used to examine biologic, metabolic, sociologic, and genetic risk factors in the development of DM2 and subsequently, AD. Using data from the National Alzheimer Coordinating Center, the association between DM2 and AD in Hispanics over 65 years of age was examined using χ^2 and logistic regression to determine whether DM2 in this population contributes to AD development. No association was found between DM2 and AD (*OR* .791, 95% CI = .441-1.509, p = .476). Risk factors independently associated with AD were HTN, a history of stroke, and lower education in Hispanics. Obesity measured by BMI, dyslipidemia, smoking, and the APOE gene was not significant in their association to AD. This study offers information that medical providers can use to help determine which risk factors affect this population and may thereby alter the course of AD in their patients. Medical providers can make a significant impact on an individual's life by diagnosing dementia early. Early diagnosis could prevent or delay cognitive dysfunction and improve quality of life by using culturally and linguistically appropriate tools.

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Dedication

There are so many people and so many situations in our lifetime that have contributed to this moment. Our beliefs, our hopes and dreams, and of course the hard knocks have made us who we are. We are nothing without the experiences in our life course because they have taught us the importance of perseverance.

To my dear friends Sharon and Brenna, without their support it would have made this journey boring and tedious, thank you my ever-faithful friends.

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Chapter 1: Introduction to the Study

Introduction

Diabetes mellitus type 2 (DM2) is a multidimensional disease that begins when the pancreas is not able to produce enough insulin to accommodate the amount of glucose in the blood stream (Duarte, 2013). What characterizes DM2 is high blood glucose levels and glucose intolerance due to an impaired production of insulin or poor usability of insulin (Umegaki, 2014). DM2 frequently is accompanied by other conditions such as obesity, hypertension (HTN), dyslipidemia, and especially insulin resistance (IR), which can complicate the body's ability to provide adequate glucose control. These conditions, HTN, IR, and dyslipidemia, have been known to predispose individuals to neuronal death, brain changes, and eventually dementia (Duarte, 2013).

Dementia is a syndrome that is characterized by deterioration in thinking skills, memory, behavior, and independence in caring for oneself (Alzheimer's Association [AA], 2015a). Alzheimer's disease (AD) is the most common form of dementia and currently affects 5.4 million adults in the United States (AA, 2016). It has been estimated that one in nine adults over the age of 65 have been diagnosed with AD (AA, 2016; O'Bryant et al., 2013). AD is the sixth leading cause of death in the United States, it is estimated that 15% of individuals between the ages of 65-74 and 44% of the 75-84 year olds are affected with dementia (Dickstein et al., 2010). Mangialasche, Kivipelto, Solomon, and Fratiglioni (2012) showed that new and existing dementia cases increase with age, and that 70% of current dementia cases are in those 75 years and older.

The AA (2015a) estimated that in 2015, the direct cost of care for individuals with AD would reach $226 billion. Determining at what moment the brain begins to show

signs of deterioration that indicate the beginning of a dementia syndrome is vital for early intervention. Culturally and linguistically appropriate prevention strategies for AD can be implemented to direct this pathway toward a positive and healthy outcome (Mangialasche et al., 2012). As an example, the prevalence of diabetes whether undiagnosed or diagnosed among all Hispanics is currently 17%, regardless of gender. Hispanic/Latinos have a high rate of diabetes, with 2.2 million over the age of 60 currently affected (Huang et al., 2014; Noble, Manly, Schupf, Tang, & Luchsinger, 2012). The American Diabetes Association (ADA) reported that incidence of diabetes for the Hispanic ethnic group is almost double that of non-Latino Whites (ADA, 2015; Hu, Wallace & Tesh, 2010; Whyte, 2014). Hispanic/Latinos, as an ethnicity, are individuals that have origins in Mexico, Puerto Rico, Cuba, the Dominican Republic, Central America or South America.

According to Dr. Kimberly Simmons, director of Latin American Studies at the University of South Carolina, the term Hispanic references place of origin (Austin & Johnson, n.d.). These areas, Mexico, Puerto Rico, Cuba, Central America and South America were settled by the Spaniards and originally called Hispania. Even though Hispanic has long been used in census and other demographic data, the term Latino is becoming more politically correct. The general consensus, according to Simmons, is that most people prefer to be recognized by country of origin. For this study, I used the term Hispanic to include all ethnicities listed as Hispanic on surveys conducted by the National Alzheimer's Coordinating Centers (NACC).

By 2050, Hispanics over 60 years of age residing in the United States are anticipated to triple. Given the high rate of diabetes among this group, the incident rate of AD among older Hispanics could increase six fold (O'Bryant et al., 2013). In this study, I

addressed the following questions: (a) Can DM2 be linked to the development of AD in older Hispanics? (b) Are there biologic, metabolic, and sociologic risk factors that predispose older Hispanic adults to AD? (c) Is the Apolipoprotein epsilon 4 (APOE ε4) gene associated with AD development in older Hispanics?

In this chapter, I discuss the important and relevant information about DM2 and AD. The introduction and background information contain the pathogenesis of DM2 and AD as well as how they relate to each other. The problem statement and the purpose of the study were intended to explain the public health problem of AD and to discuss the social change aspect of this research study in prevention of AD in older Hispanics. The research questions and hypotheses were designed to encompass biologic, metabolic, and sociologic risk factors that are associated with AD. Next, I discuss the conceptual framework that can be related to AD development, the life-course perspective. The nature of the study substantiates the methods and analytical design chosen for this study. In the definitions section, the meaning of each term used in this study is scientifically explained. The scope of the study as the target population was Hispanics with origins in Mexico, Puerto Rico, Cuba, the Dominican Republic, Central American and South America that have been diagnosed with AD. The delimitation section explains that the data gathered were truthful and all participants were of six races within the Hispanic ethnicity, had self-reported diabetes and were truly diagnosed with AD. It is believed that all variables in this study were non-biased and any limitations were due to this cross-sectional study and the self-reported nature of DM2, HTN, and dyslipidemia.

Background of the Study

In 1906, psychiatrist and neuropathologist Alois Alzheimer noticed a progressive loss in memory and cognition in a patient with an unusual mental illness. Upon autopsy, he discovered that this patient's brain was atrophied and had deposits between nerve cells. These deposits would eventually be recognized as amyloid-beta plaques (De Felice, 2013; Medhi & Chakrabarty, 2013). Since this discovery, researchers have associated multiple factors with the development of AD, and even though the direct cause is unknown, many processes are implicated in the development of this disease. The hypotheses researchers have used to explain the origin of this neurodegenerative brain disorder have generally attributed its origin to vascular, inflammatory, and/or oxidative stress. There is also a psychosocial hypothesis that encompasses a life-course approach to AD development, which I used in this research study.

Evidence indicates a pathophysiologic and metabolic connection between AD and DM2 (Cheng et al., 2011; Götz, Ittner, & Lim, 2009; Han & Li, 2010; Mushtaq, Khan, Kumosani, & Kamal, 2014). How the pathophysiology of DM2 affects the brain by neurological changes is still under investigation, but it is estimated that multiple factors contribute to the disruption of the vessels in the brain that leads to AD. There is a gap in clinical understanding of whether DM2 in a given population can predict AD, or whether other risk factors contribute significantly to AD development (Fitten et al., 2014; Mayeda, Haan, Kanaya, Yaffe, & Neuhaus, 2013; Mayeda et al., 2014; O'Bryant et al., 2013).

Another factor that researchers have theorized as contributing to AD development is IR in the brain. Insulin was discovered nearly 100 years ago, but it was only thirty

years ago that researchers came to understand how the brain uses insulin (Banks, Owen, & Erickson, 2012). Insulin is a hormone that is made in the pancreas within the beta cells. It protects the brain against cell death, oxidative stress, and amyloid-beta protein build-up within the brain (Blazquez, Velazquez, Hurtado-Carneiro, & Ruiz-Albusac, 2014; De Felice, 2013). The hippocampus, the area in the brain that is responsible for new memory formation, has a large amount of insulin receptors. Researchers have hypothesized that impaired glucose functioning, a necessary situation for DM2, is the result of IR, which also contributes to AD development (Huang et al., 2014). Researchers have pointed to IR in peripheral tissues in their hypotheses about the association of AD and DM2 (Bartl et al., 2013; Duarte et al., 2013). IR is, in itself, a complicated metabolic disorder that has been associated with obesity, DM2, and AD in several studies (Blazquez et al., 2014).

Inflammation is also a factor that contributes AD development, and has been associated with IR in peripheral tissue as well as the brain. Inflammatory cytokines include tumor necrosis factor-α (TNF-α), Interleukin-6 (IL-6), and C-reactive protein (CRP). Along with these inflammatory cytokines, HTN, dyslipidemia, obesity, DM2, cigarette smoking, and the APOE ε4 gene all contribute in some way to vascular disruption (Dickstein et al., 2010). This vascular hypothesis has gained popularity, in that researchers have considered factors that disrupt blood vessel integrity through oxidative stress, IR, and arterial stiffness as progenitors of AD (Dickstein et al., 2010).

Sporadic Alzheimer's disease or the onset after 60 years of age is also referred to as late-onset Alzheimer's disease (LOAD). LOAD is associated with dense amyloid plaque development outside and in between the neurons in the brain and neurofibrillary strands, called tangles, within the brain cells. Researcher have proposed that ischemia, or

lack of blood flow, in the brain is the most likely cause of the amyloid plaque development, which can take as many as 20 years to develop (Prince, Albanese, Guerchet, & Prina, 2014).

Diabetes is a difficult disease to manage because of the time consuming regime of blood glucose testing, medication management, and constant nutritional vigilance (ADA, 2015; Whyte, 2014). It is interesting to note that previous researchers have demonstrated that AD incidence is higher in individuals with DM2 compared to individuals without DM2 (Blázquez et al., 2014; Medhi & Chakrabarty, 2013). It was estimated in 2012 that senior adult individuals over 60 accounted for 11.8 million of those diagnosed and undiagnosed with DM2 (ADA, 2015). Living longer creates the opportunity for developing chronic diseases. With technology and medications for DM2 allowing older individuals to live longer, the caveat is that living longer increases the opportunities for these two diseases, AD and DM2, to be more prevalent (Exalto, Whitmer, Kappele, & Biessels, 2012; Yamashita & Kart, 2011). Older adults especially may suffer from visual and cognitive impairment that makes the normal routine of diabetes management very complicated (ADA, 2015).

With more adults, many with chronic diseases living longer, dementia and DM2 have become a recognized public health problem. Several researchers have noted that DM2 poses the highest risk for dementia in older adults, even when accounting for HTN, dyslipidemia, and obesity (Exalto et al., 2012; Murthy et al., 2010). There is a noticeable gap in scholarly knowledge about culturally and linguistically appropriate tools that can be used to diagnose dementia. Primary care medical providers are at the forefront of diagnosing and preventing these diseases in their patients, and researchers have

documented that the majority of individuals with dementia symptoms initially present to their primary care providers (Galvin & Sadowsky, 2012). Medical providers therefore have the opportunity to follow their patients and intervene in the development of diseases that can present future physiological problems.

Problem Statement

DM2 is a chronic metabolic disease that affects approximately 25.8 million individuals, their families, and their communities with high financial costs as well as the intangible costs of pain and suffering (Whyte, 2014). DM2 creates an inflammatory cascade that affects the vascular system, causing microvascular changes in the brain and white matter atrophy. This atrophy contributes to vascular dementia and cognitive decline (Van Ersel et al., 2013). The blood brain barrier allows cerebral spinal fluid and blood to flow in and out of the brain; therefore, any weakness or defect here can admit toxic substances and metabolites. High glucose levels in the brain's vascularity creates an environment for an increase in free radicals and oxidative stress, which has been reported to cause neuronal damage (Umegaki, 2014). Dementia is an acquired brain condition in which the pathology can be the result of several factors. AD is characterized by the inability to remember new information. New information that is learned is stored in the hippocampus, which is the first area in the brain to suffer damage (AA, 2011).

The Hispanic population has several drawbacks to achieving optimal health. As a population, Hispanics have a higher prevalence of DM2 in their adult population (Fernandez et al., 2010; Whyte, 2014). The prevalence of obesity, a known cause of diabetes, was higher in Hispanics in a 2014 study, compared to the White population, 42.5% compared to 32.6% (Center for Disease Control and Prevention [CDC], 2014).

Fernandez et al. (2010) stated that glycemic control could be affected by several factors. One of these factors is language barrier, which has been shown to increase health disparities and decrease health literacy. Health disparities, reported by Hispanic patients, increase because patients report dissatisfaction with the care they receive. Also a language barrier between provider and patient increases difficulties with medication compliance that is vital to diabetes control (Fernandez et al., 2010).

The gene that has been strongly linked to AD in several ethnicities, but not in the Hispanic population is the APOE ε4 gene variant (Aslan, Ercan, Aybeck, & Şahiner, 2010). Previous studies have revealed that that there is a lower frequency of this gene in the Hispanic/Latino population (Campos, Edland, & Peavey, 2013; O'Bryant et al., 2013a). The higher frequency of AD in this population, as researched by Haan et al. (2003), should be accounted for by other conditions and risk factors.

There are currently several studies that measure chronic health problems, which include diabetes and cognitive impairment, in the United States. The Health & Aging Brain Among Latino Elders (HABLE) study in Fort Worth, Texas is currently researching Mexican American older adults and their unique situation in developing AD (Texas Alzheimer's Research and Care Consortium, 2015). The Sacramento Area Latino Study on Aging (SALSA) has studied Latinos in Northern California, and the researchers are currently conducting studies on cognitive impairment (O'Bryant et al., 2013; SALSA, 2013). The Hispanic Community Health Study/Study of Latinos (HCHS/SOL) includes individuals of Hispanic heritage in four communities through the United States. However, these studies measure general cognitive impairment. The HABLE does measure AD, but exclusively in Mexican Americans. In this study, I set out to analyze an

association between DM2 and AD within six Hispanic/Latino populations. These include individuals with origins from Mexico, Cuba, Puerto Rico, Dominican Republic, Central America, and South America.

There are an estimated 92,242 Hispanics currently living with AD in California alone (Conroy, Pendelton, & Bates, 2014; Ross, Brennan, Nazareno, & Fox, 2009). Most of the Hispanics that live in the United States live in California, Texas, Florida, and New York. In this study, I explored the relationship between DM2 and AD development among older Hispanic/Latino adults that live in the United States.

Purpose of the Study

My purpose in conducting this cross-sectional study was to evaluate the relationship between DM2 and AD, which are both prevalent in high rates among the Hispanic population. DM2 is considered to be a preventable disease, and AD is currently without a cure.

This study's implications for positive social change come in identifying risk factors in this older ethnic population with the possibility in preventing or delaying AD. Language and cultural barriers, poor lifestyle habits, difficulty in accessing medical care, and implicit biases in the medical provider's opinions and beliefs can compound these risk factors. Researchers use cross-sectional studies to examine all variables at the same time (Frankfort-Nachmias & Nachmias, 2008). I analyzed Hispanics, as the designated population, using variables associated with AD development. I also analyzed other variables including HTN, obesity, dyslipidemia, smoking history, history of stroke, education level achieved, and genetic factors. With this being said, this research study explored the association between DM2 and AD in older Hispanic adults compared

against a White population with the same criteria. The benefit of this research study could bring to light valuable information to help prevent cognitive decline in Hispanic older adults by isolating the most prevalent risk factors for AD.

Research Questions and Hypotheses

1. Does diabetes type 2 predispose older Hispanic adults to Alzheimer's disease?

H_o1: Diabetes type 2 does not predispose older Hispanic adults to Alzheimer's disease.

H_a1: Diabetes type 2 predisposes older Hispanic adults to develop Alzheimer's disease.

2. Do other metabolic risk factors such as HTN, a history of stroke, obesity, and dyslipidemia contribute to the development of Alzheimer's disease in older Hispanic adults?

H_o2: Other metabolic risk factors such as HTN, a history of stroke, obesity, and dyslipidemia do not contribute to the development of Alzheimer's disease in older Hispanic adults.

H_a2: Other metabolic risk factors such as HTN, a history of stroke, obesity, and dyslipidemia do contribute to the development of Alzheimer's disease in older Hispanic adults.

3. Do sociological risk factors such as educational attainment and history of smoking contribute to the development of Alzheimer's disease in older Hispanic adults?

H_o3: Sociological risk factors such as educational attainment and history of smoking do not contribute to the development of Alzheimer's disease in older Hispanic adults.

H_a3: Sociological risk factors such as educational attainment and history of smoking do contribute to the development of Alzheimer's disease in older Hispanic adults.

4. Is there a relationship between Alzheimer's disease and the APOE ε4 gene in the Hispanic population?

H_o4: There is no relationship between Alzheimer's disease and the APOE ε4 gene in the Hispanic population?

H_a4: There is a relationship between Alzheimer's disease and the APOE ε4 gene in the Hispanic population.

Theoretical Base

I determined that a conceptual framework that encompassed biologic, metabolic, sociologic, and possibly environmental factors that contribute to chronic disease development was needed for this study. The accumulation of risk perspective takes into consideration every stage of development and projects the effect poor health has on illness later in life. This model incorporates ideas from chronic disease epidemiology and epigenetics under the life course model (Halfon, 2011; Solar & Irwin, 2010). As the number and intensity of exposures during an individual's lifetime accrue, there is a chance for accumulation of bodily damage that increases the opportunity for chronic illness (Ben-Shlomo & Kuh, 2002; Cable, 2014; Halfon, 2011). The accumulation from harmful environmental conditions and negative behavioral risks, such as cigarette smoking, is what sets an individual on a pathway for neuronal destruction. The life course perspective, which incorporates the accumulation of risk theory, merges social, behavioral, and environmental risks from childhood to adulthood. This framework,

therefore, can be used to explain health disparities among groups of individuals, and to attempt to understand the beginnings of where the path was diverted from good health. By understanding this divergence, health care providers may help prevent chronic illnesses such as diabetes and dementia in older adults (Halfon, 2012).

The accumulation of risk model explains illnesses in the older adult as a cascade of biological injuries, exposures, and situations that are additive in an individual's life course. Researchers have stated that adult health can be affected through continuous damage over time. Biological insults that begin during an individual's younger years can accrue and cause damage over an individual's life course (Shonkoff, Boyce, & McEwen, 2009). Stressful experiences, whether psychological or physical, disrupts the body's immune function causing deficiencies, which create chronic disease (Ben-Shlomo & Kuh, 2002; Solar & Irwin, 2010). For example, Shonkoff, Boyce, and McEwen (2009) have stated that discrimination against some ethnicities has been associated with a quicker aging process and a 4 to 6 year earlier mortality.

Biologically, any stressful event causes the amygdala in the brain to send a signal to the hypothalamus, a small structure also in the brain. This usually produces a flight or fight response. The hypothalamus communicates with the adrenal glands, which in turn release epinephrine, also called adrenaline, producing several physiological reactions. Three things take place: an individual's pulse increases, blood pressure goes up causing momentary hypertension, and the release of epinephrine causes the retrieval of glucose from storage in the body to be used for energy (Tovian et al., 2015). Continuous activation of this system, in continuous exposures to physiological stress over years, is problematic and accounts for allostatic load. Allostasis is the adaptive process from

homeostasis to damaged biological reactions due to the chronic stress the human body is placed under. Allostatic load therefore is the unsuccessful attempt to adjustment and leads to chronic illness (Brown et al., 2004; Logan & Barksdale, 2008).

Solar and Irwin (2010) have defined accumulation of risk as the duration of negative events, whether physically or socially, that can become additive and contribute to biological damage to the human body. Unhealthy lifestyle practices, smoking, HTN, dyslipidemia, poor diet, and lack of physical exercise can in part produce obesity. Obesity is part of the metabolic syndrome, which creates IR in peripheral tissues and causes DM2. DM2 has been associated with significant brain aging and AD later in life (De Felice, 2013).

Medical providers can influence health behavior through patient-provider communication. Researchers have found that patients that have higher levels of education, better health literacy, and familiarity with American culture had lower glycated hemoglobin levels at medical follow-ups (Brown et al., 2004).

Nature of the Study

I used a quantitative study design and gathered and analyzed secondary data from Alzheimer's disease centers in the United States (ADCs). I retrieved this data from the National Alzheimer's Coordinating Center Uniform Data Set (NACC UDS). This data set was developed in the early 2000s in order to provide useful data to researchers in a centralized research database. The survey that was used by the ADCs on initial visits also includes informant interviews, which can supply valuable information about the cognitively impaired individual from a caregiving standpoint. This is a longitudinal database that is updated annually. The advantage of longitudinal data is that it could be

used to identify patterns over time in the sample Hispanic population with a comparable White population (Field, 2013). Even though most of the participants in the ADCs have continuous updates to their initial information, only data gathered on the participants first visit was used in this study. The survey information used was from older adults (>60) of self-reported Hispanic heritage diagnosed with AD and self-reported diabetes. The gene that was analyzed, for presence or absence of, was the APOE ε4 gene in both the case and control groups, Hispanics and Whites. Criteria for inclusion in this study were (a) adults 60 years and older; and (b) self-reported Hispanic heritage as Mexican, Cuban, Puerto Rican, Dominican, Central American, or South American. The dependent variable (DV) was Alzheimer's disease, and the main independent variable (IV) was DM2. Logistic regression was used to measure the relationship between the IVs and the DV to develop an odds ratio (OR).

Logistic regression was appropriate because the DV was categorical and therefore a linear relationship did not need to be established (Field, 2013). The best analytic method for determining what factors produce the highest risk for AD is logistic regression. Through logistic regression, it was possible to measure how much of a risk DM2 presents, apart from other risk factors, in eventual AD development (Field, 2013).

Other variables that I included as a potential part of a metabolic link between AD and DM2, were self-reported dyslipidemia and self-reported diabetes. Obesity was defined by a BMI > 30 kg/m^2 and self-reported hypertension. I also evaluated stroke history from self-report, caregiver report, and/or clinician diagnosed (yes/no). Sociological risk factors that I analyzed included a history of smoking as measured by years of smoking (continuous changed to categorical), and education level (continuous

changed to categorical). The genetic risk factor that I analyzed was the APOE ε4/ε4 allele exclusively.

Definitions of Terms

Adiponectin: A hormone that comes from visceral or deep fat in the abdominal cavity. This hormone makes the body more sensitive to insulin and has anti-inflammatory properties. Reduced levels of adiponectin in those with pre-diabetes progresses to IR (Song, Lee, Park, & Lee, 2014). It is interesting to note that individuals with higher adiponectin levels have been found to have a lower risk of heart disease and better insulin signaling, yet higher levels have also been associated with all cause-mortality (van Himbergen et al., 2012).

Amyloid-beta plaques: These proteins involve fibrils that are made from amyloid-beta peptide and another protein called amyloid precursor protein (Licastro, Carbone, & Porcellini, 2014; Reitz, Honig, Vonsattel, Tang, & Mayeux, 2009). It is thought that amyloid-beta accumulation in the extra cellular space of neurons begins a cascade of destruction to neurons and synapses producing the specific neuropathology that is one of the hallmarks of AD.

Apolipoprotein E ε4 (APOE ε4): A protein that is involved in cholesterol transport. To date it is the strongest predictor for sporadic or late-onset AD, where it has three isoforms, ε2, ε3, and ε4. Each allele that is inherited increases the risk for AD by up to 3-fold and lowers the age of AD symptomology by 6 to 7 years (Reitz, 2012).

Amylin: A hormone made in the beta cells along with insulin in the pancreas. There are several important tasks amylin performs. Its effect on the blood brain barrier is

to reduce overeating and it slows down the release of insulin and glucose into the bloodstream thereby slowing the emptying of the stomach (Srodulski et al., 2014).

Dementia: A syndrome that covers abnormal cognition, which can start with mild cognitive impairment. The Alzheimer's Association defines dementia as an unspecified term for a decline in mental abilities that interfere with activities of daily living. Pre-dementia is described as mild cognitive impairment (MCI), the stage before cognitive dysfunction begins to interfere with daily life (AA, 2015c). There are currently no validated tests to secure the diagnosis of MCI, vascular dementia or AD, these are clinical diagnoses (Petersen et al., 2009; Reitz, Brayne, & Mayeux, 2011). Current research criterion for diagnosis of AD is by neuropsychological tests revealing decreased functional capacity in memory and two other cognitive domains (Manly & Mayeux, 2004). Two of the neurocognitive tests are MMSE and CDR. The tests that were used in the UDS to measure cognitive function were an extensive battery which included the MMSE, MoCA, MINT, Boston Naming test, WAIS-R, and CDR as a measure of attention, concentration, memory, judgment, and personal care.

One of the future predictive opportunities for diagnosis of AD are biomarkers that reveal certain markers in serum, plasma, and CSF. Two results can proceed from here. One is targeted medication for specific traits and the other would be very early diagnosis before symptoms are present (Atri, 2016; O'Bryant et al., 2010).

Dyslipidemia: A condition in which lipid values, HDL, LDL, and triglycerides that make up the total cholesterol count, are disproportionate to standards that researchers have found to reduce risk for cardiovascular disease and dementia.

Glycated hemoglobin: Also referred to as glycosylated hemoglobin, is a measure of blood sugar control. Glycohemoglobins make up part of the red blood cell, which has a 120-day existence. The higher the level of glucose in the red blood cells, the higher the glycated hemoglobin measured as HbA1c. Until recently HbA1c was not used for an initial diagnosis of DM2. This test can detect 85% of new diabetes, but it was argued that 15% were lost to non-diagnosis. Therefore, an oral glucose load measured within 2 hours after ingestion is the most widely accepted method for diagnosis of diabetes (Masharani, 2005). What must be considered is the patients' compliance. If the patient refuses or delays in fasting all day for this blood test, the diagnosis would be delayed and a quick non-fasting blood test, the HbA1C would be adequate.

Health literacy: The test mentioned in this study performed by other researchers is the Test of Functional Health Literacy in Adults (TOFHLA). This test comes in a shorter, easier to take form (S-TOFHLA), and also in a Spanish version. The TOFHLA has a 50-item section for reading comprehension and a 17-item numerical section that measures terms that patients could face in a medical setting. Cronbach's alpha for reliability was 0.98 (Mancuso, 2010).

Hyperglycemia: Is classified as glucose that is too high, measured at >130 mg/dl fasting or 180 mg/dl, if you are diabetic, after a meal. The ADA states a diagnosis of DM2 is made if HbA1c is ≥ 6.5% (Olson, Rhee, Herrick, Ziemer, Twombly, & Phillips, 2010).

Hypoglycemia: Is classified as a glucose level that is too low. Measured as < 70mg/dl and can cause nervousness, irritability, confusion, and unconsciousness (Lin & Sheu, 2012).

Insulin resistance: Insulin receptors can be found in the brain in the cerebral cortex, cerebellum, hypothalamus, and the hippocampus where new memories are formed. One of the roles of insulin is keeping neurons from dying. Insulin also reduces amyloid-beta from accumulating in the brain, thereby decreasing the incidence of dementia. IR is when there is a reduced level of insulin available for the body to use. A documented condition that is present in DM2 and individuals with AD is a continuous state of IR (Medhi & Chakrabarty, 2013).

Metabolic Syndrome (MetS): The World Health Organization (WHO) has defined MetS as a constellation of several metabolic conditions that must be present. The conditions are IR, hyperglycemia (fasting blood glucose [FBG] >100mg/dl, or glucose intolerance diagnosed by a two-hour oral glucose tolerance test [OGTT] result of >200 mg/dl), and obesity measured by a BMI of >30 kg/m^2. What is also included is a serum triglyceride level of >150 mg/dl, an HDL cholesterol level of <35 mg/dl, and blood pressure of 140/90 and greater (Craft, 2010; Garcia-Lara et al., 2010). IR is the underlying pathology of DM2 and therefore considered hyperglycemia (Craft, 2010).

Neurofibrillary tangles (NFT): Intracellular tangles made up of paired helical, tubular, hyperphosphorylated tau proteins (Marques, Sousa, Sousa, & Palha, 2013). It appears that the tangles inside the cells possibly disrupt the cellular matrix damaging the contents within the cell causing it to die (Yaari & Corey-Bloom, 2007).

Neuroimaging: Neuroimaging tests, such as magnetic resonance imaging (MRI), produce images of the brain and vascular tissue though a non-invasive procedure. Structural MRI can foretell progression from MCI to AD. It can detect changes in ventricular size and gray matter density. Positron emission tomography (PET) scan can

detect the amount of glucose and oxygen used by the brain in the areas that are most affected by AD, the hippocampus (Petersen et al., 2011; Ryan, Fine, & Rosano, 2014; Tomita et al., 2012).

Oral glucose tolerance test: A blood test used to diagnose high blood sugar, by having the patient ingest 75-110 grams of a sugar solution. The International Expert Committee (IEC) has set the standard for OGTT to be used for initial diagnosis of diabetes. Fasting blood glucose levels are considered normal when the results are less than or equal to 100 mg/dl, one hour results are < 184 mg/dl or 10.2 mmol/L. The two-hour results of the 2hr OGTT considered normal are < 140 mg/dl or 7.7 mmol/L (Olson et al., 2010).

Type 2 diabetes: A chronic condition in which the body is unable to store glucose in the muscles for energy because the pancreas is not making enough insulin. It has been considered to be only adult onset but due to its relationship to obesity, can be diagnosed in teenagers. The diagnosis of diabetes can start with simple clinical tests such as urine or blood test, even though type 2 can be present without physical symptoms for years. Most often it is the clinician that suspects an abnormality and provides a screening test. Because this illness is quite prevalent, especially in the elderly, it is important for clinicians to suspect glucose abnormalities in all individuals that are obese and have a family history of type 2 diabetes (Fitzgerald, 2005).

Assumptions

I assumed that the information that was gathered in the NACC UDS was accurate. While surveys can be subject to bias and recall bias can change the outcome due to erroneous recall on the part of the participant, I nonetheless assumed that the information

that the UDS gathered was accurate and honest. AD was diagnosed using more than one criterion during the diagnostic period. Probable, possible, or definite AD was diagnosed in participants through clinical determination and neuropsychological test. The NINCDS-ADRDA determines the criteria for dementia diagnosis. The UDS collected data in several different languages as was appropriately necessary for better fluency and recognition. I assumed that all participants that were of Hispanic heritage were correctly identified by the UDS. It was important in this study to differentiate between type 1 and type 2 diabetes; however, the UDS relied on self-reported diabetes information from patient or caregiver. I thus assumed that, due to the high incidence of DM2 in this population, these individuals had type 2 diabetes.

Scope and Delimitations

In this cross-sectional quantitative research study, I used data from the NACC UDS that gathers data on individuals with dementia. I selected a cross-sectional design because cross-sectional studies enable the researcher to examine all the necessary variables at the same time (Frankfort-Nachmias & Nachmias, 2008). I requested data from the UDS that reflected the initial visit of every participant in each Alzheimer's disease center throughout the United States after 2005. A prospective study design would have been the most informative, would have had the highest internal validity, and would have established cause and effect on the highest level. However, the time required would have been prohibitive, as would the cost.

I used the UDS from the NACC to evaluate a correlation between AD and DM2. In 1999, the National Institute on Aging founded the NACC for the purpose of gathering data collected by the Alzheimer's Disease Centers (ADCs). The UDS was begun in 2005

to prospectively collect data from yearly clinical evaluations. This enables researchers to track changes in certain variables over time, and to view results of neuroimaging and neurocognitive tests.

I obtained the sample population from any of the 31 centers within 29 states, as of 2015. This included version 1, 2, and 3 (v.1, v.2, v.3) in the information packet supplied by the ADCs. In order to assure generalizability, the characteristics of the study population, older Hispanics, had to reflect the characteristics of the older Hispanics in the general population. Generalizability is valuable because the conclusions of a research study, depending on the *p* value and confidence intervals, convey the results as statistically significant. The variables I measured in this research study thus needed to reflect the same demographics as the general population (Frankfort-Nachmias & Nachmias, 2008).

The accumulation of risk model embodies a life-course perspective. Damage to the human body, either by poor lifestyle habits or lack of sufficient medical care over a lifetime, causes chronic and/or worsening disease. I chose this theory because multiple research studies have shown that a lifetime of stressors, physiologically and psychologically, create allostatic load (Brown et al., 2004; Krieger, 2011; Logan & Barksdale, 2008). Theories that I deemed not applicable were those that incorporated strictly environmental causes for DM2 and AD development because of low statistical significance. Models that depended on self-efficacy or stages of change do not encompass social standing in adolescence, poor educational attainment in young adulthood, or the deleterious effects of HTN, high cholesterol, and obesity in later life. Accumulation of risk theory is slightly similar to the transactional model of stress and

coping which postulates coping with chronic disease and finding meaning through the process reduces stress hormones. However, by having an awareness of accumulation of risk, the concept would be to prevent occurrences in an individuals' life span that produce negative outcomes (Glanz & Schwartz, 2008).

Limitations

Limitations of this study and the data within relate to bias and internal and external validity. Because I used a cross-sectional study that included data gathered at one point in time, it reflects the AD standing of the participant at the initial evaluation (see Frankfort-Nachmias & Nachmias, 2008). Bias, in this regard, pertained to the participant's accurate self-identification as originating from Mexico, Puerto Rico, Cuba, Dominican Republic, Central America or South America. Even though a cross-sectional study cannot prove causality, by ruling out other factors that could modify AD development, I determined that it would provide adequate internal validity. Internal validity is established when changes in the IV cause changes in the DV. Internal validity can be increased when controls are matched as closely as possible to the case subjects (Frankfort-Nachmias & Nachmias, 2008). External validity is established when the population procured in the study sample represents the ethnic population in reality. By using data that had been collected throughout the United States from various ADCs, the opportunity for generalization was increased. This included different demographics, environmental influences, and cultural differences that could have affected AD development.

Cross-sectional studies have the advantage of showing a pattern between variables at a single moment in time. The goal of a cross-sectional study design is to describe a

population in regards to an outcome and predictor variables. However, cross-sectional studies can be slightly problematic for several reasons. Researchers cannot use them to draw a conclusion as to causality. Because it recorded one point in time, I could not use this cross-sectional study to specify disease outcome and whether DM2 occurred first, or whether AD caused diabetes. Researchers have hypothesized that there is a possibility of reverse causation, meaning that AD precedes DM2 (Frankfort-Nachmias & Nachmias, 2008; Levin, 2006). As individual's age and cognition starts to deteriorate, they are unaware of the symptoms of hyperglycemia and DM2, therefore, can manifest.

In the concluding sections, I discuss the significance of the study and its relevance for the prevention of DM2 in order to avert AD development in older Hispanic adults. I will also mention how medical providers can use adequate tools to diagnose AD when the signs are early in order to devise a plan for the aging Hispanic population.

Significance

AD is an incurable neurodegenerative disorder that affects millions of older individuals. Many researchers have evaluated various risk factors that have been known to contribute to dementia. The risk factors for the development of AD are broader than just DM2. However, DM2 sets up a cascade of metabolic difficulties that establish a basis for vascular damage. However, other risk factors such as atherosclerosis and HTN can create damage separately from the insulin resistance DM2 creates (Exalto et al., 2012; Tuligenga et al., 2014).

AD affects ethnicities in different proportions. It is estimated that AD affects 7.5% of 65-74 year-old Hispanics, compared to 2.9% of Whites. In the 75-84 year-old range, incidences of AD increase to 27.9% for Hispanics, and 10.9% for White. It is also

reported that 29% of those with AD also have DM2 (AA, 2014). The risk of developing DM2 in the Hispanic/Latino population was 66% higher than that for Whites (Chow, Foster, Gonzales, & McIver, 2012). With these statistics, I determined that a research study, which included six races within the Hispanic ethnicity with DM2, was clinically important to determine the association of DM2 and AD development. Logistic regression was the best analytic method for determining what factors produce the highest risk for AD. Through logistic regression, it was possible to measure how much of a risk it is to have DM2, apart from other risk factors, for the eventual development of AD (Field, 2013).

As the Hispanic population within the United States expands in number and becomes older, it is important to culturally address their needs for a timely AD diagnosis (Hildreth et al., 2014). As an outcome of this study, there are several areas that could be proposed for change in this population. The first opportunity is making available to medical providers culturally and linguistically appropriate diagnostic tools. Another situation would be to allow time in the clinical appointment to assess for dementia in patients over 50 years of age. Current literature shows that there is a need to make available resources and appropriate information for patients and caregivers of Hispanic adults to help them understand the signs of AD (Gelman, 2010).

Summary and Transition

The older U.S. population is projected to increase substantially by 2050. The total number of Whites over 65 will double, but Hispanics most likely will increase 11-fold (Aiken-Morgan, Whitfield, & Paige, 2014). If this ethnicity presents earlier with disease in America, there is a greater chance for intervention. Because AD has a long prodromal

period, even one chronic disease in older adults creates an opportunity for intervention and diagnosis (Dominiquez et al., 2015).

In this study, I used longitudinal data from ADCs in the United States. Older individuals with AD of White and Hispanic decent were evaluated using an odds ratio to determine if DM2 contributes to the development of AD.

Chapter 1 has included a background of AD and DM2 in the United States and a discussion of the potential for destruction of the older individual's cognitive function. In this chapter I also discussed the importance of a study using Hispanic/Latinos, and the possibility of bringing about social change within this population. In Chapter 2, I discuss the theoretical framework that drove this study and the literature that is currently available to point out the importance of understanding a link between DM2 and AD in its prevention. In Chapter 3, I discuss the methodology used in this study, and I present the results in chapter 4. In Chapter 5 I discuss the results of the statistical analysis and offer recommendations that have the potential to assist medical providers with culturally based tools for dementia diagnosis in Hispanic older adults.

Chapter 2: Literature Review

Introduction

The purpose of this study was to evaluate the relationship between DM2 and AD in older Hispanic adults. According to the 2010 Census, 50.5 million of the 308.7 million individuals that live in the United States, were Hispanic/Latino (Ennis, Rios-Vargas, & Albert, 2011). This ethnic population includes individuals from Mexico, Cuba, Puerto Rico, the Dominican Republic, Central America, and South America. "Hispanic" refers to those individuals that have a family origin to Spain. Hispanic is an ethnic distinction. Interestingly, all Latin Americans are Latin but not Hispanic (Austin & Johnson, n.d.). According to Junkett (2013), "Latino" signifies those individuals that are from Mexico, Cuba, Puerto Rico, and Central America or South America, regardless of race. Individuals within the Hispanic/Latino ethnicity comprise the largest minority in the U.S. population.

In a study evaluating 22,171 diabetics, Mayeda et al. (2014) discovered that more than 25% of adults older than 65 living in the United States, are Latinos. The incidence and prevalence of neurodegenerative diseases have also been steadily increasing. It is estimated that 36 million people worldwide currently suffer from dementia (Candeias et al., 2012). AD is the most common form of dementia, and between 50-80% of cases are individuals over 60 years of age (Dominiguez, Marschoff, Gonzalez, Repetto, & Serra, 2012). AD is a slowly progressive fatal disease of the brain in which the origin is multifactorial and can go undiagnosed due to the long latency of symptom development (Candeias et al., 2012; Khan & Alkon, 2014). The United States alone has 5.5 million individuals diagnosed with AD, and costs associated with the disease have been

estimated at $214 billion (AA, 2014). Medicare and Medicaid pay approximately 70%, $150 billion, of all health care costs associated with AD and other dementias in long-term care. It is estimated that by 2050 the prevalence of AD will triple, placing a substantial burden on families (Ryan, Fine, & Rosano, 2014).

DM2 and AD have become public health concerns because both diseases have been known to increase in an aging population (Ryan, Fine, & Rosano, 2014). There is evidence that indicates a pathophysiologic and metabolic association between AD and DM2 (Cheng et al., 2011; Götz, Ittner, & Lim, 2009; Han & Li, 2010; Mushtaq, Khan, Kumosani, & Kamal, 2014). How the pathophysiology of DM2 affects the brain by neurological alterations is still under investigation, but researchers have hypothesized that multiple factors contribute to the disruption of the vessels in the brain that leads to AD. According to recent research, the factors that exist in both AD and DM2 are IR, oxidative stress, and glucose dysfunction whether hypoglycemia or hyperglycemia. Amylins effect on amyloid polypeptide and amyloid-beta proteins that are metabolized, cleared, or stored in the brain exist with both conditions as well. Amyloid plaques have been discovered in the pancreas of diabetics as well as individuals with AD (Bornstein, Brainin, Guekht, Skoog, & Korczyn, 2014; Whitmer, Karter, Yaffe, Quesenberry, & Selby, 2009).

DM2 and dementia incidence and prevalence increase as individuals' age (Samaras & Sachdev, 2012). Therefore, as the population continues to age, the incidence of AD is likely to place a greater burden on society (Bornstein et al., 2014; Ryan, Fine, & Rosano, 2014). Researchers originally did not understand what affect insulin had on brain tissue; however, recent medical research into the association between AD and DM2 has shown that the brain is insulin sensitive (Banks, Owen, & Erickson, 2012). This insulin

sensitivity, as well as amylin accumulation in brain tissue, is associated with a cascade of degenerative processes. For example, within certain regions of the brain, insulin and amylin affect neuronal development and glucoregulation. Insulin also acts as an inhibitor to excess food consumption, and affects cognitive function including attention, learning, and memory (Blazquez et al., 2014; Srodulski et al., 2014). High insulin levels in the blood, hyperinsulinemia, cross the blood brain barrier and contribute to AD pathology by increasing amyloid-beta proteins. It is the excess buildup of these proteins that cause these plaques to form (Alafuzoff, Aho, Helisalmi, Mannermaa, & Soininen, 2009).

DM2 is a metabolic disease that affects 17% of older adults and 10% of all Hispanics in California alone (Conroy, Lee, Pendleton, & Bates, 2014; Ekoé & Zimmet, 2001; Whyte, 2013). Epidemiological studies have established that older Hispanic Americans are more likely than African Americans and Whites to have DM2, which places them at a twofold increased risk for dementia development (AA, 2011; Mayeda et al., 2013). A recent study in Southern California discovered that Hispanics are younger at AD diagnosis (Fitten et al., 2013). Contributing factors to the high number of older Hispanic adults that have diabetes are multidimensional. Some of the implicating factors that place this ethnicity at risk are lifestyle choices, cultural beliefs about managing illness, language barriers that encourage poor health literacy, and possibly genetics (Campos, 2006; Hu, Amirehsani, Wallace, & Letvak, 2013). According to current literature, Hispanics that have diabetes and poor health literacy are more likely to have difficulty maintaining adequate glucose control (Hu et al., 2013; Shaw, Huebner, Armin, Orzeck, & Vivian, 2008). To prevent vascular complications, which increase the risk of

AD, researchers have suggested that glucose control is a serum glycosylated hemoglobin level of 7% or less (Olson et al., 2010; ADA, 2014).

In a qualitative study, Gelman (2010) revealed that the Hispanic population believes there are three reasons for not receiving a timely dementia diagnosis. One is the belief that being forgetful is a normal part of aging. A second reason is the language barrier and/or immigration status and lack of insurance that prevents the opportunity for early diagnosis. The third reason is lack of information on symptoms of AD within the Hispanic community. This is an important avenue for social change. Medical providers are in a pivotal position to affect individuals and their beliefs about disease. For the Hispanic population, providers can be given specific tools to identify, diagnose, and treat early signs of dementia, especially of the Alzheimer's type.

This chapter presents relevant literature that has been published in regards to the pathogenesis of AD and its association to DM2. Sections within this chapter include discussions of:

- The literature search strategy that I used to gather medical and scholarly information that pertains to the variables disclosed below that show an association between AD and DM2.
- The conceptual framework that I used to support this study. Specifically, I discuss the accumulation of risk model which reinforces the idea that chronic disease begins earlier in life, accrues as a person ages, and presents the opportunity to create chronic disease.
- The background and pathophysiology of AD and what the current literature states about its incidence, prevalence, and association to DM2.

- The biological risk factors that researchers have identified as the causes and comorbid conditions that link AD and DM2. The main genetic risk factor that I discuss is the APOE ε4 allele.
- The metabolic risk factors that predispose an individual to AD such as inflammatory causes, IR, hyperglycemia, hypoglycemia, and metabolic syndrome (MetS) with each individual component, hypertension (HTN), dyslipidemia, and obesity. I also consider history of stroke as an effect modifier or confounder in Alzheimer's disease.
- The sociological risk factors associated with the development of AD such as cigarette smoking, inadequate intellectual stimulation, low educational attainment, and poor health literacy. I discuss cultural barriers that pertain to the Hispanic/Latino community as well as patient and provider perceptions as barriers to diagnosis.

Literature Search Strategy

AD and its association to DM2 has been studied by others for several years, and I examined every available study, dissertation, and research article for this literature review. I performed an Internet search using *Alzheimer's disease* and *diabetes mellitus type 2* as keywords. To these search terms, I added the following words and phrases: *APOE ε4, amyloid-beta deposits in the brain*, *cultural barriers*, *dementia, dyslipidemia, ethnic disparities, genetic predisposition of Alzheimer's disease, health literacy, Hispanic/Latino, hypoglycemia, hyperglycemia, hypertension, inflammatory causes of dementia, insulin resistance, metabolic syndrome, oxidative stress, provider barriers to diagnosis,* and *smoking.*

I performed additional searches for the same keywords using Google Scholar and PubMed, Medline full text, and EBSCO databases that I accessed via the Walden University library. This led me to over one hundred research studies, meta-analyses, and scientific reports pertaining to AD, DM2, ethnicities and AD development, cultural/ language barriers, and health literacy. I reviewed the reference list of each of these articles for other research studies published within the previous five to six years that pertained to the above literature search criteria. I eliminated research studies that were published before 2008, and also studies that pertained only to diabetes type 1, gestational diabetes, or did not specify AD in any area of the articles. However, many scientific reports about health literacy and cultural barriers were older than five years, but including them was important to the study. Research studies and scholarly works that mentioned mild cognitive impairment and vascular dementia were included if the results reported AD as well. In this way, I was able to examine and evaluate all the risk factors for all groups of dementia.

The World Health Organization (WHO), the Alzheimer's Association, and the National Institute on Aging supplied the most extensive works and scientific reports. Also included in the literature search were specific tools used for the Hispanic population for health literacy as well as any other test used to elucidate cultural barriers pertaining to Hispanic's. Health literacy is an important concept in patient care. It drives how an individual communicates, understands, and complies with health care advice (Coffman, Norton, & Beene, 2012; Nurss et al., 2004; Shaw et al., 2008; Stiles, 2011; Yamashita & Kart, 2011).

Understanding the causes of dementia is an important step public health needs in order to present prevention tactics. This understanding will also help medical providers and their patients ameliorate life situations that predispose them to cognitive dysfunction. Therefore, a theory that postulates causes of illness that expose the human body to cumulative biological damage was needed.

Theoretical Framework

By the late twentieth century, three social epidemiological perspectives emerged: the sociopolitical, the psychosocial, and the ecosocial. The ecosocial perspective combines the psychosocial aspects of health behavior and incorporates the social factors that contribute to the distribution of disease (Krieger, 2011). A life course framework connects early, mid or late life exposures of bodily harm to the possibility that it leads to chronic disease in later life (Ben-Shlomo & Kuh, 2002; Tomita et al., 2012). The accumulation of risk model under the life course perspective is organized by the idea that late life dementia has biologic, metabolic, and sociologic roots. Multiple factors such as smoking, untreated hypertension, high serum cholesterol, obesity, and diabetes, added to unfortunate genetic factors accumulating over a lifetime, create eventual neurodegenerative brain pathology (Mangialasche et al., 2012).

Other researchers have found that wear and tear or "weathering" of bodily systems under physically stressful moments causes an increase in the aging process (Shonkoff, Boyce, & McEwen, 2009). Krieger (2011) refers to this as allostatic load, originally introduced by Bruce S. McEwen. Allostatic load forces the human body to respond to stress biologically, psychologically, and metabolically by clustering physical damage (Ben-Shlomo & Kuh, 2002; Shonkoff, Boyce, & McEwen, 2009). In the case of

dementia development, which can take 20 years, the amount and severity of neurologically damaging events can be ignored until the accumulation is inevitable (Prince et al., 2014).

Solar and Irwin (2010) as well as Ben-Shlomo and Kuh (2002) have described the accumulation of risk model. This model takes the idea that negative events that expose the human body early in life are additive, and as an individual age, the experiences accumulate and produce disease later in life. Certain biological factors are unavoidable such as the APOE ε4 allele genetic risk factor. This allele is the strongest marker for late-onset AD (LOAD), which predisposes individuals to have an increased sensitivity to unhealthy lifestyle behaviors. Therefore, a lifetime of no smoking, increased physical activity, a healthy diet, and very modest alcohol intake has been shown to reduce the risk of AD in those with the APOE ε4 gene (Mangialasche et al., 2012).

Life course epidemiology has provided an avenue to put into perspective health disparities that are from an environmental, and/or a psychosocial nature, and are not just biological. Mangialasche et al. (2012) and Prince et al. (2014) both have noted that higher educational attainment and higher socioeconomic status (SES), especially from midlife to older age, have been shown to reduce the risk of cognitive impairment. This is most likely because of increasing cognitive reserves in the brain. Researchers from the Sacramento Area Latino Study on Aging (SALSA) presented information about Hispanics of Mexican decent. Obtaining higher education protected these individuals from cognitive decline. However, those that had a more privileged childhood but experienced a spiral downward in SES lost their protection from dementia (Al Hazzouri et al., 2010).

Through an individual's life course, metabolic risk factors of DM2, dyslipidemia, HTN, and obesity are modifiable. Sociological risk factors such as smoking, level of education, and poor health literacy are also modifiable. Increasing cognitive reserves early in an individual's life has the possibility to alter the symptoms of dementia and neurodegenerative disease in later life (AA, 2015c; Prince et al., 2014). With the knowledge of genetic risk factors, individuals could be more aware of their opportunity for changing negative lifestyle behaviors to positive ones in order to prevent cognitive decline.

Background and Pathophysiology of Alzheimer's disease

Dementia is a syndrome that is characterized by deterioration in thinking skills, memory, behavior, and independence in caring for oneself. Studies of transitional states from normal aging to the stages of cognitive decline have interested researchers and medical practitioners alike. Mild cognitive impairment (MCI) is on the continuum between normal aging and AD (The Healthy Brain Initiative, 2013). MCI is an accurate diagnosis when an older individual displays memory loss that is more than expected for that individual's age (AA, 2015c; Petersen et al., 2001). It is possible for individuals with MCI to progress to AD, but not everyone will. It is estimated that 60-80% of dementia cases are those individuals with AD (AA, 2015c). Most individuals with AD will experience MCI years before the diagnosis of AD. Individuals that eventually present to a dementia clinic most likely already have some form of dementia. It has been reported that it takes about two years for a person with symptoms to see a medical provider and another year to be diagnosed. Another disturbing statistic is that approximately 20% of those with AD have not received clinical diagnosis (Atri, 2016). It is important therefore,

that clinicians have the tools, resources and time availability to provide screening surveys for their older patients (Sheehan, 2012). The accurate identification of individuals with dementia makes early screening of extreme importance. By detecting these individuals early medical providers are able to recognize, diagnose, and counsel patients that are at risk for developing AD.

Within the different types of dementia there are MCI, vascular dementia (VaD) and AD. Longitudinal studies imply that up to 20% of individuals over age 65 present with symptoms of MCI. MCI produces changes so subtly and mildly that those with MCI do not meet specific dementia classification (AA, 2015c; Xu et al., 2010). VaD has a physiological origin in that it begins as a result of reduced blood flow to the brain. Changes in thinking and memory take place after a stroke, or several strokes that impair blood flow. The risk factors for VaD are similar to AD, which are cigarette smoking, HTN, excessive alcohol consumption, and physical inactivity. VaD and AD can co-exist which can make a diagnosis for AD difficult (AA, 2014b).

Rating scales are numerous and have been used for years in order to diagnose and stage individuals with symptoms of mild cognitive impairment through severe forms of dementia. The type of tool used depends on the symptomology and the type of assessment needed (Sheehan, 2012). According to the literature, assessment of dementia staging uses the least time consuming yet most revealing test common to clinicians (Petersen et al., 2001, 2009; Sheehan, 2012).

The Campaign to Prevent Alzheimer's Disease by 2020 (PAD2020) is an initiative that is working with the Alzheimer's Association to identify individuals in the very early stages of dementia possibly before cognitive dysfunction is apparent. The goal

is to design a "cognitive toolbox" that will assess briefly and accurately a set of diagnostic criteria that medical providers can use at point-of-care (Snyder et al., 2011). Another goal is the ability to use the same tests for the frequent evaluation of cognitive changes over time thereby establishing criteria that would assist medical providers with a timeline for screening cognitive impairment. It would be logical as in mammography screening, that when an individual turned 50, the MMSE would be performed whether there are discernable cognitive symptoms or not. Many tests have been designed with different facets to measure cognitive abilities. One example is the CogState MCI/AD battery specifically designed to involve minimal human support and available in 71 languages (Snyder et al., 2011). It is relatively short, 20-25 minutes, with sensitivity for detecting memory decline at 94% and specificity at 100%. What has been discovered was any change in cognitive function within a year's period of time was positively correlated to cerebral amyloid deposits on PET scans (Snyder et al., 2011).

The Alzheimer's Association supports the following three assessment tests to use in primary care, General Practitioner Assessment of Cognition (GPCOG), Mini-Cog, and Memory Impairment Screen (MIS), (Anderson, 2014). However, the three most common tests in this category that are used most frequently by clinicians are the Mini-Mental State Exam (MMSE), the Clinical Dementia Rating scale (CDR), and the Global Deterioration Scale (GDS), (Sheehan, 2012). The NACC employs a comprehensive grouping of cognitive tools, which include MMSE, CDR, and the MoCA. The MMSE is the most common and widely used in a clinical setting, but the CDR is more reliable for categorizing stages of cognitive impairment. Both the CDR and the GDS provide numerical staging from minimal to severe cases. Longitudinal studies have revealed that

individuals' that eventually develop AD scored poorly on cognitive tests at the outset compared to those that did not develop AD (Petersen et al., 2001). What must be remembered is that tests available to screen cognitive impairment must be interpreted properly, using more than one modality and possibly more than one professional opinion. Multiple assessment tools may require personal interviews with caregivers, patients themselves and possibly even brain imagery to not only identify those at risk, but to monitor changes in neuropathology (Petersen et al., 2001; Sheehan, 2012).

Dementia has either been classified as a mild or major neurocognitive disorder (AA, 2015a). There are two criteria that have been used to diagnose individuals with AD. According to the most recent information, the 2015 Alzheimer's facts and figures by the Alzheimer's Association, the Diagnostic Statistical Manual of Mental Disorders (DSM-V) and the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) have specified certain characteristics that identify individuals with AD. The original criteria, designed in 1984, incorporated individuals that already exhibited memory loss and poor thinking abilities before the diagnosis could be made. With a revision of the 1984 criteria in 2011, the National Institute on Aging determined that within the early stages, AD symptomology could manifest before memory loss develops (AA, 2015a). There are six domains that measure impairment: complex attention, executive function, learning and memory, perceptual-motor, language, and social cognition (Atri, 2016). In 2013 DSM-V changed the word 'dementia' to 'neurocognitive disorder' in which AD is a subtype.

As neurons in other parts of the brain begin to die, other mental and physical problems can manifest (AA, 2015a). The pathophysiology that is associated with the brain damage characterizing AD is compressed plaques between neurons called amyloid-beta plaques, and tangles of tau protein within the brain cells. Tau proteins stimulate tubulin construction into microtubules, which make up the cytoskeleton of the neurons thus giving them structure and dimension. Tubulin binding of tau is regulated by other proteins and in abnormal conditions, as in the beginning of cognitive dysfunction, a switch called phosphorylation causes a reduction of tubulin. This sets up a cascade of poorly structured microtubules in the neuronal cell causing the cell to collapse (Kolarova, Garcia-Sierra, Bartos, Ricny, & Ripova, 2012). With neuronal death the brain atrophies leaving more unoccupied space allowing the lateral ventricles to expand (Prince et al., 2014). To what extent inflammation and oxidative stress interact with neuronal death is questionable, meaning which came first or do they work synergistically.

Medication has been developed to slow down mental decline in AD and to help with improvement in activities of daily living but has been only mildly successful (AA, 2015b; Johnston, Covinsky, & Landefeld, 2005). Four medications have been developed since 1996 that target two different mechanisms. Donepezil (Aricept), galantamine (Razadyne), and rivastigmine (Exelon) are cholinesterase inhibitors. Since AD is characterized by neuronal death, a cholinesterase inhibitor slows down the disruption of chemicals from synapse to neuron transmission that relays communication and therefore storage of information. Memantine (Nemenda) is a N-Methyl-D-aspartate receptor antagonist. Through a complicated process glutamate is allowed to attach to neurons and help to maintain learning and memory (AA, 2015b). Each population and ethnicity

responds differently to these medications possibly depending on amount of damage, early diagnosis, and genetics. Researchers are working on designing medications that would treat the underlying disease however volunteers are needed for clinical trials. Clinical trials are currently being conducted that are focusing on targeting the tau protein abnormalities rather than just amyloid-beta increase (Atri, 2016). It has been documented that some diverse populations, which include Blacks and Hispanics, are especially needed in these clinical trials (Lines & Wiener, 2014; Singleton, 2014).

Biological Risk Factors Associated with Alzheimer's Disease

Age & Heredity

There are known factors that predispose an individual to AD. The most recognized risk factor is getting older. According to a 2015 report, one out of every nine individuals over the age of 65 has been diagnosed with AD (AA, 2015a; Ross et al., 2009; Yaari & Corey-Bloom, 2007). There is a clinical differentiation between early-onset Alzheimer's disease (EOAD) and late-onset Alzheimer's disease (LOAD) which is also considered sporadic AD. Early onset can begin in a person's 30s, 40s, or 50s (Koedam et al., 2010). What sets EOAD and LOAD apart is the genetic cause and the age of the individual at earliest recognizable symptoms. EOAD, like LOAD, is incurable and is solely dependent on genetics as to its cause, where LOAD can be associated with metabolic factors that complicate age related illness (Strobel, 2015). EOAD is also called familial because there is a strong genetic connection with a 50-50 chance siblings and parents will be affected as well. The agreed on consensus is that LOAD is always after age 75, but there is no agreement on when to diagnose LOAD versus EOAD. This is due to the deterministic genes for AD development that can be difficult to differentiate

specifically from familial AD, which is presenilin-1 (PS1) and the gene that is associated with LOAD development, which is the APOE ε4 gene (Koedam et al., 2010; Morris, Clark, & Vissel, 2014; Strobel, 2015). Many families that have limited genetic history ignore symptoms of cognitive impairment in their parents when they are over 60 years of age confusing the diagnosis of EOAD that could possibly have been present. What is difficult to miss and is considered a rare occurrence are symptoms of executive dysfunction and apraxia in a 45-year-old individual (Koedam et al., 2010; Strobel, 2015; Yaari & Corey-Bloom, 2007).

In a retrospective study to compare early symptoms of EOAD to LOAD researchers evaluated medical charts of 270 EOAD patients and 90 LOAD patients. The most common early symptom was visuospatial dysfunction in the EOAD group whereas memory loss was the most common symptom of LOAD (Koedam et al., 2010; Yaari & Corey-Bloom, 2007).

Genetics

The most outstanding genetic risk factor is the apolipoprotein gene (Morris, Clark, & Vissel, 2014). Apolipoprotein E ε4 is one of three common forms of the APOE allele. The tendency to inherit the locus, or position, of this gene in association with AD development has been confirmed by several studies. There are loci for a link to AD on chromosomes 1, 9, 10, 12, and 19 (Rogaeva, 2008). The three common alleles are epsilon 4 (association with AD), epsilon 3 (neutral), and epsilon 2 (AD protective). Epsilon 2 (ε2) occurs in about 7% allele frequency and has a poor binding capability. Epsilon 3 (ε3) has a 79% allele frequency but is considered neutral therefore within itself is harmless. Risk for disease development is rated according to copy combinations. There are five

haplotypes: 3/3,3/4, 2/3, 2/4, and 4/4 (Atri, 2016). The allele combination that presents an increased risk for AD are ε2/ε4 or ε3/ε4 however, ε4/ε4 produces the greatest risk. It is important to mention that this gene does not need to be present for AD to develop (Ghebranious, Ivacic, Mallum, & Dokken, 2005). It is interesting to note that only about 2% of individuals with AD have the epsilon 2 allele, as many as 40% of AD individuals have the epsilon 4 allele (Rogaeva, 2008). The APOE is a protein that is commonly made in the liver and the macrophages. It is also made in the central nervous system (CNS) by astrocytes and allows cholesterol to be moved in and out of the brain (Huang & Mahley, 2014; Rohn, 2014). This APOE gene makes up a prominent lipoprotein called very low-density lipoprotein (VLDL), which clears excess cholesterol from the blood to be processed by the liver. With that being said, being mindful of a normal cholesterol level in any individual is vital to several preventative disorders, dyslipidemia, heart disease, and stroke (Genetic home reference, 2008).

It is also thought that the APOE protein helps neurons repair because it is activated in nerves that are remodeling after damage (Huang & Mahley, 2014; Yaari & Cory-Bloom, 2007). Homogeneity of this gene is when both parents contribute a specific allele, heterogeneity is when only one parent contributes a specific allele (Genetic home reference, 2008; Rohn, 2014). The risk of developing AD is much higher if an individual inherits two alleles for the APOE ε4 gene (Ross et al., 2009). However, it must be stated that the APOE genotype creates a heritable predisposition for some individuals. Aslan et al. (2010) are in agreement with Yaari and Corey-Bloom (2007), that possessing the APOE ε4 allele was strongly associated with AD but does not specifically determine this form of dementia [*OR*: 2.91 (95% CI 1.237-6.823)], (Crean et al., 2010). White

individuals have up to a 15-fold increase in risk of AD. However, in the same report Yaari and Corey-Bloom (2007) state that as many as 50% of LOAD individuals do not have a ε4 allele.

In a study reported by Campos, Edland, and Peavy (2013), Mexican Hispanics were considered to have European, African, and Amerindian genomes. Caribbean Hispanics (Puerto Rican, Cuban, and Dominican) generally had more African influence in their genomic type therefore what is the susceptibility to AD development among Hispanics knowing this? This meta-analysis showed that the White cases studied had a higher frequency of the ε4 allele at 43%; Mexican Hispanics cases had 21.4%. The association discovered by Farrer et al., reported by Campos, Edland, and Peavy (2013) concluded that the risk of developing AD, as previously documented, is higher in Hispanics than Whites. Studies performed by Haan (2003) and O'Bryant et al. (2013a) show that Hispanics possessing this allele less frequently in their population, must have other chronic conditions that present risk factors to AD development.

Genetic studies have revealed that chromosome 10 comprises an extensive area that associates AD and DM2. The gene that creates the insulin degrading enzyme (IDE), the substance that allows for clearance of amyloid-beta, is located near an area that is thought to be responsible for LOAD. It has been shown that IR, and IDE in a recent longitudinal study, link hyperinsulinemia to an increased risk of AD (Williamson, Goldman, & Marder, 2009; Xu et al., 2010). A study cited by Cheng et al. (2011) from Finland, concluded that IR is associated with AD regardless of APOE e4 allele status. Even though genetics cannot be changed, those that can be identified earlier in their life-

course have the ability to modify their risks (Huang & Mahley, 2014; Prince et al., 2014; Rohn, 2014).

Negative risk factors that are modifiable such as excessive alcohol use, smoking, and eating a diet high in fat place individuals in a high-risk category (Mangialasche et al., 2012). The E4 allele has been associated with the majority of LOAD in Whites but weakly associated in Blacks and Hispanics (Lines & Weiner, 2014; O'Bryant et al., 2013; Reitz, Brayne, & Mayeux, 2011). Medicare claims from 2006 discovered that the ethnicity with the highest rate for AD diagnosis was Hispanics at 14% compared to 9% for Whites. It has been found that the APOE ε4 gene was less common in Hispanics (21.4%) than Whites (42.9%). This study concluded that the risk of AD in Hispanics was less likely due to the APOE ε4 gene compared with Whites even though multiple studies place Hispanics at the top of the AD risk stratum (AA, 2011; Campos, Edland, & Peavy, 2013; Fitten et al., 2013; O'Bryant et al., 2013).

Data from Project FRONTIER (Facing Rural Obstacles to Health Now Through Intervention, Education & Research) and TARCC (Texas Alzheimer's Research & Care Consortium) were analyzed in which 1628 individuals, White (n=1002) and Mexican Hispanics (n=626), were examined and evaluated for cognitive impairment (O'Bryant et al., 2013b). The results revealed that Mexican Americans were younger, had less years of education, had a higher BMI, and were more likely to have DM2 when diagnosed with MCI but the results were not statistically significant (Whites 19% and Mexican Americans 20%). O'Bryant et al. (2013b) agreed with previous studies that if the Mexican Hispanic population actually carry the APOE ε4 gene less frequently than other ethnicities, and yet have a higher incidence of MCI/AD then it has been suggested that

other factors must be evaluated. O'Bryant et al. (2013b) suggested according to the results of the FRONTIER and TARCC studies that diabetes played an important factor in AD development within this ethnicity and should be evaluated further. In a study performed by Blazer et al. (2003) with results reported by Aslan et al. (2010), it was discovered that the ε4 allele was present in 29% of diabetics, 31% in those with HTN, and 32% in those with a stroke history.

Some conflicting statistics, though, state that bias existed in some reports. Most of the research studies were performed on White, higher educated individuals that have fewer comorbid illnesses (Crean et al., 2010; Lines & Wiener, 2014). Crean et al. (2010) have surmised that this stemmed from how the subjects were recruited, case definition, and E4 homozygote or heterozygote carrier state per demographics studied. It was possible that subjects for RCT were chosen by their genotyping as opposed to a community wide sweep of all older individuals with cognitive impairment. If the criteria were to include probable AD diagnosis rather than possible AD diagnosis, determined through neuroimaging, psychological testing, and genotyping, the clinical diagnostic accuracy would increase from under 50% to over 75% (Crean et al., 2010).

Metabolic Risk Factors Associated with Alzheimer's Disease

The hallmark of AD, neural degeneration, can begin many years before significant symptoms arise (Candeias et al., 2012; Khan & Alkon, 2014). Because age can play a factor in cognitive functioning, older individuals (>65 years) are more likely to display AD symptomology than younger individuals especially if there is a genetic predisposition such as the APOE gene. Candeias et al. (2012) pointed out that aging, diabetes, and the APOE alleles were the main risk factors that contributed to the

pathogenesis of AD. Some of the metabolic risk factors that contribute to AD are neuronal inflammation, insulin's effect on the brain, and hypo and hyperglycemia.

Inflammatory factors

Recent literature has focused on inflammatory causes as a risk factor for the development of dementia and DM2 (Licastro et al., 2014; Wang et al., 2011). The current literature hypothesizes that inflammation in the body either, causes AD, encourages and helps AD to manifest, or is strictly a by-product of dementia itself. However, even though inflammation is present in brain tissue of individuals that have AD, it is not a requirement for the onset of dementia (Encui & Popescu, 2013). The inflammatory cascade is complicated with different pathways that are called into action whether there is acute or chronic inflammation present in the body. Acute is described as minutes to hours after bodily injury, infection or tissue damage. Chronic inflammation is characterized by days to years of the activation of several proteins that are intentionally released in the bloodstream that no longer repair damaged tissue but irritate blood vessels (Conway, 2000; Mushtaq et al., 2014; Sharma, 2012). It is problematic to blame a single event on the inflammatory cascade since multiple factors create an environment for metabolic dysregulation.

It is hypothesized that blood vessel damage by oxidative stress is the initial step in the neurodegeneration of AD. Oxidative stress takes place when the body cannot keep up with repairs from free radical damage because of altered DNA methylation (Madeo & Elsayad, 2013). Aging in itself is associated with oxidative stress, which causes cell and neuronal death; however, other processes work synergistically to promote damage (Madeo & Elsayad, 2013). Normal aging is associated with reduced cerebral blood flow

due to atherosclerosis and other mechanisms that cause the endothelial portion of the blood vessels to thicken (Morris, Clark, & Vissel, 2014). It has been found that those with AD also have evidence of peripheral inflammation denoting that damage by free radicals is global and not just limited to the brain (Licastro et al., 2014; Madeo & Elsayad, 2013).

As oxidative stress continues, the small arterioles and capillaries in the brain respond to the chronic inflammatory state. This chronic inflammation creates areas of ischemia, poor blood flow in which nutrients cannot reach the cells, which further disrupt neuronal function (Marchesi, 2011). Neuroinflammation from chronic inflammatory cytokines is what causes neuritis and sets the brain up for AD (Mushtaq et al., 2014). Cytokines are intercellular mediation proteins that trigger inflammation and are released in an immune response (Definition of cytokine, 2012). Inflammatory factors create an environment for endothelial damage, amyloid-beta plaque development and hyperphosphorylation of tau proteins leading to neurofibrillary tangles. The original amyloid hypothesis stated that an accumulation of amyloid-beta in the brain began the cascade of damage to synapses, neuronal cells, and thereby neurodegeneration. More recent information states amyloid-beta proteins are part of, but not the sole cause of, LOAD. There are several factors that contribute to AD pathology those being genetics, amyloid-beta proteins, tau proteins destroying the structure of neuronal cells, and a chronic inflammatory state (Morris, Clark, & Vissel, 2014).

It is believed that the CSF through the blood brain barrier transports amyloid-beta protein, therefore any accumulation of this substance, is what causes the hallmark features of AD (Medhi & Chakrabarty, 2013). Researchers have also reported that the

increase of tau protein in the CSF, as well as, in the brain noted on PET scans is highly diagnostic of AD, more than amyloid-beta alone (Atri, 2016). Ten to 15 years before obvious functional impairment these manifestations are taking place creating the eventual deterioration in cognitive functioning and memory (Madeo & Elsayad, 2013; Mushtaq et al., 2014).

Three inflammatory cytokines that affect brain tissue and are connected to DM2 are TNF-α, Il-6, and CRP. Cytokines such as TNF-α and Il-6 are mediators of the inflammatory cascade. CRP is the serum marker that elevates in the presence of inflammation in the serum (Mushtaq et al., 2014). In response to TNF-α the liver makes more glucose and triglycerides. At the same time, it decreases the cells ability to absorb glucose increasing insulin resistance in the presence of obesity, and the pathogenesis of diabetes. In a cohort study performed on a Danish population with AD, high levels of TNF-α and Il-6 were found in the serum as well as cerebral spinal fluid (CSF) of AD patients (Blázquez et al., 2014; Licastro et al., 2014; Mushtaq et al., 2014). Inflammation also plays a part in the development of DM2. According to authors Wellen and Hotamisligil (2005), diabetes is considered an obesity linked inflammatory disease. Twenty years ago researchers found that TNF-α was abundantly produced in adipose and muscle tissue of obese individuals. Inflammation can link obesity with insulin resistance but it is unknown at this time, which came first. Does inflammation instigate IR and therefore obesity or is inflammation a result of IR? It is also documented that hyperlipidemia is involved with inflammation but in what stage this takes place is unknown (Wellen & Hotamisligil, 2005).

The Rotterdam Study was one of the original studies to reveal that individuals with DM2 are at an increased risk for AD. How these two diseases are linked through inflammatory manifestations is thought to be a result of IR. In order to determine if these inflammatory mediators could predict future diabetes development, the West of Scotland Coronary Prevention Study was performed. CRP was elevated in those that were prediabetic, therefore speaking to the idea that inflammation is an early effect in the diabetes continuum (Mushtaq et al., 2014).

In a study that was part of the Pre-Diabetes Intervention Project (PDIP) from 2006-2008, researchers gathered and studied 340 participants, 96 men (average age of 67.85 +/- 5.35 years) and 244 women (average age 64.30 +/- 6.02 years). Seventy-one of these participants had normal glucose, 189 were considered prediabetic, and 80 were diabetic. Researchers discovered that highly sensitive-cross reactive protein (hs-CRP) as well as other variables of age, sex, waist circumference, triglyceride levels, and IR was a positive risk factor for the development of diabetes (Wang et al., 2011).

Randomized control trials have shown that obese individuals have more TNF-α in their adipose tissue establishing a connection between obesity, DM2, and inflammation. TNF-α along with being a major component of systemic inflammation, aggravates the liver into increasing glucose production, and thereby increases insulin resistance. Insulin resistance and inflammation can be linked to DM2 and AD.

Insulin resistance

IR is a condition in which tissues like muscle, liver, fat cells, blood vessels, and the brain do not have the ability to recognize or use insulin. Insulin is a hormone that is made by the pancreatic beta cells in response to glucose in the bloodstream. Insulin takes

glucose in the bloodstream and deposits it into cells for energy. In the brain, it is carried by the CSF, passing through the blood brain barrier and is stored and used in the hippocampus affecting learning, forming and recollection of new memories (Barbagallo & Dominguez, 2014; Candeias et al., 2012; De Felice, 2013). Insulin is used in the hypothalamus to reduce glucose generation by the liver and to regulate food intake. It is interesting to note that the hypothalamus lacks a certain amount of barriers, which allows insulin to proceed into its structure more efficiently (Kleinridders, Ferris, Cai & Kahn, 2014). Amyloid-beta can build up in the brain when there is not enough insulin. One of the roles of insulin in the brain is to turn on the IDE pump that clears out the excess amyloid-beta (Kawamura, Umemura, & Hotta, 2012). Too little insulin in the brain has been seen in AD patients and consequently these individuals have too much insulin in the peripheral tissues (Dickstein et al., 2010; Whitmer et al., 2009). With this being said, insulin has neurosupportive properties that protect against early cellular death, amyloid buildup, and oxidative stress (Blázquez et al., 2014). It has been reported that insulin delivered directly into the brain, either intranasally or by infusion, improved cognitive functioning in individuals with cognitive dysfunction and AD (De Felice, 2013; Duarte et al., 2013; Kuljiš & Šalković-Petrišić, 2011).

The current literature supports the idea that insulin is important to brain function and cellular energy in peripheral tissues. Both AD and DM2 have symptoms of IR. Dickstein et al. (2010) report that hyperinsulinemia is a risk factor for dementia. AD is thought to be an insulin resistant brain condition since receptors in the hippocampus are lacking insulin at the time of dementia diagnosis (Dickstein et al., 2010). Aging is a risk factor for the development of DM2 and AD; both diseases prevent a long, healthy quality

of life for the older individual. DM2 and AD present with IR, amyloid buildup, inflammation, and cognitive dysfunction. Both of these diseases take many years of progressive damage to appear. DM2 is a result of IR due to obesity and chronic inflammation. Because DM2 and AD share IR, AD has been considered type 3 diabetes (Blázquez et al., 2014; Li, Song, & Leng, 2015). In a study using 500 older individuals with and without DM2, Heijer et al. (2003) reported that individuals with a history of IR demonstrated increased brain atrophy on brain MRIs (Wilson, 2012). In a meta-analysis gathered by Ryan, Fine, and Rosano (2014), those with baseline IR had worse performance on processing information. Structural MRIs of DM2 brains revealed reduced total brain volume compared to those with no cognitive decline (Ryan, Fine, & Rosano, 2014).

Hypoglycemia

Individuals that are older, have diabetes for at least 10 years, and use insulin along with oral medications are at risk for complications of blood sugar that is too low called hypoglycemia. Hypoglycemia is usually induced by exogenous insulin use or improper use of diabetes medications (Duarte et al., 2013). Older people are considered to have less brain plasticity and reserve. This makes the older individual's brain less flexible for recovery from neuronal damage (Whitmer et al., 2009). Hypoglycemic episodes in a younger diabetic, less than 60 years old, could produce no long lasting affect but in an older individual, this can lead to dementia. How hypoglycemia affects the brain is thought to reduce nutrient transport, possibly causing neuronal death, and damaging areas of memory (Bornstein et al., 2014). Episodes of hypoglycemia also are related to transient ischemic attacks (TIA), (Liu & Sheu, 2012). When normal glucose, which is 4-7

mmol/L, falls below 4mmol/L the individual becomes confused and disoriented, thereby multiple hypoglycemic events have been linked to dementia (Whitmer et al., 2013; Wilson, 2012).

In a study performed by Whitmer et al. (2009), 16,667 older individuals were evaluated for dementia risk attributable to severe episodes of hypoglycemia that required hospitalization. It was discovered that a 2.4% increase in absolute risk per year of follow-up was attributable to those with a history of hypoglycemia contrasted to those with no history of hypoglycemia. However, with accumulation of events, neuronal death and cognitive dysfunction can increase (Lui & Sheu, 2012; Whitmer et al., 2009). Results in the Edinburgh Type 2 Diabetes Study and the Fremantle Diabetes Study revealed severe hypoglycemia could be associated with dementia risk. The bias involved with these studies was that diabetes was self-reported, and the use of a single healthcare system. In order to maintain a connection between hypoglycemia and dementia risk, researchers Lui and Sheu (2012) gathered one million individuals through the National Health Research Institutes in Taiwan. The RR was significant for diabetics with episodes of hypoglycemia exhibiting dementia at 2.76 (95% CI 2.06-3.70, $p < 0.001$) as opposed to those diabetic individuals that reported no episodes of hypoglycemia at 1.60 (95% CI 1.19-2.14, $p = 0.003$), (Lin & Sheu, 2012).

In evaluating the link between DM2 and AD, the process that brought the individual to the diabetic state is important to understand. IR and insufficient insulin secretion are the two basic functions that are taking place. Beta cells in the pancreas respond to serum glucose by putting more insulin in the blood stream. IR takes place in the presence of obesity, which causes hyperinsulinemia. Hyperinsulinemia has been

linked to amyloid-beta plaque development in the brain, as well as in the pancreas of DM2 individuals (Li, Song, & Leng, 2015). Hyperinsulinemia has been linked to DM2 in which one well-documented cause is obesity (Craft, 2010; Emanuela et al., 2012; Prince et al., 2014). Adiposity, especially central fat deposits, affects the brain through inflammatory cytokines and hyperinsulinemia (Emanuela et al., 2012). Midlife obesity has been linked to DM2 development and dementia in later life (Craft, 2010).

Hyperglycemia

Hyperglycemia takes place when the pancreas is unable to produce enough insulin for the present glucose load in the blood stream ("Hyperglycemia", 2014). Hyperglycemia is characterized by either an OGTT result of 200 mg/dl, a fasting glucose result of 126 mg/dl, or a glycated hemoglobin (HbA1c) result of over 6.5% (Craft, 2010). Previous studies have reported a fourfold increase in cognitive dysfunction in individuals with HbA1c >7% compared to those with blood glucose readings of HbA1c <7% (Kawamura, Umemura, & Hotta 2012). The prevalence of DM2 increased with age and was estimated that 25% of those 65 years and older were affected. The effect of uncontrolled glucose on the brain can be considered additive. The longer diabetes has the opportunity to affect the vascular system the greater the potential for brain atrophy and cognitive impairment (Kawamura, Umemura, & Hotta, 2012; Ryan, Fine, & Rosano, 2014). Chronic uncontrolled blood glucose levels as measured by HbA1c >7% have been associated with a three times higher risk for stroke and AD development than individuals with normal glucose (HbA1c <5.6%), (Barbagall & Dominguez, 2014; Cheng et al., 2011; Akter et al., 2011). The Kingholmen study revealed that individuals with very high HbA1c levels were at the highest risk of dementia development without regard to

concomitant vascular pathologies (Exalto et al., 2012; Sridhar, Lakshmi, & Nagamani, 2015). Studies have shown that cognitive decline can be avoided with controlled glycated hemoglobin, which points to a connection between DM2 and cognitive impairment (Wilson, 2012).

The metabolic risk factors that increase an individual's chance for dementia development are hyperglycemia, hypoglycemia, IR, obesity, HTN, and dyslipidemia. Researchers have questioned which process is specifically linked to DM2 and AD. Whether it is strictly glucose, HTN, or IR as separate complications, all of these can contribute to a variety of conditions that are included in the metabolic syndrome (Li, Song, & Leng, 2015). The Metabolic syndrome (MetS) is a cluster of factors that contain these variables that are all known to produce elevated risk for cardiovascular disease, cerebrovascular disease, DM2, and AD (Garcia-Lara, Aguilar-Navarro, Gutierrez-Robledo, & Avila-Funes, 2010).

Metabolic Syndrome

MetS is a condition of multiple factors that contribute to heart disease, diseases of the brain and encompass known risk factors for DM2 and AD. The World Health Organization (WHO) has defined MetS as a constellation of several metabolic conditions that must be present. The conditions are IR, hyperglycemia (fasting blood glucose [FBG] >100mg/dl, or glucose intolerance diagnosed by a two-hour oral glucose tolerance test [OGTT] result of >200 mg/dl), and obesity measured by a BMI of >30 kg/m^2. What is also included is a serum triglyceride level of >150 mg/dl, an HDL cholesterol level of <35 mg/dl, and blood pressure of 140/90 or greater (Craft, 2009; Garcia-Lara et al., 2010). The International Diabetes Federation (IDF) has added the pro-inflammatory state

as a risk factor for MetS (Dallmeier, 2012; Sharma, 2011; Solfrizzi et al., 2009). Each element of the MetS should not be evaluated separately as it is still under investigation whether each factor is additive or interactive in some way (Li, Song, & Leng, 2015).

A population cohort in the United States studying 980 individuals between the ages of 69-78 found an association between the MetS and AD. However, it is interesting to note that four longitudinal population based studies, the Italian Longitudinal Aging Study, the Honolulu-Asia Aging Study, the Three-City study, and a large study incorporating several different ethnicities in the United States, found no association between MetS and AD. Older Latinos in the SALSA study who had MetS progressed more quickly into cognitive decline than those without MetS (Li, Song, & Leng, 2015). A case-control study taking 90 patients with AD and 180 non-demented patients in Mexico City with an age range of 66-97 years discovered that MetS was more frequent in the AD group. The results were statistically significant at 72.2% vs. 23.3% with p value < 0.001. Therefore, among these AD patients, having MetS was seven times higher than those that did not have dementia (*OR* 6.72, 95% CI 3.72-12.13; $p < 0.01$). The NHANES III study and the San Antonio Heart Study both discovered a higher prevalence of Mexican Americans possessing all of the factors of MetS with 31% to 23% in Whites (Hildreth, Grigsby, Bryant, Wolfe, & Baxter, 2014). It is important to note that all of the entities that comprise MetS should not be evaluated separately. Individual factors that make up MetS are under debate as how they are associated to the development of AD. The route that all of these conditions follow, pathophysiologically, likely brings all the factors to a single mechanistic plateau.

Metabolic Syndrome and Obesity

Obesity can be measured three ways: (a) Body mass index (BMI), which is related to total body fat and takes weight in kilograms divided by height in meters squared (kg/m^2), (b) waist circumference (WC), which is considered to be possibly more accurate than BMI because it focuses on adipose tissue around the abdomen, and (c) waist hip ratio (WHR), which is calculated WC and hip thickness at the widest part over the greater trochanters (Abbatecola et al., 2010; Loef & Walach, 2013; Luchsinger, Cheng, Tang, Schunf, & Mayeux, 2013). It has been mentioned that obesity is the origin of IR therefore hyperinsulinemia affects peripheral tissues as well as brain CNS tissue.

Obesity has become a public health topic because it affects several disease states. Since the 1980s obesity has been increasing in most parts of the world. Ten years ago, approximately 205 million men and 297 million women had a BMI > 30 kg/m^2. If an association can be made between obesity and dementia, the public health impact would be substantial (Prince et al., 2014). The ideal composition of body fat is still under investigation, however, obesity has been agreed upon as a BMI of > 30 kg/m^2. The majority of studies have been performed on midlife individuals with measured or self-proclaimed obesity by BMI (Fitzpatrick et al., 2009; Luchsinger et al., 2012; Luchsinger & Gustafson, 2009). Visceral body fat is currently considered to be an endocrine organ within itself due to the pro-inflammatory reactions it creates. It has been discussed that high body fat leads to hyperinsulinemia and DM2 with both of these conditions being risk factors for AD (Abbatecola et al., 2010; Fitzpatrick et al., 2009; Salas et al., 2016).

Central obesity in midlife is related to a higher incidence for dementia development including AD. The Cardiovascular Health Study demonstrated that midlife

obesity, defined as 40 to 59 years old, was linked to an increased risk of dementia in later life, however, higher BMI at 65 years old was not associated with dementia (Luchsinger et al., 2013). In a meta-analytic search, authors Loef and Walach (2013) found that underweight individuals (BMI<25) had an inverse relationship to dementia, obese individuals (BMI >30) through mid-life (40-59 years of age) had a twofold risk for all dementias (RR = 1.91). Abbatecola et al. (2010) studied 693 persons aged 65-85 years old longitudinally with the intention of linking DM2 and obesity to AD development. The results were those with normal glucose, but increased BMI during the study, showed no signs of cognitive dysfunction but the individuals with DM2, and the most obese in the group, had a twofold risk of worsening cognitive decline per MMSE at a 2-year follow-up. Therefore, it is interesting to note that those over 75 years of age, when discussing the association between obesity and AD, showed a U shaped curve.

Referring back to the Cardiovascular Heart Study, higher BMI in mid-life was related to a higher risk in dementia but not in the older group (>65). The limitations of the Cardiovascular Heart Study were recall bias in which subjects were asked what they remembered their weight to be at age 50 (Prince et al., 2014). Other studies have used WC as a better marker for obesity (Abbatecola et al., 2010). The result of aging is that body composition changes by reducing lean muscle but increases overall body fat without true weight gain (Fitzpatrick et al., 2009). Most of the studies on obesity whether using BMI or WC have conflicting results except when other risk factors are added as covariates. The Framingham Heart Study demonstrated that obesity and hypertension were adequate predictors of cognitive decline, emphasizing that the covariates under the MetS possibly work synergistically.

Metabolic Syndrome and Hypotension and Hypertension

Blood pressure that is elevated is common throughout the world. The World Alzheimer's Report states that approximately 60% of the 60-69 year olds are affected by HTN whereas this number increases to 72% in individuals between 70-79 year olds in the United States (Prince et al., 2014). HTN is defined by a systolic blood pressure (SBP) of 140 mm Hg and a diastolic blood pressure (DBP) of 90 mm Hg (Craft, 2010; Dickstein et al., 2010). Blood pressure readings increase as individuals age due to hardening of the arteries which makes the arteries less flexible (Dugdale III, 2012). It can be compared to forcing water at high pressure through a narrow hose. Higher blood pressure in the oldest old is medically acceptable and understandable if below 150/90. However, those that have higher blood pressure readings in younger and midlife face the opportunity for accumulation of vascular damage during the years to older age. A singular risk factor, according to Prince et al. (2014), for mortality in the older individual is HTN. The damage that elevated blood pressure presents is thought to increase amyloid-beta plaques, which leads to various types of dementia (Dickstein et al., 2010). The NHANES survey from 1999-2004 asked individuals whether respondents had treatment for HTN. Controlled HTN, according to the NHANES who surveys thousands of residents yearly, was among 60-79 year olds at 47% and 80 years and older had 36% controlled blood pressures. The WHO has documented that the low and middle-income countries compared to other countries have consistently poorly controlled HTN (Prince et al., 2014).

The accumulation of risk model claims two things. A lifetime of vascular injury from vasodilation and vasoconstriction, as well as reducing the vascular systems ability

to maintain the blood brain barrier leads to late life dementia. Midlife HTN has been related to the development of vascular dementia and AD most likely through decreased blood vessel patency (Craft, 2010; Reitz, Brayne, & Mayeux, 2011). A study by Skoog et al., reported by Garcia-Lara et al. (2010), discovered that AD patients had a 15-year history of HTN prior to the diagnosis of AD. Epidemiologically, HTN precedes dementia by 30 years however the progression is not linear and therefore cannot be taken as evidence alone for AD. Imaging studies have revealed that tissue degeneration, ventricle enlargement, and infarcts are present in the brains of individuals with HTN. All of these conditions can lead to dementia even though there are conflicting results from longitudinal studies.

It is well accepted that HTN in midlife is associated with AD; however, the same cannot be true of late life HTN (Dickstein et al., 2010). The Framingham Study was the first study to make an association between HTN and cognitive dysfunction with the Rotterdam study, the Honolulu-Asia Aging Study, and the Epidemiology of Vascular Aging Study in agreement with those results (Dickstein et al., 2010). In the Framingham Study, 4,897 adults that were stroke and dementia free at 55 years old, longitudinally discovered that the life time risk of stroke in a 65-year old woman with normal blood pressure was half that of the same 65 year old woman with HTN. Thereby pointing out that certain lifestyle modifications, education and treatment of high blood pressure, is vastly important to reduce stroke risk and possibly AD (Seshadri et al., 2005).

It is interesting to note that some studies have found antihypertensive treatment to not have a positive effect on cognition. However, it must be noted that these studies can be considered biased since they were performed on individuals that did not have

dementia. It is thought that antihypertensive medication, a calcium channel blocker for example, decreases calcium within the neurons stopping the opportunity for brain pathology to transpire (Dickstein et al., 2010; Razay, Williams, King, Smith, & Wilcock, 2009).

Elevated blood pressure has been positively correlated with cognitive dysfunction, but it is therefore interesting to note that blood pressure that is too low can have deleterious effect on the brain as well. A DBP of <70 mm HG has been linked to increased mortality. This might be a case of reverse causation in that AD affects the autonomic centers of the brain thereby disrupting the blood pressure. Cerebral perfusion, in this situation less blood flow to the brain, is another idea that hypotension is related to AD as discovered in the OPTIMA study (Razay et al., 2009).

Metabolic Syndrome and Dyslipidemia

Blood serum cholesterol has several components that should be defined. Total cholesterol consists of triglycerides, low-density lipoproteins (LDL), and high-density lipoproteins (HDL), (Baron, 2005; Prince et al., 2012). Cholesterol levels have been defined and categorized by the 2002 Adult Treatment Panel (ATP) III guidelines in which a total cholesterol (TC) < 200 mg/dl is appropriate, borderline is between 200-239 mg/dl, and > 240 mg/dl is considered inappropriately high (Solomon, Kivipelto, Wolozin, Zhou, & Whitmer, 2009). Dyslipidemia is when the components of total cholesterol are elevated and create a high risk for cardiovascular complications from inflammation in the arteries (Prince et al., 2014; Schreurs, 2010). Lipids are fats that are the basis of all cellular structures. This includes neuronal cells and therefore makes up to 30% of brain composition cholesterol rich. Because cholesterol is so vital to brain function, the blood

brain barrier confiscates a substantial amount from peripheral use to be used for learning and memory. Levels of HDL, the good cholesterol that is considered protective, lower than 35 mg/dl, has been implicated in memory decline in midlife (Schreurs, 2010). The Whitehall study showed that low HDL is related to cognitive decline whether or not the individual was positive for the APOE ε4 gene. This study also emphasized the importance of early recognition of cognitive decline in diabetics. There is an association between IR, dyslipidemia and cognitive dysfunction regardless of ethnicity and APOE genetic susceptibility (Yamazaki et al., 2011).

Epidemiological studies analyzing the association between cholesterol levels and AD have produced inconsistent results. The working theory is that cholesterol was measured at a time in an individual's life when an accumulation of events was not significant enough to register a deficit or were measured late in life (Dickstein et al., 2010; Prince et al., 2014). The Uppsala Longitudinal Study of Adult Men and the Three-Cities cohort study revealed no association between late life total and LDL cholesterol and AD. The one idea that can be agreed upon is high cholesterol during an individual's middle years is a risk factor for AD development (Dickstein, 2010; Solomon et al., 2009). The Kaiser Permanente historical cohort study found that having a total cholesterol (TC) level over 200 mg/dl increased the risk of AD (borderline TC HR 1.23, 95% CI 0.97-1.55, high TC HR 1.57, 95% CI 1.23-2.01). The Cardiovascular Risk Factors, Aging, and Dementia study (CAIDE) as well discovered that an elevated midlife cholesterol level was associated with AD (Prince et al., 2014; Solomon et al., 2009). Craft (2010) reports the results of 18 prospective studies in which an association was discovered between

midlife TC and AD risk but discovered no association to AD risk in late life TC measures.

Insulin acts as a regulator for the manufacturer of lipids as well as degradation of lipids. Insulin resistance in fat cells causes the breakdown of lipids. Where this becomes a problem is the free fatty acids that are increased due to this process inhibit the ability of insulin to suppress the release of the dangerous lipids into the bloodstream after a meal. Most of the studies came to the conclusion that a rapid decrease in TC during an individuals' mid to late-life can potentiate the onset of AD (Prince et al., 2014).

What must be considered then is if high cholesterol in midlife is a risk factor for AD, why in late life an inverse relationship has been discovered through several studies (Dickstein et al., 2010; Schreurs, 2010)? Some research studies have determined that individuals that had high measurable TC in late life appear to not have a dementia risk. These studies reported by Schreurs (2010) performed by Panza et al. (2006), and van den Kommer et al. (2009), discovered that in the elderly, having high cholesterol was protective on cognition. It is hypothesized that if cholesterol, which is a fat, has a positive effect on learning and memory then an increase in later years should be cognitively protective (Shreurs, 2010).

The ACCORD-MIND study revealed several hypotheses on whether individuals with DM2 are at risk for reduction of brain volume and poor cognitive function. The researchers of this study mention that a combination of DM2, uncontrolled HTN, and dyslipidemia act synergistically to produce cognitive dysfunction. This study took 2,977 individuals without dementia, HbA1c < 7.5%, a case group of SBP of 120 mm Hg with the control group having 140 mm Hg. The group of treated LDL of 100 mg/dl was given

a fibrate, and the untreated group a placebo for dyslipidemia. At a 40-month follow-up it was interesting to note that the intensive reduction of the high blood pressure group had a greater reduction of total brain volume and the fibrate therapy for the high triglyceride group had no effect on brain volume (Bornstein et al., 2014; Williamson et al., 2014). In explanation, even though the sample size was large, cognitive impairment can take many years to develop (Kawamura, Umemura, & Hotta, 2012; Prince et al., 2014).

Stroke History and Alzheimer's Disease

Hypertension and dyslipidemia are independent risk factors for AD, as previously discussed. Risk factors for vascular disease compromise the integrity of blood vessels, which in turn enhance inflammatory cytokines to increase. Both of these conditions together measured in midlife increase the risk of developing AD (Iadecola, 2014; Kivipelto et al., 2001; Prince et al., 2014). Due to better survival after a stroke the prevalence of post-stroke dementia (PSD), any type of dementia, is on the increase (Lenzi, De Benedetto, & Altieri, 2012). It has been reported that > 25% of individuals that had a first or recurrent stroke developed dementia. Because PSD and AD share the same risk factors, it is unknown whether stroke is additive to AD development or considered more a cause-effect relationship. Individuals that previously had ischemic cerebrovascular disease (vascular changes in the brain) progressed from pre-clinical AD to probably AD after a stroke according to researchers Lenzi, De Benedetto, and Altieri (2012).

Pre-stroke dementia shares comorbidity with diabetes, hypertension, and lower education, and older age. Post-stroke dementias share similar risk factors, however, these authors state being White seems protective in comparison to Hispanics (Lenzi, De

Benedetto, & Altieri, 2012). The risk of AD doubles ten years or more after a stroke, and those with DM have a compromised ability to heal after a stroke (Lenzi, De Benedetto, & Altieri, 2012).

Diabetes Mellitus Type 2 and Alzheimer's Disease

The prevalence of diabetes increases with age. It is estimated that individuals with DM2 that are over 65 years of age amount to anywhere from 21.6% to 25% (Prince et al., 2014). The United States is not alone in this estimation where developed and developing countries are recording similar statistics and associating obesity and a lifetime of inactivity to DM2 (Prince et al., 2014; Ryan, Fine, & Rosano, 2014). AD is a neurodegenerative brain disorder that is estimated to affect 5 million Americans over the age of 65 (Prince et al., 2014). Multiple studies are relating DM2 to the development of AD. This is particularly disheartening because with an aging population there is a higher risk of dementia from multiple causes as well as a higher incidence and prevalence of DM2. As treatment for DM2 evolves, individuals with moderately controlled diabetes will live longer and thereby increase the opportunity for AD. Not only do genetic risk factors elevate the possibility of developing both diseases, modifiable risk factors can play a significant role. Increasing the risk for insulin resistance and obesity is an accumulation of a lifetime of untreated HTN, dyslipidemia, and cigarette smoking as well as an inactive life-style. IR increases the opportunity for amyloid-beta plaques to develop, as well as neurofibrillary tangles, creating a slippery slope of cognitive decline beginning in the hippocampus and spreading throughout the brain.

The risk factors for the development of AD are broader than just DM2. DM2 sets up a cascade of metabolic circumstances that create an arena for vascular damage. But

other risk factors such as atherosclerosis and HTN create damage separately from the insulin resistance DM2 creates (Tuligenga et al., 2014). Many research studies performed observed an association between midlife HTN and later dementia development (Exalto et al., 2012). It is hypothesized that DM2 makes brain vascularity more susceptible to early plaque and tangle development thereby disrupting brain function (Ryan, Fine, & Rosano, 2014). This effect is believed to be most important during an individuals' midlife span of 40- 59 years when most modifiable risk factors are fully in place (Tolppanen et al., 2013).

Several studies have made an association between DM2 and AD. The Hisayama study revealed evidence of DM2 and AD in autopsied individuals. They noticed that these diseases occurred together 2.18 times more often than individuals without DM2 by observation of neuronal plaques (Yamazaki et al., 2011). In a systematic review gathered by Lu, Lin, and Kuo (2009) reported byYamazaki et al. (2011), it was discovered that most of the literature reported a 1.39 times greater risk of developing AD in those with DM2. A meta-analysis reported by Exalto et al. (2012), observed brain MRI results of DM2 individuals that displayed a significant association between lacunar infarcts and DM2. However, many of these results are from individuals with no signs of dementia. In order to solve this mystery, amyloid PET scans could set the AD pathologies apart from a brain that is damaged exclusively by a vascular component (Exalto et al., 2012). In a study performed by Tomita and associates (2012), a PET scan was used to evaluate 14 AD patients with DM2 and 11 AD patients without DM2. The PET scan used an amyloid tracer BF-227 in which the tracer was found to have a higher uptake in all AD patients. This finding suggested that amyloid-beta plaques develop in AD brains with or without DM2 (Tomita et al., 2012).

In order to study whether DM2 can be linked to cognitive dysfunction, Moran and associates (2013) evaluated MRI results and cognitive tests using 350 individuals with DM2 and 363 individuals without DM2. It was noted that hippocampal atrophy as well as limbic, temporal, and frontal gray matter atrophy could be positively associated with DM2. The hippocampus displayed reduced gray matter volume in midlife subjects with DM2. These authors suggest further studies to elucidate all the metabolic factors that can reinforce the pathways between DM2 and dementia. Other researchers have confirmed what these authors have uncovered. Brain atrophy caused by IR, uncontrolled glycemia, oxidative stress, amyloid-beta clearance, and inflammatory cytokines have been linked to AD neurodegeneration (Moran et al., 2014).

A prospective study that measured functional abilities by activities of daily living followed 608 individuals with AD, 63 of these individuals had DM2 at baseline. When confounders were adjusted, the results were significant for individuals with DM2 that had AD for 1 year [*OR* = 2.04 (95% CI 1.02-4.110)], (Sanz, Hanaire, Vellas, Sinclair, & Andrieu, 2011). As well as a functional decrease, executive dysfunction has been found to be associated with HbA1c results and MMSE scores. The ACCORD-MIND study recognized that a drop of 0.14 points on the MMSE coincided for each 1% increase in HbA1c (Kawamura, Umemura, & Hotta, 2012).

As with the timing of HTN and obesity, the development of DM2 impacts the risk for AD. The researchers of the Swedish Twin Registry found that midlife onset of DM2 presented the greatest risk for AD [*OR* 2.25 (95% CI 1.29-3.92)] compared with individuals that developed DM2 after 65 years of age [*OR* 1.56 (95% CI 1.05-2.32)], (Carlsson, 2010; Xu et al., 2009). This reinforces the idea that accumulation of risk has

placed public health at the corner stone of disease education, recognition, diagnosis, and treatment of AD and DM2 as degenerative diseases that can be linked.

Sociologic Risk Factors associated with Alzheimer's Disease

Within sociological risk factors for AD there are modifiable and non-modifiable factors. Factors that cannot be modified are age, gender and genetics. Those that are modifiable are diet, HTN control, control of cholesterol levels, a physically active life-style, smoking cessation, higher education, and preventing diabetes. It has been argued that DM2 genetically predisposes an individual to the development of DM2. However, if a physically active life-style is adopted, a diet higher in fruits and vegetables, and a BMI < 30 kg/m^2 is achieved, the opportunity for diabetes development and complications therein can be minimized. One needs then to logically look at the reality of all the risk factors for the development of DM2 and subsequently AD.

Lifestyle Factors and Alzheimer's Disease

A modifiable risk factor for the delay or prevention of AD is avoidance of cigarette smoking. Cigarette smoking is still considered the most modifiable risk factor for early morbidity and mortality (McPhee & Pignone, 2005; Prince et al., 2014). Active and passive cigarette smoke can be implicated in AD development through atherosclerosis. Smoke residue components destroy the elastic portion of the intima of arteries, which makes them stiff. Oxidative stress and inflammation from toxins in the smoke cause a cascade of degeneration in all arteries including the brain (Reitz, Brayne, & Mayeux, 2011). A stroke by either a hemorrhage from the capillaries in the brain caused by uncontrolled HTN, or from a clot caused by plaque from uncontrolled cholesterol levels, increases the opportunity for vascular dementia. Cigarette smoke

affects the brain in AD by reducing the ability of the CSF to clear amyloid-beta, increases pro-inflammatory responses, and thereby causes changes in synaptic relays (Prince et al., 2014).

The Chicago Health and Aging Project cohort study discovered with current smokers and AD risk, it did not matter pack-years of smoking (p = .88) but with ex-smokers a trend toward lower AD risk in spite of pack-years was significant (p = .02), (Prince et al., 2014). In longitudinal studies reported by the World Alzheimer's Report 2014, carriers and non-carriers of the APOE ε4 allele were evaluated for cigarette smoke damage. The pooled *RR* was higher for non-carriers of this allele (*RR* = 1.73, 95% CI: 1.12-2.45) than carriers of the APOE e4 allele (*RR* = 1.49, CI 95% 0.95-2.03). However, in the 21 year follow-up of 1,449 participants in the Cardiovascular Risk Factors, Aging and Dementia Study the reverse was found. Midlife smoking was associated with higher risk of AD of APOE e4 carriers (OR: 6.56, 95% CI 1.80-23.94) whereas among non-carriers there was no significance (Rusanen, et al., 2010). Some studies suggest that 14% of AD cases are attributable to cigarette smoking (Mangialasche, Kivipelto, & Fratiglioni, 2012).

Errors in recall, performing these studies in late life, and confounders can underestimate the effect of smoking on AD thereby allowing for the null association (Prince et al., 2014). In a large cohort studying adults that measured midlife smoking as the greatest risk factor for dementia, those that were former smokers and those that smoked about one half of a pack per day were at the same risk as never smokers (Rusanen et al., 2011).

An interesting and slightly disturbing fact is that nicotine has been found to protect the brain through reducing the action of amyloid-beta. One recent study found that a lifetime of cigarette smoking reduced the incidence of Parkinson's disease and Lewy Body dementia (Prince et al., 2014). Even though other cigarette smoke toxins have been known for decades to be deleterious to the human body there is a future potential for nicotinic pharmacological therapies for dementia (McPhee & Pignone, 2005; Prince et al., 2014; Reitz, Brayne, & Mayeux, 2011).

Modifiable risk factors for DM2 and AD development are lifestyle behaviors. As with MetS, factors can be clustered together and generally work synergistically to affect health (Prince et al., 2014). A diet that is healthy coincides with physical activity. Physical activity promotes cardiovascular health by causing the intima of the blood vessels to strengthen and pump blood more efficiently. Physical activity modifies HTN, DM2, dyslipidemia and obesity thereby reducing the incidence of dementia through blood vessel health (Prince et al., 2014; Ross, Brennen, Nazareno, & Fox, 2009). The authors of the World Alzheimer's Report gathered 16 studies that found that physical activity reduces the opportunity for AD development (*HR* = 0.50, 95% CI 0.36-0.84). The increased physical activity has an accumulative affect. It must be started midlife or earlier, researchers mentioned the earlier the better (Ruthirakuhan et al., 2012). Several of these studies were biased in that the measurement of risk was only measured after 65 years of age. Also what must be considered is reverse causation. As a bias, the ratio for risk reduction should be greater and having age related physiologic factors could prevent older adults from engaging in adequate physical activity (Prince et al., 2014).

Meta-analyses evaluating the affect that exercise has on cognition revealed a positive association between increased attention, executive function, processing speed, and memory. Studies performed by Buchman et al. (2012) and Larson et al. (2006) reported by Ruthirakuhan et al. (2012), agreed that those that participated in the least amount of exercise per week cohort had twice the risk of dementia development than those in the highest amount of exercise per week. Physical exercise seems to be helpful for patients with AD as they respond to cardiovascular and muscular strengthening which helps with activities of daily living. Aerobic exercise increases peak oxygen consumption and increases gray and white matter brain volume, notably in the hippocampus. Neuroplasticity appears to be the improvement seen in AD patients (Ruthirakuhan et al., 2012). In a recent symposium, Atri (2016) relayed his experience with patients with AD. Table 1 displays previously mentioned risk factors for AD according to Atri (2016).

Table 1

Positive and Negative Risk Factors for Alzheimer's Disease

AD is more common	AD is less likely
Age	Education
Female	Exercise
HTN, dyslipidemia, DM2	Heart health, antioxidant diet
APOE genotypes	Social activity
History of stroke/head trauma	
Family history	

With AD being the sixth leading cause of death in the United States it has become apparent that preventive mechanisms need to be discovered and enforced. It is important to note that a study funded by the National Institutes of Health called the Diabetes Prevention Program Outcomes Study, discovered that lifestyle interventions and Metformin use obtained good results. However, there was no significance in reducing microvascular complications (ADA, 2014). In the Diabetes Prevention Program those that were in the exercise, diet, Metformin, and behavior modification group saw the greatest results. The over 60-year-old group reduced their risk of developing diabetes by 71% (DPP, 2013). If microvascular complications were unavoidable what are the recommendations for the older individual on blood glucose maintenance and AD prevention? Researchers are not in agreement concerning what can be considered safe

recommendations and procedures for the older diabetic monitoring blood glucose levels in order to delay or prevent dementia (Nicklett, 2011).

Social and Intellectual Stimulation and Alzheimer's Disease

Two other lifestyle factors that can reduce the incidence of AD are social engagement and cognitive stimulation (Ross, Brennen, Nazareno, & Fox, 2009). Socialization refers to social interactions in which individuals have allotted meaningful time with friends and family to comply with the norms of the society around them. Increased socialization has been known to increase brain vascularity called angiogenesis (Ruthirakuhan et al., 2012). Whether this is due to stress reduction, increased self-worth, or merely reduces the feelings of isolation, they are considered deterrents to AD development and progression (Ruthirakuhan et al., 2012). The cognitive reserve hypothesis referred to the plasticity of brain reserve depending on the innate individual characteristics such as, years of education, intelligence, and job type. What has been used to measure cognitive reserve is education and IQ; however, some researchers also add occupational attainment, social engagement, and literacy (Reitz, Brayne, & Mayeux, 2011; Ruthirakuhan et al., 2012; Tucker & Stern, 2011). Job complexity and leisure activity, which alludes to socialization skills, create more neuronal cells in the hippocampus called neurogenesis (Prince et al., 2014; Ruthirakuhan et al., 2012).

Intellectual stimulation refers to any mind activity that takes up to six hours per week to perform such as card games, reading, and/or word puzzles. Results from the Kungsholmen Project reflect this concept that complicated jobs decrease the risk of developing dementia. It also reinforced the fact that APOE ε4 carriers were more susceptible to AD development especially in light of poor lifestyle and behavioral risk

factors (Mangialasche et al., 2012). It is questionable whether intellectual stimulation creates a cognitive reserve by delaying the signs of AD in spite of the developed pathology associated with AD (Ruthirakuhan et al., 2012). It has been documented that individuals with AD that have higher education and better job accomplishments show faster decline than AD individuals with less education. Tucker and Stern (2011) hypothesized that those with more cognitive reserve will have more extensive pathology associated with AD. Interestingly, those with greater cognitive reserve will need increased levels of atrophy, more amyloid molecules in the CSF, and greater brain cortical shrinkage to display signs of dementia because, basically, there is more to lose.

In a longitudinal study performed on 154 Italian adults these results were further corroborated that lower education is associated with slower disease progression. The theory is less cognitive reserve causes more vulnerability to pathological brain damage which in part promotes earlier signs of dementia (Musicco et al., 2009). This reinforces the premise that activities that stimulate and increase cognitive reserve can be part of a nonpharmacological tactic in the prevention of AD (Ruthirakuhan et al., 2012; Tucker & Stern, 2011). The Memory and Aging Project (MAP) and Minority Aging Research Study (MARS) used a detailed questionnaire with Hispanic and Black adults older than 70 years of age. This cross-sectional study revealed those adults that participated in cognitively stimulating activities had more cognitive reserve and performed better on neuropsychological tests. The results, according to the authors, exemplified the social disadvantages of some Hispanics because they scored lower on the supplied cognitive tests (Prince et al., 2014).

Social factors have positive effects on cognitive functioning. Social support and interpersonal relationships interact to produce protective factors for most ethnic groups. In a study performed by Hill (2008) and reported by Aiken-Morgan, Whitfield, and Paige (2014), Mexican Americans that participated in religious activities had better cognition compared to those with educational attainment alone. Mexican Americans that attended church displayed signs of slower cognitive aging. Social ties proved to be cognitively protective.

AD affects ethnicities in different proportions. It is estimated in the 65 to74 year-old-range; Hispanics comprise 7.5% compared to 2.9% Whites. In the 75 to 84-year-old range, it increased to 27.9% Hispanics and 10.9% in White. It is also reported that 29% of those with LOAD also have DM2 (2014 Alzheimer's Statistics, 2014). However, it is interesting to note that an Italian cohort discovered that individuals with DM2 had a 65% reduction in AD progression. The summarization of these results can possibly be explained by the use of medications for diabetes. Results are controversial but one class of diabetes medication thiazolidinediones, specifically Rosiglitazone, was taken by all but one individual in this study. Therefore, biasing the study by modifying the insulin production and receptor responsiveness to insulin by use of this medication (Musicco et al., 2009).

Minority Group Status and Alzheimer's Disease

Increases in DM2 prevalence has been studied in relation to BMI and racial/ethnic groups. It has been discovered that diabetes prevalence is greater in the normal and overweight individuals in minorities. Therefore, the disparities between Hispanics and Whites were more pronounced in DM2 development than between African Americans

and Whites (Zhang, Wang, & Huang, 2009). The risk of developing DM2 in the Hispanic population was 66% higher than Whites (Chow, Foster, Gonzales, & McIver, 2012). Mexican Americans had higher rates of DM2, worse glucose control, and displayed earlier complications from the disease than Whites (Mayeda et al., 2013). In 2010, Puerto Ricans were more frequently diagnosed with diabetes at 11.2%, Mexicans at 10.2%, followed by Cubans at 7.5% (Rosofsky & Aponte, 2010).

In the Sacramento Area Latino Study on Aging (SALSA) 1,617 participants that were dementia free at the beginning of the study were evaluated for 10 years. Participants at the end of the study with DM2 were 677, 159 with dementia, and 361 that had died. Those with DM2 had a higher risk of dementia (2.05 [1.41-2.97]) compared to non-diabetics (1.55 [0.93-2.58]), (Mayeda et al., 2013). The SALSA study also presented an interesting conclusion. Within their participants those individuals with treated DM2 were more likely to be immigrants, have less abdominal obesity, less HTN, lower glucose, fewer reports of heart attacks, strokes, and kidney disease (Mayeda et al., 2013)

This has been presented in other studies as the Hispanic paradox. Most studies are performed on Mexican Americans in the United States. It has been documented that those older diabetic adults that stay in Mexico are considered healthier than their American counterparts (Blue, 2009; Diaz, Crespo, Taylor, & Torres, 2009; Vega, Rodriguez, & Gruskin, 2009). On a similar note, Puerto Ricans that live in Puerto Rico have higher diabetes rates, undiagnosed and diagnosed, at 13.98% compared to the 10.9 % of Puerto Ricans that live in the United States. (Castaneda & Bermudez, n.d.). In a report submitted by the CDC in the Morbidity and Mortality Weekly (2015), several facts were presented concerning Mexican Hispanics. Sixty-four percent of the 82.4% of Hispanics in America

are of Mexican origin. Death rates due to DM2 in Hispanics were higher than for Whites. Hispanics born in the United States had more risk factors for illness and ultimately worse health than foreign-born Hispanics. Hispanics in the United States were generally 15 years younger than their White counterparts for all illnesses, were more likely to be living below poverty level, and had a lower education attainment (Dominiquez et al., 2015). The Hispanic paradox therefore has two schools of thought to sustain this theory. One is that Mexican Americans are a resilient group of individuals to have enough motivation to leave their families and go to another country, but it has also been hypothesized, the individuals that migrate are just healthier people (Junkett, 2013). It has been also documented that Latinos in Mexico smoke less. The statistics reveal that for those individuals that smoke, more than 50% of the difference between foreign and native-born males at 50 years of age had a longer life expectancy (Blue, 2009; Hildreth, Grigsby, Bryant, Wolfe, & Baxter, 2014; Vega, Rodriguez, & Gruskin, 2009). A more plausible explanation why Mexicans that stay in Mexico are healthier is healthier food availability and a more active physical lifestyle.

The older U.S. population is projected to increase substantially by 2050. The total number of White adults over age 65 will double but Hispanic adults will most likely increase 11-fold (Aiken-Morgan, Whitfield, & Paige, 2014). It is important to state that if this ethnicity presents earlier with disease in America, there is a greater chance for intervention. Because AD has a long prodromal period, older adults that have even one chronic disease create an opportunity for intervention and diagnosis (Dominiquez et al., 2015).

In a report by the CDC of data performed and gathered by the National Center for Health Statistics, Hispanic adults between 55-64 years of age were asked how they would rate their health. Thirteen to fourteen percent of Hispanics in this age group in 2013 responded by stating they had fair to poor health where only 8% of Whites responded in the same way (Bush & Bengeri, 2015). In a longitudinal study gathered by the Health and Retirement Study, 2,494 individuals with DM2 were evaluated on their health outcomes between White, Black, and Hispanic populations. Hispanics were more likely to have poorer health (*OR* 0.59, $p < .05$). Higher education was associated with cumulative odds of better health ($p < .05$). According to Nicklett (2011), factors that can contribute to worse health outcomes are acculturation and health literacy.

Acculturation

The definition of acculturation is the merging of cultures because of an extended contact to the population an individual has chosen to reside with (Diaz, Crespo, Taylor, & Torres, 2009). This usually means that the migrating population adopts the cultures of the target population. Studies have attributed low acculturation and chronic stress to abdominal obesity and thereby, IR. It has been well studied that stress activates the hypothalamic-pituitary-adrenal (HPA) axis and produces cortisol, which causes the collection of visceral abdominal fat (Björntorp, 2001). Country of origin can change how each race interprets disease risk. Isasi et al. (2015) took 14,753 Mexican, Cuban, Dominican, Central American and South American adults, 2,758 of them between the ages of 60-74, from data gathered by the HCHSO/SOL cohort study. Acculturation was measured through the Short Acculturation Scale for Hispanics (SASH) and obesity was measured by BMI from 25 (25-29, overweight) to over 40 kg/m^2 (morbid obesity). In this

study Puerto Ricans had the highest prevalence of obesity with South American adults having the lowest incidence of obesity (Isasi, et al., 2015). Other studies have revealed that living longer in the United States is associated with a higher prevalence of obesity. This study also discovered that the longer an individual resides in the United States, the greater the opportunity to develop obesity which was measured consistently across all races (Isasi et al., 2015).

Other cultural patterns can be associated with health disparities. Variations in what an individual believes about disease origin, treatment for chronic diseases, and their response to medical providers' instructions affect health care (Shaw et al., 2008). Cultural barriers to adequate knowledge and health care are also language differences, religious beliefs, and the individual's ties to family (Lines & Wiener, 2014; Shaw et al., 2008). A patient's capability to understand the medical providers' direction and instruction is manifested by cultural factors that extend past literacy and educational attainment (Shaw et al., 2008). More than 43% of Mexican Americans older than 20 years of age are obese. Obesity leads to DM2, and more than 11% of Latinos have DM2, the most prevalent disease for this population (Junkett, 2013).

Where obesity becomes a cultural problem is their belief that being overweight is considered healthier. Some individuals believe that their illness is either of a hot or cold origin (Junkett, 2013). What can also complicate timely diagnosis and adequate medical care is the difference between how American providers base their medical acumen. Hispanics have a family structure that is based on everyone having an opinion therefore, a supportive unit. The Hispanic heritage consider family and caregiving a family affair, a task they believe as obligation. As a contrast, American providers base their medical

decisions on a model of health care that is autonomous. This reflects American medical provider opinion of individualism rather than the Latino perspective of collectivism (Campos, 2006; Junkett, 2013).

Religious beliefs only become a medical issue when individuals with chronic disease feel that God has control whether with the origin or continuation of disease and therefore do not seek medication to control the effects of disease (Campos, 2006; Lines & Wiener, 2014). However, in a cross-sectional study conducted by BRFSS, Hispanics when told they had been diagnosed with DM2 were more likely than Whites to take prescribed oral diabetes medication but were reluctant to use injected insulin (Campos, 2006). In the NHANES survey, 2,696 Hispanic adults with low acculturation admitted to not having a medical provider they regularly attended, no health insurance as well as low education attainment (Campos, 2006).

In a qualitative study performed by the National Hispanic Council on Aging (NHCOA), several beliefs and opinions surfaced about Hispanic's ideas and misconceptions about AD. AD is almost 1.5 times higher in Hispanic older adults than White adults. Hispanics also show signs of AD earlier than other racial/ethnic groups (Fitten et al., 2013; NHCOA, n.d.). The older adults interviewed suggested that AD was due to stress or personality types. Family members that were interviewed believed that AD was just signs of normal aging (Sansom, 2009; NHCOA, n.d.).

Health Literacy

Many factors influence the relationship between good health and poor health; biology, genetics, attitudes about health, socioeconomic status, and health literacy ("disparities", 2010). Health literacy has been defined as the patient's ability to

understand basic information and skills to function adequately in a healthcare environment (Coffman, Norton, & Beene, 2012; Quick guide to health literacy, n.d.). Latinos base their symptoms on either past experience, others knowledge of the disease, or whether they feel ill. In a convenience sample of 150 Mexican Americans, women in the study stated they believed diabetes was advanced only when they started to feel the complications of the disease. In the same study Mexican Americans made "educated guesses" about their blood sugar levels without using a glucometer. According to the authors, not relying on biophysical data is most likely related to poor health literacy (Coffman, Norton, & Beene, 2012). This study also stated that 62% of Latino individuals tested using Spanish had limited health literacy. Even though education was positively associated with greater DM2 understanding ($\beta = .41$, $p = .0001$) health literacy, according to its definition, was not linked to DM2 knowledge (Coffman, Norton, & Beene 2012).

Bilingualism is an important concept that has been studied in cognitive aging (Aiken-Morgan, Whitfield, & Paige, 2014). Dementia affects language function not only because of the brain structures that are utilized in cognitive performance but in the way the terms are interpreted. AD was shown to affect an older individual's dominant language. Therefore, if an older Hispanic was more comfortable speaking Spanish, this language was considered dominant, even if they spoke English. It was also discovered that since AD affects the meanings of words. Those that were Spanish-dominant speakers were able to correctly name an object in Spanish but not correctly in English (Aiken-Morgan, Whitfield, & Paige, 2014). These researchers also discovered that those who learned English before the age of 12 performed better on English repetition tests compared to those that learned English after 12 years of age.

Cultural differences, language preferences, and SES are all pivotal in the healthcare of individuals with chronic disease (Stiles, 2011). Other barriers to adequate healthcare noted by Hu et al. (2013) are low education, low income, poor acculturation, language and literacy problems, and medical comorbidities. Health literacy is needed in order for medical orders to be followed, DM2 blood glucose regimes to be managed, and understanding aspects of either DM2 or AD progression (Shaw et al., 2008). Limited English inhibits individuals with need for disease management to receive enough information for self-management. Poor communication negatively impacts healthcare. It is the responsibility of the medical provider as well as the patient to adequately express symptoms, side effects, and then solutions in a manner that is acceptable for both.

Communication and trust that is reciprocal has the most health advantages (Mancuso, 2010). Symptoms dictated by a patient to a provider that does not comprehend their language can result in misdiagnosis. Cultural difference can result in the same communication barrier. In a study performed on California Latinos it was discovered that they had the most chronic illnesses but were unfamiliar with the proceedings of the U.S. medical process. The burden of controlling DM2 depends on a partnership between provider and patient. Hispanics want a personal relationship with their providers. This relationship is based on kindness (simpatia), friendliness (personalismo), and respect (respeto), (Junkett, 2013). Using the Teach-back Method can increase the patient's role as a willing and able participant in the healthcare model. By use of this method the patient is able to explain to the provider what was discussed. DM2 can be controlled and therein reduce the incidence of AD.

Medical Provider Perspective of Barriers to Diagnosis

DM2 in the older person can present with complications that stem from physical problems that inhibit self-care. Visual changes that emerge with aging make testing their glucose levels challenging when reading the glucometer output. Long standing diabetes can create retinopathy, which makes reading fine print difficult. Diabetes knowledge has been associated with educational level as well as diabetes education classes (Coffman, Norton, & Beene, 2012). Medical providers have the responsibility of informing patients of the self-care management of diabetes as well as the complications of uncontrolled glucose. Barriers according to the Latino patient can stem from poor health literacy, lack of recognition of symptoms, and lack of healthcare insurance (Coffman, Norton, & Beene, 2012). Patients with a positive attitude about managing the symptoms of diabetes were more likely to follow the treatment regime involved with controlling their disease (Nam, Chesla, Stotts, Kroon, & Janson, 2011). Nam et al. (2011) and Lincoln (2014) discovered a barrier to proper care according to Latino patients. Within the Hispanic/Latino ideal, the family unit is more important than the individual person and the concept of sticking closely to a diabetic lifestyle seemed selfish.

The attitude that the provider presents at the time of clinical diagnosis can be the catalyst for the patient's psychological perspective on diabetes management. Providers surveyed stated cultural incompetence, language differences, and the patient's inability to continue with follow-up appointments as barriers to acceptable glucose control (Nam et al., 2011).

Primary care medical providers are usually the first place where individuals obtain a possible dementia diagnosis (Galvin & Sadowsky, 2012). Therefore, the burden

of recognition of signs and symptoms, ordering adequate laboratory and imaging tests as well as treatment, becomes an important and valuable role for the provider. Supplying knowledge and adequate material for the medical provider to use for diagnosis up till now has been scarce. Recognition of the early symptoms of LOAD is a starting point for diagnosing the pathological changes that individuals with dementia will exhibit. Since damage usually begins in the hippocampus where new memories are formed, impairment of recent events and the inability to recall newly learned information is the first presenting symptoms (Galvin & Sadowsky, 2012). The focus of Alzheimer's research has been the support of clinical diagnosis and treatment but recently has changed to developing therapies that would be neuroprotective before symptoms of cognitive decline (Snyder et al., 2011) The NINCDS-ADRDA criteria states either a definite, probably or possible diagnosis. The only routine test available is the MMSE. Other tests that have good reliability are the Clinical Dementia Rating (CDR) and the Montreal Cognitive Assessment (MoCA). Patients or family member barriers stem from denial or ignoring symptoms, provider barriers in this early time frame revolves around time for consultation (Galvin & Sadowsky, 2012).

Primary care providers need to ask about memory impairment because dementia starts slowly and insidiously and can be difficult to recognize by patients and providers. Recent literature comments that all too frequently patients report to a clinic with irreversible brain tissue loss due to not recognizing the signs of dementia (Snyder et al., 2011). An effective strategy is to administer the MMSE to all patients over 50 years of age regardless of cognitive function and periodically retest the patient, giving the ability to follow possible progression over time (Galvin & Sadowsky, 2012). Norton, Matthews,

Barnes, Yaffe, and Brayne (2014) discuss that if dementia could be delayed by one year the worldwide cases of AD in individuals over 60 years of age in 2050 could be reduced by 11%.

Having culturally appropriate materials is as important as the provider possessing culturally sensitive intuition. Many providers believe that cognitive impairment can be a normal sign of an aging brain (Gelman, 2010; Stewart et al., 2014). Latino patients as well as caregivers have the same misconception which delays diagnosis and possible treatment. Gelman (2010) cites multiple studies that mention it is not the lack of AD knowledge that is prevalent in the Latino community but lower education, poor health literacy, and language differences that account for delay in dementia diagnosis.

Social Change

The psychosocial hypothesis of dementia origin provides an avenue for prevention and treatment. This hypothesis encompasses the accumulation of risk model and lifestyle behaviors that put this population at risk for dementia. Hispanic/Latinos have risk factors such as genetics, lifestyle patterns, and cultural beliefs that make fighting dementia difficult. Protective factors that could attenuate or delay a diagnosis of AD are a physically active and socially engaged lifestyle as well as early and consistent medical care of chronic diseases such as diabetes. As the U.S. Hispanic population expand in number and become older it is important to culturally address their needs for a timely AD diagnosis (Hildreth et al., 2014). It has been stated that Hispanics are diagnosed later in the disease process, have less opportunity to adequate resources, less likely to be given AD medication, and less likely to participate in clinical research (Hildreth et al., 2014).

Health care providers have the opportunity to reach this population using culturally designed diagnostic tools. Fitten et al. (2013) has studied a group of Hispanics in Southern California and discovered that this population shows signs of dementia at an earlier age than Whites. Caregivers of AD family members have mentioned that they were unaware of all the signs of AD. They mentioned that they would agree to screening if their medical practitioners suggested it (NHCOA, n.d.). However, the same providers stated that there are no culturally and linguistically adequate AD resources for Hispanic older adults (NHCOA, n.d.). There are three areas that could be proposed for change in this population. Culturally and language appropriate diagnostic tools, time in the clinical appointment to assess for dementia, and resources and information appropriate for patients and caregivers of Hispanic/Latino origin to understand the signs of AD (Gelman, 2010).

Summary and Conclusions

AD is a slowly progressive fatal disease of the brain in which the origin is multifactorial and can go undiagnosed due to the long latency of symptom development (Candeias et al., 2012; Khan & Alkon, 2014). There is evidence that suggests a pathophysiologic and metabolic association between AD and DM2 (Cheng et al., 2011; Götz, Ittner, & Lim, 2009; Han, & Li, 2010; Mushtaq et al., 2014). How the pathophysiology of DM2 affects the brain by neurological alterations is still under investigation but it is estimated that multiple features contribute to gray mater atrophy through a cascade of factors that leads to AD.

DM2 is a metabolic disease that affects 17% of older adults and one in ten Hispanics in California alone (Conroy, Lee, Pendleton, & Bates, 2014; Whyte, 2013).

Some of the implicating factors that place this ethnicity at risk are lifestyle choices, cultural beliefs in managing illness, language barriers that produce poor health literacy as well as genetics (Campos, 2006; Hu, Amirehsani, Wallace, & Letvak, 2013). The third reason is lack of information within the Hispanic community on symptoms of AD. This is an important avenue for social change. Medical providers are at a pivotal position to affect individuals and their beliefs about disease.

It is important for clinicians to have the tools, resources and time availability to provide screening surveys for their older patients (Galvin & Sadowsky, 2012; Gelman, 2010; Stewart, 2014). The accurate identification of individuals with dementia makes early screening of extreme importance. By detecting these individuals early, medical providers are able to recognize, diagnose, and counsel patients that are at risk for developing AD. It is important to state that if this ethnicity presents earlier with disease in America, there is a greater chance for intervention. Because AD has a long prodromal period, older adults that have even one chronic disease create an opportunity for intervention and diagnosis (Dominiquez et al., 2015).

Chapter 3 includes the methods used in this study, which will attempt to reveal a correlation between DM2 and AD in older Mexican Americans. This research study took variables known to contribute to AD and provide an established link from DM2 to AD, with DM2 as a prominent contributor. The dataset, population and correlation techniques will be discussed in chapter 3. Identifying Mexican Americans that are biologically, metabolically and sociologically at higher risk for AD will provide social change for this population.

Chapter 3: Methods

Introduction

I conducted this study to understand the association between DM2 and AD in older Hispanics. For this quantitative research study, I used a cross-sectional design because data were retrieved at participants' initial visits to ADCs in the United States. AD was the dependent variable, and DM2 was the primary independent variable. The other independent variables were HTN, BMI, dyslipidemia, education level, stroke history, smoking history, and APOE ε4 gene as the genetic marker. The study population was older Hispanics over 60 years of age, with a White control group matched with the same variables.

Chapter 3 includes several sections that outlined the process of this study. In the introduction I describe the type of analysis I used as well as the purpose of the study. In the data collection and operationalization of variables sections, I discuss how I used logistic regression as the analytical method for determining, with an OR, the extent to which DM2 predisposes older Hispanics to AD.

Research Design and Approach

I used a quantitative cross-sectional design approach to evaluate the main research question and determine the extent of the association between DM2 and AD in older Hispanic adults. Cross-sectional studies include data from one point in time and all variables are evaluated simultaneously. In my study, this meant that the data reflected the AD standing of the participants at initial visit. An advantage of cross-sectional studies is that they can be performed occasionally to monitor trends in prevalence of a chosen disease status (Szklo & Nieto, 2014). I used the UDS from the NACC that gathers data on

individuals with AD. In the UDS data, information about the extent these older Hispanics have follow-up treatment is not included; therefore, I measured these variables at one point in time, participants' initial visits from years 2005-2015. Researchers can use cross-sectional studies to evaluate different groups of people that might vary in some variables (educational level and blood pressure status, for instance) but share other characteristics. The most reliable and valid study is one that can reveal cause and effect. Epidemiological findings of causality are what make changes in the way things are managed for primary prevention of chronic diseases. The highest internal validity would have been provided by a prospective study design, and would have best established cause and effect. However, the time required for a prospective study would have been prohibitive and costly.

I used the UDS from the NACC to evaluate a correlation between AD and DM2. In 1999, the National Institute on Aging founded the NACC in order to gather all the data collected by ADCs. The UDS was begun in 2005 to prospectively collect data from yearly clinical evaluations. This enables researchers to track changes in certain variables over time, and to view results of neuroimaging and neurocognitive tests. I compared the independent variables with DM2 in the six races under the Hispanic ethnicity and a matched sample of Whites to determine the amount of confounding that is accounted for in AD development apart from DM2.

Even though a cross-sectional study cannot prove causality, by ruling out other factors that could modify AD development, I determined that it would provide adequate internal validity. By using data that is collected throughout the United States in various ADCs, the opportunity for generalization was increased. This includes different

demographics, environmental influences, and cultural differences that could have affected AD development.

The primary research question asked whether DM2 predisposes older Hispanic/Latinos to AD. The DV for this study was AD (yes/no). Inclusion criteria were that participants had to be adults over 60 years old of Hispanic/Latino origin that self-reported diabetes at the time of initial evaluation. Table 2 lists the inclusion and exclusion criteria.

Table 2

Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Adults >/= 60 years of age	White or Hispanic/Latino origin < 60 years
Adults of Hispanic/Latino origin	Adults with other dementia besides AD
Adults with self reported DM	Adult with a history of gestational DM
Adults with AD diagnosis	

The IVs I measured as risk factors in AD development were HTN, dyslipidemia, BMI, education, history of stroke, and history of cigarette smoking. The APOE ε4 gene was the gene variant that I measured for it's possible effect on AD development among White and Hispanic individuals. Even though AD status was determined at the initial visit to an ADC, participants can be re-evaluated as to progression of dementia (Sklo & Nieto, 2014). Participants in this dataset were evaluated for AD at the initial visit by several neurocognitive tests, which for some participants were updated yearly. The data were gathered by the NACC from NIA funded ADCs. The UDS created in 2005 was designed

to be a prospective database for researchers to review standardized clinical evaluations that were obtained on initial visits and thereafter updated. I conducted a bivariate analysis for all independent variables, which would allow for associations between the IVs and DV. I used multivariate regression to determine whether risk factors other than DM2 are modifiers or confounders in AD development.

Methodology

Target Population

The target population for this study was self-proclaimed Hispanics of Mexican, Puerto Rican, Cuban, South American, or Central American descent with self-reported diabetes that have registered by either referral from a medical provider or self-referred to an ADC in the United States. The sample size of Hispanics was (N= 1011), participants with diabetes (n = 260), and a diagnosis of AD (n = 245). According to G*Power, the total sample size for power of 81% and an effect size of .40 (medium effect) was 33-50 participants. The White participants were (N = 9823), those with diabetes (n = 953), and those with AD (n = 873). In order to add strength to study, the White control group had triple the amount of participants in the sample size and thus provided a more accurate way to relate to the Hispanic group. I excluded individuals from this study that self-reported as White or Hispanic but younger than 60, those with a history only of gestational diabetes, and any individual diagnosed with a dementia other than AD.

Sample Size and Power Calculations

Studies that gather information on individuals that have diverse demographics is the benchmark of randomization, a benchmark I worked to meet by including a diverse population of Hispanics within the United States. Using a widely, dispersed population

sample therefore produces generalizability, since the White and Hispanic matched groups were from a wide variety of communities (see Creswell, 2014). Accuracy would obviously increase with large sample sizes, but it is possible to achieve good accuracy with a small sample. This is possible if the sample chosen is representative of the general population, referring again to generalizability (Stamatopoulos, 2002).

I used logistic regression to analyze if the outcome, AD, can be significantly associated to DM2 and other specific variables that could alter the outcome of AD. A medium effect size of 0.40 presents researchers with enough significance to pertain to everyday life and practical significance (Lakens, 2013). Burkholder (n.d.) and Ellis (2010) have both asserted that for a two-tailed, non-directional test and power set at 80%, alpha at 0.05, and effect size of 0.30, the minimum sample size for detecting a correlation coefficient should be 84-89. Likewise, Pezzullo (2013) stated that a formula could be used in which $8/r^2$ is used to determine the sample size for a significant correlation between variables, therefore if $r = 0.30$ (small/medium effect), $(0.30)^2 = 0.09$, $8/.09 = 89$. It appears that if an agreement could be made to choose between 84 and 89 participants for each group, this would produce a statistical significance, if one exists, between the chosen variables. The 260 Hispanics with DM in all of the ADCs in the United States were obtained from a grouping of 12,174 individuals evaluated by the UDS up to 2015.

The variables I included in the study can, in some way, possibly contribute to vascular damage in the brain. I used logistic regression to attempt to separate, which variables were moderators and which were mediators. Age and the APOE e4 gene are known moderators between DM2 and AD (Field, 2013). I attempted to show that DM2 is a mediator variable in AD development. I evaluated data for HTN, obesity, educational

attainment, smoking, and dyslipidemia in two ethnicities for effect modification. Hispanics were self-identified, the individual was able to choose between Puerto Rico, Cuba, Dominican Republic, Central America or South America, and Mexico as place of origin or heritage. Those in the White matched sample group also self-identified their ethnicity. Descriptive statistics were conducted to describe demographics of the sample groups, the independent variables, and the outcome variable of AD.

Sample Size

An adequate sample size was needed to determine whether there was a significant effect between the primary research hypothesis and the outcome. With two rival hypotheses, the null and alternate hypothesis, there were possible Type I and Type II errors that I needed to consider. With the alpha for this study set at 0.05, there was a 5% chance of making a mistake when the null was rejected, a Type I error (see Ellis, 2010). The null for this study stated that older Hispanics with DM2 do not have an increased risk of developing AD. The power of a study protects against making a Type II error. If the power can be set at .90 and the sample size is large, the possibility of not rejecting a false hypothesis is reduced. The standard power for most studies is set at .80 with an alpha of .05 and an effect size of 0.45. This can ensure that the alternate hypothesis will be truly identified and the null hypothesis will be correctly rejected.

Threats to Validity

There are three situations that arise with the use of cross-sectional studies. First, because the exposure and the outcome are noticed at the same time, there is no temporality. There can be no exact evidence that the exposure, DM2, caused the outcome, AD. Second, cross-sectional studies focus on prevalence rather than incidence

of an outcome. Third, it is important to have ruled out other explanations for the study results, meaning that prevalence of AD is truly increased by DM2 in the study population (Carlson & Morrison, 2009).

Precision is a lack of error that happens by chance, but validity refers to no chance of systematic error (Carlson & Morrison, 2009). Researchers increase internal validity by implementing a control group. The performance of this type of analytic method and how well the study variables are managed also increases internal validity. Another way to increase internal validity is to reduce the chance of confounding. The sign of external validity is being able to state that the results of this study can be applied to the majority of Hispanics. There were several threats to external validity in this study. First, the sample size I used was modest, at slightly greater than 200 Hispanic individuals. If the effect size misjudges by anticipating a close-fitting correlation between variables, meaning 0.20, the sample size will be too small and the study will be poorly powered (Ellis, 2010). By choosing between small to modest size effect for these study variables, meaning 0.30, it is possible that this study would reach statistical significance more than half the time (Ellis, 2010). Second, it can be argued that the individuals that seek the ADCs are drastically different from the average population in cognitive function. Third, it can also be argued that the cross-sectional nature of this study has reduced the idea that DM2 and AD have long prodromal periods of development, and this study was unable to tap into the nature of these diseases prospectively. The self-reported diabetes, HTN, and dyslipidemia can be a limitation; however, if the majority of these individuals have been diagnosed with any of these conditions in mid-life, these conditions, according to current literature, can have a profound impact on the development of AD (Prince et al., 2014).

Instrumentation and Operationalization of Constructs

There are three types of validity to consider when evaluating the instrument used for the study. Content validity, refers to the items in the instrument correctly measure what needs to be measured. Predictive or concurrent validity refers to the results that are correlated with and to other results. Construct validity is the usefulness of the scores from the instruments and how well it measures the concept of cognitive dysfunction (Sklo & Nieto, 2014).

Construct validity was the concept behind developing an algorithm for diagnosis of dementias used by the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS). Early stages of AD can affect speech, memory and judgment (Sheehan, 2012). Discovering a consistent diagnosis for dementia due to the progressive nature of cognitive impairment a battery of several testing measure have proven more beneficial (Duara et al., 2010). A portion of the cognitive tests that are administered in the ADCs to evaluate stages of dementia from mildly impaired to profound dementia are the Montreal Cognitive Assessment (MoCA), Mini Mental State Exam (MMSE), the Multilingual Naming Test (MINT), the Boston Naming Test (BNT), and the Wechsler Adult Intelligence Scale-Revised (WAIS-R). The diagnosis provided by a clinician that signifies the level of cognitive impairment, whether dementia or not, is the Clinical Dementia Rating (CDR).

MoCA: This test was originally designed to evaluate mild cognitive impairment. It can assess nine domains of cognitive function and is an adequate screening tool for early AD but education levels need to be considered. It has been stated that this test is too extensive for those individuals that are moderately or severely impaired (Getz, n.d.). It

takes 10 minute to administer and has the ability to assess those with moderate to severe cognitive impairment with a score of <25 points out of 30 (Chang et al., 2012). Between controls and those with very mild dementia the sensitivity was 92.6% and with specificity at 84.0% (Change et al., 2012). Hsu et al. (2015) state that this test is more useful than the MMSE in perceiving dementia with a sensitivity of 78% and specificity of 94%.

MMSE: This test is widely used and also takes approximately 10 minutes to administer. It is utilized best as a screening tool not diagnostic test (Sheehan, 2012). It is more difficulty to identify early cognitive changes with individuals that have a higher education, even though it is widely used. Its advantage is in picking out changes once dementia is diagnosed (Weintraub et al., 2010). Cut off scores for assessing between normal and mild AD is 26/27 out of 30 points with sensitivity of 94.2% and specificity of 83.5% (Chang et al., 2012).

MINT and BNT: The Multilingual Naming Test, which was introduced in 2012 to detect naming skills impairment for bilinguals. It is similar to the BNT but is more sensitive to multiple language speakers and includes a 68 black and white line drawing. When the MINT is used for Spanish-English bilinguals it is highly correlated to the BNT but the BNT undervalues an individuals' Spanish competence (Ivanova, Salmon, & Gollan, 2013). This test is recent and has no inter-rater reliability scores. Ivanova, Salmon and Gollan (2013) used the MINT in a 2013 study and discovered that it detected differences between individuals with AD and controls but not mild cognitive impairment and controls.

CDR: This test is used to determine severity of dementia in AD. It is argued that the results are more reliable if an informant is available that can corroborate amount of

disability if one exists on things such as personal care (Nyunt et al., 2013). CDR can be used to assess even mild cognitive impairment (CDR = 0.5). Three specialists functioned as raters evaluating 90 older adults with the CDR in which these participants previously scored <26 on the MMSE and the MoCA (classified as dementia). Internal consistency displayed a Crohnbach's α of 0.83-0.84, with inter-rater reliability of 0.95 for global rating (Nyunt et al., 2013).

WAIS-R: This test was originally designed to measure intelligence (IQ). It consists of six verbal and five performance subtests. Within the neurocognitive battery through the UDS several domains were measured, digit span, and digit symbol subtests, to evaluate attention.

Table 3 below displays a few of the cognitive tests used by the NACC. The MoCA is a new addition and is very promising in measuring mild to moderate Alzheimer's disease but few centers used this test with Hispanics. The MINT is a good alternative to the BNT because it incorporates words used from the individuals' original language. However, there were too few Hispanic individuals tested and this test was not analyzed in the final outcome for this study.

Table 3

Tests Administered by the NACC for Neurocognitive Evaluation

	CDR	MINT	MoCA	WAIS-R	MMSE
Attention			X	X	X
Concentration			X	X	
Executive Function	X		X	X	X
Memory	X	X	X	X	X
Language		X	X		X
Visuoconstructional Skills			X	X	X
Conceptual Thinking			X	X	
Calculations	X		X	X	X
Orientation	X		X		X
Judgment/Problem Solving	X			X	X
Personal Care	X				
Word knowledge		X		X	
Time to administer			10-12 minutes		7-8 minutes
Score for dementia	2-3/4		25/30		24/30

NACC criteria depend on the consensus diagnosis (ConsDx) as a result of clinicians agreeing on history and neuropsychological test results of patients (Duara et al., 2010). Consistency among physicians (PhyDx) and neuropsychologist diagnosis (NPDx) is necessary for reproducibility in cross-sectional studies. Computational algorithm (AlgDx) was developed by the NACC to be used as an agreed upon tool to best diagnose dementia and pre-dementia. Reliability of the AlgDx was measured by comparing to the ConsDx. The association to brain atrophy on MRI and the frequency of the APOE ε4 allele evaluated the validity of the AlgDx. These two markers have been correlated to AD pathology in other literature (Duara et al., 2010).

The results were tabulated from a sample size of 532 adults between the ages of 52 and 92. Cohen's weighted kappa, which counts disagreements was measured and reported for three items, PhysDx, NPDx, and ConsDx. Within these three categories, three diagnoses were measured for inter-rater reliability, no cognitive impairment (NCI), mild cognitive impairment (MCI), and Dementia. Results of the Inter-rater Reliability of the Consensus Diagnosis are displayed in Table 3 using Cohen's weighted kappa (Duara et al, 2010).

Table 4

Inter-Rater Reliability of the Consensus Diagnosis

PhysDx	NPDx	ConsDx
0.69 (SE = .11)	0.88 (SE = .07)	0.78 (SE = .07)
70% agree NCI	89% agree NCI	90% agree NCI
70% agree MCI	91% agree MCI	70% agree MCI
80% agree dementia	88% agree dementia	80% agree dementia

The use of this data set was appropriate for several reasons. The open access data are managed by a specific group (University of Washington) with the intent to be used by researchers. Some of the neurocognitive tests used as a cognitive battery to be placed in a LOAD database were MMSE screening for cognitive impairment, MoCA, MINT and BNT, and the WAIS-R as a more sensitive screening tool and with the CDR assessing functional status (Cognitive testing, n.d.; Duara et al., 2012). These tests measure all of the neurocognitive areas individuals have to assess for cognitive abilities. This data set evaluates individuals from all over the United States allowing for good generalizability.

They have a large sample group for Whites with AD and other dementias but a small sample size in relation to the group of Hispanics. This is possibly true due to the family ties Hispanics have together. There is a cultural belief that has been maintained within this ethnicity that what happens within the family must stay in the family. Another cultural belief is the lack of knowledge of dementia symptoms as being a disease process and not just old age. This is where social change is valuable and necessary. Cultural beliefs may not be changeable within this generation, but having specific tools to diagnose AD and giving medical providers the right tools and attitudes will change how the Hispanic adult ages cognitively.

Characteristics of Selected Data

Variables measured as part of a metabolic link between AD and DM2 will be self-reported dyslipidemia, diabetes, and HTN. Obesity as defined as a BMI > 30 kg/m^2 and history of stroke defined as (yes/no). Sociological risk factors that were analyzed were history of smoking measured by how many years the individual has been smoking, when the individual may have stopped smoking, and education level as measured by < a high school education, high school only, or > high school education. The literature confirms that higher education is cognitively protective (Prince et al., 2014). The genetic risk factor that was analyzed was the APOE ε4 genotype.

Data Management

Within some research studies there are situations that the researcher must decide between contribution to scientific knowledge and an individual's right to privacy. The UDS gathered data on the ADC location of each individual but for complete privacy not only does each individual receive only a number, the researchers are blinded to the

location of each ADC. The data that was gathered and analyzed for this study has been previously de-identified. Walden University issued the IRB number 02-01-16-0370587 and approval before any data collection began.

Creating positive social change was the outcome and goal of this study (Frankfort-Nachmias & Nachmias, 2008). Analyzing this data is an important step in discovering an association between DM2 and AD in the older Hispanic population. The data that was analyzed has been password protected on a personal computer and on a zip drive as back up. No other individual had access to this data.

Data Analysis

Data was entered into SPSS version 21.0 to evaluate whether DM2 predisposes older Hispanics to AD. All variables addressed a biological, metabolic, or sociological attribute that is related to the development of AD. Years of exposure to hyperglycemia, HTN, dyslipidemia, and obesity that have been poorly controlled could cause an accumulation of damage, therefore these variables were necessary to evaluate. Researchers have stated the risks of morbidity and mortality was higher the longer the individual had these above conditions (Sikdar, Wang, MacDonald, & Gadag, 2010). A bivariate analysis was performed on all independent variables to evaluate the relationship between the IVs and the DV.

The outcome variable, AD (yes = 1, no = 0), was categorical and therefore a logistic regression presenting an *OR* was used. Logistic regression is used to describe data when the DV is dichotomous and IVs that are either categorical or continuous (see Pezzullo, 2013). There are several assumptions with logistic regression. Non-linearity is acceptable between the IVs and DV, except for continuous independent variables, and

therefore a logit transformation of the dependent variable AD was performed. Another assumption is multicollinearity. The independent variables should not be closely related. The reason a variety of variables were chosen was to account for the different risks the human brain endures with hyperglycemia. Table 5 presents the categorical independent variables.

Table 5

Categorical and Continuous Variables for Analysis

Categorical IV with one level	Continuous IV with more than one level
History of stroke (yes/no)	BMI as kg/m2 (<24, 25-29, >30)
APOE ε4 as ε4/ε4 (yes/no)	
DM (yes/no)	Smoking history (current, past, never)
Hyperlipidemia (yes/no)	Education level (< HS, HS, >HS)
HTN (yes/no)	

Research Questions and Hypotheses

The four research questions this study addressed and analyzed were described below.

1. Does diabetes type 2 (DM2) predispose older Hispanics to Alzheimer's disease (AD)?

H_o1: DM2 does not predispose older Hispanics to AD.

H_a1: DM2 does predispose older Hispanic to AD.

Dependent variable: AD. *Independent variable*: DM2.

Statistical tests: Pearson chi-square test of association to analyze the association between DM2 and AD. This was reported with X^2, degrees of freedom (df) and *p* values. Logistic regression was used to analyze an odds ratio (*OR*) for DM2 and AD. It will be reported as *OR*, 95% confidence interval (CI) and *p* value.

2. Are there other metabolic risk factors such as HTN, history of stroke, obesity, and dyslipidemia contribute to the development of AD in older Hispanic?

H_o2: Other metabolic risk factors such as HTN, history of stroke, obesity, and dyslipidemia do not contribute to the development of AD in older Hispanic.

H_a2: Other metabolic risk factors such as HTN, history of stroke, obesity, and dyslipidemia do contribute to the development of AD in older Hispanic.

Dependent variable; AD. *Independent variables*: HTN, obesity as measured by BMI, dyslipidemia, and a history of stroke.

Statistical tests: Chi-square to determine any association between HTN, obesity, dyslipidemia, and stroke with AD reported with X^2, *df*, and *p* values. Logistic regression will be used to analyze an *OR* for each covariate as well as 95% CI and *p* values.

3. Do sociological risk factors such as education and smoking contribute to development of AD in older Hispanics?

H_o3: Sociological risk factors such as education and smoking do not contribute to the development of AD in older Hispanics.

H_a3: Sociological risk factors such as education and smoking do contribute to the development of AD in older Hispanics.

Dependent variable: AD. *Independent variables*: Educational attainment measured as < high school, high school, > high school, history of smoking as current, past or never.

Statistical tests: Multiple regression techniques for dummy coding the three levels in the one category of educational level and smoking, therefore binary dummy variables. These will be reported with *OR*, 95% CI, and *p* values.

4. Is there a relationship between AD and the APOE ε4 gene in the Hispanic population?

H_o4: There is no relationship between AD and the APOE ε4 gene in the Hispanic population.

H_a4: There is a relationship between AD and the APOE ε4 gene in the Hispanic population.

Dependent variable: AD. *Independent variable*: APOE ε4 genetic allele.

Statistical tests used: Pearson chi-square test of association. This calculates data from two categorical variables, APOE ε4, ε4/ε4 and ε2/ε4 combination (yes/no) and AD (yes/no) a X^2 will be reported as well as *df* and *p* values. Logistic regression will analyze the relationship between the APOE ε4 gene and AD as to the association with *OR*, 95% CI, and *p* value (Pezzullo, 2013).

Summary and Transition

A goal was to determine to what extent each variable either contributed to or interfered with an association between DM2 and AD. The life course theory was used to establish the concept that an accumulation of negative life events can create poor health. The positive social change could change the way medical providers supply diagnostic

dementia tools to their patients. There is a need for culturally and linguistically appropriate tools for Hispanics. Medical providers as well as Hispanic/Latino patients will benefit from early diagnosis of AD. Chapter 4 presents the statistical tests and analyses of data that was collected.

Chapter 4: Results

Introduction

The purpose of this study was to measure an association between DM2 and the development of AD in older Hispanics. I hypothesized that were biologic, metabolic, and sociologic factors that influence the development and progression of AD (ADA, 2015; O'Bryant et al., 2013; Whyte, 2014). Therefore, the main variable that I presented to determine the degree of association was DM2 in Hispanic adults between 60-96 years of age. Other variables that I tested were whether HTN, dyslipidemia, stroke history, and obesity as measured by BMI, education attainment, and a history of smoking could be associated as either confounders or mediators to the development of AD (see Prince et al., 2014). The genetic allele that researchers have associated with AD is the APOE ε4 allele. Chapter 4 consists of the data collection and processing analyses of the sample population, Hispanic adults compared to a White adult control group, using data from the UDS.

I conducted this cross-sectional study to determine if there was a relationship between DM and AD in older Hispanic adults. I also addressed the research questions and accompanying hypotheses with the premise that DM2 influences the odds of developing AD. Variables that could also be involved with AD were evaluated as well, including HTN, dyslipidemia, obesity, stroke history, cigarette smoking, and one genetic risk factor. I evaluated each risk factor, by variable, as to the influence these conditions have individually on AD development. The results of these statistical analyses began with the characteristics of both populations, Hispanic and White. I performed univariate analysis on all variables as to their association to AD and whether they qualified for

analysis by multivariable logistic regression. In order to understand how AD affected participants in this study, evaluating the cognitive tests used for a clinical diagnosis was necessary. In this chapter, I also discuss the results compared to the mean scores for both Hispanic adults and White adults by four cognitive tools used by the NACC to evaluate AD.

Cognitive Characteristics of Sample

The NACC Neuropsychological Battery consists of multiple tests employed to evaluate level of cognition; however, not every ADC gathered the same test results. Table 6 provides a list of the tests most frequently used by the ADCs to determine level of cognition. These four cognitive tests most accurately measured cognitive levels and skills of individuals that participated in the ADCs. Spanish was used for 594 of the MMSE tests administered; however, with other cognitive tests, the language used was not documented.

Table 6

Neuropsychological Tests Used to Determine Level of Cognition in Hispanic and White Adults

Each test measures	CDR Possible 0-3	BNT Possible 0-30	WAIS-R Possible 0-93	MMSE Possible 0-30
Attention			X	X
Concentration			X	
Conceptual Thinking			X	
Executive Function	X		X	X
Memory	X	X	X	X
Language		X		X
Visuoconstructional Skills			X	X
Calculations	X		X	X
Orientation	X			X
Judgment/Problem Solving	X		X	X
Personal Care	X			
Word knowledge		X	X	
Time to administer		10-12 minutes		7-8 minutes
Score for dementia	2/3	25/30	21/93	24/30

Forty-four percent of the White adults and 44% of the Hispanic adults evaluated using the CDR global rating for dementia were correctly classified in the moderate AD category. This is a score of 2, whereas 7% of the White adults and 12% of the Hispanic adults were evaluated with severe AD, a score of 3.

Table 7 displays results of all four tests. The CDR, which is a global rating of cognition, also assesses judgment and personal care. All four cognitive tests in the battery were significantly associated with a diagnosis of AD within White adults. However, within Hispanic adults, staging of cognition by the CDR was positively associated to AD but not the other cognitive tests.

Table 7

Association Between Cognitive Tests and AD Diagnosis

	Hispanic			White		
	X^2	*df*	Significance	X^2	*df*	Significance
CDR	24.317	4	<0.001*	140.846	4	<0.001*
MMSE	3.799	2	.150	23.769	2	<0.001*
BNT	4.456	3	.216	16.630	3	<0.001*
WAIS-R	.717	2	.699	22.255	2	<0.001*

Note: Chi-Square Significance level <0.05.

Descriptive Statistics and Demographic Characteristics

I have used descriptive statistics to describe the population and the variables that I measured. Table 8 displays the characteristics of each population with each variable that I evaluated in this study. Percentages of each variable are presented. More women than men participated in the study, 67% and 33% respectively for Hispanic adults, and 51% and 49% respectively for White adults. Women were slightly older in both populations: Hispanics, 76.7 years and 75.9 years respectively; and Whites 77.6 years and 77.1 years respectively. The majority of Hispanic adults had up to a 6th grade education (33%), and the majority of White adults had advanced degrees (31%).

Table 8

Characteristics of NACC-UDS of Hispanic Adults and White Adults Aged 60-96 Years

Characteristic	Category	Hispanic % (*n*=921)	White % (*n*=8,422)
Mean age	Male	75.9 (SD 7.9)	77.1 (SD 7.9)
	Female	76.7 (SD 8.0)	77.6 (SD 8.2)
Gender	Male	304 (33)	4,148 (49)
	Female	617 (67)	4,274 (51)
Diabetes (DM)	Self-reported	235 (26)	797 (9)
Hypertension (HTN)	Self-reported	585 (64)	3,951 (47)
Dyslipidemia	Self-reported	466 (51)	4,132 (49)
Body Mass Index	18-24 kg/m^2	257 (28)	3,317 (39)
(BMI)	25-29 kg/m^2	327 (36)	2,687 (32)
	>30 kg/m^2	201 (22)	1,163 (14)
Education	Grade 1-6	305 (33)	53 (.01)
	Grade 7-8	109 (12)	169 (2)
	Grade 9-11	82 (9)	286 (3)
	HS grad	160 (17)	2,043 (24)
	Grade 13-20	213 (23)	2,583 (31)
Stroke history	Clinical diagnosis	64 (7)	427 (.05)
Smoke history	1-25 years	148 (17)	2,136 (25)
-years smoked-	26-51 years	115 (12)	1,209 (.14)
	52-77 years	27 (3)	211 (.03)
	78-96 years	11 (1)	218 (.03)
APOE allele	ε4/ε4	42 (5)	773 (.1)
AD	Clinical diagnosis	874 (95)	7,798 (93)

Table 9 displays the results of Hispanic and White adults between 60-96 years old that have been diagnosed with primary cause of observed cognitive impairment – Alzheimer's disease (AD); both races combined equaled 9,343. Within this AD diagnosis, Hispanic adults comprised 8.4% within the AD subcategory of the entire population studied, but 95% within the Hispanic adult group, 874 individuals out of 921. White adults with a primary AD diagnosis comprised 75% of the individuals in the AD subcategory, and 93% within the White adult group, 7,798 out of 8,422. Genetic data

gathered on the same population size measured five haplotypes of the APOE gene. For this study the ε4/ε4 allele combination was of most importance since it is estimated that 40-65% of those with AD have at least one copy of this allele (AA, 2015). There were 42 Hispanic adults with this combination, and 773 White adults.

Table 9

Characteristics of Hispanic and White Adults with and without Alzheimer's Disease

Characteristics	Category	Hispanic Alzheimer's Disease		White Alzheimer's Disease	
		No	Yes	No	Yes
DM	Self-reported	14	221	71	726
HTN	Self-reported	38	547	301	3,649
Dyslipidemia	Self-reported	29	437	310	3,822
BMI	18-24 kg/m^2	8	249	206	3,111
	25-29 kg/m^2	21	306	172	2,514
	30-45 kg/m^2	10	191	98	1,065
Education	Grade 1-6	11	294	4	49
	Grade 7-8	6	103	13	156
	Grade 9-11	3	79	11	275
	HS	8	152	140	1,903
	College	17	196	448	5,369
Stroke	Clinical diagnosis	7	57	59	368
Smoking -years smoked-	1-25 years	13	135	139	1,997
	26-51 years	6	109	85	1,124
	52-77 years	1	26	15	196
	78-96 years	2	9	44	174
APOE	ε4/ε4 allele	5	42	26	773

Note: The adults that were deemed AD (no) were considered to have either vascular dementia or possibly 'contributing to cognitive impairment' without a 'primary contributing to cognitive impairment' diagnosis of AD dementia.

DM, HTN, and dyslipidemia were self-reported diagnoses. At the time of the initial visits, there were no laboratory confirmations and each individual was classified per self-report. Stroke history was a combination of self-report and clinical diagnosis through neurocognitive testing, MRIs, and previous medical history reports. The NACCAPOE variable is a derived variable within the NACC. This variable was coded for five different haplotype combinations of the APOE allele, and was confirmed through the ADC and reported to the NACC.

Three variables that were continuous were recoded to reflect a categorical variable. Education was continuously measured for each individual and was grouped into five categories of elementary, middle school, high school, high school graduate, and college. The majority of individuals measured, with and without AD completed high school and had some college. Sixty-nine percent of White adults with AD had higher education. In the Hispanic adults, 21% of those individuals with AD had higher education.

Smoking was also a continuous variable that I dummy coded for five groupings to reflect the length of time an individual smoked. The individuals in this dataset were separated into a category of 60-96 years of age. Some individuals were still smoking up to 96 years according to the self-reported data. Only slightly more of White adults (control group) were still smoking into later years. The majority of adults in both populations smoked up to 25 years, with and without AD.

I grouped BMI into three categories: normal weight, BMI (<24 kg/m^2); overweight, BMI (25-29 kg/m^2); and obese, BMI (>30 kg/m^2). There was a slight difference with the same population, considering those with AD and those without AD in

the Hispanic adult group, where the majority was in the overweight category (41% with AD, and 54% without AD). Within the White adult group, the majority of individuals were of normal weight (43% without AD, and 47% with AD).

Research Questions

I designed the following research questions to concentrate on Hispanics with diabetes that had been diagnosed with AD. For this study the dependent variable was AD and the main independent variable was DM2. I introduced other variables to determine the correlation to AD, whether as mediators or moderators. The research questions and the hypotheses that accompany them that I addressed in this study were:

1. Does diabetes type 2 predispose older Hispanic to Alzheimer's disease?

H_o 1: Diabetes type 2 does not predispose older Hispanics to Alzheimer's disease.

H_a 1: Diabetes type 2 predisposes older Hispanics to Alzheimer's disease.

2. Do other metabolic risk factors such as HTN, history of stroke, obesity, and dyslipidemia contribute to the development of Alzheimer's disease in older Hispanics?

H_o 2: Other metabolic risk factors such as HTN, history of stroke, obesity, and dyslipidemia do not contribute to the development of Alzheimer's disease in older Hispanics.

H_a 2: Other metabolic risk factors such as HTN, history of stroke, obesity, and dyslipidemia do contribute to the development of Alzheimer's disease in older Hispanics.

3. Do sociological risk factors such as educational attainment and history of smoking contribute to the development of Alzheimer's disease in older Hispanics?

H_o 3: Sociological risk factors such as educational attainment and history of smoking do not contribute to the development of Alzheimer's disease in older Hispanics.

H_a 3: Sociological risk factors such as educational attainment and history of smoking do contribute to the development of Alzheimer's disease in older Hispanics.

4. Is there a relationship between Alzheimer's disease and the APOE ε4/ε4 gene in the Hispanic population?

H_o 4: There is no relationship between Alzheimer's disease and the APOE ε4/ε4 gene in the Hispanic population?

H_a 4: There is a relationship between Alzheimer's disease and the APOE ε4/ε4 gene in the Hispanic population.

Data Management and Variable Derivation

The hypotheses have an evidence-based perspective in that AD, DM2, and hyperlipidemia is more prevalent in the Hispanic population (O'Bryant, 2013). Therefore, the UDS, which is a longitudinal dataset gathered by ADCs, includes more than 26,000 people throughout the United States. The ADCs are multidisciplinary centers located at 31 institutions in 17 states that contain data on individuals suffering from dementia. The NACC began in 1999 to advance AD research and all individuals can either be self-referred or referred through medical professionals. Since 2005, data were gathered annually by using standardized behavioral, cognitive as well as functional information for each participant. Genetic and neuroimaging data are available for most participants. Cognitive tests and intake information can be given in several languages and with the use

of family informants if necessary (Chapman et al., 2016). Researchers are blinded as to the location of each ADC for ethical reasons and informed consent was collected from all participants before any test was begun. A data request was submitted to the NACC and received approval number (ID 674) in which a dataset was provided with 12,174 individuals from various races. This sample was further divided by age, eliminating 979 individuals that were either younger than 60 or older than 96 years of age, equaling 11,194. Of these 11,194 individuals 1,851 were placed aside because they did not have an exclusive diagnosis of AD. Initial visits from each participant from the years 2005 to 2015 was included on each variable in this study as well as cognitive tests used to diagnose AD. Data inquiries were eventually restricted to age grouping of 60 to 96 years, Hispanic/Latinos and Whites, a dataset of 9,343.

During data manipulation it was discovered that the derived variables that categorized RACE included individuals that claimed White or Caucasian heritage. The variable HISPOR included self-proclaimed individuals with Hispanic origins from Mexico, Puerto Rico, Cuba, Dominican Republic, Central and South America. A dummy variable was created to reflect that 558 proclaimed both races White and Hispanic. Hispanics were pooled together, 558 from the White/Hispanic proclamation, 363 from the HISPOR proclamation therefore a sample size of 921. Whites were then recognized as 8,890 from the dataset of 12,174. The data that was evaluated for this study consisted of 9,343 individuals between the ages of 60 and 96, 921 were Hispanic, and 8,422 were White, losing 468 to a non-specific AD diagnosis. All of these individuals were evaluated on their initial visit to an ADC therefore a cross-sectional study.

Based on the inclusion criteria in chapter 3, I further filtered participants by diabetes, which was self-reported, since at time of evaluation a clinical diagnosis was not available. Most individuals in this study were evaluated by a team of clinicians and neuropsychologists and received a diagnosis of probable or possible AD per neurocognitive tests. The variable NACCALZP was assigned either (a) primary cause of observed cognitive Impairment-Alzheimer's disease or (b) contributing cause of observed cognitive Impairment-Alzheimer's disease. Individuals for this research study were accepted for analysis if they received a 'primary diagnosis' versus 'contributing diagnosis'.

Discrepancies within the presumptive data gathering mentioned in chapter 3 consisted of a few factors. In the best interest of this study a strict diagnosis of diabetes mellitus type 2 would have been preferred. When I obtained the dataset, there was no information concerning the type of diabetes each individual possessed. It can only be assumed that the majority of these individuals had DM2 since the majority of individuals suffer from this type (ADA, 2015). The NACC has stated that if any information is missing or was not gathered it was not considered "required." Each ADC can decide what information will be gathered with an explanation as to the reasoning coded as 95=unable to gather due to cognitive decline, 96=patient refused or -4=not gathered for that variable. Data was further separated by yes and no, either the individual had the condition or they did not.

Other discrepancies could be with external validity. The White sample size was large with an unfiltered group of individuals of over 8,000 adults. The NACC gathers data on individuals with dementia from multiple cities within the United States. The

Hispanic group of individuals was small in comparison to the population of Hispanic/Latinos within the United States. The Alzheimer's Association has stated there are approximately 200,000 Hispanics in the United States that have been diagnosed with AD (AA, 2015). Less than 1,000 Hispanics is therefore a small sample size.

Research Questions and Hypotheses

1. Does diabetes type 2 predispose older Hispanic adults to Alzheimer's disease?

H_o 1: Diabetes type 2 dose not predispose older Hispanic adults to Alzheimer's

H_a 1: Diabetes type 2 does predispose older Hispanic adults to Alzheimer's disease.

Chi-square analysis compares the observed count of each variable to the count, which would be expected when considering the assumption of no association between variable and outcome (Field, 2013). I used a Chi-square test for association to determine if there is an association between DM and AD in older Hispanic adults. The assumptions for chi-square are two variables used in the study are at a categorical level, all observations are independent, and all cells have more than five participants that are being measured for that variable.

Results for the chi-square analysis are presented in Table 10. There was no statistically significant association between DM and AD in either population. The case group Hispanics, and control group Whites results were, X^2 (1) = .510, p = .475 and X^2 (1) = 3.161, p = .075 respectively. When there is a small X^2 there is a greater probability that any association occurs by chance therefore DM and AD cannot be associated and along with the p value relate to non-significance. Table 10 displays the results of each variable

and its association to AD using a chi-square test with a significance level measured at 0.05. The results indicate that Hispanics with HTN, a lower education, and a stroke history have a positive association to AD. Obese White adults that had a stroke history, and a history of smoking had a positive relationship to AD.

Table 10

Covariates and Alzheimer's Disease Within the Sample Population of Hispanic and White Adults 60-96 Years of Age

	Hispanic			White		
	X^2	*df*	Sig	X^2	*df*	Sig
DM	.510	1	0.475	3.161	1	0.075
HTN	7.319	1	0.007*	1.547	1	0.214
Dyslipidemia	3.736	1	0.053	.460	1	0.498
BMI						
(18-24 kg/m^2)	3.037	1	.081	2.936	1	.087
(25-29 kg/m^2)	.006	1	.937	.130	1	.718
(30-45 kg/m^2)	1.933	1	.164	7.154	1	.007*
Education	12.242	5	0.032*	7.220	5	0.205
Stroke history	4.738	1	0.029*	27.689	1	< 0.001*
Smoking history -years smoked-	3.655	3	0.301	54.023	3	< 0.001*
APOE	3.202	1	0.074	19.532	1	<0.001*

Note: Significance level was set at <0.05. * Denotes those variables that are considered statistically significant using a Chi-square analysis to verify if an association exists between each variable and AD.

Tables 11 displays the binary regression conducted on the DM variable to AD outcome to verify the odds of Alzheimer's disease based on an individual with a history of diabetes or no history of diabetes between Hispanics and Whites.

Table 11

Unadjusted Odds Ratio for Alzheimer's Disease and Diabetes in Hispanics and Whites

	β	SE	Wald	*df*	*p*-value	Odds Ratio	95% CI Exp (β)
Hispanics with Diabetes	-.235	.330	.508	1	.476	.791	.441-1.509
Whites with Diabetes	.234	.132	3.147	1	.076	1.264	.976-1.638

Note: Significance level 0.05 *OR* and 95% CI determined using logistic regression linking DM and AD.

There was no association in either group between DM and AD. The unadjusted odds ratio for DM and AD for Hispanic and White older adults (60-96 years) is displayed in Table 11 (*OR* .791, 95% CI = .441-1.509, p = .476 and *OR* 1.264, 95% CI = .976-1.638, p = .076). The results for both populations indicate that there was failure to reject the null hypothesis that DM is related to AD. Even though the *OR* suggests that the risk of developing AD increases if the individual has DM in Whites, the CI contains 1, which allows for the idea that in this population increased risk and no significant risk can equally be considered (see Field, 2013). The null hypothesis that DM is not associated to AD development could not be rejected according to the results of the *OR*.

2. Do other metabolic risk factors such as HTN, dyslipidemia, obesity, and a history of stroke contribute to the development of Alzheimer's disease in older Hispanic adults?

H_o 2: Other metabolic risk factors such as HTN, dyslipidemia, obesity, and a history of stroke do not contribute to the development of Alzheimer's disease in older Hispanic adults.

H_a 2: Other metabolic risk factors such as HTN, dyslipidemia, obesity, and a history of stroke contribute to the development of Alzheimer's disease in older Hispanic adults.

In order to determine the contribution of each variable to the development of AD I used multiple regression techniques. However, when comparing all the effects of the predictor variables simultaneously, it is unknown to what extent each variable is related to the other (Szklo & Nieto, 2014). Multicollinearity occurs when two variables are related linearly. This can be common when working with raw datasets because information gathered may be redundant. This causes the importance of one variable, DM, to be less reliable than the other variables and results can be confounded. Szklo & Nieto (2014) mention that the variation inflation factors (VIF) should be under 5, Tolerance should be > .20 and these should be compared to a non-significant level in order to verify that no variables are linearly related. The results of the collinearity statistics were Tolerance < .908 and the VIF ranged from 1.006 to 1.101 when all variables were measured against each other.

In order to test the null hypothesis for the second research question, I used chi-square and logistic regression. Logistic regression adjusts for confounders with an adjusted *OR*, taking into consideration the other covariates (see Szklo & Nieto, 2014). Chi-square analysis revealed that for Hispanics, HTN and stroke were significantly associated with AD, X^2 (1) = 7.319, p = .007 and X^2 (1) = 4.738, p = .029. The results of

the BMI statistic for White adults revealed that being obese and having a stroke history were significantly associated with AD, X^2 (1) = 7.215, p = .027 and X^2 (1) = 27.689, p = < .001.

Table 12 displays the results of the logistic regression *OR* and CI for covariates hypertension (HTN), dyslipidemia, body mass index (BMI), and a stroke history. HTN and a stroke history were significantly and positively associated to AD in Hispanics, however in obese White adults (>30 kg/m^2 BMI) and a having a stroke history was associated with AD. Each variable was measured with AD using logistic regression and a significance level set at 0.05 for *OR*s and CI.

Table 12

Unadjusted Odds Ratio for Alzheimer's Disease and Metabolic Variables in Hispanic and White Adults

	β	SE	Wald	*df*	*p*-value	Odds Ratio	95% CI Exp (β)
Hispanic HTN	1.081	.418	6.701	1	.010*	.339	.150-.769*
Dyslipidemia	-.649	.314	3.624	1	.057	.552	.268-1.019
BMI							
(18-24 kg/m^2)	-.628	.366	2.942	1	.086	.534	.261-1.094
(25-29 kg/m^2)	.019	.237	.006	1	.937	1.019	.640-1.621
(>30 kg/m^2)	-.467	.339	1.901	1	.168	.627	.323-1.218
Stroke history	-.911	.432	4.447	1	.023*	1.224	1.028-1.457*
White	*β*	SE	Wald	*df*	p-value	Odds Ratio	95% CI Exp (B)
HTN	.108	.087	1.546	1	.214	1.114	.940-1.319
Dyslipidemia	.059	.087	.459	1	.498	1.060	.895-1.257
BMI							
(18-24 kg/m2)	.301	.176	2.916	1	.088	1.351	.957-1.909
(25-29 kg/m2)	.059	.165	.130	1	.718	1.061	.769-1.465
(>30 kg/m2)	.600	.227	6.973	1	.008*	1.822	1.167-2.843*
Stroke history	.757	.147	26.493	1	<0.001*	2.131	1.598-2.843*

Note: Hypertension (HTN), Body Mass Index (BMI).

Logistic regression measured whether a variable would be statistically significant by an odds ratio within the sample populations that had AD. HTN, dyslipidemia, a history of stroke, and obesity measured by three categories of BMI in the Hispanic and White population were analyzed. Each population that did not have a self-reported history of HTN, dyslipidemia, history of stroke or an obesity factor compared with those

that did have these conditions were measured against a diagnosed outcome of AD. The assumptions for logistic regression are a linear relationship between a continuous variable and the logit of the outcome exist, multicollinearity does not exist, and the independent variables are measured without errors (see Field, 2013). The farther away β is from zero signifies a higher predictive value. The Wald statistic tests the null hypothesis that the constant is equal to zero. If the β coefficient is significantly different from zero it is assumed that any of the variables in the model contributes positively to the outcome of AD. The odds ratio reports the association between having the condition as the predictor of AD. *OR*s less than 1 are interpreted, as the predictor increases the odds of AD occurring decreases. Conversely, *OR*s greater than 1 are associated with the odds of the outcome, AD, occurring (see Field, 2013). The chi-square and logistic results for the following variables are displayed in Tables 10 and 12.

Hypertension. The chi-square analysis revealed that in the Hispanic population HTN was significantly associated with AD X^2 (1) = 7.319, p = .007. The logistic regression output also agrees that HTN was associated to AD in Hispanics (*OR* .339, 95% CI = .150-.769, p = .010). Even though the *OR* reveals a decreased risk of AD with HTN, the p value is below .05 and the CI does not contain 1, which points to HTN being associated with AD. In White adults, HTN was not associated to AD either through a chi-square analysis or logistic regression.

Dyslipidemia. In the chi-square analysis for Hispanics as well as regression, dyslipidemia was slightly non-significant. In comparison X^2 (1) = 3.736, p = .053 and (*OR* .522, 95% CI = .268-1.019, p = .057). The *OR* suggests that dyslipidemia is protective in the development of AD but the slightly non-significant p value indicates

possibly for the larger percent of the population this could be a predictor. For White adults this predictor variable in the chi-square analysis and regression revealed it was not associated to AD.

Stroke history. For both Hispanic adults and White adults, a history of stroke was positively and significantly associated with AD. Chi-square results for Hispanic adults and White adults respectively X^2 (1) = 4.738, p = .029 and X^2 (1) = 27.689, p = < .001. The *OR* results were corroborative for both races and suggests that having experienced a stroke creates a 1 to 2 times increased risk of developing AD. The *OR* results for Hispanic adults were (*OR* 1.224, 95% CI = 1.028-1.457, p = .023) and White adults were (*OR* 2.131, 95% CI = 1.598-2.843, p = < .001).

BMI. BMI was categorized into three groups denoting normal weight (18- 24 kg/m^2) overweight (25-29 kg/m^2) and obese (>30 kg/m^2). Chi-square and logistic regression were performed to discover if there was an association between any of these three groups and AD. It was discovered for Hispanic adults the majority of individuals in a sample size of 921 were overweight (25-29 kg/m^2). The majority of White adults in a sample size of 8,422 were of normal weight (<24 kg/m^2). The Chi-square results for Hispanics was not statistically significant for any category however, for Whites it was significant at BMI of (30-45 kg/m^2), the level considered obese, X^2 (1) = 7.154, p = .007. The regression results agreed with the chi-square for non-significance for Hispanics and significant for Whites at the same BMI level (*OR* 1.822, 95% CI = 1.167-2.843, p = .008). The odds of developing AD as an individuals weight increases is 1.8 times greater than being of normal weight for White adults.

I used chi-square analysis for both races to detect an association between risk factors besides DM and AD. There was a significant association in Hispanic adults with HTN and a stroke history; among White adults, a history of stroke and being obese, with a BMI (30-45 kg/m^2). An *OR* was obtained through logistic regression, which revealed that there were increased odds of developing AD in Hispanics with HTN and a history of stroke. In White adults, there was a risk of developing AD with a history of stroke and a higher BMI.

3. Do sociological risk factors such as educational attainment and a smoking history contribute to AD development in Hispanic older adults?

H_o 3: Sociological risk factors such as educational attainment and a history of smoking do not contribute to the development of AD in older Hispanic adults.

H_a 3: Sociological risk factors such as educational attainment and a history of smoking contribute to the development of AD in older Hispanic adults.

Tables 13 displays the *OR* and CI for the variables in research question 3 for each population. The results indicate that from the two sociologic variables studied, having less education for Hispanics was significantly associated with AD. A smoking history was positively associated with AD in Whites.

Table 13

Unadjusted Odds Ratio for Alzheimer's Disease and Sociological Variables in Hispanic and White Adults

	β	SE	Wald	*df*	p-value	Odds Ratio	95% CI Exp (B)
Hispanic							
Education	.202	.089	5.180	1	.023	1.224	1.028-1.457*
Smoking history -years smoked	-.062	.288	.046	1	.803	.940	.534-1.653
White	*β*	SE	Wald	*df*	p-value	Odds Ratio	95% CI Exp (B)
Education	.081	.045	3.195	1	.074	1.084	.992-1.185
Smoking history -years smoked-	.351	.064	30.450	1	<0.001	1.421	1.254-1.610*

Note: Significance level ≤0.05 *OR*s and CI derived from logistic regression and sociological variables and AD.

Two variables that are known in current literature to be associated with AD are educational level and cigarette smoking. These variables were used in a multivariate regression to assess any association between years of education and years of smoking as to how they relate positively or negatively to AD development in Hispanics and Whites.

Education. Education was categorized by grade school 1-6, grades 7-8, high school, grades 9-11, high school graduation, 12, and college years up 13-20 years of education. Within the Hispanic adult group with AD, 36% had up to a 6th grade education. Within the White adult group with AD, 44% had a college education. As noted in Table 10, chi-square results for Hispanic adults, lower education was significantly associated with AD, whereas in White adults, education has the potential to be protective

against the development of AD. There were fewer individuals in the higher than high school attainment category with the results as X^2 (5) = 12.242, p = .032. For White adults, the results were not significantly associated with AD, X^2 (5) = 7.220, p = .205, this can be concluded that higher education is not associated with AD in White adults. Table 13 displays the *OR* for Hispanics (*OR* 1.224, 95% CI = 1.028-1.457, p = .023). These results suggest there is a higher risk for developing AD with less education for this population. For White adults, the *OR* results were (*OR* 1.084, 95% CI = .992-1.185, p = .074). An *OR* over 1 indicates that higher education can be protective. Because the CI contains 1 and the p value is slightly above .05, these results do not allow the null hypothesis, that lower education is associated to AD in White adults, to be rejected.

Smoking history. Smoking was divided into four groups of 25 years. I performed a chi-square to determine an association between years of smoking and AD in both populations. Chi-square results for Hispanics X^2 (3) = 3.655, p = .301 and an agreement of *OR* with results of (*OR* .940, 95% CI = .534-1.653, p = .803) were discovered. The majority of Hispanics and Whites smoked between 1 and 25 years. The null hypothesis could not be rejected for years of smoking. Therefore, according to this data no association can be made between years of smoking and AD development. White adults had a different result with chi-square and *OR* agreeing that as years of smoking increase so does the opportunity for AD. Chi-square of X^2 (3) = 54.023, p = < .001 and *OR* (*OR* 1.421, 95% CI = 1.255-1.610, p = < .001) is suggestive that as smoking years increase there is an increased risk of AD.

In determining whether subcategories of three variables changed any outcome to either statistically significant or not significant, BMI, smoking years, and education levels

were placed in a separate layer to measure the significance or confounding in relationship to the other variables. This is referred to as an adjusted *OR* for confounding through the Mantel-Haenszel Common Odds Ratio Estimate. The results for the Mantel-Haenszel Conditional Independence test was X^2 (1) = .259, p = .611. The results for the odds ratio estimate were (*OR* 1.111, 95% CI = .786-1.571, p = .552). Each of these categories measured against each layer of BMI, education and smoking were homogenous across each stratum and the findings were non-significant.

4. Is there a relationship between Alzheimer's disease and the APOE ε4 gene in Hispanic older adults?

H_o 4: There is no relationship between Alzheimer's disease and the APOE ε4 gene and in older Hispanic adults.

H_a 4: There is a relationship between Alzheimer's disease and the APOE ε4 gene in older Hispanic adults.

Table 14 displays the results of the unadjusted odds ratio for each population with the APOE gene and AD.

Table 14

Unadjusted Odds Ratio for Alzheimer's Disease and the APOE ε4ε4 Allele for Hispanic and White Adults

	β	SE	Wald	*df*	*p*-value	Odds Ratio	95% CI Exp (β)
Hispanic							
APOE	.223	.128	3.014	1	.083	.972	.838-1.608
White	*β*	SE	Wald	*df*	p-value	Odds Ratio	95% CI Exp (B)
APOE	-.221	.051	18.370	1	<0.001	.802	.725-.887*

The null hypothesis for research question 4 could not be rejected in Hispanic adults, but there was statistical significance in White adults and the null hypothesis was rejected. Chi-square analysis for each population is displayed in Table 9. The chi-square of association results for Hispanic adults were X^2 (1) = 3.202, p = .074, and for White adults, X^2 (1) = 19.532, p= < .001. This signifies that the APOE ε4 gene is significantly associated with the development of AD in Whites but not Hispanics. The *OR* reflects statistical significance in White adults but not Hispanic adults. Both *OR*s are less than 1, which possibly signifies there is a decreased risk of AD in Hispanics and Whites with the ε4/ε4 APOE allele. The *OR* for each population respectively was (*OR* .972, 95% CI = 8.38-1.608, p = .083) and (*OR* .802, 95% CI = .725-.887, p = < .001).

Model Summary

There are three tables within the logistic regression analysis that measure whether the predictors accurately classify and can be related to AD. The Hosmer-Lemeshow Test is a goodness of fit test that reveals if the model is different from the observed values. Since the *p* value is greater than .05 for all variables added to the model for Hispanic

adults, the model is a good fit X^2 (8) = 3.379, p = .908 and for White adults, X^2 (8) = 8.764, p = .363. The Omnibus Tests of Model Coefficients uses all the predictors provided for the study and then relates them to AD. The results of this test for Hispanics adults, X^2 (8) = 14.081, p = .080 and White adults, X^2 (8) = 53.951, p =< .001. The Classification Table provides a percentage of individuals correctly classified by the type of variables that were placed in the study. The results for Hispanic adults were 93.3% correctly identified and White adults were 93.8% correctly classified.

Summary and Transition

This study attempted to determine whether diabetes was associated with AD in older Hispanic adults. A White control group three times the size of the case group was used to provide a comparison. There was failure to reject the null hypothesis for research question 1 for either population through a chi-square and logistic regression. This means with this study there was no association between DM and AD in older Hispanics or Whites.

The outcomes of research question 2 of other metabolic conditions that could participate in the development of AD suggest that a history of stroke is significantly associated to AD. These variables were HTN, dyslipidemia, a history of stroke, and obesity measured by three subcategories of BMI. These risk factors were measured as either independent risk factors or as confounders in the development of AD in older Hispanics. For Hispanic adults, HTN, and a history of stroke were positively associated with AD and significantly contributed to the model for predicting AD. In White adults, a history of stroke and obesity, as measured by BMI, were positively associated with AD.

Research question 3 introduced sociological risk factors that could be involved with AD development. Education attainment measured on five levels and smoking history measured on four levels for AD development in the association to DM and AD. For Hispanic adults, smoking years and education were not significantly associated with AD statistically, and for White adults, smoking but not education attainment was statistically significantly associated to the development of AD.

Research question 4 revealed that for Hispanics the APOE ε4/ε4 was not a good predictor of AD development however, for the White group it was statistically significant. These results could deliver information for medical providers to decide on the best approach for older Hispanic adults for dementia prevention.

Chapter 5 will present interpretation of these results, ideas and a framework for social change within the older Hispanic community. Limitations within the data and results as well as recommendations for future research will also be discussed.

Chapter 5: Discussion, Conclusions, and Recommendations

Introduction

The purpose of this study was to discover if there is an association between DM2 and AD in older Hispanics. I hypothesized that biologic, metabolic, and sociologic factors influence the development and progression of AD (ADA, 2015; O'Bryant et al., 2013; Whyte, 2014). Therefore, I analyzed the main independent variable, DM2, to determine if there was an association of DM2 with AD in Hispanic adults between 60 and 96 years of age. Other variables that I analyzed as independent risk factors as either confounders or mediators for AD were HTN, dyslipidemia, stroke history, obesity measured by BMI, lower educational attainment, and a history of smoking (Prince et al., 2014). The APOE ε4 allele is the genetic allele that has been associated with AD. Chapter 5 consists of my interpretation of data findings, a discussion of limitations of this study, recommendations based on my findings, and a discussion of what tools are currently in place for medical providers. I also discuss this study's implications for social change and my larger conclusions.

Research questions that I designed and addressed were: (a) Does DM2 predispose older Hispanics to AD? (b) Does HTN, hyperlipidemia, obesity, and a history of stroke affect the relationship of AD development in older Hispanic adults? (c) Do sociological risk factors such as low education attainment and a smoking history contribute to AD development in older Hispanic adults? And (d) Is there a relationship between the APOE ε4/ε4 allele in AD development in older Hispanic adults? I collected data from the NACC UDS that consisted of 60-96 year-old Whites and Hispanics with AD.

Interpretation of Findings

Multiple epidemiological studies have shown a link between DM2 and AD (Li, Song, & Leng, 2015; Moran et al., 2013; Yang, 2013), and my intention was to add more insight to the current literature regarding these two health risks in Hispanics. Despite a large, generalizable dataset including more than 8000 White older adults and 900 Hispanic older adults, I was unable to reject the null hypothesis for Research Question 1. In what follows, I discuss which variables of each research question were statistically significant in each population, and which variables remained statistically non-significant.

1. Can there be an association between DM2 and AD development in Hispanic older adults?

I could not use the findings for this primary research question to support a rejection of the null hypothesis in either population, White or Hispanic. Many researchers have emphasized that DM2 increases the risk of AD compared to individuals without diabetes. The Hisayama Study, reported by Yamazaki et al. (2011), showed that DM2 and AD were noticed occurring together 2.18 times more frequently then separately diagnosed (Sims-Robinson, Kim, Rosko, & Feldman, 2010). Researchers who conducted the Rotterdam Study determined that IR was the relationship that ties DM2 and AD together (Mushtaq et al., 2014). Many more epidemiological studies have been performed over the years to positively link DM2 to AD development either by inflammation (Blázquez et al., 2014; Li, Song, & Leng, 2015; Medhi & Chakrabarty, 2013; Mushtaq et al., 2014) or IR and reductions in glucose metabolism (Dickstein et al., 2010; De Felice, 2013; Duarte et al., 2013; Sims-Robinson, Kim, Rosko, & Feldman, 2010; Whitmer et

al., 2009). Moran et al. (2013) found that DM2 is associated with cortical atrophy therefore neurodegeneration contributing to AD.

For this study no association was found by *OR* .791, 95% CI = .441-1.509, p = .476 for Hispanic or White adults. There are few studies that support the concept that DM2 alone exclusively associates to AD (Beeri et al., 2005; Tomita et al., 2012; Tuligenga et al., 2014). Tomita et al. (2014) concluded that the extent of amyloid-beta deposits in the brain does not differ between DM2 adults with AD and those with AD alone. Their results point out that diabetics with and without AD had similar senile plaques that were typical of AD pathology, whether insulin or oral diabetes medications were used.

Tuligenga et al. (2014) concluded that shared factors with diabetes such as HTN cause cognitive decline, which can be dependent on duration of both diseases. The results further clarify that newly diagnosed diabetes and prediabetes did not relate to faster cognitive decline when compared to normoglycemic individuals. However, middle-aged adults with long standing diabetes displayed a 45% faster decline in memory. Tuligenga et al. (2014) and Sims-Robinson et al. (2010) further concluded that insulin resistance, most common in DM2, the sole instigator of cognitive decline, is erroneous since DM2 is often associated with cardiovascular as well as environmental and lifestyle risk factors. Beeri et al. (2005) concurred with the other studies that determine that there is not one agent responsible for AD development in individuals with DM2. Cardiovascular risk factors, HTN, dyslipidemia, older age, APOE genetics, and inflammatory conditions contributed significantly to AD pathology, according to these authors. In light of the non-significant findings of Research Question 1, I considered other risk factors.

2. Are there other metabolic risk factors such as HTN, dyslipidemia, obesity, and a history of stroke, that contribute to the development of AD in older Hispanic adults?

I analyzed each variable for collinearity, as any similarity in conditions would skew the results producing imprecise results. The VIF ranged from 1.006 to 1.101; since was below 5, these variables were not linearly related.

MetS is a condition that consists of several cardiovascular risk factors including hyperglycemia (whether or not frank diabetes), dyslipidemia, HTN, and central obesity (McEvoy et al., 2012). I analyzed all of these risk factors by chi-square and *OR* as to their relationship independently to AD. The collective features of MetS and individual risk factors have been found to enhance cognitive aging. Researchers have determined that this is due to hyperglycemia and inflammatory by-products, but it can differ within population size, age, and, mostly, whether the factors are additive or interactive (McEvoy et al., 2012; Li, Song, & Leng, 2015).

HTN. Epidemiological studies have shown that chronic high blood pressure not controlled in midlife is associated with AD (Feldstein, 2012). Midlife HTN has been associated with amyloid-beta build up in the brain affecting the vascularity of the vessels. Other studies have shown that anti-hypertensive medications provide a protective effect and, therefore some of the studies that proclaim no association to AD neglect to evaluate medication use (Østergaard et al., 2015). I found a significant association between HTN and AD in Hispanics by analyzing data using chi-square and *OR*, X^2 (1) = 7.319, p = .007 and *OR* .339, 95% CI .150-.769, p = .010. There were 64.8% Hispanics with HTN and AD compared to 35% without HTN and AD. In a study using the HCHS/SOL data of

16,415 Hispanics, Sorlie et al. (2014) concluded several factors. Women over 50 years of age had a higher prevalence of HTN, and the amount of awareness, treatment, and control within the Hispanic population was low despite age range (Sorlie et al., 2014). However, it is interesting to note that education and income level did not alter the rates of HTN, but those with health insurance had a higher rate of awareness, treatment, and control of their HTN (Feldstein, 2012; Sorlie et al., 2014). This could also be the reason why the White population did not have a significant finding of HTN as it relates to AD, as discussed in the NHANES data for 2009-2010 (Sorlie et al., 2014). The theory being they received treatment earlier in their lives and continued with normal blood pressure levels through late life.

Those with adequate health access, a consistent primary care provider, and access to medications generally have treatable risk factors that reduce the effects of chronic disease (Hall et al., 2012). I was unable to determine whether this is the reason that the null hypothesis could not be rejected, in that HTN had been adequately treated within the White adult population. In the NACC database of over 8000 White individuals with AD, 50% had HTN, whereas 51% were not hypertensive. The *OR* 1.114, 95% CI = .940-1.319, p = .214 reflect non-significance, and due to the self-reported nature of the data, I could not discern whether HTN was measured from midlife or late in life. According to a prospective study from Finland, patients that had been treated for HTN and dyslipidemia in midlife had less incidence of AD in later life (Kivipelto et al., 2001). In the same Finnish study, researchers discovered that the risk of AD was increased when both HTN and dyslipidemia were present in midlife from an *OR* of 2.7 to 3.5 (Kivipelto et al., 2001).

Dyslipidemia. The Uppsala Longitudinal Study of Adult Men, and the Three-Cities Cohort Study showed no association between late life TC and AD, which concurs with the results of this study. I was unable to reject the null hypothesis concerning dyslipidemia, as associated with AD in Hispanics and Whites. The *OR* reveals slight non-significance and could be interpreted as protective, *OR* .552, 95% CI = .268-1.019, p = .057. Some studies have reported better memory and mental function in the elderly with higher TC and LDL specifically (Schreurs, 2010). Eighteen prospective studies that were reported by Craft (2010) showed that no association was discovered between AD and late life TC measures. HTN and dyslipidemia could increase dementia risk through atherosclerosis and by impairing blood flow to brain structures, inducing neurodegeneration as seen in stroke results.

Stroke. Few Hispanic adults presented with a stroke history and AD in this data set, 6.6% compared to 93% with no stroke history and AD. White adults as well were few in the same category, reflective of 5% with a stroke and AD history and 95% with no stroke history. However, with both populations a stroke history was positively and significantly associated with AD. *OR* for the Hispanic population was 1.224, 95% CI = 1.028-1.457, p = .023. It is interesting to note that according to Lenzi, De Benedetto, and Altieri (2012), being White provided some protection against stroke; however, the NACC data had 368 Whites with a past history of stroke compared to 7,338 who did not. These adults with AD presented a different result with an *OR* of 2.131, 95% CI = 1.598-2.843, p = < 0.001. These results show that a history of stroke doubles the chance of developing AD. Researchers who conducted the Framingham Study, which included 4,897 adults, measured life time risk of stroke and concluded that blood pressure is the most

modifiable risk factor for stroke, and that HTN in midlife reflects risk of stroke in late life (Seshadri et al., 2005). Stroke and risk factors for stroke carry genetic links such as the APOE gene. AD occurring after a stroke could be the consequences of vascular pathology and/or degenerative changes occurring pre- and post-stroke (Lenzi, De Benedetto, & Altieri, 2012).

BMI. Metabolic conditions such as DM2 and vascular conditions, HTN and stroke, have been known to contribute to late life dementia. Midlife obesity has been known to contribute to dementia in late life through several studies. The causal means are as mentioned before are inflammatory cytokines, increased insulin not clearing from the brain, and amyloid beta plaque build-up (Gunstad, Lhotsky, Wendell, Ferruci, & Zonderman, 2010; Li, Song, & Leng, 2015; Prince et al., 2014). Prince et al. (2014) in the World Alzheimer's Report 2014 report on 15 prospective studies that looked for an association between obesity and dementia. Obesity in midlife presented a 30% increased risk of eventually developing dementia in late life and interestingly enough, those that had a low BMI, were at twice the risk of developing dementia. The Finnish Cardiovascular Risk Factors, Aging and Dementia study (CAIDE) and the Kaiser Permanente study found a positive association between central obesity in mid-life and dementia in late life. However, the Prospective Population Study of Women in Sweden (PPSW) found no association (Prince et al., 2014). Anstey, Cherbuin, Budge, and Young (2011) agreed because they discovered in their study that body fat contains leptin and estrogen which has proven to protect cognitive function.

In this research study, I discovered in the Hispanic adult population studied, there were no associations between any BMI measurements and dementia. There were more

Hispanics that had a BMI of 25-29 kg/m2, considered over weight, in the sample group. In the White adults studied, there was a statistically significant association between obesity (BMI of 30-45 kg/m^2) with (*OR* 1.822, 95% CI = 1.167-2.843, $p = .008$) and AD.

3. Do sociological risk factors such an educational attainment and a history of smoking contribute to AD in older Hispanic adults?

Education. There are several theories on why educational attainment is considered brain protective. It is believed that higher brain functions created by higher education create more efficient neural pathways. Those individuals with higher education may be more motivated to engage in intellectually stimulating activities. Also those that have more education usually have better paying jobs that are also more stimulating, creating more cognitive reserve to draw from (Ngandu et al., 2007; Prince et al., 2014;). Meta-analysis results from 19 studies reported that dementia was increased in individuals with lower education. This is in agreement with the results from this study in which Hispanic adults with lower education had a 1.2 increased risk of developing AD with *OR* (*OR* 1.224, 95% CI = 1.028-1.457, $p = .023$). The majority of Hispanic adults had a grade school education at 36% compared to White adults having the majority of the individuals in the study at 39% with a college education. However, within White adults, the null hypothesis was unable to be rejected that higher education was protective of dementia. In an interesting study presented by Alladi et al. (2013), those that are bilingual have a longer delay at dementia onset adjusting for education level, sex, and occupation. Song, Mitnitski, and Rockwood (2014) agree, in their study those that survive longer with cognition intact had higher education.

Smoking. Heavy smoking in midlife has been reported to be associated with a 100% increase in AD. The Honolulu Asia Study found that the risk of AD increased with the amount of midlife smoking and a third study found an association between smoking and AD when considering APOE ε4 carriers (Rusnan et al., 2011). This agrees with the results of this study for the White adult population in that the odds of developing AD from smoking through midlife increased by 1.4 compared to non-smokers. There was no statistical association between Hispanic adults and smoking in this study. The majority of Hispanic adults smoked up to 25 years, which was almost 50% of the studied population. This is in agreement with a study performed by Rusnan et al. (2010) that states smoking can be neural protective. Nicotine, according to more than one study, protects the brain against cell damage. However, other substances in cigarettes are known carcinogens (Prince et al., 2014). Studies that report this protective affect should be evaluated for recall and selection bias.

4. Is there a relationship between Alzheimer's disease and the APOE gene in older Hispanic adults?

The APOE ε4 allele has been reported to increase the risk of AD in Hispanic adults and White adults but more so in a dose dependent manner. Those that have a ε4/ε4 genotype can be up to three times more susceptible to AD but this was found more frequently in individuals with poor lifestyle practices (Crean et al., 2010). Mexican Hispanics were found to carry less often the ε4 allele than White adults but have a heavier burden of AD. In a study by Campos, Edland, and Peavy (2014), White adults had a significant association between AD and APOE ε4 genotype but not Hispanic adults. This study also discovered this fact and was in agreement with Aslan et al. (2010). *OR* for

Hispanic adults and APOE ε4/ε4 carrier status was (*OR* .972, 95% CI = 8.38-1.608, *p* = .083) however, for White adults the null hypothesis was rejected with the *OR* as (*OR* .802, 95% CI = .725-.887, *p* = <0.001). This is also in agreement with Aslan et al. (2010), Starks et al. (2015), Teruel et al. (2011), and Prince et al. (2014).

The APOE genotype creates a risk for development of AD but has not been found to be the sole cause of AD itself. APOE as a cholesterol can aggravate brain pathology to encourage neuronal damage through amyloid build-up plaques and increased NFT. In a study by Malek-Ahmadi et al., reported by Starks et al. (2015), individuals with AD and DM2 as well as APOE carriers displayed more plaques and tangles postmortem than non-carriers.

Theoretical Framework

A life course framework hypothesizes that early and midlife exposures of bodily harm possibility lead to chronic disease in later life (Ben-Shlomo & Kuh, 2002; Tomita et al., 2012). The accumulation of risk model under the life course perspective embodies the idea that late-life dementia has biologic, metabolic, and sociologic roots. Multiple factors such as smoking, untreated hypertension, high serum cholesterol, obesity, and diabetes added to unfortunate genetic factors, accumulating over a lifetime creates eventual neurodegenerative brain pathology (Mangialasche et al., 2012). As in the ecosocial perspective, the accumulation of risk model proposes times in an individuals' life, mostly through midlife (40-59 years old) when certain conditions develop and start a continuum of damage.

The factors that are not modifiable in an individuals' life are age, nationality, genetics, and the APOE genotype. However, as this study attempted to discover, the

modifiable risk factors that could influence dementia in late life were DM status, HTN, dyslipidemia, a history of stroke, obesity, smoking, and educational attainment. DM2 was not found to be significantly related to dementia in late life in either population studied. Most of the modifiable risk factors measured were performed in mid-life with longitudinal data documentation. Some of the results had inconsistent findings, there was disagreement between studies, and bias in studies was reported concerning some findings. However, the majority of studies report a prospective, longitudinal significance between midlife (40-59 years old) and late life complications of chronic disease including dementia, specifically, AD (Al Hazzouri et al., 2011; Cable, 2014; Prince et al., 2014; Song, Mitinski, & Rockwood, 2014). With the knowledge that accumulative patterns can be additive in an individuals' life creating irreversible disease, steps can be taken to ameliorate the effects caused by DM2, dyslipidemia, HTN, and obesity. HTN, stroke, and lower education were found to be significantly associated with eventual dementia in Hispanics as well. In the social change section, ways to change this pattern in this population were discussed.

Strengths of the Study

One of the strengths with this data was that it was collected by the NACC UDS over the last 10 years and included a variety of variables and detailed cognitive tests used to determine cognitive status. The dataset was large with *n*=8,422 White adults and *n*=921 Hispanic adults. The data were meant to be generalizable because there were 31 locations throughout the United States that gathered information for the NACC, which included several races. Other datasets did not go into as much detail as to the results of the cognitive tests that explained different types of dementia including AD. Another

strength was the amount of information included in the literature review for many aspects and risk factors of AD. Factors that affect the brain such as HTN, stroke, and dyslipidemia were included. However, other factors that affect the brain, as well as, the body needed to be included such as obesity and smoking. Education and socialization were included to present a complete picture of how these factors affect an individuals' cognitive status. Results of this study reflect what the literature expounds as to the relevant risk factors of dementia.

Limitations of the Study

There were several limitations to this study. The cross-sectional nature of this study is problematic because it cannot be used to observe events longitudinally and therefore causation cannot be established. Even though the data set used for this study was large, it was difficult to know the specific ethnicity of each individual since this was recall for some participants that may have been older than 80 years of age. Early in evaluation of this data it became apparent that some of the Hispanic/Latinos when asked about heritage replied, "yes" to Caucasian as well. I ultimately included these individuals in the Hispanic/Latino grouping for the purposes of this study. Another limitation in this regard is some interviewers did not gather the same data in every location under every variable causing missing data. I eliminated missing data before any analysis was performed.

A significant limitation was the self-reported nature of several conditions. In reviewing the data and data dictionary of the NACC UDS data once received, no lab confirmation of diabetes type, cholesterol levels, or blood pressure readings were available. Most of the interviewers gathering data in ADC locations took the participants

claim that they had been diagnosed with the above conditions, therefore self-reported. It was also unknown how long the conditions had affected each participant or what types of medications had been used.

BMI was used as a marker for obesity. This is a measure strictly of weight in kg divided by height meters squared. Therefore, it does not take into consideration body density. A person could be classified as obese by kg/m^2 but be large in stature and have more muscle density. Fitzpatrick et al. (2009) stated measuring height and weight in the elderly is not a good way to assess adiposity. Waist circumference is a more accurate measurement in older individuals however the measurement used by the UDS was BMI.

Recommendations for Future Research

The intent of this study was to evaluate if an association can be found between DM2 and AD in older Hispanic/Latinos. There was no association found between DM2 and AD in these two populations, White adults or Hispanic adults, yet other risk factors were statistically significant. HTN, and lower education in Hispanics, obesity and a smoking history for White adults, and a history of stoke for both populations. There is currently a vast amount of information and research studies that confirm a statistically significant association between the causes of DM2 and AD. Obesity alone, caused by poor lifestyle habits, creates an environment of insulin resistance and inflammatory reactions that affect the brain.

Randomized Control Trials. (RCT) are needed to develop new therapies, medications, and vaccines to prevent or alter disease progression. There are several challenges that some trials face. RCT for AD patients are problematic due to acquisition and retention of participants (Gelman, 2010). Factors that must be included are

recruitment with those that will complete the trial, those that will represent AD patients from ethnicities that reflect the general population of AD sufferers. Grill and Karlawish (2010) discovered in a recent Alzheimer's Disease Cooperative study only 10% were non-White. Since Black and Hispanic minorities are growing faster than their White counterparts, minority enrollment techniques need to improve (Grill & Karlawish, 2010). Two suggestions include increasing the sites where trials are held and increasing awareness of AD trials possibly through primary care providers.

Medications/Vaccines. Several medications have been designed to alter the pathophysiology of how AD progresses. Currently there are no medications that reverse symptoms or arrest the disease. There are trials of a medication that target tau-proteins instead of amyloid-beta proteins before they damage the neuronal cell that is not far from completion (Atri, 2016). Roy Jones, Director of Research Institute for the Care of Older People (RICE) stated there are multiple trials to test the success of a vaccine that inhibits the tau proteins from creating tangles within the cell. Experimentation with another vaccine that targets the amyloid-beta proteins that cause plaques and has been discussed within this research study as a possible cause of AD (Atri, Sabbagh, & Tan, 2016; Sauer, 2016).

Researchers have noticed that several types of medications have been shown to alleviate a few of the signs of AD. Those individuals that have been treated for HTN with calcium channel blockers and those treated successfully for DM2 with a GLP-1 analogue had less incidence of AD. Both are currently starting trials and both medications have the ability to reduce amyloid proteins in the brain (Edison, n.d.).

Biomarkers. O'Bryant et al. (2013) performed studies specifically on Mexican Americans at the Texas Alzheimer's Research & Care Consortium (TARCC) because these researchers have stated this population compared to White adults have different biomarkers for AD. Mexican Americans as part of the Hispanic/Latino heritage are at an increased risk for AD, they are treated later in the disease, and have a lower frequency of the APOE ε4 allele, which was discovered in Research Question 4 (Fitten et al., 2013; O'Bryant et al., 2013). The findings of this study were Mexican Americans were more susceptible to metabolic phenotypes that were responsible for DM2 and AD (O'Bryant et al., 2013).

Implications for Social Change

The Alzheimer's Association has stated that Hispanic adults have a 1.5 greater risk of developing AD than their White counterparts. I performed this study to determine if there is an association along with other possible contributing risk factors that could assist this population in the prevention of AD (AA, 2016). One potential social change from this study was to provide medical professionals with culturally competent cognitive tools to encourage an earlier diagnosis of AD for this older population. By using a starting age of 50 as a baseline for cognitive status determination, as well as discussing any challenges older patients may be having in activities of daily living, there is an increased possibility to capture early cognitive decline.

Cultural Barriers/Acculturation/Patients Perceptions and Beliefs. Cultural factors have been discussed within this research study as to the effect of acculturation, beliefs about aging, and health literacy in the Hispanic population. Future changes in the healthcare system could encourage other ethnicities to seek healthcare on a regular basis.

Public health practitioners have encouraged individuals to increase physical activity (Shonkoff, Boyce, & McEwen, 2009), increase health literacy to understand medication regimes (Shaw et al., 2008), increase understanding of the English language and encourage higher education. Hispanics born in the United States are more likely to be high school graduates, have medical insurance, and receive routine medical care (Fernandez et al., 2010).

Language barriers have been documented to negatively impact Latino patients with several studies providing results that using interpreters increase health care outcomes (Fernandez et al., 2010). Culturally and language appropriate healthcare could impact the Hispanic community in a positive way starting with cultural competence of the health care workforce (Bauer & Guerra, 2014).

Patient Perceptions/Beliefs. There are three documented reasons why older Hispanic adults receive a delayed diagnosis of AD per a qualitative study performed by Gelman (2010). These perceptions and beliefs influence health outcomes for this population. Within the Hispanic population is the belief that being forgetful is part of old age. The belief that the older generation can become *chocho* (addled) is not unusual, therefore diagnosis and early treatment are not considered (Valle, Yamada, & Matiella, 2006). Family members of older Hispanics admittedly ignore dementia symptoms to not be put in a position of accepting a diagnosis that implicates "craziness" (Gelman, 2010). Another reason Hispanic families are reluctant to address dementia symptoms according to Gelman (2010), is that there is a lack of information about AD. This could also explain why there are fewer Hispanics in RCT. The last reason mentioned by Gelman (2010) is immigration status, a financial barrier, and language barrier that are sufficient enough to

make family members care for their aging parents alone. Individuals that were interviewed mentioned that the providers' attitude about the patient and the patient's condition can alter the way a patient seeks and maintains health care. It is interesting to note that a providers' negative or neutral attitude even inadvertently communicated to their patients changed the way the patient perceived their health (Nam, Chesla, Stotts, Kroon, & Janson, 2011).

In a pilot study performed by Valle, Yamada, and Matiella (2006) a fotonovela was designed to increase awareness and knowledge in dementia naive older Hispanic adults. The authors stated it was not enough to provide AD information in Spanish but to gear educational sources around health literacy levels as well.

Provider Perceptions/Beliefs. Primary care generally is the first place where patients present for most ailments (Murphy et al., 2014). Medical management of dementia is difficult due to time constraints with a limited staff and providers with not enough knowledge about dementia as well as limited access to community services (Lathren, Sloane, Zimmerman, & Kaufer, 2013). As the population of the United States gets older, dementia incidence could increase leaving many of the population lacking resources, receiving a delayed diagnosis, and inadequate, or inappropriate treatment to delay AD. In a national survey, 16% of White English speaking patients and 26% of English speaking Latino patients stated that they had trouble in communicating with the provider because they felt their questions were not answered and the providers did not listen to them (Anderson, Scrimshaw, Fullilove, Fielding, & Normand, 2003). Patient provider understanding should be sought as a top priority to dispense proper and thoughtful care no matter the ethnicity or diagnosis to reduce heath disparities (Shaw et

al., 2008). It has been discussed that primary care providers have the responsibility of enquiring about dementia symptoms, addressing the needs of patients with dementia, families as caregivers, and a treatment and care plan. Stewart et al. (2012) mentioned that the greatest hurdle for patients, families, and medical providers was to recognize and mention changes in cognition that signal dementia. One of the reasons why the majority of patients go undiagnosed early is caregivers of Hispanic older adults inadvertently disguise and/or underplay symptoms of cognitive changes (Anderson et al., 2003; Shaw et al., 2008; Stewart et al., 2012).

Cultural competency/cognitive tools in dementia care. When providers were asked about the shortcomings of dementia diagnosis they claimed shortness of time within scheduled appointments to assess for dementia (78%), and inadequate and culturally sensitive diagnostic/screening tools (40-48%). Forty-eight percent of providers surveyed were reluctant to disclose a diagnosis of AD to some patients when treatment to date has no cure and the diagnosis would disturb many patients (Stewart et al., 2012).

What are the options medical providers have to improve diagnostic time for assessment, acknowledgement, treatment, and a care plan for those that are cognitively challenged? The National Council for Community Behavioral Healthcare mentions the 5 A's. Assess risk factors for dementia, Advise how symptoms can be reduced, Agree on goals for caregivers and patients with the beginning signs of dementia, Assist with problem solving barriers to obtaining greater knowledge of disease, and Arrange for labs, brain imagining, social interaction and other services as the disease progresses (de Negri, DiPrete Brown, Hernandez, Rosenbaum, & Roten, n.d.; Werner, n.d.). Along with these five recommendations, providers need a standardized schedule for cognitive testing.

There are standards for mammography and cervical cancer screening. A standard that could be recommended would be at 50 years of age for any ethnicity, an automatic MMSE should be presented to the patient and every year to every five years be repeated to catch patients that may not be aware that their cognitive status is changing. MMSE is the most commonly used cognitive assessment tool and takes 5-10 to administer. For the Hispanic community the primary provider should have the resources to refer their patients to clinical trials for greater knowledge about this population. This would ultimately determine what biomarkers might be specific to this ethnicity for treatment to be most effective.

Conclusions

The Latino population is currently the fastest growing minority group in the United States. As adults over 60 years of age increase in number of all ethnicities it is important to assess and acknowledge early dementia symptoms. The main goal of this research study was to determine if DM2 is associated in the development of AD in older Hispanic adults. This finding was not statistically significant in Hispanic adults or White adults, therefore the null hypothesis could not be rejected. However, there is a wealth of research studies that claim a significant connection between DM2 and AD (Banks, Owen, & Erickson, 2012; Barbagallo, & Dominguez, 2014; Dallmeier et al., 2012; Prince et al., 2014). Other risk factors that have been implicated in the development of AD were also analyzed. I discovered that HTN, a history of stroke, and lower education were significantly associated with AD in the Hispanic adults. A history of stroke, a smoking history, and obesity were significantly associated with AD in White adults.

Limitations were discussed as to the possible reasons why this research study found no significant association between DM2 and AD. The risk factors that were significant tie in to a collection of conditions that can contribute to AD development. The important feature of a life course framework is to acknowledge that AD takes many years to develop. Many researchers reference that midlife conditions such as obesity, HTN, smoking, and impaired glucose all contribute to mental decline in later years (AA, 2015a; Ben-Shlomo, & Kuh, 2002; Craft, 2010; Fitzpatrick et al., 2009; Garcia-Lara et al., 2010).

Low educational attainment was a significant predictor of AD in the Hispanic adult group. The 2015 Alzheimer's Disease Facts and Figures (AA, 2015a) agrees with this study that fewer years of education creates a risk for AD. The cognitive reserve hypothesis postulates that higher education allows the brain to discover alternate routes from neuron to neuron to problem solve. Other conclusions that could explain this phenomenon are higher education provides better jobs, higher SES, better nutrition, better healthcare, and possibly a wider array of social networking (AA 2015a; Prince et al., 2014; Shugart, 2014; Stern, 2012).

This research study uncovered that a history of stroke doubles the chance of developing AD for both Hispanic adults and White adults. The Framingham Study including 4,897 adults, measured lifetime risk of stroke and concluded that blood pressure is the most modifiable risk factor for stroke (Seshadri et al., 2005). AD occurring after a stroke could be the consequences of vascular pathology and/or degenerative changes occurring pre and post stroke (Lenzi, De Benedetto, & Altieri, 2012). Stroke and risk factors for stroke carry genetic links such as the APOE gene. The

APOE ε4 allele was found to be significantly associated to AD in White adults but not as much of a risk factor in Hispanic adults.

AD is an incurable disease to date. It takes many years of midlife poor health conditions to create a backdrop for malfunctioning neurons for dementia to manifest. Early detection could be the key. With the identification of risk factors, medical providers can encourage individuals to enroll for control trials to advance new medications. Vaccines are being developed to eventually prevent this deadly disease.

It was apparent with this research study that more research needs to be conducted in order to identify and diagnosis risk factors for AD in the Hispanic population. Findings from this research study could alert medical providers of older Hispanic adults as to the risk factors that are modifiable in order to curb AD; DM2, HTN, obesity, and smoking. Medical providers could also be more aware of culturally and linguistically appropriate tools, as well as cultural competency using the five A's as a guide to delay or hopefully prevent AD.

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