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A Predictive Model for Dementia Risk in Elderly Adults with Prediabetes

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Walden University
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Abstract

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BS, Syracuse University, 1984

MS, Syracuse University, 1990

Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

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Abstract

Dementia is a serious public health concern in the United States, with a prevalence of 5.2 million. There is currently no effective way to prevent or cure dementia, and the precise etiology is unknown, but it appears there are multiple risk factors. Prediabetes (PD) has been identified as a risk factor although the scientific evidence is conflicting. This study is important to those at high risk for dementia and to healthcare professionals who lack substantiated dementia prevention strategies. The purpose of this case control study was to determine whether PD is associated with dementia in adults aged 65–95 years and whether the association varies according to demographic (age, gender, race, and socioeconomic status [SES]) and health (atherosclerosis, body weight, cerebrovascular disease, dyslipidemia, hypertension, and stroke) risk factors. The ecosocial theory was selected to bridge the study findings to life-course exposures and risk factors. Cases (n = 574) and controls (n = 2,157) were sampled from a large ambulatory care dataset, and multivariable logistic regression was used to test the research hypotheses. No unadjusted association between PD and dementia was found (OR 1.08, 95% CI = .854, 1.241, p = .604). The regression analysis revealed no association between PD and dementia; however, atherosclerosis, hypertension, low body weight, and low/average SES were found to be significantly and independently associated with dementia. A stratified analysis revealed that race and SES did not alter the effect of PD on dementia. The implications for positive social change include the potential reduction of incident dementia through initiatives targeted toward demographic and health risk factors including atherosclerosis, hypertension, low body weight, and low/average SES.

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Dedication

I dedicate this study to my parents, Ken and Lois Spitzer, who taught me the importance of life-long education, hard work, determination, and contributing to the greater good.

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I want to acknowledge my chair, Dr. Mary Lou Gutierrez, who has guided and encouraged me throughout this dissertation process. Dr. Gutierrez always set the bar high and made sure that I rose to the level of scholar–practitioner. I also want to acknowledge Dr. Hebatullah Tawfik, who has been so kind and helpful, especially with study design and statistical approach. I want to recognize Dr. KK Rajamani for helping secure the dataset for this study, and Drs. Steve Wittlin and Paresh Dandona for helping construct the research concept. I want to thank my family, friends, and work family for their unwavering support and abundant encouragement. Lastly, and most importantly, I need to thank my husband Todd and children, Ryan and Raechel, for encouraging me, challenging me, and putting up with me throughout this many-year long process. Life is a journey, and I am so blessed to have all of these amazing people to share the journey with me. Thank you all.

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Chapter 1: Introduction to the Study

Introduction

Dementia is a serious and growing public health concern in the United States and around the world (Budson & Solomon, 2011; Lam & LeRoith, 2012). Dementia is a global epidemic with a worldwide prevalence of approximately 24 million. The prevalence of dementia is estimated to be 5.2 million in the United States and predicted to triple to 16 million by the year 2050 (Alzheimer's Association, 2014; Reitz & Mayeux, 2014). The risk of dementia doubles approximately every 5 years between the ages of 65 and 85 years. It is estimated that 30% to 50% of adults will have dementia by ages 85–90 years (Budson & Solomon, 2011; Peters et al., 2008; van der Flier, 2005). With an aging population, the incidence of dementia has increased significantly in the United States, posing a challenge to health care professionals who are faced with managing the epidemic burden of dementia (Lam & LeRoith, 2012; Reitz, Brayne, & Mayeux, 2011).

Prediabetes (PD) has been implicated as a risk factor for dementia although the literature is conflicting. PD is also considered a serious public health concern and has reached epidemic proportion. PD is estimated to affect about 86 million people or approximately 35% of adults in the United States today and 50% of adults over the age of 65 years (Centers for Disease Control and Prevention [CDC], 2014). PD is the prodromal period that precedes diabetes and characterized by blood glucose levels that are elevated above normal but do not reach the diagnostic threshold for diabetes (American Diabetes Association [ADA], 2013). Scientific evidence suggests that the morbidity of Type 2 Diabetes (T2D) including cardiovascular disease, neuropathy, retinopathy, stroke, renal

failure, and dementia begins during PD; however, the literature is equivocal as to whether PD increases the risk for or can be used to predict dementia (Craft, 2009; Duarte et al., 2013). Although T2D appears to be an independent risk factor for dementia, it is not known whether glucose levels within the PD range increase the risk of dementia in people without frank diabetes (Crane et al., 2013; Talbot et al., 2012).

Dementia and PD share many of the same characteristics, pathology, and risk factors (Budson & Solomon, 2011; Craft, 2009; Williamson et al., 2014). PD is characterized by significant insulin resistance (IR), and insulin is essential for neural tissue growth, repair, and regeneration (Garber et al., 2008). An insulin-resistant state in the brain has been identified in those with dementia and may be a core defect that precipitates neurodegenerative processes (Correia et al., 2011). Although the precise etiology of dementia is not known, IR and impaired insulin signaling are thought to underlie and link the pathologies of PD and dementia. The gap in understanding is whether PD is independently associated with dementia and can be used to identify those at risk for dementia, whether PD should be considered a predictive risk factor, and whether other risk factors precipitate or predict dementia (Duarte et al., 2013; Li & Holscher, 2007).

Mechanistic pathways between PD and dementia have been identified which suggests that the neuropathology of dementia may begin in the prodromal, PD period; however, evidence in the scientific literature is conflicting (Craft, 2009). It is not clear whether the association between PD and dementia is significant, independent, or predictive and whether other metabolic, vascular, or inflammatory factors underlie the

neurodegenerative process and dysfunction of dementia. The questions that this study addressed were: (a) What is the association between PD and dementia in elderly adults aged 65–95 years? (b) Do other risk factors alter the association between PD and dementia in elderly adults?, and (c) Do race and SES differentially alter the association between PD and dementia?

I chose a case control design to examine the association between the independent variable (IV), PD, and the dependent variable (DV), dementia. This design is useful for studying long latency diseases such as dementia (Carlson & Morrison, 2009; Schulz & Grimes, 2002). Logistic regression tested the strength of association between PD and dementia. The data were stratified by race and SES and adjusted for potential confounders. I obtained the IV, DV, and covariates from the Rochester, New York Unity Health System (UHS) dataset and identified them using the World Health Organization's Ninth Revision, International Classification of Diseases (ICD-9) codes, medical problem lists, laboratory values, and test results.

This study has the potential for positive social change by helping identify those at risk for dementia and justifying resources for dementia reduction initiatives. A reduction in incident dementia would lower the social burden of dementia, dementia morbidity and mortality, and overall health care costs. The ecosocial theory helped bridge the study findings to social and economic factors associated with dementia such as low socioeconomic status (SES) and race. The ecosocial theory provided a context for social and economic factors that were not directly measured due to the nature of the case control study design.

Chapter 1 contains background information on the diseases of dementia and PD, a statement of the problem, the purpose of the study, and the research questions addressed in the study.

Background of the Study

Dementia is an epidemic globally (Reitz & Mayeux, 2014), and within the United States (Duarte et al., 2013; Steinman et al., 2012). Within the United States, it is the sixth leading cause of death and the fifth leading cause of death among those over the age of 65 years (Alzheimer's Association, 2014). Deaths from dementia increased 68% from the year 2000 to 2010, and the estimated annual cost of dementia in the United States was $213 billion in 2013 and is projected to reach $1.2 trillion by the year 2050 (Alzheimer's Association, 2014).

With an aging population and no effective prevention or treatment for dementia, the incidence, morbidity, and mortality of dementia in the United States is increasing significantly. This is a difficult challenge for health care professionals who are faced with managing the epidemic burden of dementia (Azad, Al Bugami, & Loy-English, 2007; Kuyumcu et al., 2012). Currently there are no effective treatments or cure for dementia, and the drugs used to slow the progression of dementia are only marginally to moderately effective and only in certain individuals (Budson & Solomon, 2011; Kivipelto & Solomon, 2008). The primary focus of dementia prevention strategies has been on risk factor reduction and lifestyle modification such as healthy diet, adequate exercise, not smoking, and maintaining proper weight; however, these strategies do not have proven outcomes and have yet to demonstrate any measurable reduction in dementia rates in the

U.S. population (Mangialasche, Kivipelto, & Fratiglioni, 2012; Qiu, Xu, Winblad, & Fratiglioni, 2010).

Dementia appears to be a heterogeneous disease. The precise etiology of dementia is not known, but scientific evidence suggests that there are multiple risk factors (Correia et al., 2011). Well substantiated risk factors for dementia include advanced age, presence of the risk gene, the APOE e4, presence of deterministic genes that cause presenelin mutations and abnormal amyloid precursor protein (APP), and dementia in a first-degree relative. Additional risk factors thought to increase the risk for dementia include alcohol abuse, cardiovascular and cerebrovascular diseases, diabetes, female sex, head trauma, hypertension, obesity, and race (Budson & Solomon, 2011; Reitz & Mayeux, 2014). Social and lifestyle risk factors are believed to increase the risk for dementia, include low educational attainment, sedentary lifestyle, and smoking (Mangialasche et al., 2012).

The pathological hallmarks of dementia, specifically Alzheimer's disease (AD), are beta amyloid plaques and NFTs; however, this pathology appears later in the development of dementia and may not be the initiating factor of the disease. There is strong evidence to suggest that the initiating factors of dementia are brain tissue injury, inflammation, disruption of cell signaling pathways, oxidative stress, and disruptions in glucose or lipid metabolism in the brain (Lombardo, 2012).

The hallmarks of PD, including IR, inflammation, vascular injury, and impaired insulin signaling are thought to underlie and overlap with the pathology of dementia and perhaps precipitate neurodegenerative processes (Budson & Solomon, 2011; Craft, 2009; Duarte et al., 2013; Li & Holscher, 2007; Williamson et al., 2014). Although T2D is

considered an independent risk factor for dementia, the literature is not clear on whether PD is independently associated with dementia or whether other associated risk factors cause the neuropathology characteristic of dementia. It is not known whether glucose levels within the prediabetic range increase the risk of dementia in people without frank diabetes (Crane et al., 2013).

An estimated 86 million people in the United States have PD, which is one in every three people, highlighting the significant public health burden of PD (CDC, 2104; Cowie et al., 2009; Garber et al., 2008). The concern is that people with PD have a three- to ten-fold increase in absolute risk of developing T2D, which is a known risk factor for dementia (Exalto et al., 2013; Garber et al., 2008). Approximately 33% to 65% of people with PD develop T2D within six years compared to fewer than 5% of people with normal blood glucose (Geiss et al., 2010). One large epidemiologic study found that subjects with PD (impaired fasting glucose [IFG], impaired glucose tolerance [IGT] or metabolic syndrome [MetS]) converted to T2D at a rate of 8% to 10% per year, and a rate significantly greater than10% per year if the subject had all three impairments (Haffner et al., 2008).

The precise etiology of dementia is not known, but scientific evidence suggests that dementia is heterogeneous and has multiple risk factors. Epidemiological studies provide significant evidence that PD is a risk factor for dementia secondary to deranged metabolic, vascular, and inflammatory processes (Craft, 2009; Garber et al, 2008). It is well known that people with T2D have significant diabetes-related complications including heart disease, stroke, retinopathy, nephropathy, peripheral vascular disease, and

dementia. It is important to recognize that the morbidity associated with T2D likely begin years earlier in the period defined as PD (DECODE Study Group, 2001; Garber et al., 2008). IR, inflammation, and vasculopathy are thought to underlie and link the pathologies PD and dementia (Duarte et al., 2013; Li & Holscher, 2007). The rate of conversion from PD to T2D is approximately 5.6 % annually after an average of 29 months of PD; therefore, identifying people with PD may be important for developing strategies to reduce incident dementia (Geiss et al., 2010; Nichols, Hillier, & Brown, 2007).

Table 1

Diagnostic Criterion for Prediabetes

State	Fasting Glucose (mg/dl)	2 hour Glucose (mg/dl), 75 g OGTT	A1C (%)
Normal	< 100	< 140	< 5.7 %
IFG	≥ 100 - ≤ 125	< 140	
IGT	< 100	≥ 140 - ≤ 199	
Pre-diabetes	≥ 100 - ≤ 125	≥ 140 - ≤ 199	5.7 - 6.4 %
Diabetes	> 126	≥ 200	≥ 6.5 %

The diagnostic criteria for PD are outlined in Table 1 and include IFG, IGT, or elevated A1C (Derr, 2013). Each criterion reflects a different degree of insulin sensitivity, insulin secretion, and hepatic glucose output; however, the primary defect associated with each PD diagnostic criterion is still unknown and may suggest distinct pathways toward T2D (Faersh et al., 2009).

Metabolic syndrome (MetS) is considered a PD equivalent and is diagnosed using the National Cholesterol Education Program (NCEP) IV Adult Treatment Panel III

definitions (Expert Panel, 2001; Panza et al., 2010). The individual components of MetS (hypertension, large waist circumference, high triglycerides, low HDL cholesterol, and elevated fasting glucose) are believed to be independent risk factors for vascular diseases including coronary artery disease (CAD) and stroke. Accumulating scientific evidence suggests an increased risk for dementia in those with MetS (Sofrizzi et al., 2011). Early identification and treatment of people with MetS (a PD equivalent) could potentially reduce or delay vascular complications. Despite the cost and worldwide public health threat from PD, which may include dementia, relatively little progress has been made to prevent, diagnose, or treat PD and its associated morbidity (Garber et al., 2008).

The aim of this study was to determine whether PD is associated with dementia in an elderly ambulatory care population and whether dementia-related risk factors including atherosclerosis, cerebral vascular disease, hyperlipidemia, hypertension, obesity, and stroke alter the risk. The data were stratified by race and SES to analyze the racial and economic differences in dementia risk. The aim of the study was to provide scientific evidence to support prevention and treatment initiatives designed to reduce the incidence of dementia.

Problem Statement

Dementia is a global epidemic and a serious public health concern in the United States today. The scientific literature reveals that T2D is an independent risk factor for dementia; therefore, there is great concern over the estimated 86 million people in the United States with PD because of the high conversion rate to T2D (Geiss et al., 2010; Nichols et al., 2007). A review of the literature revealed that dementia risk may be higher

in those with PD and that PD could be used as a predictive marker of dementia; however, the data are conflicting. The problem remains that the causes of dementia are not fully known, and there is no cure for dementia. There are no good predictive models for dementia nor are effective dementia reduction initiatives in place. PD may be a factor in the initiation and development of the neurodegenerative processes associated with dementia and may elevate the risk of dementia; however, the association between PD and dementia has not been clearly established. Research in the fields of epidemiology and neurology has provided substantial evidence that metabolic, inflammatory, and vascular risk factors significantly contribute to the expression and progression of dementia (Mangialasche et al., 2012).

At the time of the dissertation study, there were no predictive models available for dementia in people with PD. In a large epidemiologic study, one group of investigators developed a predictive model for dementia in participants with T2D. Components of the model found to be most strongly predictive of an individual's 10-year dementia risk were age, education, depression, and complications of diabetes including microvascular disease, diabetic foot, cerebrovascular disease, cardiovascular disease, and acute metabolic event (Exalto et al., 2013). Diabetes duration and A1C were not included in the final model because their predictive value was lower than the predictors related to end-organ complications (Exalto et al., 2013). This large epidemiologic study provided good evidence that prevention of dementia should begin in the prediabetic period *before* the complications of diabetes develop.

A review of the literature revealed that African Americans may have a higher risk of dementia based on genetic susceptibility; however, the data for genetic susceptibility to dementia according to race is emerging, and there is conflicting data on the relationship between PD, race, and dementia risk (Reitz & Mayeux, 2014). Low educational attainment has been shown to increase the risk of dementia (Gatz et al., 2007). Low educational attainment is more likely in those with lower SES; therefore, SES may be a surrogate marker for dementia. It is not known whether race and low SES alter the association between PD and dementia and whether other metabolic, vascular, or inflammatory factors alter the association and should be considered for dementia reduction strategies. In summary, it is not known whether preventing or treating PD will reduce incident dementia in people of various races and SES in an elderly population and whether other associated risk factors need to be considered, such as atherosclerosis, cerebrovascular disease, dyslipidemia, HTN, obesity, and stroke.

Purpose of the Study

The purpose of this study was to determine whether PD is associated with dementia in elderly people and whether the association varies according to race, SES, or other health risk factors. This study was a quantitative, case control design that examined the relationship between the variables, PD and dementia, in elderly adults in order to provide scientific evidence of those at high risk for dementia and support the allocation of resources for targeted dementia prevention interventions. Dementia risk reduction interventions have the potential to reduce incident dementia and related morbidity, mortality, and healthcare costs. The IV or exposure variable was PD and the DV or

outcome variable was dementia. The covariates included in the analysis were age, atherosclerosis, cerebrovascular disease, dyslipidemia, gender, HTN, obesity, race, SES, and stroke. These covariates were selected because scientific evidence suggests that they are related to the underlying pathologies of dementia including vascular injury, inflammation, IR, and dysmetabolic processes (Lombardo, 2012).

Research Questions and Hypotheses

The primary research question addressed in this study was whether PD is associated with dementia risk in adults aged 65–95 years. Other questions that this study addressed were whether demographic and health risk factors alter the association between PD and dementia and whether race and SES modify the risk of dementia in those with PD. The primary research hypothesis (H_a) was that PD is associated with dementia in elderly people. The research hypothesis was based on scientific evidence that exposure to PD increases the risk of dementia by initiating or exacerbating pathological changes in the brain through metabolic, vascular, and inflammatory pathways (Craft, 2009; Duarte et al., 2013). The null hypothesis (H_0) was that there is no increase in the risk for dementia according to PD exposure in elderly adults, age of 65–95 years.

Theoretical Basis for the Study

Epidemiology has evolved from germ theories including the 1884 Koch postulates that proposed a causal relationship between microbes and disease to an expanded view that considers the ecologic and social impact on disease susceptibility (Cassell, 1964). Modern epidemiology, first termed *social epidemiology* by Yankauer in 1950, is foundationally supported by the ecologically oriented ecosocial theory (Krieger, 2011).

The ecosocial theory embraces the life-course perspective that incorporates the impact of life circumstances and exposures over a lifetime with health outcomes (Krieger, 2011).

The ecosocial theory helped guide this study and served as its theoretical foundation and deductive framework. The ecosocial theory considers social and ecologic causes of disease and is an integrative and dynamic theory that links societal and biologic determinants of disease (Krieger, 2011). The risk of dementia appears to increase with exposures to different social and lifestyle risk factors experienced over the course of a lifetime such as poor diet, sedentary lifestyle, smoking and low educational attainment; therefore, cumulative and combined exposure to different risk factors can alter the risk of dementia (Mangialasche et al., 2012).

I tested the ecosocial theory in this study by examining the exposure variable (PD) and covariates that have a biological, social, or behavioral relationship to the outcome variable (dementia). Furthermore, this study was stratified by race and SES. I hypothesized that there may be differences in biological susceptibility to PD, the covariates (atherosclerosis, cerebral vascular disease, dyslipidemia, HTN, obesity, and stroke), or to the outcome of dementia based on race and SES. Those who are APOE ϵ4 allele carriers are at increased risk for dementia. The risk for dementia in African Americans and Hispanics may be more independently associated with the APOE genotype (Farrer et al., 1997; Reitz & Mayeux, 2014; Tang et al., 1998). One population-based study suggested that APOE ϵ4 carriers are more vulnerable to the morbidity that results from lifestyle behaviors such as smoking, excess alcohol and saturated fat

consumption, and sedentary activity level; therefore, dementia may develop differentially according to race (Kivipelto et al., 2008).

In this study, the ecosocial theory served to frame and contextualize the relationship between the exposure variable (PD), the potential covariates (atherosclerosis, cerebrovascular disease, dyslipidemia, HTN, obesity, and stroke), and the outcome variable (dementia). Potential differences in dementia risk were stratified and analyzed according to race and SES. The ecosocial theory helped connect the study findings to broader racial and economic factors associated with dementia by framing social, behavioral, and lifestyle factors. The ecosocial theory provided insight into social and economic factors that may differentially impact dementia incidence such as poverty, low educational attainment, or inequity in health care between the races. I used the primary insurance (private, Medicare, or Medicaid) of the participants as a surrogate marker of SES; the ecosocial theory bridged the study findings to socioeconomic factors within the sample population that were not directly measured. Chapter 2 contains a more detailed explanation of the theoretical framework for this study.

Nature of the Study

The study was quantitative, and I selected a case control design to best answer the research question of whether PD increases the risk of dementia in 65–95 year old participants of varying races and SES. Case control studies include participants based on outcome and allow for examination of previous exposures that may be associated with an outcome (Carlson & Morrison, 2009; Schulz & Grimes, 2002). A case control design is appropriate for long latency diseases such as dementia and when the case (dementia) and

the exposure (PD) have already occurred. I did not use a longitudinal design because of the prohibitive cost and many-year long duration necessary to measure incident dementia.

The sampling frame for this study was the ambulatory care population of the Unity Health System in Rochester, New York. The dataset contained 155,000 active patient records and up to 10 years of data including demographics, diagnostic codes, medical problem lists, laboratory results, and medical test results. The dataset was sampled for adults 65–95 years of age with dementia (cases). The sampling method was a simple random sampling procedure using a computerized system.

The IV or exposure variable was PD, and the DV or outcome variable was dementia. The relationship between the IV and DV was analyzed using multivariate logistic regression with an odds ratio (OR) produced. Using stratification techniques, odds ratios were produced for each race and SES category to assess the strength of association between PD and dementia accordingly. The final aim of the statistical analysis was the creation of a multivariate model that appropriately accounted for confounding. The covariates included in the analysis were age, atherosclerosis, cerebrovascular disease, dyslipidemia, gender, HTN, obesity, SES, and stroke. All cases of dementia, PD status, and covariates were obtained from the UHS dataset and identified using ICD-9 codes, medical problem lists, laboratory values, and test results.

Definitions

Alzheimer's disease (AD) is a neurodegenerative disease characterized by significant memory loss and pathology in specific regions of the brain. Diagnosis is based on the classifications established by the National Institute of Neurological and

Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association (NINCDS–ADRDA) criteria. The NINCDS–ADRDA criteria include clinical and neuro-pathological characteristics which determine the diagnosis of *possible*, *probable*, and *definite* (Budson & Solomon, 2011).

Amyloid beta (Aβ) is a peptide that forms following the proteolysis of amyloid precursor protein and is the main component of amyloid plaques in the brains of subjects with AD (Reitz, Honig, Vonsattel, Tang, & Mayeux, 2009).

Amyloid precursor protein (APP) is an important membrane protein expressed in many tissues but concentrated in the synapses of neurons. The function of APP has not been fully elucidated but is thought to regulate synapse formation and neural plasticity; APP is known as the precursor to Aβ, the primary component of amyloid plaques characteristic of AD (Reitz et al., 2009).

Atherosclerosis is a specific type of arteriosclerosis characterized by an accumulation of fats and cholesterol in artery walls which results in plaque formation and potential restricted blood flow (National Heart, Lung, and Blood Institute, 2012).

Cerebrovascular disease (CeVD) is a group of brain dysfunctions related to disease of the blood vessels supplying the brain. CeVD is the underlying cause of cerebrovascular accidents, cerebral infarcts, or strokes which result in brain injury, cell death, and dysfunction. Cerebrovascular diseases are a diverse group of disorders that are further classified according to etiology, location, and duration of symptoms and subdivided into ischemic and hemorrhagic events (Budson & Solomon, 2011).

Dementia is a clinical state characterized by loss of function in multiple cognitive domains and a decline from baseline, severe enough to cause impairment in social and occupational functioning. Dementia may be classified as AD, vascular dementia, Lewy body dementia, or other dementia. Using the *Diagnostic and Statistical Manual for Mental Disorders (DSM-IV),* the criteria for diagnosis are specific to the subtype of dementia and include memory impairment with at least one of the following: aphasia, apraxia, agnosia, or disturbances in executive functioning (American Psychiatric Association [APA], 2013).

Dyslipidemia is a disorder of lipoprotein metabolism, manifested by elevation of total cholesterol, low-density lipoprotein (LDL)-cholesterol and triglyceride levels, as well as a decrease in high-density lipoprotein (HDL)-cholesterol. Diabetes, including elevated serum insulin and insulin resistance, are highly associated with dyslipidemia (Fodor, 2011).

Glycosylated hemoglobin or A1C is a form of hemoglobin which reflects average plasma glucose concentration over the past two to three months. In nondiabetic subjects, an A1C between 4% and 5.7% is considered normal. A simple blood draw is used to measure A1C or an A1C rapid test can be done using a finger stick. An A1C between 5.7% and 6.4% is diagnostic for prePD, indicative of compromised blood glucose control and identifies individuals at high risk for T2D (ADA, 2013).

Hypertension (HTN) or high blood pressure is a chronic elevation of blood pressure in the arteries. Blood pressure is defined by two measurements, systolic and diastolic blood pressure, depending on whether the heart muscle is contracting (systole)

or relaxed (diastole) between beats and equal to the maximum and minimum pressure, respectively. Normal systolic blood pressure at rest is between 100–140 mmHg and normal diastolic blood pressure is between 60–90 mmHg. HTN is defined as blood pressure readings consistently greater than or equal to 140/90 mmHg. Chronic HTN damages the endothelium and causes platelet aggregation making the vessels more narrow, stiff, deformed, uneven, and vulnerable to further fluctuations in blood pressure (Carratero & Oparil, 2000).

Inflammation is a biological response of vascular tissues to heal from harmful stimuli. Acute inflammation is the initial response to harmful stimuli and involves the local vascular system, the immune system, and various cells within the affected tissue. Chronic inflammation leads to a progressive shift in the type of cells present at the site of inflammation and causes simultaneous destruction and healing of the tissue. Chronic inflammation can lead to diseases such as atherosclerosis and certain cancers and is suspected in many other diseases including AD. Markers of inflammation may include interleukin-6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor alpha (TNFα) (Ferraro-Miliani, Nielsen, Andersen, & Girardin, 2007).

Insulin resistance (IR) is reduced responsiveness of target tissues to the insulin signal and a key metabolic disturbance of PD and T2D (Schiöth, Craft, Brooks, Frey, & Benedict, 2012).

Logistic regression begins with regression analysis, a mathematical model constructed to describe the relation between one variable X and another Y. Regression predicts Y (the DV), knowing X (the IV). Logistic regression is the simultaneous

assessment of the relationship between several variables (X1, X2, etc.) and Y. Multiple logistic modeling is a variant where the dependent variable (Y) is the probability of an event or outcome, which is of particular interest in epidemiological research (Bhopal, 2002).

Metabolic syndrome (MetS) is defined by the National Cholesterol Education Program (NCEP) IV Adult Treatment Panel III (Expert Panel, 2001). MetS is considered a PD equivalent (Panza et al., 2010). A diagnosis of MetS is made when at least three of the following risk factors are present: abdominal obesity, waist circumference for men of more than 40 inches and women more than 35 inches; triglycerides greater than or equal to 150 mg/dl; HDL-cholesterol in men less than 40 mg/dl, and in women less than 50 mg/d; blood pressure greater than or equal to 130/85 mmHg; and fasting glucose greater than or equal to 110mg/dl (Panza et al., 2010).

Mild cognitive impairment (MCI) is defined as a decline in cognition that exceeds that for age and education level but it is not frank dementia or disruptive to activities of daily living (Budson & Solomon, 2011; Gauthier et al., 2006; Peterson, 2004). MCI is diagnosed using the Petersen Criteria (Peterson, 2004).

Neuropathology is the study of diseases of nervous system tissue; it is a subspecialty of anatomic pathology, neurology, and neurosurgery (International Society of Neuropathology, 2013).

Obesity is a term for a weight that is greater than what is considered healthy for a given height. Obesity has been shown to increase the likelihood of certain diseases and other health problems. Obesity is diagnosed using weight and height to calculate the body

mass index (BMI), which correlates with body fat in most people. An adult with a BMI of greater than or equal to 30 is considered obese (CDC, 2012).

Oral glucose tolerance test (OGTT) is the administration of 75 grams of glucose followed by serial blood glucose measurements conducted over a 2-hour period and is used to diagnose T2D and PD (ADA, 2013).

Prediabetes (PD) is defined as impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) and an intermediate state between normal plasma glucose and overt diabetes. One of the following criteria must be met for a diagnosis of PD: fasting plasma glucose (FPG) between 100 mg/dl and 125 mg/dl; plasma glucose 2 hours after administration of a 75 gram oral glucose tolerance test between 140 mg/dl and 199 mg/dl; or glycosylated hemoglobin (A1C) of between 5.7% and 6.4%. These diagnostic criteria identify individuals at high risk for T2D (American Diabetes Association, 2013; Derr, 2013).

Stroke is brain cell injury, brain cell apoptosis, and loss of brain function secondary to interrupted blood flow to a specific region of the brain. Stroke is associated with cerebrovascular disease. There are two major types of stroke: ischemic stroke and hemorrhagic stroke. Ischemic strokes occur when a thrombosis or arterial embolism obstructs blood flow to the brain. A hemorrhagic stroke occurs when an intracranial blood vessel becomes weak and bursts (Kumar, Abbas, Robbins, & Cotran, 2010).

Type 2 diabetes (T2D) accounts for 90 to 95% of all diabetes and is characterized by insulin resistance and relative insulin deficiency. There are many causes of T2D, yet specific etiologies are not known. Ninety percent of people with T2D are overweight or

obese, and obesity itself causes some degree of IR. T2D causes significant macrovascular and microvascular complications (American Diabetes Association, 2010).

Assumptions

One of the primary assumptions of this study was that cases and exposure are complete and accurate in the dataset. It was assumed that dementia was diagnosed accurately according to the NINCDS-ADRDA and DSM-IV criteria (APA, 2013; Budson & Solomon, 2011). Inherent in the case control design, it was necessary to assume that cases and exposure were not undiagnosed or misdiagnosed.

Another assumption in this study was that the exposure variable (PD) was accurately diagnosed using the three diagnostic criteria outlined in Table 1. The United Health System (UHS) dataset was queried for ICD-9 codes, medical problem lists, laboratory values (fasting plasma glucose and A1C), and OGTT results. The diagnostic criteria for PD are relatively new, and it was assumed that participants were diagnosed accurately according to the World Health Organization (WHO), American Diabetes Association (ADA), and the American Association of Clinical Endocrinologists (AACE) criteria and that PD was not undiagnosed. It was also assumed that all the individual patient information contained in the UHS ambulatory care dataset was complete and accurate.

In the UHS dataset, race is self-identified, and it was assumed that people accurately identified their race. However, there are inherent problems with self-identification of race because of mixed races and social and psychological issues pertaining to race identity.

It was assumed that the primary insurance provider was an accurate surrogate marker of SES. For example, it was assumed that those who have Medicaid as their primary health insurance fit the criteria for low SES.

Scope and Delimitations

This study used a case control design with a sample of dementia cases from 65–95 year old adults drawn from an ambulatory care health system dataset. A case control design was chosen to examine the association between PD and dementia because the case-control design is appropriate for long latency diseases such as dementia (Carlson & Morrison, 2009; Schulz & Grimes, 2002). Cause and effect understanding is the highest level of scientific knowledge because it permits prediction and generalization (Bhopal, 2002). A large, prospective cohort design would have been a good design to provide temporality between PD exposure and incident dementia; however, a large, prospective study conducted over a many-year period to measure incident dementia would be prohibitive in terms of cost, human resources, and time required.

The UHS dataset was used to examine the association between PD and dementia. The data were stratified by race and SES because there is a paucity of data on differentiated dementia risk in those with PD based on race and SES. In addition, African American and Hispanic people appear to have different risks for dementia compared to Whites due to genetic factors. African American people may have lifestyle-risk susceptibility, which also makes race especially important to study (Mangialasche et al., 2012; Reitz & Mayeux, 2014). Additionally, those with low SES tend to have low educational attainment (LEA), and LEA is associated with dementia (Gatz et al., 2007).

Low SES was used in this study as a surrogate marker of LEA and a risk factor for dementia.

The ecosocial theory embraces the life-course perspective which considers the impact of life circumstances and lifelong exposures on health outcomes (Krieger, 2011). The ecosocial theory was chosen for this study in part because it directly addresses the genetic-lifestyle interaction that appears to elevate the risk of dementia in African Americans (Mangialasche et al., 2012). The ecosocial theory was thought to be best suited for this case control study because it considers many systems within the physical and social environment that may influence health behaviors and exposures. These may include family, community, workplace, social norms and traditions, and economics (Krieger, 2011). Other public health theories were not selected for this case control study because they are largely based on qualitative issues such as attitudes, perceptions, values, beliefs, desire, expectations, self-efficacy, and stages of change, which were outside the scope of this study (Krieger, 2011). Social and environmental factors were not consistently available in the UHS dataset and were therefore not included in the data collection and analysis. Primary insurance of participants was used as a surrogate marker of SES. The ecosocial theory was used to bridge the study findings to social and economic factors that were not directly measured.

The sampling method in this study was a simple random sample using a computerized system. All sampling units had the same probability of being included in the sample. The probability sampling strategy allowed for an accurate estimate of the odds ratio (OR) and indicates the degree to which the study findings differed from the

population (Frankfort-Nachmias & Nachmias, 2008). The ORs and confidence intervals provided an indication of the generalizability of this study as well. Generalizability can be improved when cases are obtained from multiple institutions, such as a number of community-based hospitals (Carlson & Morrison, 2009). Ambulatory care patient data from one health system was used to construct the dataset for the dissertation study; however, the dataset included participants from multiple medical disciplines and a relatively large and diverse geography. Therefore, the case selection for this study was thought to be similar to a multiple institution case selection.

Internal validity in a case control study refers to systematic error and whether the observed changes in outcome can be attributed to the exposure (Carlson & Morrison, 2009). Sampling controls in case control studies are critical to internal validity; low internal validity can result when controls are not comparable in terms of exposure in measurable and unmeasurable ways (Carlson & Morrison, 2009). Interpretation of the validity of a case control study largely depends on the sampling procedures because the meaning of the OR depends on the way in which controls are selected (Knol, Vandenbroucke, Scott, & Egger, 2008). Case control studies must therefore be explicit on sampling procedures (Knol et al., 2008). The dissertation study used carefully constructed procedures for selecting cases and controls and the internal validity is thought to be high. Explicit details on the process for case and control sampling techniques and selection are provided in the methods section of Chapter 3.

Limitations

Limitations largely pertain to validity, which is the extent to which a given measure truly represents what it is intended to measure (Frankfort-Nachmias & Nachmias, 2008). Generally, internal validity of case control studies can be lower than other study designs and generalizability higher (Carlson & Morrison, 2009). The sample for this study was drawn from a health system ambulatory care dataset which consisted of outpatient clinics, medical services, and physician practices located in 70 different locations. The geographic reach of the UHS is 100 square miles, crossing the greater Rochester, New York region. The geography is made up of six counties that include urban, suburban, and rural communities; therefore, the generalizability of this study was considered high and representative of the population.

There are inherent challenges to measurement validity that were considered in this study including content validity, empirical validity, and construct validity. Content validity can be subdivided into sampling validity and face validity. Sampling validity refers to whether the population is adequately sampled by the measuring instrument. Recall bias could be possible if subjects or family members were interviewed to obtain additional information; however, interviews were not conducted for this study because it was thought that differences in the data gathering processes for cases and controls would result and reduce the study's reproducibility.

Selection bias is a significant concern in case control studies because it is a design that tends to produce differential sampling probabilities of the disease-exposure groups. In case control studies, the control group needs to be a reasonably representative sample

of the case population (Szklo & Nieto, 2014). Cases and controls were selected from the same reference population in this study to improve the internal validity (Szklo & Nieto, 2014).

Various methods can be employed to minimize selection bias including using a multi-stage approach to sampling cases and controls, using nested case-control within cohort studies, or making an adjustment in the analysis phase (Geneletti, Best, Toledano, Elliott, & Richardson, 2013). In this study, an adjustment in the analysis phase was employed to minimize selection bias. Additionally, cases and controls were selected from a well-defined reference population as previously described. A compensating bias was not employed in this study because it may or may not be successful in minimizing selection bias (Szklo & Nieto, 2014).

Another potential limitation in this study was one of difficulty in obtaining an accurate measure of the exposure (PD) and the degree of accuracy and completeness of exposure measurement. Face validity is a subjective interpretation of the survey instrument to determine that the instrument measures all aspects of the study (Frankfort-Nachmias & Nachmias, 2008). Based on dementia literature and study design literature (Carlson & Morrison, 2009), I evaluated this case control design to determine whether it was a valid tool for answering the research questions. Face validity for this study was determined by consulting the literature to ascertain consensus about the instrument for measuring the outcome in relation to the exposure; however, confirming the face validity of this study was challenging because there is no defined procedure or criteria that precisely determines face validity (Frankfort-Nachmias & Nachmias, 2008).

Significance

Case-control studies contribute greatly to epidemiologic research and are important for identifying groups at risk (Schulz & Grimes, 2002). Using a case control design, I was able to identify racial and SES differences in elderly participants who may be at increased risk for dementia based on exposure to PD. This study was novel and important scientifically and socially because it determined whether PD in elderly subjects is associated with dementia and whether race and SES alter the association. This study also provided information to identify whether other factors alter the association between PD and dementia in elderly people.

Because dementia is prevalent in the United States, it is important to identify those at high risk so that dementia prevention initiatives can be put in place (Lam & LeRoith, 2012; Reitz, Brayne, & Mayeux, 2011). Dementia risk factor reduction and treatment initiatives have the potential to reduce the burden of dementia, save lives, and reduce health care costs significantly.

This study is important clinically because it could aid health care professionals in identifying elderly people at high risk for dementia. Additionally, the results of this study may help reduce the incidence of dementia in the greater population by providing health care professionals with information about significant dementia risk factors that can be discussed with patients as part of a risk reduction strategy that includes education and counseling.

The potential for positive social change from this study includes a reduction of dementia incidence by identification and treatment of patients with known dementia risk

factors. This research provided scientific evidence of dementia risk factors that has the potential to support the allocation of resources for dementia prevention initiatives. The result of these initiatives may be a reduction in incident dementia and dementia-related morbidity, mortality, and healthcare costs.

Summary and Transition

Dementia is a serious and growing public health concern in the United States today. The prevalence of dementia is 5.2 million people in the United States and is predicted to quadruple by the year 2050 (Reitz & Mayeux, 2014). In the United States, the estimated annual healthcare cost of dementia is $172 billion (Reitz & Mayeux, 2014). PD is estimated to affect about one third of people 65–85 years of age. In the United States, an estimated 86 million people have PD. The precise etiology of dementia is not known, but scientific evidence suggests that there are multiple risk factors that increase the risk. Mechanistic pathways between PD and dementia have been identified which suggest that the neuropathology of dementia may begin in the prodromal, PD phase; epidemiology researchers have shown that dementia risk is higher in those with PD although the scientific evidence is largely conflicting.

Characterizing the association between PD and dementia helps determine when the neuropathology of dementia begins and identifies a target for prevention and treatment. Based on current understanding, it is not clear whether the relationship between PD and dementia is significant, independent, or predictive. It is not known whether race is a factor in the PD–dementia relationship and whether other metabolic, vascular, or inflammatory factors associated with PD alter the relationship. This study has

the potential for contributing to positive social change because the findings characterized the relationship between PD and dementia and identified other significant dementia risk factors. As a result of this study and others, dementia prevention strategies could be implemented that ultimately result in a reduction of the social burden of dementia, dementia morbidity and mortality, and health care costs.

This study addressed the societal problem that the causes of dementia are not fully known and there are no good predictive models for dementia or effective dementia risk reduction initiatives in place. PD has been implicated as a risk factor for the initiation and development of dementia; however, the association between PD and dementia has not been clearly established. Chapter 2 contains a synopsis of the current literature that establishes the scope of the problem and the relevant data that support or refute an association between PD and dementia and the pathways that link them.

Chapter 2 Literature Review

Introduction

The purpose of this study was to determine whether PD is associated with dementia in elderly people and whether the association varies according to race, SES, or other health risk factors. Dementia is a global epidemic and a serious public health concern in the United States. An extensive review of the literature revealed that PD may be associated with an increased risk of dementia; therefore, there is great concern over the 86 million people in the United States estimated to have PD (Geiss et al., 2010; Nichols et al., 2007). Dementia risk appears to be higher in those with PD; however, data on the association between PD and dementia are conflicting. The problem is that the causes of dementia are not fully known. There are no good predictive models for dementia or effective dementia risk reduction initiatives in place within the elderly population. PD may be a factor in the initiation and development of dementia and elevated the risk of dementia; however, the association between PD and dementia has not been clearly established.

Chapter 2 contains information regarding the literature search strategy for this study, the theoretical foundation of the study, and the key variables and concepts. Chapter 2 contains a thorough review of the PD and dementia literature including the background and natural history and key factors linking the two diseases, specifically metabolic syndrome, vascular risk factors, inflammation, IR, brain insulin signaling, and brain atrophy. A review of dementia prediction models is included as well.

Literature Review of Prediabetes and Dementia

I conducted a review of the literature to identify what is known and not known about the association between PD and dementia in various populations. It was important to identify the definitions of PD and methods employed to determine PD status in the studies that were reviewed and evaluated for possible inclusion in the literature review. Studies conducted using T2D as the exposure variable were not included unless the study had been cited as a classic study or provided significant background information. The definitions of dementia and methods used to determine dementia diagnosis, both AD and VaD, were important as well when evaluating specific studies for possible inclusion in the literature review. Several themes emerged from a search of the PD and dementia literature. I used these themes to structure and frame the discussion of the relationship between PD and dementia and organize the literature. I discuss proposed mechanisms associating PD and dementia related to metabolic, vascular, and inflammatory processes. This literature review is an extensive review of the major and significant studies on the topic. I used the literature review to construct a summary of the current understanding of the relationship between PD and dementia and identify gaps in knowledge that lead to future research.

Literature Search Strategy

I conducted a systematic review of the literature to identify important and relevant studies on the association between PD and dementia as well as related works. The literature search was comprehensive and included recent as well as classic PD and dementia studies. Predictive models for dementia can be developed based on a

comprehensive review of the literature that assesses glucose levels most closely associated with dementia as well as other health risk factors that alter dementia risk. A predictive model for dementia could be used by medical and public health professionals for the purposes of dementia prevention in high risk subjects.

I used the medical school library at the University of Rochester School of Medicine and Dentistry to conduct the cross-database literature search on PD and dementia. The databases included Medline, Biosis, Current Contents, and Embase, which are the largest and most comprehensive medical/scientific databases currently available. I also used the Walden University library to search relevant EBSCO databases. I also conducted an internet search using Google Scholar.

Three different cross-database searches were conducted using the specified search string and the Boolean operators described below.

1. (pre-diabetes or impaired-glucose-tolerance or igt or impaired-fasting-glucose) AND (dementia or Alzheimer$ or Vascular-dementia)
2. (etiology or history or risk-factor$) AND (pre-diabetes or impaired-fasting-glucose or impaired-glucose-tolerance))[ti,ab]
3. (glucose)+AND+(dementia)+AND+(impaired+fasting)

The terms in parentheses were searched as keywords. Key search words were generated based on a review of the terminology used in review articles and scientific papers on the topic. The $ was used for truncation to ensure that the search included keywords and phrases.

The initial search of the literature from all sources yielded nearly 4,000 references that were published in English and fit the initial search criteria. After a review of the returns, I determined that most of the studies were on T2D and not PD; therefore, I eliminated most of the T2D studies. I retained studies of T2D and dementia only if they provided substantial background information and improved understanding about the pathophysiology, etiologic pathways, or underlying mechanisms for dementia. There were 90 studies that remained for potential inclusion because they specifically addressed the relationship between PD and dementia. I identified 20 additional studies for inclusion from a hand search of recently published studies and a review of the reference lists of key papers.

Once I narrowed the potential studies for inclusion, the next step was a review of each article to determine eligibility based on the inclusion and exclusion criteria. The inclusion criteria for the literature search for this study included:

- adult males and females of any race, ethnicity, or geographic region,
- experimental, longitudinal, and epidemiologic study designs,
- primary focus on the PD and dementia relationship,
- primary focus on diabetes and dementia relationship only if substantial pathophysiology and etiologic pathways are identified,
- primary focus on PD glucose levels or glucose regulation and cognitive function,
- primary focus on comorbidity associated with PD including dementia,

- primary focus of metabolic, inflammatory, or vascular pathways linking PD and dementia,
- definition of PD described within the study as IFG, IGT, metabolic syndrome, or A1C between 5.7% and 6.4%, and
- outcome measure of dementia, AD, VaD, mild cognitive impairment, or impaired cognitive function.

The exclusion criteria for the literature search for this study included:

- PD studies that did not include dementia or cognitive impairment as an outcome measure,
- diabetes, not PD, identified as the exposure variable,
- cognitive function or dementia studies that did not examine PD or MetS as an exposure variable or independent variable,
- drug intervention studies,
- studies conducted prior to 2005 unless considered a classic PD/diabetes and dementia study in the literature,
- variants of dementia other than senile dementia, AD or VaD,
- the exposure variable was something other than PD or MetS such as exercise or dietary intake, and
- study designs focused on treatment or management of dementia or PD.

General themes emerged from the comprehensive literature search on PD and dementia. These themes served as the framework for the literature review and include:

- impaired glucose tolerance, impaired fasting glucose, and elevated A1C,

- metabolic syndrome (a PD equivalent),
- vascular disease,
- inflammation,
- IR,
- brain glucose metabolism and brain insulin signaling, and
- brain volume, white matter atrophy, and cerebral blood flow.

Theoretical Foundation

Reynolds (2009) defined scientific theory as "abstract statements that are considered part of scientific knowledge in either the set-of laws, the axiomatic, or the causal process form" (p. 9). Theory should help to explain the central hypothesis or research question and bridge the independent and dependent variables (Creswell, 2009). Epidemiology has evolved from germ theories, including the 1884 Koch postulates that proposed a causal relationship between microbes and disease, to an expanded view that considers the ecologic and social impact on disease susceptibility (Cassell, 1964; Krieger, 2011). Modern epidemiology, first termed *social epidemiology* by Yankauer in 1950, is foundationally supported by the ecologically oriented ecosocial theory (Krieger, 2011). The ecosocial theory embraces the life-course perspective, which incorporates the impact of life circumstances and exposures over a lifetime and their effect on health (Krieger, 2011).

The ecosocial theory guided this study and served as its theoretical foundation and deductive framework. The ecosocial theory considers social and ecologic causes of

disease and is an integrative and dynamic epidemiologic theory that connects societal and biologic determinants of disease (Krieger, 2011). The risk of dementia appears to increase with exposures to different biological and lifestyle risk factors experienced over the course of a lifetime. The theory holds that cumulative and combined exposure to various risk factors can modify dementia risk (Mangialasche et al., 2012).

The ecosocial theory helped frame the discussion around environmental risks for dementia. Incidence rates for familial dementia in unaffected family members in the National Institute on Aging Genetics Initiative for Late-Onset Alzheimer Disease/National Cell Repository for Alzheimer Disease (NIA-LOAD/NCRAD) and Estudio Familiar de Influencia Genetica en Alzheimer (EFIGA) family studies are significantly higher than population-based estimates and may be explained by the grouping of Alzheimer–related genes in these families or by shared environmental risks (Vardarajan et al., 2014).

Neuroimaging research has provided substantial evidence that vascular, inflammatory, and metabolic risk factors significantly contribute to the development and progression of dementia (Mangialasche et al., 2012). Additionally there are genetic and biological risk factors for dementia which include presence of the APOE ϵ4 allele, race, a family history of diabetes, obesity, hypertension, stroke, and cardio- and cerebrovascular disease. Lifestyle risk factors for dementia may include smoking, high saturated fat intake, alcohol abuse, and sedentary lifestyle (Crane et al., 2013; Rowan, Riddell, & Jamnik, 2013).

The ecosocial theory was tested in the dissertation study by examining PD and potential covariates that have either a biological or social/behavioral basis in relation to dementia. The differences between the races and SES groups are discussed in Chapter 5 in terms of their biological susceptibility and social/behavioral risks and exposures related to dementia.

Dementia is considered a disease with multiple etiologies that have interactive genetic and environmental components (Kivipelto et al., 2008; Tan et al., 2011). APOE ϵ4 is the strongest genetic risk factor for dementia although recent genomewide association studies (GWAS) found the ABCA7 locus in African Americans to have an effect size of 70–80% increased dementia risk, which is as strong as that of APOEϵ4 observed in Whites. One large population-based study suggested that APOE ϵ4 carriers are more vulnerable to the results of lifestyle risk factors such as smoking, excess alcohol and saturated fat consumption, and sedentary activity (Kivipelto et al., 2008). The ecosocial theory helped explain the relationship between PD and dementia with respect to lifestyle and lifetime exposures (Krieger, 2011). Race and SES may be important predictive factors for dementia because of different genetic susceptibility and lifetime exposures. The ecosocial theory provided some insight into the race, SES, and dementia relationship by framing the key concepts and constructs of this study.

Literature Review Related to Key Variables and Concepts

Dementia: Background and Natural History

Dementia prevalence has increased significantly in the United States and around the world, and dementia is now considered an epidemic (Duarte et al., 2013; Tan et al.,

2011). Approximately 5.3 million people in the United States have dementia, which translates to 1 in 8 people or 13% of the population (Alzheimer's Association, 2014). Proper diagnosis is essential for estimating the magnitude of the disease and developing specific, targeted prevention strategies and treatments. The subtypes of dementia are AD and VaD, with other less frequent variants identified such as Lewy body or Parkinson's dementia (Budson & Solomon, 2011; The Mayo Clinic, 2013; Staessen, Richart, & Birkenhager, 2007). A diagnosis of AD is made using the NINCDS-ADRDA criteria and the DSM-IV criteria (Budson & Solomon, 2011). It is estimated that 75% of all dementia is the AD subtype and the next most frequent subtype is VaD, together making up the overwhelming majority of dementia; however, these sub-types are increasingly being viewed as less distinctive with significant overlap especially with advanced age (Gatz et al., 2007). The term *dementia* is used to represent AD and VaD collectively, and the terms AD and VaD are used throughout when referring to the specific dementia subtypes.

Figure 1 depicts the substantiated and putative risk factors for dementia. Well substantiated risk factors for dementia include (a) advanced age, (b) female gender, (c) presence of the risk gene, APOE ϵ4, or presence of deterministic genes that cause presenelin mutations and abnormal APP, (d) dementia in a first degree relative, and (e) head trauma (Budson & Solomon, 2011; Reitz & Mayeux, 2014). Additional putative risk factors include alcohol abuse, cardiovascular and cerebrovascular diseases, diabetes, hypertension, low educational attainment, obesity, and race (Budson & Solomon, 2011; Launer, Petrovitch, Ross, Markesbery, & White, 2008; Reitz & Mayeux, 2014). Social

and lifestyle risk factors believed to increase the risk for dementia include poor quality diet, sedentary activity, and smoking (Mangialasche et al., 2012).

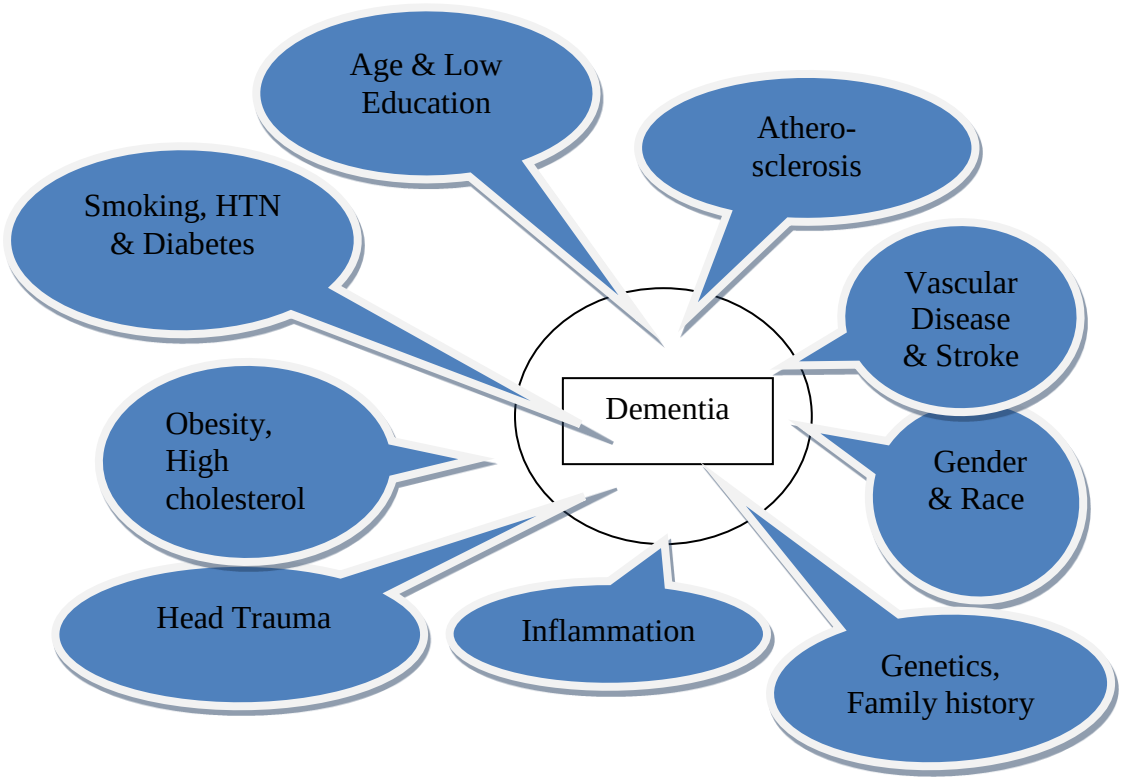

Figure 1. Substantiated and putative risk factors for dementia.

Dementia (AD) is a neurodegenerative disease characterized by significant memory loss and pathology in specific regions of the brain consisting of Aβ plaques, and accumulation of intraneuronal protein aggregates known as neurofibrillary tangles (NFT) and neuropil threads (NTs) (Budson & Solomon, 2011; Reitz et al., 2009; Takashima, 2009). Amyloid plaques are aggregates of Aβ peptide which form following the proteolysis of APP. APP becomes nonfunctional when it breaks down to Aβ peptide, negatively affecting synapse formation and neuroplasticity (Reitz et al., 2009). NFTs are

aggregates of microtubules associated with tau protein. In an aggregated form, microtubules lose their neural function of guiding molecules between the cell body and axons of the neuron (Alzheimer's Association, 2014). Contrary to normal neurites, NTs contain straight and paired helical filaments that contain tau protein and ubiquitin, and these abnormal filaments may replace the normal cytoskeleton (Reitz et al., 2009). The trigger for these pathologic processes is not known; however, the result is brain atrophy, dysfunction, and cell death.

The underlying pathology that directly causes the dysfunction associated with AD is not fully understood; however, low memory scores on standardized tests appear to be related to the quantity of amyloid plaques, NFTs, and NTs in the cerebral cortex and hippocampus specifically (Reitz et al., 2009). It is difficult to determine the independent effects of vascular, inflammatory, and metabolic factors related to AD as they are heterogeneous, interactive, and differently expressed over time and with treatment (Craft, 2009). Metabolic factors thought to be related to AD include IR, hyperinsulinemia, and prolonged exposure to components of the MetS including hyperglycemia, hypertension, and inflammatory cytokines (Craft, 2009; Talbot et al., 2012).

There is strong scientific evidence that AD is characterized by amyloid plaques and NFTs in the brain; however, there is one conflicting report in the literature from a well-known aging study (Budson & Solomon, 2011; Talbot et al., 2012; van der Flier & Scheltens, 2005). Investigators involved in a long-term follow-up to the classic Honolulu-Asia Aging Study (HAAS), which began in 1991 as a continuation of the Honolulu Heart Program (HHP), found that out of the 56% of Japanese men diagnosed with AD during

their adult life, only 19% had amyloid plaques or NFTs as the primary or dominant lesions in the brain upon autopsy (White et al., 2011). These findings are inconsistent with current understandings of AD pathology and suggest that the underlying pathology of AD may need further characterization.

The brain tissue pathology found in subjects with AD may be due in part to hyperglycemia. Hyperglycemia causes increased production of oxygen-free radicals and localized advanced glycation end products (AGE) (Di Bonito et al., 2007). AGE promote cellular dysfunction by modifying the structure, function, and mechanical properties of tissues, modulating cellular processes, and binding to cellular surface receptors (Bierhaus et al., 2005). AGEs have been found in the plaques and neurofibrillary tangles in those with AD, which supports a mechanistic pathway between PD and dementia secondary to hyperglycemia (Strachan, 2010).

Mild cognitive impairment (MCI) precedes dementia and appears to be an intermediate state between normal cognition and dementia, a prodromal period of dementia (Budson & Solomon, 2011; Reitz & Mayeux, 2014). The population-based prevalence of MCI reported in the epidemiological literature ranges from 3% to 19% in elderly adults (Gauthier et al., 2006). MCI can be characterized using the Petersen Criteria and is defined as a decline in cognition that exceeds that for age and education level but is not disruptive to activities of daily living; frank dementia is not a feature of MCI (Budson & Solomon, 2011; Gauthier et al., 2006; Peterson, 2004).

Cognition follows a cognitive spectrum with overlap at the borders of normal, MCI, and dementia (Peterson, 2004). Data from some experimental and epidemiological

studies supported the hypothesis that MCI is an early stage of AD and that making a distinction between the two is not useful. Other studies showed that not all subjects with MCI develop AD and that making the distinction is clinically relevant (Petersen, 2004). Estimates are that 50% to 80% of those with MCI progress to AD or other dementia subtypes at a rate of 7% to 15% per year, with a reported range of 1% to 25% per year (Budson & Solomon, 2011; Gauthier et al., 2006; Petersen et al., 2004). There are some individuals with MCI that progress to dementia rapidly. Predictors of rapid progression from MCI to dementia include presence of the APOE ϵ4 allele, low performance on cued memory tests, and reduced hippocampal volume (Peterson, 2004).

Investigators from one longitudinal study reported that in subjects with MCI, the presence of MetS, which is a PD equivalent, independently predicted increased risk of progression to dementia over 3.5 years (Solfrizzi et al., 2011). Identifying those with MetS and PD may allow for better prediction of rapid progression from MCI to AD.

Individuals with AD display apathy, agitation, depression, progressive memory loss, and reduced executive function such as impaired decision making and poor judgment (Budson & Solomon, 2011). Alzheimer's Dementia accounts for up to 75% of all dementia and estimates are that over 5 million people in the United States have AD today (Alzheimer's Association, 2014; Budson & Solomon, 2011; Qiu et al., 2010; van der Flier, 2005). Average life expectancy following the diagnosis of AD is three to eight years (Alzheimer's Association, 2014).

The cause of dementia is likely not due to a single factor but rather likely due to multiple underlying processes that result in the characteristic neuropathology. It is

difficult to separate the risk factors for dementia and determine which factors or combination of factors is responsible for the pathologic changes in the brain. Several investigators have tried to identify the etiology of dementia by developing predictive models based on specific risk factors in order to identify the best dementia prevention strategies (Crane et al., 2013; Exalto et al., 2013). Developing predictive models has proven challenging with varying predictive values reported in the literature (Crane et al., 2013; Exalto et al., 2013).

The covariates that were included in the dissertation study and used to build a predictive model for dementia include age, atherosclerosis, cerebrovascular disease, dyslipidemia, gender, HTN, obesity, race, SES, and stroke. The selection of these covariates was based on their genetic, social, or health-related properties and the scientific literature that describes these as likely or putative risk factors associated with dementia. Scientists have not fully elucidated the underlying etiology of dementia but have determined that PD may increase the risk of both AD and VaD (Budson & Solomon, 2011; Craft, 2009, Williamson et al., 2014). PD is the prodromal period that precedes T2D, and evidence has suggested that the microvascular, metabolic, and inflammatory pathology associated with T2D begins in this prediabetic, prodromal period (Dik et al., 2007; Solfrizzi et al., 2011; Yaffe et al., 2003). I describe the vascular, metabolic, and inflammatory pathways linking PD to dementia in this literature review.

The dissertation research addressed the gap in understanding of the association between PD and dementia and was based on a case control design to examine the relationship. Case control studies are appropriate for long latency diseases such as

dementia and have the potential to contribute significantly to the body of knowledge on this subject (Wacholder, Silverman, McLaughlin, & Mandel, 1992). Multivariable logistic regression was used to assess the association between PD and dementia and to build a predictive model.

Cerebrovascular disease accounts for approximately 10% of all dementia and is associated with infarcts that cause reduced blood flow resulting in white matter atrophy, cognitive dysfunction, and reduced functional abilities (Budson & Solomon, 2011). A diagnosis of VaD is made using neuropsychological tests in conjunction with neuroimaging, either computerized tomography (CT) or magnetic resonance imaging (MRI) (Budson & Solomon, 2011). Estimates are that 10–15% of the population have mixed dementia with both vascular and neurodegenerative characteristics. Many patients with AD have some vascular pathology in the brain likely due to aging (Alzheimer's Society, 2013; Budson & Solomon, 2011). Making a diagnosis of dementia with a single definitive subtype is challenging.

Currently there are no drugs available to prevent dementia or treat the underlying pathology of any dementia subtype (Alzheimer's Association, 2014). There are five drugs currently approved by the U.S. Food and Drug Administration (FDA) to control the symptoms of dementia or slow the progression. These include:

1. donepezil (Aricept, 1996),
2. galantamine (Razadyne, 2001),
3. memantine (Namenda, 2003),
4. risvastigmine (Exelon, 2000), and

5. tacrine (Cognex, 1993).

The effectiveness of the available dementia drugs is limited. The therapeutic window for these drugs is 6 to 12 months on average, and only approximately 50% of people respond to drug therapy (Alzheimer's Association, 2014).

Age, Heredity, Genetics, and Dementia

The strongest risk factor for AD is age (Qiu et al., 2010). Early onset AD (EOAD) is defined as AD onset in those younger than 65 years of age and accounts for 1% to 5% of all cases. Late-onset AD (LOAD) is defined as AD onset in those over 65 years and accounts for more than 95% of all AD (Reitz & Mayeux, 2014). The features of EOAD and LOAD are indistinguishable; however, EOAD is associated with more rapid progression and a Mendelian pattern of inheritance (Reitz & Mayeux, 2014).

Heredity is also a strong risk factor for dementia (AD). Those with a first-degree relative with AD have approximately a two-fold higher risk of AD although approximately 80% of AD is sporadic and the underlying mechanisms are not completely understood (Budson & Solomon, 2011; Qiu et al., 2010; van der Flier, 2005).

Presence of the APOE ϵ4 allele is the strongest genetic risk factor for dementia (AD); however, positive APOE ϵ4 allele status is not diagnostic of dementia (AD) or essential for developing it (Budson & Solomon, 2011). The APOE ϵ4 allele is located on chromosome 19q13 and has been the only dementia (AD) susceptibility gene identified in non-Hispanic Whites to date. The APOE ϵ4 allele is described as a genetic modifier of dementia (AD) risk. As the number of the ϵ4 alleles increases, dementia (AD) risk increases and the age of onset decreases by approximately six to seven years (Kivipelto &

Solomon, 2008; Reitz & Mayeux, 2014; van der Flier, 2005). A single APOE ϵ4 allele is associated with a two- to three-fold increased risk of dementia, and two copies of the APOE ϵ4 allele are associated with at least a 5-fold increase (Reitz & Mayeux, 2014). Presence of the APOE ϵ4 allele has been linked to the neuropathology characteristic of AD including amyloid-β plaque and NFT formation, oxidative stress, aberrations in lipid homeostasis and intracellular insulin signaling, and cell death (Kivipelto et al., 2008; Reitz & Mayeux, 2014).

Race and Dementia

Race may be a significant risk factor for dementia although this finding has not been consistent across populations. There are data to support the hypothesis that African Americans have a higher risk of dementia compared to Whites (Froehlich, Borgardus, & Inouye, 2001). African Americans appear to have a higher prevalence of VaD and a lower prevalence of Parkinson's (or Lewy body) dementia compared to Whites, and the genetic etiology of AD appears to differ in African Americans as well (Froehlich et al., 2001).

There is support for the hypothesis that African Americans have a higher risk of dementia compared to Whites based on genetic risk factors, specifically the APOE ϵ4 allele. African Americans also appear to have a higher prevalence of VaD than Whites (Froehlich et al., 2001). Recently, using GWAS, scientists identified ABCA7 as a major dementia susceptibility locus in African Americans (Reitz & Mayeux, 2014). The effect size of ABCA7 for dementia indicates a 70–80% increase in risk which is as strong as the effect size of APOEϵ4 in Whites. In contrast the ABCA7 locus identified in Whites poses

only a 10–20% increase in dementia risk. In addition, these GWAS scientists confirmed that APOE is a susceptibility gene in African Americans, which had been an inconsistent finding in previous studies (Reitz & Mayeux, 2104).

At the 2013 Alzheimer's Association International Conference, Yaffe et al. presented recent findings from the ongoing prospective Health, Aging and Body Composition study. The aim of this 12-year follow-up study was to assess dementia risk in African American and White elderly participants who were free of dementia at baseline (AAIC, 2013). Yaffe et al. reported that African Americans were 1.5 times more likely to develop dementia than Whites; however, when the data were adjusted for several SES factors, the excess dementia risk in African American participants was not statistically significant; therefore, the excess risk for dementia in African American elderly people may be related to SES rather than genetics (AAIC, 2013). The dissertation study indirectly determined SES by using the primary insurance provider (private, Medicare, and Medicaid) as a surrogate marker. Those with Medicaid as their primary health insurance were categorized as low SES.

In a longitudinal cohort study, investigators evaluated dementia in the Cardiovascular Health Study (CHS) participants, which included 2,865 White and 492 African American participants who were free of dementia at baseline and followed for over five years (Fitzpatrick et al., 2004). The investigators did *not* find racial differences in incident dementia in this cohort (Fitzpatrick et al., 2004). Therefore, the impact of race and race related factors such as education and SES on dementia risk requires further investigation.

Presence of the APOE ϵ4 allele is a recognized risk factor for AD in various ethnic groups in adults of each gender; however, several investigators suggested that the risk for AD in AAs and Hispanics may be more independently associated with the APOE genotype (Farrer et al., 1997; Tang et al., 1998). More recently, investigators have found mixed utility of the APOE allele for predicting AD (Sun, Nicholas, Walker, Wagner, & Bachman, 2012). In one study, investigators found that APOE allele carrier status had a high sensitivity and high positive predictive value for the diagnosis of AD but a low negative predictive value and low specificity (Sun et al., 2012). Another group of investigators found APOE genotyping in patients with mild cognitive impairment had limited clinical utility for predicting AD (Devanand et al., 2005). There is a paucity of data on PD and dementia risk when stratified by race.

According to the Alzheimer's Association's 2010 *Alzheimers Disease Facts and Figures* report, Hispanics are reported to have a dementia risk approximately 1.5 higher than Whites but are less likely to have a diagnosis (Alzheimer's Association, 2014). Hispanics in the United States have higher rates of cardiovascular risk factors including diabetes, high blood pressure, and high cholesterol, which may increase the risk for dementia (Alzheimer's Association, 2014). Additionally, Hispanics have a long life expectancy, which is also a risk factor for age-related dementia.

The Aging, Demographics, and Memory Study (ADAMS) provided data on the prevalence of dementia (AD) in White and African American participants aged 71 years and older. The findings from ADAMS indicated that elderly African Americans have a dementia risk almost twice that of Whites in the same age group, 21.3 % versus 11.2 %,

respectively (Potter et al., 2009). The ADAMS study included Hispanics but the number of participants was too small to provide valid estimates of the AD prevalence for that group. Overall, there is a paucity of data in the scientific literature on the association between PD and dementia examined by race and SES; the dissertation study addressed that gap.

Low Educational Attainment, SES, and Dementia

Other risk factors have been shown to have an association with dementia including low educational attainment, obesity, smoking, and hyperlipidemia (Budson & Solomon, 2011). Low educational attainment is a variable often found to be associated with a higher risk of dementia, after adjusting for age and family history, although it is not well understood (Budson & Solomon, 2011; Gatz et al., 2007). The predominant hypothesis is that education creates a higher mental threshold and cognitive reserve, provides mental stimulation, and strengthens connectivity in the brain by increasing synaptic density (Budson & Solomon, 2011; Gatz et al., 2007, Karp et al., 2004). A second hypothesis is that differences in educational attainment reflect genetically-driven differences in intelligence.

Investigators in the HARMONY study used the Swedish Twin Registry to assess dementia in twins over the age of 65. Analyses included co-twin controls, tests for association between educational attainment and genotype, and bivariate twin modeling. Low educational attainment was found to be a highly significant risk factor for dementia in their case-control and co-twin control analyses (monozygotic twin pairs) (Gatz et al., 2007). APOE ϵ 4 was not associated with educational attainment and did not alter the

relationship between educational attainment and dementia. The investigators concluded that low education is a significant risk factor for dementia (Gatz et al., 2007). Strengths of the study were large dataset and use of a co-twin design. A limitation was that APOE genotyping was not available for all participants.

In two large population-based cohort studies known as the EClipSE study (Epidemiological Clinicopathological Studies in Europe), Brayne et al. (2010) examined the association between neuropathology at death and clinical dementia as it relates to exposure to education. They found that a higher educational attainment reduced dementia risk independently of the degree of postmortem neuropathology (Brayne et al., 2010). They found that more education did not prevent the neuropathology consistent with AD and VaD but rather reduced the clinical expression of dementia before death (Brayne et al., 2010).

Karp et al. (2004) selected a cohort of 931 subjects 75 years of age or older without dementia at baseline from the Kungsholmen Project in Sweden to examine whether the association between low educational level (LEL) and increased risk of AD and whether dementia incidence could be explained by occupation-based socioeconomic status (SES). The investigators reported that subjects with LEL had an adjusted relative risk (RR) of 3.4 for incident AD and those with lower SES had an adjusted RR of 1.6 (Karp et al., 2004). When they introduced both education and SES into the same model, only education remained significantly associated with AD; well-educated subjects with low SES were not found to have high AD risk. These investigators concluded that the association between LEL and increased AD risk was not mediated by adult SES or

socioeconomic mobility. Their findings suggested that early life factors may be important in the development of dementia later in life, and this is supported by the life-course theory (Karp et al., 2004; Krieger, 2011).

Obesity and Dementia Risk

Chronic obesity and being overweight also appear to be risk factors for lower cognitive performance, cognitive decline, and dementia (Elias, Goodell & Waldstein, 2012). Obesity is a state of ectopic fat accumulation with associated changes in adipokine secretion. These changes are thought to cause a state of chronic inflammation, insulin resistance, and endothelial dysfunction, although the exact mechanisms are not known (Flehmig et al., 2014). Inflammation, insulin resistance, and endothelial dysfunction are believed to be related to the neuropathology of dementia and provide a mechanistic link between the two diseases. Obesity also raises the risk of PD and T2D by almost six fold (Skolnik & Ryan, 2014).

In a longitudinal analysis of over 6,000 members of Kaiser Permanente, central obesity in midlife was found to increase the risk of incident dementia nearly threefold over a 30-year period, and this was independent of T2D and cardiovascular comorbidities (Whitmer et al., 2008). The investigators used Cox proportional hazard models to adjust for age, sex, race, education, marital status, diabetes, hypertension, hyperlipidemia, stroke, heart disease, and medical utilization (Whitmer et al., 2008). One major limitation of the study was the high number of participants lost to follow up.

Similar findings were seen in participants of the Cardiovascular Risk Factors, Aging, and Dementia (CAIDE) study who were followed for an average of 21 years. The

investigators found a twofold risk of dementia for each risk factor as well as up to a six fold additive effect for the following: midlife obesity, high total cholesterol, and high systolic blood pressure (Kivipelto et al., 2005). They concluded that obesity at midlife is associated with an increased risk of dementia and AD later in life and that vascular risk factors increase the risk in an additive manner.

In a meta-analysis of observational studies, Loef & Walach (2013) found that midlife obesity increases the risk of dementia later in life. They noted that when obesity is added to predictive models, the prevalence of dementia goes up exponentially. These investigators suggested that increases in midlife obesity prevalence contribute significantly to incident dementia and that public health initiatives to reduce midlife obesity will serve as primary prevention of dementia (Loef & Walach, 2013).

Dyslipidemia and Dementia Risk

Several epidemiologic studies have found a relationship between elevated serum cholesterol levels and development of dementia, although results have not been consistent (Ramdane & Daoudi-Gueddah, 2011). Several mechanisms have been suggested to explain the association between cholesterol and AD. One hypothesis was that high serum cholesterol is related to atherosclerosis, cardiovascular and cerebrovascular disease. The first pathologic development in atherosclerosis is the formation of an atheroma, which is an accumulation of debris in the intima or inner layer of the artery wall. The debris contains cholesterol, fatty acids, calcium, and some fibrous connective tissue. Atheromas cause a swelling, narrowing and restricted blood flow within the artery (Lusis, 2000). Atherosclerosis in larger cerebral vessels is thought to develop primarily due to HTN and

secondarily to dyslipidemia; atherosclerosis in smaller cerebral vessels is thought to be related to HTN only and not impacted by dyslipidemia including hypercholesterolemia (Solomon, Kivipelto, Wolozin, Zhou & Whitmer , 2009).

Recently, investigators examined a cohort of elderly subjects and found that those with higher LDL-cholesterol and lower HDL-cholesterol levels had greater amyloid plaque deposits in specific brain regions suggesting a higher risk for future dementia (AD) (Reed et al., 2014). Additionally, cholesterol is essential for brain function and high cholesterol turnover has been associated with neurodegenerative diseases (Solomon et al., 2009).

Using the Kaiser Permanente Northern California Medical Group medical records as a database, investigators evaluated nearly 10,000 participants for midlife cholesterol and incident dementia, both AD and VaD, over a 30-year period (Solomon et al., 2009). Cox proportional hazards models were used and adjusted for age, education, race/ethnicity, gender, and T2D, HTN, BMI, and late-life stroke. Even moderately elevated cholesterol levels ($\geq$220 mg/dl) in mid-life were found to be a significant risk factor for AD and dementia VaD.

One group of investigators retrospectively examined the relationship between fasting plasma total cholesterol (TC), triglycerides (TG), and glucose levels, and AD in a cohort of elderly patients. They found that TC was higher in patients with AD, and TG and glucose levels did not significantly differ between the AD and control groups (Ramdane & Daoudi-Gueddah, 2011).

Results of the study suggested that patients with AD have mildly elevated TC, normal TG, and normal FPG. Mild hypercholesterolemia appeared to be consistent across age and severity of dementia, and paralleled the projection of age-related change in TC in the control group (Ramdane & Daoudi-Gueddah, 2011). The investigators hypothesized that mild hyper-cholesterolemia may be present many years prior to the onset and diagnosis of AD (Ramdane & Daoudi-Gueddah, 2011).

Smoking and Dementia Risk

It is well known that cigarette smoking significantly increases mortality secondary to cardiovascular disease and several types of cancers; however the mechanisms between smoking and dementia, both AD and VaD are complex and less well understood. Smoking appears to cause injury to cerebral vessels as well as brain cells, damaging the vascular system by increasing blood pressure as well as blood clotting factors (Rusanen, Kivipelto, Quesenberry, Zhou, & Whitmer, 2011). Studies examining the link between smoking and AD have been varied and controversial, with some studies actually suggesting that smoking *reduces* the risk of cognitive impairment (Rusanen et al., 2011). Dementia experts agree that lifestyle choices and behaviors that help maintain vascular health are important for reducing AD risk (Rusanen et al., 2011).

Recently, one group of investigators analyzed data from more than 21,000 Kaiser Permanente Northern California participants to determine the effects of heavy smoking on dementia risk. They found that smoking two packs or more per day in midlife more than doubles the risk of developing dementia (AD or VaD) (Rusanen et al., 2011).

Pre-Diabetes and Dementia Risk

There is accumulating scientific evidence that PD adversely effects cognition and may be a risk factor for dementia (Craft et al., 2009; Duarte et al, 2013; Kloppenborg, van den Berg, Kappelle & Biessels, 2008; Strachan, 2010, Williamson et al, 2013). Under normal physiologic conditions, glucose is the primary fuel source for the brain and necessary for normal cognitive function (Lamport, Lawton, Mansfield, & Dye, 2008). The hallmarks of PD, IR, impairments in glucose tolerance and glucose metabolism, as well as insulin signaling provide several mechanistic pathways to link PD and dementia (Craft, 2009; Lamport et al. 2008; Strachan, 2010).

There are 86 million people in the United States who have PD and up to 65% of those with PD will convert to T2D within a six year time frame (Duarte et al, 2013; Garber et al., 2008; Steen et al., 2005; Strachan, 2010). There is support in the scientific literature that dementia is an end-organ disease of T2D, what Steen et al. (2005) first referred to as *type 3 diabetes*; therefore, there is great concern for the 86 million Americans who have PD because of the high conversion rate to T2D, placing these individuals at high risk for dementia (Strachan, 2010). Data in the literature regarding the relationship between PD and dementia has been mixed. A number of large epidemiologic studies have tried to determine when dementia associated with T2D begins and whether glucose levels in the pre-diabetic range initiate the pathologic processes or whether other factors are responsible. The question remains as to when the pathology of dementia begins and whether PD can be considered an independent or predictive risk factor.

It is not known whether glucose levels within the PD range increase the risk of dementia in people without frank diabetes (Crane et al., 2013). Determinations of glucose thresholds are somewhat arbitrary and are based on data that suggest significant health risks associated with these specific plasma glucose levels (Garber et al., 2008). Health risks associated with these glucose thresholds specifically include retinopathy and fatal cardiovascular events, although the DECODE study group found that the 2-hour blood glucose was a better predictor of all cause and cardiovascular deaths than FPG (DECODE Study Group, 2001; Garber et al., 2008; Lamport et al., 2008). Glucose tolerance appears to be a continuum from low-normal blood glucose values to overt diabetes, and the data consistently has shown that health risks increase as blood glucose levels rise into the high-normal and pre-diabetic range (DeFronzo et al., 2013; Garber et al., 2008; Lamport et al., 2008).

Impaired fasting plasma glucose (IFG) is one of the three diagnostic criteria for PD and may be a marker for cognitive impairment (Derr, 2013). Using data from the Betula study and Västerbotten Intervention Program, fasting plasma glucose was assessed for its effect on episodic and semantic memory in non-diabetic subjects (Rolandsson, Backeström, Eriksson, Hallmans, & Nilsson, 2008). The Betula study was a cognitive function study of 35–85 year olds and the Västerbotten Intervention Program was a health survey of 40, 50, and 60-year-olds for fasting and post meal glucose levels and cardiovascular disease. The investigators assessed 411 nondiabetic subjects without dementia who had participated in one of these two surveys within the past six months.

Using an adjusted multivariate model, the investigators found that FPG and two-hour post meal glucose was significantly and negatively associated with episodic memory in women but not in men (Rolandsson et al., 2008). The conclusion was that glucose levels in the high normal or pre-diabetic range were associated with lower memory scores. The investigators hypothesized that higher fasting glucose and higher plasma glucose levels following a glucose-load have a negative effect on the hippocampus resulting in reduced memory (Rolandsson et al., 2008).

Similarly, Ohara et al. (2011) conducted a study of community-dwelling older subjects without dementia at baseline to assess the association between glucose tolerance and incident dementia over a 15-year follow-up period using a standard OGTT design (Ohara et al., 2011). Those subjects who did not have diabetes but had elevated 2-hour OGTT results (in the prediabetic range) had a significantly increased risk of developing all-cause dementia, AD, and VaD even after adjustment for covariates (Ohara et al., 2011). Elevated 2-hour OGTT is diagnostic for PD. The same elevated dementia risk was not observed for FBG. The authors concluded that diabetes is a significant risk factor for all-cause dementia, AD, and likely VaD. They also concluded that in subjects without frank diabetes, an elevated 2-hour OGTT is closely associated with increased risk of all-cause dementia, AD, and VaD (Ohara, et al., 2011). The Ohara et al. study provided evidence that PD is a risk factor for incident dementia.

In a five year intervention study of individuals from the Danish population-based study, Inter99, investigators examined interventions for reducing the incidence of ischemic heart disease and T2D (Faersh et al., 2009). They found that the transition from

NGT to IFG was caused by reduced insulin secretion progressing to a decline in hepatic insulin sensitivity. In contrast, these investigators found that low whole-body insulin sensitivity with a secondary lack of insulin secretion is associated with progression to IGT (Faersh et al, 2009). This study documented that that low insulin sensitivity or "IR" precedes IGT by five years. Based on the findings of Faersh et al. (2009) it appears that IR precedes IGT by many years and yet IGT is used to diagnose PD. A limitation of the large-scale epidemiological study was that the reliability may have been reduced when estimates of insulin secretion were not done using the most reliable and reproducible technique, the glucose clamp technique (Faersh et al., 2009).

In a 2006 study of non-diabetic older women with osteoporosis, researchers tested the hypothesis that elevated A1C is predictive of cognitive impairment or dementia (Yaffe, Blackwell, Whitmer, Krueger, & Barret-Connor, 2006). In the four year dementia study, the investigators found that for every 1% increase in A1C there was an age-adjusted 50% increased risk for MCI (Yaffe et al., 2006). The subjects had a baseline A1C of 5.8%, which is diagnostic for PD. For those subjects with an A1C level of 7% at baseline (diabetes), the age-adjusted risk for developing MCI was four times higher. Contrary to the findings of Fuh, Wang, Hwu, & Lu (2007) and Christman et al. (2012), Yaffe et al. (2006) did find an association between A1C and risk of developing MCI and dementia in women with PD. The investigators accepted the hypothesis that elevated blood glucose in the PD range is a predictor of cognitive impairment.

There is additional support for the hypothesis that cognitive function may be impaired during the period of PD, well before glucose levels reach the diagnostic

threshold for T2D (Messier, Tsiakas, Gagnon, & Desrochers, 2010). Using an OGTT method in a younger cohort, investigators measured blood glucose, insulin levels, and cognitive performance on standardized tests following a glucose load. They observed that deteriorating glucose regulation into the PD range predicted lower performance on cognitive tests (Messier et al., 2012). Underscoring these findings, a separate cross-sectional study of elderly Chinese subjects showed that higher fasting blood glucose (FBG) levels were associated with dementia independent of vascular risk factors and MRI-confirmed vascular disease (Mortimer et al., 2010). The investigators analyzed their data for clinical outcomes, neuropsychological test results, vascular risk factors, and quantitative MRI volumetric indices. They suggested that high normal FBG may be a risk factor for dementia (Mortimer et al., 2010). Of note, the Mortimer et al. study identified cases primarily from an outpatient Memory Disorders Clinic, and controls were identified from a community sample; therefore, there was potential for increased frequency of diabetes among cases relative to controls, lowering the validity of their results (Mortimer et al., 2010).

The Uppsala study was a 12-year longitudinal study conducted to measure the association between glucose metabolism, insulin sensitivity and secretion, and dementia (AD and VaD) in over 1,000 cognitively-normal adult men (Rönnemaa et al., 2009). The investigators conducted OGTT's and insulin clamp studies. They found that low early insulin response, but not low insulin sensitivity, also called IR, was associated with a higher risk of AD. Low insulin sensitivity was associated with a higher risk of VaD (Rönnemaa et al., 2009). The study provided evidence that specific characteristics of PD,

IR, and low early insulin response may be in the causal pathway for the two primary sub-types of dementia, AD and VaD.

APOE ε4 allele status is the strongest genetic risk factor for dementia (Kivipelto & Solomon, 2008; van der Flier, 2005). The APOE ε4 allele was tested for in a subset of participants in the Uppsala study. The investigators found that the association between low early insulin response and AD was stronger in those without the APOE ε4 allele suggesting that impaired insulin response is an important risk factor for AD even in the absence of APOE ε4 (Rönnemaa et al., 2009).

The Uppsala longitudinal study was large with a long duration follow-up period and provided detailed information on baseline glucose metabolism and dementia subtyping. The investigators noted that due to multiple independent analyses, the data might be at risk of false positives and possible type 1 errors (Rönnemaa et al., 2009). The generalizability of the study was also limited because the subjects were males only.

An examination of data from the Adult Changes in Thought (ACT) study was conducted to test the hypothesis that elevated glucose levels are associated with risk of dementia (Crane et al., 2013). The ACT study included 2,067 randomly selected members of the Group Health Cooperative in Washington State who were free of dementia at baseline. Participants were assessed for dementia every two years using the Cognitive Abilities Screening Instrument over a median follow-up period of 6.8 years.

The ACT study design made use of fasting blood glucose, random glucose, and A1C to develop a composite of average blood glucose. A time-varying estimate of each participant's average glucose level was calculated using a combination of measured

glucose values and the calculated daily average glucose values, and a hierarchical Bayesian method (Crane et al., 2013). The data was analyzed using Cox regression models, stratified by diabetes and cerebrovascular disease status, and controlled for sex, age, APOE genotype, and multiple potential confounders.

Results of the ACT study showed that older non-diabetic adults with average blood glucose levels within the PD range (average glucose of 115 mg/dl) had an increased risk of dementia compared to those in the lower to mid-normal range (100 mg/dl) with an adjusted hazard ratio for dementia of 1.18 (95% CI, 1.04 to 1.33) (Crane et al., 2013). Participants with T2D who had the highest glucose levels (average glucose of 190 mg/dl) had an increased risk of dementia compared with participants with glucoses in the mid-diabetes range (160 mg/dl) with an adjusted hazard ratio for dementia of 1.40 (95% CI, 1.12 to 1.76) (Crane et al., 2013). The results did not change after adjustment for APOE ϵ4 status. The investigators suggested that glucose levels in the PD range may be a risk factor for dementia in non-diabetics subjects (Crane et al., 2013).

A strength of the ACT study is that it was a large prospective cohort design and had a long and thorough follow-up using a large volume of data (Crane et al., 2013). Two limitations of the study were that the results may not be generalizable to other ethnic groups, and there may be misclassification of the outcome variable due to the investigator's creation of a composite average blood glucose value.

Using a similar population to that of the ACT study, another group of investigators examined the association between glucose control over time, measured by A1C, and cognitive changes in community dwelling non-diabetic, non-demented elderly

subjects who were enrolled in longitudinal studies of cognition (Ravona-Springera et al., 2012). The Mini Mental State Exam (MMSE) was used to assess cognitive changes and was the primary outcome measure.

The investigators found that after adjusting for age there was a significant reduction in MMSE scores (-1.37 points) per unit increase in A1C. Their findings remained unchanged after adjusting for additional confounders and incipient diabetes (A1C between 6% and 7%). In the 15-year follow-up study, cognitive decline was evident in non-diabetic non-demented elderly subjects when A1C increased within the normal range and into the PD range (Ravona Springera et al., 2012). Strengths of the study included the long follow-up period with a multi-disciplinary agreement on the non-diabetic and cognitively-normal status of the subjects. Limitations were that there was no brain imaging done and some of the confounding variables were based on self-reports such as physical activity and smoking.

Despite a body of evidence suggesting a relationship between PD (either IFG or IGT) and dementia, there remains equivocation in the literature. Several recent studies do not support the hypothesis that IFG or IGT is associated with cognitive dysfunction or dementia (Christman et al., 2012; Fuh, Wang, Hwu, & Lu, 2007; Rouch et al., 2012). In a longitudinal population-based cohort of elderly non-demented community dwellers participating in the PROOF study (Prognostic indicator of cardiovascular and cerebrovascular events), the investigators found that diabetes but not PD (IFG) was associated with a higher two year decline on standard cognitive function tests, the Trial Making Test B, and Stroop test, which measure attention and executive function

(decision making) (Rouch et al., 2012). Their findings were significant after adjusting for age, gender, education, anxiety, depression, and cardiovascular risk factors (Rouch et al., 2012). The strength of this study was that it provided long term follow-up of healthy subjects who did not have dementia at baseline.

Using a middle-aged population-based Taiwanese cohort of women and a case control design, investigators examined the effect of glucose tolerance on performance in five separate cognitive tests (Fuh, Wang, Hwu, & Lu, 2007). The investigators used OGTT's to categorize the participant's glucose tolerance status as normal, PD (IGT), or frank diabetes. They found no association between glucose tolerance status and cognitive performance noting that the duration of diabetes in these subjects was less than five years (Fuh et al., 2007). It should be noted that the study did not describe the case and control selection process and did not appear to follow a case control design. The subjects in the study were described as poorly educated. Because low educational attainment is a significant risk factor for dementia, the findings may be confounded (Budson & Solomon, 2011). Although frequently cited in the PD/dementia literature, the study appears to have significant design flaws.

Investigators in a large prospective study did not find evidence that PD is associated with dementia. In a prospective cohort of 8,442 people known as the Atherosclerosis Risk in Communities (ARIC) study, investigators studied people with and without diabetes and examined the spectrum of A1C (normal, pre-diabetes, and overt diabetes) along with three measures of cognition (Christman et al., 2012). They measured cognitive changes over a six year period. The purpose of the study was to determine

whether higher A1C values are independently associated with cognitive decline and risk of dementia-related hospitalization. The investigators found that A1C's in the pre-diabetic range did not have predictive power for dementia but A1C's in the diabetic range did (Christman et al., 2012).

Unlike many studies of dementia that focus on older or elderly subjects, the cohort studied by Christman et al. (2012) was a middle aged population, with a mean age of 56 years. Based on their findings, the investigators concluded that further study of non-glucose related causes of cognitive decline is warranted (Christman et al., 2012). Primary strengths of the study are that it was a large cohort design with a six year follow-up and used two different cognitive tests. A limitation of the study was that the investigators used A1C only to measure blood glucose status, which may not detect those with early PD. Generalizability was also limited because of the selection of middle-aged participants only.

Metabolic Syndrome and Dementia

Metabolic syndrome (MetS) is a heterogeneous disorder diagnosed using the Third Adults Treatment Panel of the National Cholesterol Education Program (NCEP-ATP-III) (Panza et al., 2010). MetS is a constellation of symptoms including at least three of the following: hypertension, large waist circumference, high triglycerides, low HDL cholesterol, and elevated fasting glucose (Raffaitin et al., 2008). The American Diabetes Association considers the MetS a PD equivalent (Garber et al., 2008)

A study of 151 participants with pre-existing dementia and 64 controls was conducted to assess co-occurrence of MetS and dementia (Wehr et al., 2012). Metabolic

syndrome was diagnosed according to the modified Grundy criteria (hypertension, obesity, high triglyceride and low HDL-cholesterol levels, and hyperglycemia). IR was assessed using the standardized mathematical model of IR known as HOMA-IR (homeostasis model assessment of insulin resistance), which is calculated based on fasting insulin levels. The investigators found that MetS was more common in those with vascular dementia (VaD) than in the control group (Wehr et al., 2012). The MetS components of hyperglycemia (IGT) and low HDL-cholesterol were found to be higher only in APOE ϵ4 negative subjects even though APOE ϵ4 is a strong genetic marker for AD (Wehr et al., 2012). The investigators also reported that blood glucose levels were higher two hours after a glucose load in participants with dementia compared to the control group (Wehr et al., 2012). MetS is a PD equivalent and IGT is diagnostic for PD; therefore these findings are suggestive of an association between the PD equivalent, MetS, and dementia.

Examining dementia risk with respect to the individual metabolic and vascular components of the MetS helps elucidate which factors are most significant. Associations between MetS and its individual components and risk of incident dementia are inconsistent in the scientific literature. In a four year prospective cohort study of 7,087 older subjects recruited from the French Three-City cohort, investigators used a Cox proportional hazard model to estimate a hazard ratio for incident dementia (both VaD and AD) in those with and without MetS, with an analysis of each component of the MetS (Raffaitin et al., 2008).

Over the four year study period, nearly 16% of participants were found to have MetS with an increased risk of incident VaD but not AD. High triglyceride level was the only component of the MetS that was significantly associated with the incidence of VaD (Raffaitin et al., 2008). The investigators found that diabetes but not PD (IFG) was significantly associated with all-cause dementia and VaD. The investigators concluded that improved detection and treatment of vascular risk factors are needed in older people in order to reduce the risk of dementia (Raffaitin et al., 2008).

The cognitive decline characteristic of dementia may be related to the presence of MetS and inflammation together. In the cross-sectional Longitudinal Aging Study Amsterdam (LASA), investigators sampled 1,183 elderly subjects and assessed the relationship between MetS, the individual components of MetS, inflammatory markers (C-reactive protein and 1-antichymotrypsin) and cognition (Dik et al., 2007). The NCEP criteria were used to diagnose MetS, and the MMSE was used to assess cognitive status (Dik et al., 2007). The overall aim of the study was similar to that of Raffaitin et al. (2008) except that inflammation was also analyzed to determine if it modified the relationship between MetS, the components of MetS, and cognition.

These investigators found that 36% of those sampled had MetS, which was significantly and negatively associated with all measures of cognition (Dik et al., 2007). When the individual components of MetS were analyzed, hyperglycemia was most significantly associated with cognitive function. There was an interaction effect found between MetS and inflammation, which was negatively associated with cognition in those subjects in the upper tertile for inflammation (Dik et al., 2007). The investigators

concluded that cognition was reduced in those with MetS, particularly in subjects with high levels of inflammation, and that the components of MetS most closely associated with reduced cognition was hyperglycemia (Dik et al., 2007). The study provided evidence of an association between PD and the cognitive changes that are consistent with dementia.

One limitation of the LASA study was that it was a cross-sectional design. Longitudinal studies assessing MetS and its individual components, inflammation, and cognition are needed to validate these findings. Another limitation is that serum fructosamine was used as a proxy for fasting glucose, and the researchers could not fully determine whether the samples taken were fasting (Dik et al., 2007).

MetS is a constellation or clustering of metabolic and vascular risk factors and it is difficult to separate the risks associated with each factor (Craft, 2009). When taken as a whole, there appears to be an increase in dementia incidence in those who meet the criteria for MetS, a PD equivalent (Dik et al., 2007). The public health response to the epidemic of PD or MetS has been slow and there are no specific treatments available for PD. However, prevention of PD or early intervention in MetS (a PD equivalent) has the potential to reduce incident dementia.

Vascular Risk Factors and Dementia

Development of dementia, both AD and VaD, is associated with vascular risk factors, and several have been identified as potentially causative or in the causative pathway, including HTN, cardio- and cerebrovascular disease, and hypercholesterolemia (Craft, 2009; Panza et al., 2010, Talbot et al, 2012). Although there is a growing body of

evidence to suggest that vascular risk factors contribute to AD, it has not been determined whether vascular disease causes lesions that are consistent with AD or simply increases the clinical severity of AD (Launer et al., 2008). T2D is a disease associated with significant macro- and micro-vascular morbidity including cardiovascular disease, neuropathy, retinopathy, and nephropathy. Scientific evidence has suggested that these vasculopathies begin in the prediabetic period (Garber et al., 2008; Lamport et al., 2008; Samaras & Sachdev, 2012). PD is characterized by hyperglycemia, and there is scientific evidence that chronic hyperglycemia causes micro-vascular disease in the cerebral cortex as it does in other small vessels in the retina, nephrons, and distal vasculature of the legs and feet (Strachan, 2010). A second theoretical mechanism for increased dementia risk secondary to PD is the development of atherosclerosis of large and small cerebral vessels in the brain, which results in neuronal ischemia and brain dysfunction (Di Bonito et al., 2007; Strachan, 2010).

Hypertension appears to be in the causative pathway for dementia. HTN is highly associated with stroke, and stroke, both hemorrhagic and vessel occlusion can cause morphologic changes in the brain. Stroke is a known risk factor for dementia (Budson & Solomon, 2011, Williamson et al., 2014). Dementia risk is twice as high in those who have had a stroke, with an estimated prevalence of 30% following a stroke (Gorelick et al., 2011). The most common type of VaD is called multi-infarct dementia, which is caused by a series of small strokes. Sub-cortical VaD is a form of small vessel disease caused by damage to the microvasculature deep within the brain (Alzheimer's Society, 2013).

Hypertension (HTN) is associated with VaD and is now thought to play a role in the pathogenesis of AD as well (Craft, 2009; Kivipelto & Solomon, 2008). HTN disrupts diurnal blood pressure variation, which can lead to endothelial injury of the small cerebral arteries resulting in white matter lesions and brain matter atrophy (Nagai, Hoshide, & Kario, 2010). HTN is a major risk factor for stroke, and stroke is in the causative pathway of dementia. Stroke and cerebral vessel infarcts result in brain atrophy, cerebral hypo-perfusion, ischemia, and white matter hyper-intensities (WMH) (Firbank et al., 2007; Williamson et al., 2014). Silent infarcts are detected using MRI (Liao et al., 1997).

Although there is an association between stroke and dementia, there appear to be other factors that may precipitate cerebral vascular injury such as IR. Vascular injury may be a mediator and in the mechanistic pathway between PD and dementia. IR, a hallmark of PD, is associated with pro-inflammatory processes and is thought to have a negative effect on endothelial function (Craft, 2009). IR favors vasoconstriction by decreasing nitric oxide production and capillary recruitment resulting in reduced micro-vascular blood flow (Craft, 2009). There are gaps that still remain in understanding the complex and heterogeneous etiology of dementia (Kloppenborg et al., 2008; Panza et al., 2010).

T2D is an established cardiovascular (CV) risk factor. PD is also thought to be a CV risk factor because the CV pathology appears to begin well before the onset of T2D (Baker et al., 2011; Bowden et al., 2010; Craft, 2009; Steen et al., 2005). Using a longitudinal cohort design, Newman et al. (2005) sought to determine whether coronary artery disease (CAD), peripheral artery disease (PAD), or cardiovascular disease (CVD)

markers can predict incident dementia and AD. Over 3,500 participants who were dementia-free at baseline were followed for over five years. MRI was used to assess evidence of stroke and brain pathology.

The investigators of the longitudinal study found that CVD was independently associated with elevated AD risk with the highest risk found in those with PAD. Although cases of stroke were excluded in the study, the investigators noted that subclinical strokes resulting in diffuse cerebral ischemia may mediate the association between PAD and AD (Newman et al., 2005). They concluded that PAD is a significant risk factor for AD. Based on these findings, PAD may be a viable predictive marker for dementia and strategies to reduce or prevent vascular disease may result in reductions in dementia incidence (Newman et al., 2005). PD is thought to cause insult to and occlusion of peripheral vessels through metabolic, vascular, and inflammatory processes and may play a role in the development of PAD.

Newman et al. (2005) noted that lifetime cumulative effects of multiple risk factors can result in subclinical vascular disease. The investigators speculated that dementia and atherosclerosis may have common risk factors that affect the brain directly. When their data was adjusted for HTN, T2D, cholesterol, and smoking, the relationship between PD and dementia remained (Newman et al., 2005). These findings suggested that vascular disease increases the risk of dementia independent of glycemic status.

Because dementia appears to be heterogeneous with multiple etiologic factors, vascular risk factors such as HTN have been of interest to neuroscientists and epidemiologists. In a nine year longitudinal study conducted as part of a cohort study on

aging and dementia known as the Kungsholmen Project, a Cox proportional hazards model was used to assess PD and the risk of dementia in a cohort of over 1,000 Chinese people, aged 75 years or more (Xu, Qiu, Winblad, Fratiglioni, 2007). The participants were cognitively normal at baseline and did not have diabetes.

The investigators found that PD was associated with increased risk of dementia in and that the risk was increased in those with severe systolic hypertension (Xu et al., 2007). It is clear from this study's findings that controlling vascular risk factors is important and that HTN can change the relationship between PD and dementia. Strengths of this study are that it was large and had a long follow-up period. The primary limitation is that it has limited generalizability because of the inclusion of Chinese subjects only in their cohort.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was designed to examine intensive glucose control versus standard of care glucose control in those with T2D on occurrence of major cardiovascular events (Barzilay et al., 2013). Barzilay et al. (2013) used participant data taken from the ACCORD sub-study, Memory in Diabetes or ACCORD-MIND, which was based on the hypothesis that T2D is a risk factor for cognitive impairment. The ACCORD-MIND study had 2,977 participants with a mean age of 62 years, who were followed for 40 months. The primary aim of ACCORD-MIND was to examine whether micro-vascular disease as measured by the presence of albuminuria and reduced estimated glomerular filtration rate (eGFR) is associated with cognitive decline in participants with T2D (Barzilay et al., 2013). Participants in ACCORD-MIND underwent three neuropsychological tests: baseline, 20

months, and 40 months, which assessed information processing speed, verbal memory, and executive function (Barzilay et al., 2013). Additionally, data on albumin in the urine (albuminuria) was collected and defined as ≥30 mg albumin per gram creatinine in a spot urine sample. Albuminuria is a significant risk factor for CVD and considered a marker for macro-vascular disease development especially in those with T2D (Satchell & Tooke, 2008).

The ACCORD-MIND investigators analyzed the data using mixed-effects models to assess the association between albuminuria, eGFR, and cognitive decline (Barzilay et al., 2013). The investigators found that information processing, but not verbal memory and executive function speed, was significantly reduced in participants with T2D who had albuminuria at baseline and persistent albuminuria throughout the trial compared to those with no albuminuria (Barzilay et al., 2013). Logistic regression was used to generate an odds ratio for dementia of 1.37 (95% CI, 1.09 to 1.72) in those with progressive albuminuria. These data supported the hypothesis that markers of vascular disease may be predictors of incident dementia in those with diabetes. What remains to be answered is whether vascular disease can be a predictive marker of dementia in those with PD.

In another analysis of the ACCORD MIND sub-study, a different group of investigators sought to examine whether intensive medication therapy for HTN and lipid levels would slow the decline in cognitive function and total brain volume (TBV) in patients with T2D who were intensively managed versus those receiving standard of care management over a 40 month period (Williamson et al., 2014). Investigators of the

MIND study found that in participants with long-duration T2D and high CV event risk, intensive BP and lipid control did not significantly reduce cognitive decline over the 40 month follow-up period (Williamson et al., 2014). The conclusion from this trial was that intensive glucose, blood pressure, and lipid-lowering medication therapy is not effective for reducing cognitive decline in patients with long-duration T2D (Williamson et al., 2014). This trial provided evidence that the cognitive decline associated with T2D begins long before the diagnosis of diabetes, likely in the pre-diabetic period, and that disease prevention and early intervention strategies are needed to reduce cognitive decline in these patients.

The Diabetes Heart Study (DHS) was a large epidemiological study of White and African American families who were identified as having an excess of T2D (Bowden et al., 2010). The aim of the original DHS study was to specifically examine this cohort for evidence of subclinical cardiovascular disease using CT to measure vascular calcified plaque, ultrasound to assess carotid intima medial thickness, and ECG to examine heart rhythm intervals (Bowden et al., 210). The purpose of the DHS study was to accumulate comprehensive knowledge about people with T2D who belong to two distinct racial/ethnic groups in a population with especially high CVD mortality rates. DHS-Mind and DHS African American Mind (DHS-AA-Mind) examined CVD and cognitive function with special attention given to racial differences. The DHS-Mind study looked at baseline coronary artery calcification (CAC) and cognitive performance collected at baseline and a seven year follow-up. In this population, they found that T2D was

associated with lower performance on verbal memory, processing speed, and semantic fluency compared to those without T2D (Bowden et al., 2010).

Inflammation and Dementia

A theoretical mechanism linking dementia with PD is inflammation in the brain that results in the characteristic cognitive dysfunction (Craft, 2009; Festa et al., 2000; Ravaglia et al., 2004; Solfrizzi et al., 2011; Yaffe et al., 2003). A state of chronic inflammation in the brain is thought to cause diffuse benign plaques to develop into mature destructive beta amyloid plaques and cause NFT's (Budson & Solomon, 2011; Rubio-Perez & Morillas-Ruiz, 2012). In addition, overexpression of the cytokine interleukin-1 (IL-1) is an important factor that has been shown to cause the onset of inflammatory processes in the brain. Other important cytokines associated with neuronal inflammation are IL-6 and TNF-α.

Inflammation produces many complex reactions in the brain, including excess production of APP that result in neuronal death and brain dysfunction (Rubio-Perez & Morillas-Ruiz, 2012). Some scientists have proposed that inflammation should be added as a component in the definition of MetS because inflammation plays an important role in the pathophysiology associated with MetS (Sofrizzi et al., 2009). Chronic subclinical inflammation is part of the IR syndrome, and IR is a hallmark of PD. Specific inflammatory markers have recently been identified in subjects with PD and MetS (Craft, 2009; Festa et al., 2000; Ravaglia et al., 2004).

The aim of the Health, Aging, and Body Composition Study was to assess whether specific inflammatory markers were associated with cognitive decline in over

3,000 elderly African American and White subjects (Yaffe et al., 2003). The investigators used interleukin-6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor-alpha (TNF-α) to assess inflammation, and the Modified Mini-Mental State Examination (3MS) to assess cognitive function, assessed at baseline and in a two year follow-up.

Investigators of the Health, Aging, and Body Composition Study found that subjects with the highest inflammatory marker levels (IL-6 and CRP but not TNF-α) had 3MS scores that were similar at baseline but significantly lower at the two year follow-up with greater cognitive decline. They found no significant interaction between race and inflammatory marker levels with cognitive function (Yaffe et al., 2003). These findings supported the hypothesis that inflammation is prospectively and negatively associated with cognitive function in an elderly population as determined by IL-6 and CRP levels (Yaffe et al. 2003). Based on these findings, inflammatory markers could be used to identify those at high risk for dementia.

Using a prospective population-based design, inflammation and its effect on cognitive function were examined over a 3.5 year period as part of a sub-study of the Italian Longitudinal Study on Aging (Sofrizzi et al., 2009). The relationship between the components of the MetS, inflammation, and incident dementia was investigated in over 2,000 elderly subjects. They used the MMSE to measure cognitive changes over time and analyzed the effect of the individual components of the MetS as well as the inflammatory marker, fibrinogen. The investigators found that the risk for VaD was significantly increased in those with MetS and especially increased in those with MetS and high levels of inflammation (Sofrizzi et al., 2009). These findings are similar to those of Yaffe et al.

(2003) demonstrating that high levels of inflammation in those with MetS (PD equivalent) increases the risk of dementia.

Vascular inflammation is likely one of the underlying causes of dementia (Ravaglia et al., 2004). Using a cross-sectional design, investigators examined the association between plasma total homocysteine (tHcy) and serum C-reactive protein (sCRP) as markers of inflammation in both CVD and old-age dementia; these investigators hypothesized that low-grade vascular inflammation is the underlying cause of dementia (Ravaglia et al., 2004). The investigators found that tHcy was associated with systemic low-grade inflammation in both CVD and dementia but that the association appeared to be a specific marker of poor health rather than a specific marker of vascular inflammation (Ravaglia et al., 2004). A limitation of the study was the cross-sectional design which cannot determine a cause and effect relationship between plasma tHcy and sCRP and cardiovascular disease and dementia (Ravaglia et al., 2004).

Insulin Resistance and Dementia

PD, T2D, obesity and the MetS are all characterized by a state of IR. Insulin resistance is often concurrent with high plasma insulin levels and is characterized by tissues that are unresponsive to insulin specifically in the liver, muscle, adipose tissue, endothelium, and brain (Craft, 2009). There is strong evidence to suggest that dementia is an IR state in the brain, and IR may be a core syndrome of dementia (Baker et al., 2011; Bruehl, Sweat, Hassenstab, Polyakov, & Convit, 2010; Craft, 2009; Di Bonito et al, 2007; Sanz et al., 2012; Willette et al., 2013). IR is a complex response to excess adiposity and

is considered to be in the causal pathway for PD and vascular morbidity such as hypertension and CV disease.

Insulin resistance is a hallmark of PD and is thought to cause vascular injury and micro-vascular infarcts (Craft, 2009). In a case control study, a 56-year-old man presented with fatigue, weakness, and proteinuria. The patient had been diagnosed with impaired fasting glucose (IFG) four years prior; PD diagnosed with IFG is associated with IR. A thorough work up of the patient revealed nodular glomerulosclerosis which is a chronic complication of diabetes but not often diagnosed in PD (Bhatt, Gupta, Vibha, Sharma, & Maharjan, 2013). The investigators concluded that the morbidity associated with T2D occurs years earlier in the prodromal period of PD, when IR is present and often significant.

Additional support for the association between IR and dementia comes from the work of Willette et al. (2013) who used neuroimaging analysis techniques, voxel-based, and tensor-based morphometry to assess gray matter volume (GMV) in a cohort of 372 asymptomatic participants. GMV was indexed at baseline and four year follow-up using MRI. Participants were also assessed for APOE ϵ4 status. The investigators hypothesized that IR would be inversely associated with GMV with progressive atrophy in brain regions associated with dementia (AD) and that are sensitive to insulin-signaling fluctuations. Using HOMA-IR, the investigators determined that IR was a useful predictor of reduced GMV and brain atrophy in regions specifically affected by early AD (Willette et al., 2013). IR associated may therefore provide a mechanistic pathway from PD to the underlying morphology of AD.

In several studies, IR and IFG have been significantly associated with reduced cognitive function (CF). In a longitudinal study, investigators aimed to evaluate the interplay of IFG, IR, and hyper-homocysteinaemia (Hhcy) on CF in non-diabetic elderly subjects (Di Bonito et al., 2007). IR was defined as the upper quartile of insulin distribution. MMSE scores were used to assess CF and scores were adjusted for age and education. Homocysteine is a circulating α-amino acid; homocysteinaemia is associated with vascular inflammation and endothelial injury (Di Bonito et al., 2007). The investigators identified IFG, IR, and Hhcy as important independent markers of impaired CF in elderly subjects (Di Bonito et al., 2007). The study supported the hypothesis that metabolic derangement and inflammation play a role in impaired CF and provide a potential pathway between PD and dementia.

Additional support for the IR and dementia hypothesis came from a randomized crossover study of 23 older adults with normal CF and newly diagnosed PD. The aim of the study was to determine whether abnormal patterns in the glucose metabolic rate (CMRglu) in the brain could be detected using positron emitting tomography (PET) imaging in those with early PD (Baker et al., 2011). IR was estimated using HOMA-IR. The investigators found Alzheimer-like reductions in CMRglu in subjects with PD, concluding that metabolic defects in the brain likely occur years before the presentation of dementia (Baker et al., 2011). Insulin resistance was found to be associated with reduced CMRglu and mild cognitive impairment. The investigators suggested that IR might be a viable marker for AD risk (Baker et al., 2011).

Neuropsychological test results in subjects with IR were compared to matched controls to determine whether cognitive impairments exist in the prediabetic state (Bruehl et al., 2010). The investigators found that subjects with IR had reductions in declarative memory and executive functioning compared to subjects without IR (Bruehl et al., 2010).

The pathology of dementia is thought to begin 10 to 30 years before the appearance of clinical symptoms (Lombardo, 2012). Scientific data has supported a shared etiology hypothesis between PD and dementia with IR as a common etiologic factor between the two diseases (Talbot et al., 2012). A group of neuroscientists recently determined that the pathophysiologic characteristics of AD and T2D overlap to a large extent suggesting that these two diseases may have a common etiology (Talbot et al., 2012). The pathophysiologic characteristics of AD and PD overlap as well. For example, both AD and PD are characterized by IR, dysregulated glucose metabolism, cellular oxidative and inflammatory stress, β amyloid accumulation, and neural atrophy (Talbot et al., 2012). Determining whether there is a common etiologic factor(s) between PD and AD is important because these two diseases are epidemic, and prevention strategies and targeted drug treatments are very much needed.

In a recent study using ex vivo stimulation, Western blotting, and immunohistochemistry of tissue samples from case cohorts from the University of Pennsylvania and the Religious Orders Study, investigators tested the hypothesis that brain IR occurs in AD in the absence of T2D and peripheral IR (Talbot et al., 2012). The investigators evaluated basal and insulin-stimulated brain signaling from tissue samples from those with MCI and AD.

There were several important findings from the study by Talbot et al. (2012). The investigators determined that there is an insulin resistant state in the brain in those with AD in the absence of T2D and APOE ϵ4 allele status (Talbot et al., 2012). IR was evidenced in the hippocampal region of the brain known to be vulnerable to early and significant AD pathology (Talbot et al., 2012). Beta amyloid is the main component of amyloid plaques in the brains of subjects with AD. Levels of insulin receptor substrate (IRS-1) correlated positively with Aβ plaques and negatively with episodic and working memory even after controlling for Aβ plaques, neurofibrillary tangles, and APOE ε4 allele status (Talbot et al., 2012). Elevated nitrotyrosine levels in the brains of people with AD provided evidence of inflammatory and oxidative stress associated with IR.

The findings of Talbot et al. (2012) provided insights into IR and brain pathology in those with and without AD. The investigators identified two IRS-1 candidate biomarkers for brain IR and concluded that brain IR is an early and common feature of AD even when T2D is absent (Talbot et al., 2012). Therefore, PD, which is characterized by significant IR, may be an early predictor of AD risk and PD prevention may help reduce the brain pathology and cognitive impairment associated with AD.

The effects of IR on brain volume are not well characterized and the relationship between IR and cognitive impairment/dementia is equivocal based on disparate scientific findings. In a cross-sectional trial known as the MONA LISA study, IR, adiposity, waist circumference, and body fat levels were assessed in over 1,100 late middle-aged adults in relation to cognitive function (CF). CF was assessed using four different neuropsychological tests. Insulin resistance was estimated using HOMA-IR.

Investigators in the MONA LISA trial developed three predictive models using multiple logistic regressions to estimate the relationship between cognitive performance and metabolic markers. In one model the investigators adjusted for age, sex, education, and occupational status. In the second model they additionally adjusted for income, smoking, alcohol consumption, sedentary activity level, and psychotropic substance use. The third model included hypertension, dyslipidemia, vascular disease, C-reactive protein, and depression.

The MONA LISA investigators found that adiposity and elevated A1C were each associated with reduced cognitive function as evidenced by reduced processing speed scores (Sanz et al., 2012). Their results showed that IR within the upper quartile was associated with poor cognitive performance on the Stroop Test; however, these findings were not significant when adjusted for adiposity (Sanz et al., 2012). Excess adiposity was associated with poor cognitive performance, and an inverse relationship was found between BMI and cognitive function (Sanz et al., 2012). High A1C was associated with poor cognitive performance as assessed by the DSST.

The MONA LISA study had a large sample size, used a population-based design, and had very little missing data; however, there are inherent limitations of cross-sectional studies including lack of causal temporality. It was not possible for the investigators to determine whether cognitive impairment may have caused poor health behaviors, which resulted in greater adiposity and IR in those participants (Sanz et al., 2012).

The association between PD and cognitive decline is not entirely understood and the available data is equivocal. To investigate the relationship between FBG levels, IR,

and cognitive impairment in an elderly population, data from the PROSPER study, a large randomized placebo controlled clinical trial including participants with high risk for or pre-existing vascular disease, and the Rotterdam Study, a large prospective cohort study, were merged into one large sample of 8,447 participants (Euser et al., 2010). The aim of the combined study was to determine the association between FBG and cognitive function at baseline and longitudinally over a three to four year period. Neuropsychological tests were used to assess changes from baseline. The researchers also used HOMA-IR to assess the relationship between IR and cognitive function in the Rotterdam participants.

The investigators found that people with frank diabetes had cognitive decline at baseline, but those without diabetes did not (Euser et al., 2010). In participants without diabetes there was no significant association between FBG at baseline and changes in cognitive function when the longitudinal analyses were performed. In contrast to the findings of others, the investigators did not find a clear association between IR and cognitive decline in this cohort, suggesting that IR associated with PD may not be a risk factor for cognitive decline. The investigators concluded that there may be a threshold effect for elevated glucose values on cognitive function or that factors other than elevated glucose lead to dementia in people with frank diabetes (Euser et al., 2010).

Brain Glucose Metabolism, Brain Insulin Signaling and Dementia

Dementia is characterized by some scientists as a neuroendocrine disorder, with abnormalities in the brain described as an end-organ complication of PD and T2D (Baker et al., 2011; Craft, 2009; Steen et al., 2005). Using PET imaging, Baker et al. (2011)

determined that there is a reduction in the cerebral glucose metabolic rate in subjects with PD and IR, which is independent of age, oral glucose tolerance test results, and APOE ϵ4 allele status. This added to the strong scientific evidence that the hallmarks of PD (impaired glucose metabolism, IR, and impaired insulin signaling in the brain) are present in those with AD (Candeias et al, 2011; Craft, 2009; Holscher, 2011; Talbot et al., 2012).

There is a density of insulin receptors in the hippocampus, which is the brain region primarily involved in the accrual, management, and retention of new information (Budson & Solomon, 2011; Schiöth et al., 2012). The role of the hippocampus in learning and memory has been evidenced in rodent studies where damage to the hippocampus results in severe impairments in learning and spatial memory (Schiöth et al., 2012). In rodent studies, a decrease in insulin receptor signaling results in cognitive impairment and reduced synaptic transmission in the hippocampus (Holscher, 2011). In a cross-over study using 38 normal weight students, an eight week insulin treatment period and a word recall test, investigators were able to demonstrate that insulin action in the hippocampus enhances learning and memory processes in young healthy adults. This occurred when insulin was introduced directly into the central nervous system using an intra-nasal delivery system (Schiöth et al., 2012).

Several pathological processes have been thought to promote cognitive impairment and dementia in people with PD. There is evidence of brain IR and hyperinsulinemia in those with PD (Craft, 2009). IR results in reduced brain insulin signaling, accelerated β amyloid accumulation due to down regulation of the insulin-degrading enzyme (IDE) which facilitates clearance of β amyloid, and hyper-

phosphorylation of tau protein (Bordier, Doucet, Boudet, & Bauduceau, 2014; Craft, 2009; Holscher, 2011; Talbot et al., 2012). These morbid complications resulting from IR and hyperinsulinemia are the hallmarks of AD and provide a mechanistic pathway between PD and dementia that helps explain the pathology that results in memory loss and cognitive dysfunction.

Dementia is heterogeneous and complex and the factors that initiate the neurodegenerative processes are not precisely known. In preclinical and clinical studies, insulin has been shown to be a growth factor in the brain, neuro-protective, and associated with brain cell regeneration and proliferation (Holscher, 2011). Significant abnormalities in insulin signaling mechanisms have been demonstrated in the brains of subjects with AD. Deranged insulin signaling may be one of initiating factors that initiates the neurodegeneration (Holscher, 2011; Steen et al., 2005; Talbot et al, 2012). As de la Monte (2012) noted, the significant rise in peripheral IR secondary to obesity and PD likely plays a major role in the current dementia epidemic; however, there are multiple etiologic factors that should drive research and treatment.

Total Brain Volume, White Matter Atrophy, Cerebral Blood Flow and Dementia

Various epidemiologic and experimental studies have tried to determine when the cognitive decline of dementia begins. It is not clear whether glucose levels in the PD range initiate the pathologic processes or whether other factors are responsible such as the comorbidities of HTN and hyperlipidemia (Cherbuin, Sachdev, & Anstey, 2012; Roriz-Filho et al., 2009; Thambisetty et al., 2013). The ACCORD MIND sub-study provided evidence that in patients with long-duration T2D, white matter lesions are more

prevalent and total brain volume (TBV) and cognition are reduced especially in those with concomitant HTN and lipid abnormalities (Launer et al., 2011; Williamson et al., 2014).

In a large population-based longitudinal study known as the Framingham Offspring Study, a sub-set of participants underwent MRI and multiple cognitive tests to assess the impact of various metabolic factors (Tan et al., 2011). Linear regression was used to assess the relationship between independent variables (T2D, IR, fasting insulin, and A1C) and the outcome variables (total cerebral brain volume [TCBV], hippocampal volume, and cognitive function). In this large population-based study, characteristics of PD including metabolic dysregulation, and especially IR, were found to be strongly and negatively associated with cognitive impairment and reduced brain size (Tan et al., 2011). Based on over 65 years of data, investigators from the original Framingham Study determined that if AD could be delayed by five years, the lifetime AD risk would be cut in half, from 14% to 7% (Tan et al., 2011). Modifying dementia risk factors could delay the onset and reduce the epidemic burden of dementia, which would benefit individuals and society.

Three neuroimaging studies examined brain changes in patients with PD or high-normal blood glucose levels. One group of investigators sought to assess the association between glucose levels and brain volume in older non-diabetic, cognitively normal subjects who were enrolled in a longitudinal study on aging (Cherbuin et al., 2012). FBG was measured in relation to hippocampal and amygdalar volume over a four year period. The investigators found that high-normal and pre-diabetic glucose values were associated

with greater brain atrophy in both the hippocampal and amygdalar regions. These investigators concluded that glucose levels in the PD range are associated with brain atrophy and suggested that, due to this morbidity, a new definition for diabetes may be warranted (Cherbuin et al., 2012). Complications of diabetes, including dementia, might be prevented or delayed if diabetes was diagnosed at a lower glucose threshold, in the period currently defined as PD.

Identifying younger people with a high risk of dementia would allow health professionals to implement targeted dementia prevention strategies. In a neuroimaging sub-study of a large prospective trial known as the Baltimore Longitudinal Study of Aging, 64 cognitively normal subjects underwent PET imaging and OGTT's, with the first OGTT administered 12 years earlier (Thambisetty et al., 2013). The aim of the study was to investigate whether IGT identified in midlife is associated with longitudinal changes in regional cerebral blood flow (rCBF) (Thambisetty et al., 2013). IGT is diagnostic of PD. The investigators used an OGTT to determine IGT status which was used as a surrogate marker of early abnormalities in insulin signaling. MRI and PET scans were used to image various regions of the brain. Participants with normal glucose tolerance (NGT) and IGT (which is PD) had a series of rCBF measurements taken over an eight year period. Cognitive status was measured using the MMSE.

Investigators of the Baltimore Longitudinal Study of Aging found significant differences in rCBF in several regions of the brain between the NGT and IGT groups, with greater reductions in rCBF in the IGT group. The findings were independent of APOE ε4 status. The investigators proposed that IGT (which is PD) identified in midlife

in cognitively normal older subjects is a risk factor for development of reduced blood flow in the brain (Thambisetty et al., 2013).

Mechanistic explanations for observed changes in longitudinal studies are difficult to determine. A limitation in the Baltimore Longitudinal Study of Aging study is that it was not designed to elucidate mechanistic explanations for the observed reductions in rCBF (Thambisetty et al., 2013). The investigators suggested that the decreases in rCBF might be early disturbances and adaptive mechanisms in brain function in those with IGT (which is PD). The investigators noted that it was not clear whether these observed changes in rCBF associated with IGT are related to AD pathology such as neuritic plaques and NFT's (Thambisetty et al., 2013).

Dementia incidence increases markedly with age; therefore it is important to examine differences in dementia risk factors, and dementia prevalence and incidence in different age groups (Budson & Solomon, 2011). Older subjects with hypertension were used to assess the association between PD and T2D, and structural brain changes, metabolic brain lesions, and AD using MRI and standardized neuropsychological tests (Roriz-Filho et al., 2009). The investigators found that those with diabetes and systolic hypertension had lower Stroop Test scores with greater cognitive dysfunction in attention and executive function. They found that those subjects with AD had cortical and white matter subcortical lesions. The investigators concluded that there is a measurable association between PD, diabetes, and AD (Roriz-Filho et al., 2009).

Neurologically asymptomatic elderly subjects enrolled in the Austrian Stroke Prevention Study were followed for six years to determine the rate of brain atrophy and

impact of cerebrovascular risk factors, APOE ϵ4, and white matter hyperintensities (WMH). MRI was used to assess brain volume and WMH (Enzinger et al., 2005). Subjects were assessed for metabolic and vascular risk factors including HTN, T2D, cardiac disease, smoking and alcohol intake. The investigators measured fasting plasma glucose, A1C, total cholesterol, and triglycerides (Enzinger et al., 2005).

Results of the Austrian Stroke Prevention Study revealed that those with elevated A1C had a greater rate of brain atrophy, which was more pronounced when factors associated with MetS were also present ($p = 0.0001$). The data was suggestive of a link between MetS and late-life brain atrophy (Enzinger et al., 2005). Their multivariate analysis indicated that baseline brain parenchymal fraction, A1C, and WMH were most closely associated with brain atrophy in this elderly cohort (corrected $R^2 = 0.27$; $p = 0.0001$) (Enzinger et al., 2005).

Dementia Prediction

PD is associated with vascular pathology and vascular risk factors are associated with dementia; however, there are no good predictive models for dementia or risk scores developed based on PD status (Candeias et al., 2012; Craft, 2009). One group of investigators developed a novel approach for predicting dementia risk using a dementia risk score to identify high risk subjects. The result of this approach may be interventions to reduce lifestyle-related dementia risks and early pharmacological intervention. The investigators used data from the population-based Cardiovascular Risk Factors, Aging, and Dementia study. They examined over 1,400 middle-aged subjects at baseline for evidence of dementia and then again 20 years later (Kivipelto et al., 2005). The aim of

the study was to develop a simple risk score that would predict late-life dementia based on several mid-life vascular risk factors (Kivipelto et al., 2005).

In the Cardiovascular Risk Factors, Aging, and Dementia study, the t test and $\chi 2$ were used to detect differences in mid-life vascular risk factors between participants with and without dementia (Kivipelto et al., 2005). Two logistic regression models were developed that included different independent variables which may have included age, sex, education level, simple and readily available vascular risk factors, and APOE $\epsilon 4$ status. Based on the risk score generated, the investigators found that the dementia risk predictor tool quantitatively predicted dementia well (area under curve 0.77; 95% CI 0.71- 0.83) (Kivipelto et al., 2005). Incident dementia was 4% over the 20 year follow-up period, and the strongest predictors of future dementia were age, low educational attainment, HTN, high blood cholesterol, and obesity. Participants with the highest categorical risk score had a dementia risk of 16.4% with a sensitivity of 0.77, specificity of 0.63, and negative predictive value of 0.98 (Kivipelto et al., 2005).

The investigators concluded that the dementia risk tool is a novel approach for dementia risk prediction but noted that the tool needs further validation and improvements in order to increase its predictive value (Kivipelto et al., 2005). The study is important because it determined that vascular risk factors present in mid-life are associated with the development of dementia. The social benefit of the study is that it provides a simple tool that can help identify people at high risk for dementia based on vascular risk factors. The tool would allow physicians to assist individuals in reducing

their likelihood of developing dementia by making lifestyle changes and using appropriate pharmacological agents (Kivipelto et al., 2006).

A limitation of the Cardiovascular Risk Factors, Aging, and Dementia study is that the distribution of the vascular risk factors differentially shifted within the population over the length of the study: specifically, blood pressure, cholesterol, and obesity. Blood pressure and cholesterol have shifted downward in the population due to better treatment regimens, and obesity has shifted upward due to changes in lifestyle. The investigators did not feel that these changes greatly affect the predictive ability of the tool for future dementia risk because the relative changes were not large and the boundaries of the risk categories in their model were wide (Kivipelto et al., 2005).

To develop a 10-year predictive risk score for dementia in those with T2D investigators reviewed nearly 30,000 patient records from the Kaiser Permanente Northern California (KPNC) diabetes registry in order to identify candidate predictors of dementia (Exalto et al., 2013). There were 45 candidate predictors selected for inclusion which consisted of comorbid diseases that met prevalence and incidence criteria in the dementia group and identified using ICD-9 codes or procedural terminology codes. The T2D specific dementia risk score (DSDRS) was determined using a Cox proportional hazard model, substituting points for the β coefficient in the final prediction model, and adjusted for age, ethnicity, sex, and education (Exalto et al., 2013).

The model most strongly predictive of an individual's 10-year dementia risk included age, education, micro-vascular disease, diabetic foot, cerebrovascular disease, cardiovascular disease, acute metabolic event, and depression (Exalto et al., 2013).

Subjects with the highest sum scores were 37 times more likely to develop dementia over a 10-year period with a shorter time to dementia incidence relative to those with the lowest sum scores (Exalto et al., 2013). Diabetes duration and A1C were not included in the final model because their predictive value was lower than the end-organ complication predictors (Exalto et al, 2013).

The study by Exalto et al. (2013) included the use of a large and diverse cohort, and extensive comorbidity data analyzed over a 10-year period. A significant limitation of the study is the reliance on ICD-9 codes for dementia diagnosis, which may bias the findings by over or underreporting dementia (Exalto et al., 2013). The observational design of the study also increased selection survivor bias by including subjects at an age associated with dementia risk (Exalto et al., 2013). The investigators concluded that the DSDRS predicted absolute dementia risk over a 10-year period and could be used for vigilant monitoring of cognitive decline and identification of high risk patients (Exalto et al., 2013). An identifiable gap is the lack of predictive models for PD and dementia controlling for associated risk factors.

There are three large ongoing randomized, controlled trials being conducted in Europe using a multi-domain approach with the aim of targeting multiple vascular risk factors for dementia in older adults, primarily by promoting lifestyle changes and adherence to medical treatments (Mangialasche et al., 2012). These studies include: the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), the Multi-domain Alzheimer Preventive Trial (MAPT), and the Prevention of Dementia by Intensive Vascular Care (PreDIVA) study. These studies will provide

prospective data about population-level dementia prevention through intervention (Mangialasche et al., 2012).

There are over 86 million people in the U.S. who have PD and over 5 million with dementia (CDC, 2014). A gap in the research is a reproducible predictive model for dementia that would aid healthcare practitioners in identifying those at high risk for dementia and provide evidence for resource allocation for dementia prevention initiatives (CDC, 2014).

Summary and Conclusions

PD appears to be associated with dementia but and whether PD is clearly or independently associated with dementia. It is difficult to determine the independent effects of metabolic, inflammatory, and vascular factors related to AD as they are heterogeneous, interactive, and differently expressed over time and with treatment (Craft, 2009; Strachan, 2009).

The disturbing rise and epidemic proportion of both PD and dementia with mechanistic pathways that appear to link the two diseases poses a potential public health crisis (Exalto et al., 2013). There is accumulating scientific evidence that PD increases the risk of dementia, both AD and VaD. What is not known is what blood sugar threshold increases the risk or whether there are other factors associated with PD that modify the risk. It is important to better understand the many etiologic factors associated with dementia and identify those people at high dementia risk in order to develop preventive strategies as well as treatment regimens.

The review of the literature presented in this chapter highlighted the discrepant findings and gaps in understanding of the prodromal period of diabetes, referred to as PD, and its association with dementia. Conflicting findings of the association between PD and dementia are evident in the scientific literature, with some studies showing a significant decline in cognitive function or structural and functional changes in the brain while others do not. The following themes emerged from this literature review: (a) T2D is a risk factor for dementia, but it is unclear whether PD is an independent or predictive risk factor for dementia; (b) IR, hyperinsulinemia, vascular pathology, amyloid plaque formation, and inflammation are shared characteristics of PD and dementia; and (c) brain insulin resistance and atrophy are present in those with PD. In addition, it is clear from a review of the literature that there is a paucity of data on the relationship between PD and dementia with respect to race and SES.

Chapter 3 includes a description of the methods used in this study, which addresses a gap in the literature by providing additional data on the association between PD and dementia. The study assessed PD as an independent risk factor for dementia in people of different races and SES. The specific methods, population, sampling techniques, and proposed analyses are provided in Chapter 3. Identifying those at risk for dementia and implementing dementia reduction initiatives will be important to individuals, healthcare providers and society (CDC, 2014).

Chapter 3: Methods

Introduction

The purpose of this study was to determine whether PD is associated with dementia in elderly people and whether the association varies according to demographic and health risk factors. Chapter 3 consists of a description of the study design, variables, and research questions as well as the target population and sampling procedures. I provide the procedures for data access and data management along with validity and reliability measures, the data analysis plan, methods for data analysis, ethical procedures, and overall summary of the design and methodology.

Research Design and Approach

This study was a quantitative, case control design selected to best answer the research question. The design was appropriate for this study because case control studies select participants based on outcome (dementia/no dementia) and allow for examination of a previous exposure (PD) that may be associated with the outcome (Carlson & Morrison, 2009; Schulz & Grimes, 2002). A case control design is also appropriate for long latency diseases such as dementia and for when the case (dementia) and the exposure (PD) have already occurred (Carlson & Morrison, 2009).

Determining cause and effect is the highest level of scientific knowledge because it permits prediction and generalization (Bhopal, 2002). A large, prospective cohort design would have been a preferred design and could provide temporality; however, it would have required a large budget, more human resources, and many years to conduct. I chose the case control design because it is the most appropriate design to answer the

research question about dementia as it relates to PD exposure. Case control design has advantages in that it is an efficient design, sample sizes tend to be large, they are relatively fast, and require few resources to conduct; however, the case control design does not allow for cause and effect determinations or provide information about the temporality between exposure and outcome (Carlson & Morrison, 2009; Frankfort-Nachmias & Nachmias, 2008).

The primary research question that this study addressed was whether PD is associated with dementia risk in adults aged 65–95 years. Other questions addressed were whether other health risk factors alter the risk of dementia and whether race and SES differentially alter the risk of dementia in those with PD. Risk factors that were specifically examined include age, atherosclerosis, cerebral vascular disease, dyslipidemia, gender, HTN, obesity, race, SES, and stroke. The multivariate regression used to develop a predictive model examined whether or not these other risk factors for dementia alter the association between PD and dementia. The data were also stratified by race and SES.

The IV or exposure variable was PD and the DV or outcome variable was dementia. The relationship between the IV and DV was analyzed using logistic regression. The purpose of this study was to determine whether PD is associated with dementia in elderly people and whether the association varies according to race, SES, or other health risk factors. Odds ratios with their confidence intervals were produced for each race and SES category to assess any modification to the association between PD and dementia for each stratum. Case and exposure status was determined using the UHS

dataset and identified using ICD-9 codes, medical problem lists, laboratory values, and test results.

Population

The sampling frame for this study included the ambulatory care population of the UHS, which is located in Rochester at the center of Monroe County in western New York State. Monroe County has 19 suburban and rural towns and is a hub for a five-county metropolitan area with a population of 1,054,323 residents that share health care resources (Unity Health System, 2013). The UHS serves people from the five-county metropolitan area. In the city of Rochester, 34% of African American and 33% of Hispanic residents live in poverty in socioeconomically disadvantaged neighborhoods where health disparities are prevalent (Doherty, 2013).

Sampling and Sampling Procedures

I conducted a point in time query of the UHS data to ascertain cases of dementia present in January 2014. The computer language used to query, modify, and define the relational database was Microsoft T-SQL (Structured Query Language). T-SQL has capabilities above SQL standard which include procedural programming, local variables, support functions for string processing, data processing, and mathematics (T-SQL Tutorial, 2013). The inclusion and exclusion criteria for cases and controls in this study are listed in Table 2.

Controls were randomly selected from the source population and represent those who would have been cases had they developed dementia. Controls were randomly selected in the same time period from the source population, which is the UHS

ambulatory care dataset. The models control for the potential confounders and include variables that are associated with dementia, and noncausally or causally associated with PD. They are not thought to be intermediate variables in the causal pathway between PD and dementia. Scientific evidence has suggested that age, HTN, dyslipidemia, and obesity potentially increase the risk of both PD and dementia (Elias et al., 2012; Skolnik & Ryan, 2014; Solomon et al., 2009; Sowers, Epstein, & Frohlich, 2000).

Table 2

Inclusion and Exclusion Criteria

	Case (n = 630)	Control (n= 630)
Male or female, age $\geq$ 65 to $\leq$ 95 years	X	X
Race reported	X	X
Dementia diagnosis	X	O
May or may have pre-diabetes diagnosis	X	X
Diabetes diagnosis (T1 or T2)	O	O
Demographic and medical/laboratory data available, UHS ambulatory care dataset for point in time sample on January 15, 2014.	X	X

Mediation is thought to occur when (a) the IV significantly affects the mediator, (b) the IV significantly affects the DV in the absence of the mediator, (c) the mediator has a significant and unique effect on the DV, and (d) the effect of the IV on the DV is reduced when the mediator is added to the model (Szklo & Nieto, 2014). The data were stratified by race and SES to assess effect modification. All sampling units had the same probability of being included in the sample. This sampling strategy allowed for a more accurate estimate of the odds ratio for dementia and increased the degree to which the

study findings reflected the odds of dementia in the source population (Frankfort-Nachmias & Nachmias, 2008).

A proper sample of the data was necessary to assess whether the research hypothesis (*H*1), which states that some effect exists between the predictor variables and outcome variable, was true and accurately represented the association in the source population. An adequate sample size was needed to power the study and generate meaningful statistics with an acceptable risk of Type I error (Frankfort-Nachmias & Nachmias, 2008). The sample size needed for this study was calculated using the epidemiology statistical software *Epi Tools* using the specified parameters of 80% power and an alpha of .05 (1.96). These parameters were chosen to minimize the likelihood of a Type I error (finding a significant association when one does not exist) (Sergeant, 2014). A calculated sample size of 1,026 participants was required to adequately power this study, meaning 513 cases and 513 controls were required.

Effect size is a descriptive statistic that indicates the magnitude of a relationship within the sample data without indication of whether the relationship is a true relationship in the source population. In case control studies, effect size is a measure of the strength of the phenomena between the binary variables and estimated using an OR (Ellis, 2010; Wacholder et al., 1992). Effect sizes complement inferential statistics where significance is most often determined by *p* values or confidence intervals (Ellis, 2010).

Instrumentation and Operationalization of Constructs

Measurements by definition are descriptive but must be related to a theoretical framework in order to create construct validity**.** Construct validity is a wider

understanding of what the measurements in a study truly mean (Frankfort-Nachmias & Nachmias, 2008). Worldview is important in research and can be used to conceptualize, orient to, or develop perspective on the phenomena being studied (Reynolds, 2009). The ecosocial theory was the deductive framework for this study. Ecosocial theory is an integrative, multilevel and dynamic epidemiologic framework that links societal and biologic determinants of disease and health inequities (Krieger, 2011). The ecosocial theory considers social and ecologic causes of disease such as social inequality, discrimination, sexism, racism, stress, social injustice, and poverty. The ecosocial theory can help guide and transform epidemiologic research and practice and was tested in this study.

Threats to Validity

It is important to address the internal and external threats to validity. In case control studies, internal threats to validity are a significant concern and external threats are minimal with high generalizability (Carlson & Morrison, 2009). A significant threat to internal validity in case control studies is selection bias because it is a design that tends to produce differential sampling probabilities of the disease-exposure groups (Szklo & Nieto, 2014). Selection bias can result in a case control study when selection of cases, but not selection of controls, varies according to exposure status, violating one of the primary assumptions in case control studies. In this case, the selection of cases would not be independent of exposure and would bias the exposure odds in cases but not controls (Aschengrau & Seage, 2008; Szklo & Nieto, 2014). To minimize selection bias, cases and control subjects were selected from a well-defined reference population as previously

described. A compensating bias was not employed in this study as it may or may not have been successful in minimizing selection bias (Szklo & Nieto, 2014).

In case control studies, the assumption that cases and controls are selected from the same reference population is critical to the internal validity of the study because the control group needs to be a reasonable representative sample of the case population (Szklo & Nieto, 2014). The target population is the population the researcher intends to sample and make inferences about (Geneletti et al., 2011). A negative bias in study results can be introduced when the controls are too similar to the cases with regard to exposure status. Sampling for cases and controls in case control studies is critical to internal validity, and the study design must be very detailed on sampling procedures (Knol et al., 2008). Proper sampling procedures and case and control selection processes were implemented in the design phase to minimize selection bias and are described in detail in the Sampling and Sampling Procedures section.

Selection bias is a significant concern in case control studies regardless of whether the controls are selected from the same reference population (Szklo & Nieto, 2014). Various methods can be employed to minimize selection bias including use of a multistage approach to sampling cases and controls, using nested case-control within cohort studies, or an adjustment in the analysis phase using Bayesian poststratification (Geneletti et al., 2011).

In case control studies, study validity also pertains to issues of information bias, specifically misclassification (Szklo & Nieto, 2014). In this study, cases could have been misclassified due to the many subtypes of dementia and subjectivity inherent in making a

differential diagnosis. Cases in this study could have been misclassified if other terms were used for dementia such as MCI. Misclassification of cases was minimized in this study by restricting case definition of dementia to ICD-9 codes for dementia/unspecified (294.20), AD (331.) and VaD (290.40) (International Classification of Disease, 2012).

Misclassification of exposure (PD) is more likely to occur in case control studies. The criteria used to diagnose PD have changed in recent years and therefore may be unknown or misunderstood by clinicians. To minimize misclassification of the exposure, the design of this study included use of the ICD-9 code for *other abnormal glucose* that is not diabetes (790.29), the ADA criteria for PD diagnosis that includes IFG, OGTT results, and A1C (ICD, 2012). Misclassification can be minimized particularly by extracting IFG and A1C from the dataset because they are commonly measured and can be used to identify participants with PD. The IFG and A1C are concrete and objective measures of PD even when a formal diagnosis has not been made and entered into the patient's medical problem list.

Threats to external validity in case control studies include interaction or effect modification, which is a true effect that should be described, reported, and not controlled (Szklo & Nieto, 2014). Stratification of the data for race and SES was used to determine effect modification. In case control studies, the homogeneity of effect is assessed based on the OR. The OR for dementia was examined according to exposure to PD across race and SES categories (Szklo & Nieto, 2014).

Instrumentation and Materials

The sample for this study was drawn from the UHS ambulatory care dataset, which consists of outpatient clinics and services, and physician practices associated with a 700 bed hospital. The geographic reach of the UHS is 360 square miles, crossing the greater Rochester, New York region and six counties that consist of urban, suburban, and rural communities. The dataset was available through the UHS NextGen electronic medical record, which is an integrated electronic medical record system. The dataset included patient-specific deidentified health information and demographic data compiled from the UHS ambulatory care service departments which includes primary care, internal medicine, family medicine, the Unity Geriatric practice, Neurology and Rehabilitation practice, and the Endocrinology and Diabetes practice. There were approximately 155,000 active patient records in the UHS ambulatory care dataset and up to 10 years of data available depending on the type of data needed.

Secondary Data: Gaining Access

By design, case control studies are retrospective. Cases and controls for this study were extracted from the UHS dataset. Initially, permission to use the UHS dataset was obtained from the Chief of Endocrinology at UHS. A signed Data Use Agreement was obtained from the UHS dataset manager, and a copy is included in the Appendix. Exempt status was given by the UHS IRB because this study involved a retrospective chart review of deidentified patient records and did not require any direct participant contact. Exempt status was also granted for this study because it aligned with one of the six federally-defined exempt categories, meaning that it presented the lowest risk to subjects

(University of California MERCED, 2008). In addition, this study met the ethical standards of Walden University, and permission to conduct the study was granted by the Walden University IRB.

Data Management

The dependent or outcome variable in this study was dementia. It is very important to define what constitutes a case in order to increase the likelihood of true case ascertainment (Aschengrau & Seage, 2008). In this study, cases of incident dementia were identified within the UHS dataset using ICD-9 codes. The International Classification of Diseases (ICD) is a standard diagnostic tool for epidemiology and provides infrastructure to monitor incidence and prevalence of specific diseases (WHO, 2010). The ICD-9 codes are used in the United States for the purposes of health care coding and billing. Each code is assigned a definition for a specific disease, injury, symptom, or condition, and use of ICD-9 codes is enforced by the Centers for Medicare & Medicaid Services (WHO, 2014).

ICD-9 codes have been found to be useful for ascertaining case and exposure data and provide high positive predictive value; however, ICD-9 coding may differ by age group and type of exposure (de Achaval, Feudtner, Palla, & Suarez-Almazor, 2013). In a study of incident stroke using Medicaid health data, investigators validated the use of ICD 9 codes and found a positive predictive value (PPV) of 80% for obtaining the outcome diagnosis, especially when the diagnosis was narrowly defined (Roumie et al., 2008). To improve the validity of using ICD-9 codes for case and exposure identification, it is suggested that a hypothesis-driven strategy should be employed to avoid

misclassification (de Achaval et al., 2013). The dissertation study was hypothesis-driven and utilized the well-defined ICD-9 codes to ascertain cases and exposure.

I used the ICD-9 diagnosis codes to ascertain cases that included AD (331.0), dementia/unspecified and VaD (290-290.4, 294.1-294.21) (International Classification of Disease, 2014). Both AD and VaD were included as cases because estimates are that 10% to 15% of the population have mixed dementia with both vascular and neurodegenerative characteristics. Many patients with AD have some vascular pathology in the brain making a definitive diagnosis of dementia and the subtype challenging (Alzheimer's Society, 2013; Budson & Solomon, 2011).

The codes for AD and VaD were chosen because they are the first and second most prevalent causes of dementia, respectively (Budson & Solomon, 2011; van der Flier & Scheltens, 2005). The code for dementia/unspecified was used to identify cases because it is a broad diagnostic category for dementia and helped identify a greater number of individuals with dementia who would have been missed if the codes for AD and VaD were used exclusively.

The exposure variable in this study was PD and was identified within the UHS dataset using (a) ICD-9 code 790.29 (other abnormal glucose), (b) the terms PD, IGT, or IFG in the participant's medical problem list, (c) laboratory test results of fasting glucose >100 mg/dl and $\leq$125 mg/dl, (d) a 2-hour OGTT result between 140 mg/dL and 199 mg/dl, or (e) A1C (glycated hemoglobin) between 5.7% and 6.4%.

Demographic data was used to determine age great than or equal to 65 years and less than or equal to 95 years, gender, race and SES. The UHS dataset was adequately

large and diverse to ascertain dementia cases with and without PD and stratify by race and SES; there were 155,000 active patients in the dataset. Cases and controls were extracted from the dataset using a point in time query in January, 2014.

The control group was a sample taken from the source population that produced the cases and provided information on the disease/exposure distribution in the population. The UHS dataset served as the reference population and was the same population that produced the cases of dementia. The inclusion and exclusion criteria for cases and controls are listed in Table 2. Controls were extracted from the dataset using the same criteria as cases without the diagnosis of dementia; therefore, the odds of dementia were compared between those exposed to PD and those unexposed. Survivor sampling was employed meaning that controls were chosen after cases had been ascertained; therefore, selection of controls was a random sample taken from a pool of non-cases (Aschengrau & Seage, 2008). The controls were sampled independently of exposure and had the same probability of selection as cases (Aschengrau & Seage, 2008). The ratio of cases to controls was 1:4.

Data Analysis

The phenomena that was operationalized in this study was whether PD increases the risk of dementia, whether the odds for dementia are different when stratified by race and SES in those with and without PD, and whether other health risk factors differentially alter the association between PD and dementia. The procedures that were chosen to identify and extract cases of dementia, PD exposure, and other health risk factors associated with dementia were (a) ICD-9 codes, (b) the medical problem list, (c)

laboratory test results, and (d) other test results. Demographic data was used to extract information on age, gender, race and SES. The following research questions that this study attempted to answer were:

1. Is PD associated with dementia risk in pre-diabetic adults, age 65–95 years?

   $H_0$1: PD is not associated with the risk of dementia in pre-diabetic adults, age 65–95 years.

   Ha1: PD is positively associated with dementia risk in pre-diabetic adults, age 65–95 years.

2. Do other risk factors such as age, atherosclerosis, cerebrovascular disease, gender, hyperlipidemia, HTN, and obesity alter the association between dementia and PD in adults age 65–95?

   $H_0$2: Other risk factors do not alter the association between PD and dementia in adults, age 65–95.

   Ha2: Other risk factors alter the association between PD and dementia in adults, age 65–95.

3. Is there an interaction between certain risk factors for PD?

   H03: Race and SES do not modify the risk of dementia in adults with PD, age 65–95 years.

   Ha3: Race and SES modify the risk of dementia in adults with PD, age 65–95 years.

The potentially confounding variables are displayed in Figure 2 and include age, gender, dyslipidemia, HTN, and obesity and were selected because they are extraneous

variables that correlate either directly or inversely with both the dependent variable and the independent variables (Szklo & Nieto, 2014). Confounding variables are causally associated with the outcome, and non-causally or causally associated with the exposure, but are not intermediate variables in the causal pathway between exposure and outcome (Szklo & Nieto, 2014). Overlooking confounders could have created a spurious association between PD and dementia.

The potentially confounding variables were identified within the UHS dataset using ICD-9 codes and the medical problem list. The ICD-9 codes that were used are (a) dyslipidemia (272.0 pure hypercholesterolemia and 272.2 mixed lipidemia), (b) hypertension (401.0 – 401.9, essential hypertension: malignant, benign or unspecified), and (c) obesity (278.0 obesity unspecified and 278.01 morbid obesity). Age and gender were analyzed as confounders as well.

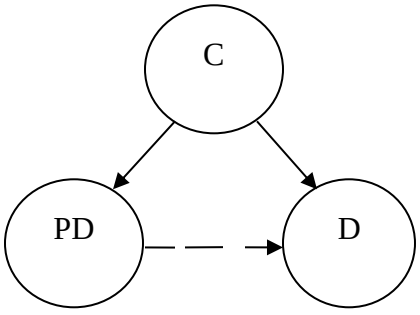

Figure 2. Directed acyclic graph (DAG) shows the relationship of the confounding variables to both the independent and dependent variable. C = Confounding variable (age, dyslipidemia, gender, HTN, obesity); PD = prediabetes (IV); D = dementia (outcome variable).

The potentially mediating variables are displayed in Figure 3 and include (a) atherosclerosis (440.9, generalized and unspecified atherosclerosis), (b) cerebrovascular disease (430–438, occlusive, thrombotic and hemorrhagic cerebral disease), and (c) stroke (431-435, intra-cerebral hemorrhage, other intra-cranial hemorrhage or occlusion with or without cerebral infarct, stenosis of pre-cerebral arteries or occlusion of cerebral arteries). In addition, race and SES were specifically analyzed as potential mediators using stratification. When an effect modifier or mediator is present, the effect of the exposure (PD) on the outcome (dementia) is altered (Szklo & Nieto, 2014).

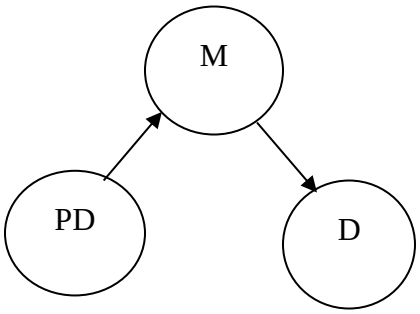

Figure 3. DAG shows the direction of the relationship between PD and dementia going through the mediating variables. M = Mediating variables (atherosclerosis, cerebrovascular disease, stroke); PD = prediabetes (IV); D = dementia (outcome variable).

Operationalization and Data Analysis Plan

I used the SPSS statistical analysis software (IBM Software, 2013) to analyze the data. The data was analyzed using logistic regression as the most appropriate way to assess the association between PD and dementia. Table 4 is a summary of the statistical tests used for the analysis in this study. The data was stratified by race and SES. Low SES served as a surrogate marker for low educational attainment and life-course exposures.

Logistic regression is a probabilistic mathematical model used to predict a binary outcome from a binary predictor, and the outcome of a categorical dependent variable based on one or more predictor variables; it is the simultaneous assessment of the relationship between several variables (X1, X2,…X10) and Y (Bhopal, 2002; Bishop, 2006). The goal of logistic regression is to explain the relationship between the independent or predictor variables and the outcome so that an outcome can be predicted for a new set of predictor variables (Bhopal, 2002).

In this study, PD, age, atherosclerosis, cerebrovascular disease, dyslipidemia, gender, HTN, obesity, race, SES, and stroke were analyzed for their association with dementia. Table 3 is a summary of the statistical tests used to address each research question.

Table 3

Statistical Test Summary

Research Question	Variables of Interest	Statistical test
1.) Is PD associated with dementia risk in prediabetic adults, age 65–95 years?	Dementia; Prediabetes	Univariate analysis: Chi-square is used to determine the unadjusted association between PD and dementia; report X2, df and *p* values. Binary logistic regression: used to determine unadjusted odds ratio for PD and dementia; report OR, 95% CI, and *p* value
2.) Do other risk factors alter the association between PD and dementia in adults, age 65–95 years?	Age, atherosclerosis, cerebral vascular disease, dyslipidemia, gender, HTN, obesity, race, and stroke	Univariate analysis: Chi Square analysis: to determine association of each risk factor with dementia; report X2, df, and *p* values. Binary logistic regression: Used to determine adjusted association between PD and dementia, adjusting for each covariates; report OR, 95% CI, and p values.
3.) Is there an interaction between certain risk factors for PD?	Dementia; Prediabetes; Race; SES	Stratified binary regression: used to determine adjusted association between PD and dementia, stratified by race and SES; report OR, 95% CI, and *p* values.

Logistic regression yields an odds ratio which represents the strength of the association between the exposure and outcome and was reported as the primary outcome measure in this study. In addition, odds ratios were generated for each race and SES category to assess any modification in the association between PD and dementia across the strata. The confidence intervals for each odds ratio were reported as well. A confidence interval that includes 1.0 is a non-statistically significant finding and indicates that the association between the exposure and outcome could be the result of chance alone (Forthofer, Lee & Hernandez, 2007).

The final aim of the statistical analysis in this study was the creation of a multivariable model that appropriately accounted for confounding. The sequential steps for model building in this study were (a) descriptive analysis, (b) univariate analyses to test unconditional associations of the variables with the outcome, (c) testing of collinearity to test associations/correlations between explanatory variables, (d) to test the association of a variable after adjusting for other variables or confounders, and (e) model diagnostics to assess whether the final model fulfilled the assumptions on which it was based (Field, 2009). Descriptive analysis provided an understanding of the distribution of data for each variable and a preliminary idea about the association of the explanatory variables with the outcome. Variables that had a high number of missing or grossly inaccurate values were identified and reported. The distribution of the explanatory variables was determined by inspecting the frequency tables.

In order to create a parsimonious model, univariate analyses were used to test the association of each of the explanatory variables, one at a time with the outcome (dementia). Those found to be statistically significant were considered the predictor variables and entered into the model using a forced entry method, starting with PD only (Field, 2009). This was a critical step in this study for determining which variables to include in the multivariable analysis, excluding the variables that did not show any significant and independent association with dementia. The results reported for the univariate analyses included chi-square, *df,* and *p* values. If the p value was <0.05, the predictor variable was included as a potential confounder in the multi-variable model.

The third step in the logistic regression model building in this study was testing for collinearity. Problems can occur in the multivariable analysis of two explanatory variables are highly correlated with each other (Field, 2009). It is beneficial to examine the explanatory variables for correlation and exclude highly correlated variables before conducting multivariable analysis. Within SPSS, a diagnostic tool known as the variance inflation factor was used to determine whether any of the predictor variables had a strong linear relationship with any other predictor (Field, 2009).

The fourth step in the logistic regression model building in this study was multivariable logistic regression analysis. Using SPSS, the Exp (B) or odds ratio (OR) and confidence interval were calculated and then reported along with the model fit statistics. Table 7 (in Chapter 4) shows all the predictor variables in the model and the OR for each. The variables that significantly predicted the outcome (dementia) were determined using the multivariable logistic regression (Field, 2009).

Model fit statistics were calculated as the last step of the logistic regression analysis. The Hosmer Lemeshow test was used to determine how well the model fit the data (Field, 2009; Hosmer & Lemeshow, 2000). The Hosmer Lemeshow test was used to indicate how the model predicted values not significantly different from what was observed; therefore, a *p* value greater than the established cutoff of 0.05 indicated a good fit of the data. The contingency table for the Hosmer Lemeshow test contains the observed and expected values for each category of the outcome variable and was used to calculate the Hosmer and Lemeshow chi-square. The p value was compared to a critical

value to decide whether to reject the null model in favor of the alternative model. If the chi-square and *df* was 1, I concluded that the model perfectly fit the data for this study.

The data used to assess the association between PD and dementia was stratified by race and SES. Logistic regression was used to determine whether the odds ratios across the stratum were equal (homogeneous) or unequal (heterogeneous) and provided an estimate of the odds ratio of the exposure variable (PD), adjusted for the strata variable (race and SES) (Szklo & Nieto, 2014). A summary of the statistical tests used to address each research question is provided in Table 3.

Human Protection and Ethics

Professional code of conduct was central to this case control study. It was critical that every measure was taken to protect the privacy of individuals and confidentiality of each participant's health and demographic data when using the UHC dataset. The study was reviewed and approved by the UHC IRB and Walden University IRB before access to, manipulation, or extraction of any data began.

There is a balance between collecting private patient information for the purpose of research and potential risks and harms that may result from infringements on personal privacy or violation of the confidentiality of data. There is a general rule that epidemiologic data should not be collected if it will not be used for creating positive social change, increasing knowledge, or improving understanding (Crosby, DiClemente & Salazar, 2006; Frankfort-Nachmias & Nachmias, 2008). The UHC dataset was de-identified to protect participant's rights to privacy; therefore, names or patient identifiers will not be visible when viewing and querying the data. No direct patient contact was

made in this study; therefore, no informed consent was required. The raw data was not shared or disseminated in any way.

Collecting the data for the study was justified because the data has provided important information on dementia risk according to race and SES in those who have PD compared with those who do not. The research helped answer an important question about whether PD should be a target for dementia prevention interventions, with special consideration for race and SES.

Summary and Transition

This study was quantitative, and a case control design was selected to best answer the research question. The purpose of the study was to determine whether PD is associated with dementia in elderly people and whether the association varies according to race, SES, or other health risk factors. The research questions that this study answered are (a) whether PD is associated with dementia risk in adults aged 65–95 years, (b) whether other risk factors alter the association between dementia than PD and (c) whether race differentially alters the risk of dementia in those with and without PD. Using a case control design, multivariable logistic regression was used to test the strength of association between PD and dementia, stratified by race and SES, and adjusted for confounding. The ecosocial theory bridged the study findings to social and economic factors that were directly measured in the study. The positive social change that may result from the study includes the potential for reduction of dementia incidence through prevention, early identification, and treatment of patients with dementia risk factors such as atherosclerosis, hypertension, low body weight, and low average SES.

Details on data collection, results of the logistic regression analysis and post hoc analyses are presented in Chapter 4.

Chapter 4: Results

Introduction

The purpose of this study was to determine whether PD is associated with dementia in elderly people and whether the association varies according to race, SES, or other health risk factors. The research questions addressed in this study were:

1. Is PD associated with dementia risk in prediabetic adults, age 65–95 years?

   $H_0$1: PD is not associated with the risk of dementia in prediabetic adults, age 65–95 years.

   H_a1: PD is positively associated with dementia risk in prediabetic adults, age 65–95 years.

2. Do other risk factors such as age, atherosclerosis, cerebral vascular disease, dyslipidemia, gender, HTN, obesity, race, SES, and stroke alter the association between dementia and PD in adults, age 65–95 years?

   $H_0$2: The aforementioned risk factors do not alter the association between PD and dementia in adults, age 65–95 years.

   H_a2: The aforementioned risk factors alter the association between PD and dementia in adults, age 65–95 years.

3. Is there an interaction between certain risk factors for PD?

   $H_0$3: Race and SES do not modify the association between PD and dementia in adults with PD, age 65–95 years.

   *H*a3: Race and SES modify the association between PD and dementia in adults with PD, age 65–95 years.

The research hypotheses were based on scientific evidence that exposure to PD increases the risk of dementia by initiating or exacerbating pathological changes in the brain through metabolic, vascular, and inflammatory pathways, although the evidence is conflicting (Craft, 2009; Duarte et al., 2013).

Chapter 4 contains the data collection procedures used in this study including the time frame of collection and any discrepancies with the prespecified methods for data collection. The results section begins with descriptive statistics of the sample population, a summary of all statistical assumptions, and an assessment of the representativeness of the sample population relative to the reference population. Chapter 4 also contains results of the univariate analyses which are reported in order to justify each covariate entered into in the multivariable logistic regression models. This chapter also includes a summary of all statistical findings related to each research question and hypothesis. Table 3, located in Chapter 3 provides a summary of the statistical tests used to address each research question.

Data Collection

The sample for this study was extracted from the UHS ambulatory care dataset using a point in time query (January 15, 2014) to obtain cases, controls, and covariates. The original dataset was compiled by UHS from data obtained from their outpatient clinics, health services, and physician practices. There are 70 locations within the UHS altogether. The geographic reach of the UHS is 360 square miles, crossing the greater Rochester, New York region, with an estimated population of 1,054,323 (U.S. Census Bureau, 2012). Figure 4 depicts the geography of the population, which is made up of six

counties (Livingston, Monroe, Ontario, Orleans, Wayne, and Yates) and includes urban, suburban, and rural communities. The racial makeup of the metropolitan statistical area (MSA) in 2010 was 83.35% White, 10.73% African American, 1.90% Asian, 0.27% Native American, 0.03% Pacific Islander, 1.99% from other races, and 1.73% from two or more races. Hispanic or Latino of any race was 4.50% of the population (U.S. Census Bureau, 2012). Median per capita income for metropolitan western New York was $42,733 in 2012 (U.S. Census Bureau).

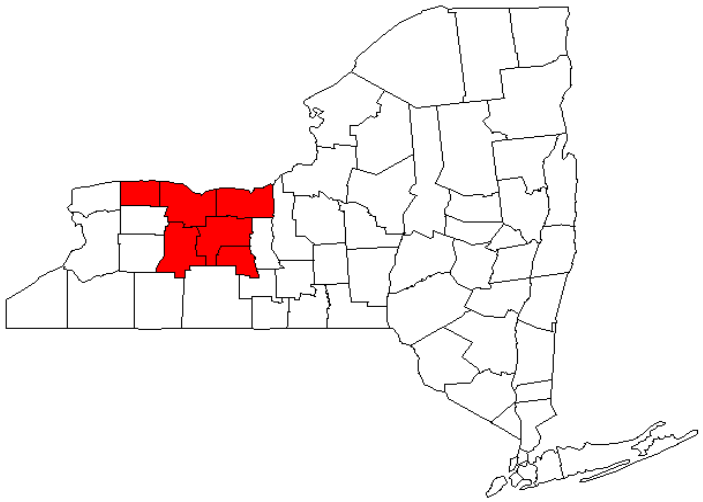

Figure 4. Map of the Rochester, NY MSA. The MSA is the geographic area of the study population, by Wikipedia, 2014. The image is licensed under the *Creative Commons Attribution-Share Alike 3.0*

Approval to conduct the study was obtained from the Walden University Institutional Review Board (IRB) and the UHS IRB. The Walden approval number for this study is 09-05-14-0302878. In addition, a signed data use agreement was obtained

from the UHS data owner. The data was collected according to the methods outlined in Chapter 3. There were no discrepancies between the actual data collection methods and the planned methods.

Preanalysis Data Cleaning

Frequency tables and visual inspection of the data were used to detect implausible, erroneous, or missing values within the dataset. The crude dataset from UHS contained 25,969 participants. Those records with a diagnosis of or laboratory values consistent with diabetes were removed. Changes to the data were documented and stored in a separate file from the crude dataset. The necessary recoding of data (e.g... race, SES, PD) and all missing data were also documented. Missing data ranged from 0% to less than 5% for any of the variables within the dataset. A review of the missing data revealed no pattern to the missing data that would result in significant bias; therefore, the analyses were run with the cells of missing data deleted.

Data Analyses

The data were analyzed using the IBM statistical analysis software SPSS version 22. The sequential steps for model building in this study were (a) descriptive analyses, (b) univariate analyses to test unconditional associations of the variables with the outcome, (c) testing of collinearity to test associations/correlations between explanatory variables, (d) multivariable logistic regression analyses to test the association of a variable after adjusting for other variables or confounders, and (e) model diagnostics to assess whether the final model fulfilled the assumptions it was based on (Field, 2009). The final sample

size was 2,731 with an *n* of 574 cases and 2,157 controls. The case to control ratio was 1:4 based on the random sampling methods described in Chapter 3.

Descriptive Statistics and Demographic Characteristics

Descriptive statistics provide an understanding of the distribution of data for each variable. Table 4 contains a summary of demographic characteristics of the study's participants. Based on the inclusion criteria, participants had to be between 65 and 95 years of age for inclusion in the study. The gender distribution was 38.3% males and 61.7% females. Mean participant age was 76.1 years—76.19 (SD7.7) and 76.13 (SD 7.9) in the case and control groups, respectively. The mean age of those with PD and without PD was 76.2 (SD 8.0) and 76.0 (SD 7.9) years, respectively. Using the UHS dataset and the sampling techniques described in Chapter 3, there were 574 cases of dementia, 2,157 controls, and a total sample of 2,731. The percentage of participants who met the diagnostic criteria for PD (detailed in Table 1, Chapter 1) was 26.6 % in the control group and 27.2% in the cases.

There were three race categories devised for this study: White, Black/African American, and Other. The Other category was created because of the low percentage of subjects in all remaining race categories. The Other category included Pacific Islanders, unreported/refused, more than one race, and American Indian/Alaska Native. The majority of the sample population was White (88.5 %) and a small minority was Black/African American (4.1%). The remaining 7.4% of the sample population was placed in the other race category. Race distribution in those with dementia (cases) and without dementia (controls) was similar, and both groups followed the distribution of the

sample population. The racial make-up of the sample population was similar to that of the total population except that the Black/African American group was underrepresented in the sample (4.1% versus 10.73%). Ethnicity was not identified in the UHS dataset.

Table 4

Demographic Characteristics of UHS Population: Point of Time Query of Cases and Controls (n=2,731)

Characteristic	Category	Dementia No (%)	Dementia Yes (%)
Prediabetes*	No	1598 (74.1)	418 (72.8)
	Yes	559 (25.9)	156 (27.2)
Age (years)	65–74.9	1063 (49.3)	264 (46.0)
	75–84.9	701 (32.5)	213 (37.1)
	85–95	393 (18.2)	97 (16.9)
Gender	Male	1045 (38.3)	215 (39.0)
	Female	1686 (61.7)	359 (61.0)
Race	White	1895 (88.1)	516 (90.1)
	Black	91 (4.2)	22 (3.8)
	Other	166 (7.7)	35 (6.1)
SES (Insurance)	Private	382 (17.7)	52 (9.1)
	Medicare	1746 (80.9)	522 (90.9)
	Medicaid	29 (1.3)	0 (0.0)
BMI category	BMI < 18	18 (0.8)	19 (3.3)
	BMI 18–24.9	488 (22.6)	209 (36.4)
	BMI 25–29.9	1016 (47.1)	275 (47.9)
	BMI > 30	635 (29.4)	71 (12.4)
Atherosclerosis	No	2100 (97.4)	545 (94.9)
	Yes	57 (2.6)	29 (5.1)
Cerebrovascular	No	2066 (95.8)	543 (94.6)
	Yes	91 (4.2)	31 (5.4)
Dyslipidemia	No	1920 (89.0)	516 (89.9)
	Yes	237 (11.0)	58 (10.1)
Hypertension	No	1133 (52.5)	231 (40.2)
	Yes	1024 (47.5)	343 (59.8)
Stroke	No	2045 (94.8)	546 (95.1)
	Yes	112 (5.2)	28 (4.9)

*No missing data

Three SES categories were devised using primary health insurance provider as a surrogate marker for SES: low SES, low/average SES, and average/above average SES. A participant was classified as low SES if the primary health insurance provider was straight Medicaid and low/average SES if the primary health insurance provider was Medicare or Medicare/Medicaid. A participant was classified as average/above average SES if the primary insurance provider was private. More participants were average/above average SES in the controls compared to the cases. In those with dementia (cases), 90.9% of participants were low/average SES compared to 80.9% in those without dementia (controls).

The mean BMI of the total sample population was 28.6 kg/m^2 with 1.4% underweight (BMI < 18), 25.5% normal weight (BMI 18–24.9), 47.3% overweight (BMI 25–29.9), and 25.9% obese (BMI $\geq$ 30). There was a greater proportion of participants who were underweight (BMI < 18) in the cases compared to controls (3.3% versus .8%) and a smaller proportion of participants who were obese (BMI > 30) in cases compared to controls (12.4% versus 29.4%).

There were differences between cases and controls in the proportion of subjects with the vascular risk factors of HTN and atherosclerosis. There was a greater proportion of HTN found among cases and controls (59.8% versus 47.5%). Three percent of the overall sample participants had atherosclerosis; however, 2.6% of controls and 5.1% of cases had atherosclerosis. There were very small differences between cases and controls for the other health risk factors including CeVD, hypercholesterolemia, and stroke.

Chi square univariate analyses were done to test for association between PD and dementia, and all the potential covariates with dementia and PD, respectively (Tables 5 and 6).

Table 5

Chi Square Analysis of Covariates and Dementia in the UHS Sample Population of Elderly Adults

	X^2	df	Sign
Prediabetes	0.374	1	0.541
Age	4.328	2	0.115
Atherosclerosis	8.632	1	0.003
BMI	105.435	3	< 0.001*
Cerebrovascular Dse	1.484	1	0.223
Dyslipidemia	0.367	1	0.545
Gender	0.564	1	0.453
HTN	27.359	1	< 0.001*
Obesity	68.914	1	< 0.001*
PD	0.374	1	0.541
Race	1.950	2	0.377
Race White	0.041	1	0.84
Race Black/AA	1.435	1	0.231
Race Other	2.476	1	0.116
SES (insurance)	34.519	2	< 0.001*
Stroke	0.092	1	0.762

Note. * Sig. level $\leq$ 0.05. Chi square analysis used to determine association between each predictor and dementia, with accompanying *p* values

Table 6

Chi Square Analysis of Covariates and Prediabetes in the UHS Sample Population of Elderly Adults

	X^2	df	p-value
Age	0.218	2	0.897
Atherosclerosis	13.429	1	< 0.001*
BMI	276.6117	3	< 0.001*
Cerebrovascular Dse	.000	1	0.985
Dyslipidemia	223.278	1	< 0.001*
Gender	24.566	1	< 0.001*
Hypertension	1428.537	1	< 0.001*
Race	110.741	2	< 0.001*
SES (insurance)	4.72	2	0.094
Stroke	2.928	1	0.087

Note. * Significance level ≤0.05. Chi square analysis used to determine association between each predictor and dementia, with accompanying *p* values.

Research Questions and Hypotheses

Research Question 1

Is PD associated with dementia in prediabetic adults, age 65–95 years?

$H_0$1: PD is not associated with dementia in prediabetic adults, age 65–95 years.

H_a1: PD is positively associated with dementia in prediabetic adults, age 65–95 years.

The chi square statistic (X^2) was used in this study to address Research Question 1 and analyze whether the two categorical variables, dementia and PD, were associated with each other, to test the null hypothesis of no association. Assumptions for chi square included: (a) the DV is measured on a dichotomous scale; (b) there is one or more IV, either continuous or categorical; (c) there is independence of observations meaning that the DV has mutually exclusive and exhaustive categories; (d) there is a linear relationship

between any of the continuous IVs and the logit transformation of the DV; and (e) no data point is zero (Field, 2009).

Results of the chi square analysis for association between PD and dementia as well as other risk factors are presented in Table 5. There was no significant association found between dementia and PD; the X^2 (1) =.374, p = .541. Additionally binary regression was conducted to determine the unadjusted odds of dementia based on exposure to PD. The unadjusted odds ratio (Table 7) indicated that PD is not associated with dementia; there was no association found between dementia and exposure to PD in adults aged 65–95 years (OR 1.06, 95%; CI= 0.867–1.313; p = 0.541); therefore, there was failure to reject the null hypothesis for Research Question 1.

Table 7

Unadjusted Odds Ratio for Prediabetes and Dementia

	B	SE	Wald	df	p-value	Odds Ratio	95% Cl for Exp(B)
Prediabetes	.065	.106	.374	1	.541	1.067	.867 - 1.313

Note. Significance level ≤0.05 ORs and 95% CI obtained using logistic regression relating each predictor variable to dementia.

Research Question 2

Do other risk factors such as age, atherosclerosis, cerebral vascular disease, dyslipidemia, gender, HTN, obesity, race, SES, and stroke alter the association between dementia and PD in adults, age 65–95 years?

$H_0$2: The aforementioned risk factors are not confounders of the association between PD and dementia in adults, age 65–95 years.

H_a2: Other risk factors are confounders of the association between PD and dementia in adults, age 65–95 years.

Chi square and multivariable logistic regression analyses were conducted to address the second research question, and test the null hypothesis. Chi square analyses were done to assess the association between PD and dementia (Table 5); PD with each demographic characteristic and health risk factor (Table 6); and dementia with each demographic and health risk factor (Table 5). Based on the chi square analyses, the covariates were found to have a significant association with dementia included atherosclerosis, BMI, HTN, SES, and obesity. The covariates that were found to have a significant association with PD included HTN, hypercholesterolemia, stroke, metformin use, race, SES, obesity, and metabolic syndrome.

Multivariable logistic regression (MLR) was used to identify the risk factors that are associated with dementia and contributed to a model used to predict the outcome variable, dementia (Table 8). Assumptions of MLR included (a) linearity between any continuous predictor variable and the logit of the outcome variable, (b) independence of errors, and (c) no multicollinearity between any of the variables (Field, 2009).

The Hosmer Lemeshow test was used to assess how well the model fit the data. Results in this study were X^2 (8) = 5.924, p = .656, indicating a good fit of the data and that the model predicted values not significantly different from what was observed (Field, 2009).

In case control studies, effect size is a measure of the strength of the phenomena between the binary variables and estimated using an OR (Ellis, 2010; Wacholder et al., 1992).

Table 8

Multivariable Logistic Regression Analysis: Predictors of Dementia in Elderly Adults in the UHS Sample Population (n= 2731)

	B	S.E.	Wald	df	Sig.	Exp(B)	95% CI
Prediabetes	-0.016	0.115	0.019	1	0.890	0.984	.786–1.233
Age 65-74.9 Ref.			5.431	2	0.066		1.025–2.843
Age 75-84.9	0.237	0.108	4.800	1	0.028	1.267	1.025–1.566*
Age 85-95	0.000	0.137	0.000	1	0.998	1.000	.764–1.309
Race (African American)	-0.036	0.094	0.145	1	0.703	0.965	.803–1.160
Constant	-1.869	0.227	67.631	1	0.000	0.154	
SES (Medicare)	0.732	0.160	20.948	1	< 0.001	2.079	1.519–2.843*
Atherosclerosis	0.591	0.247	5.702	1	0.017	1.806	1.112–2.933*
BMI Reference			92.463	3	0.000		
BMI (<18)	0.987	0.348	8.030	1	0.005	2.684	1.356–5.313*
BMI (25-29.9)	-0.329	0.111	8.829	1	0.003	0.719	.579–.894*
BMI (>30)	-1.335	0.153	76.079	1	< 0.001	0.263	.195–.355*
Dyslipidemia	-0.211	0.164	1.663	1	0.197	0.810	.587–1.116
HTN	0.535	0.106	25.549	1	< 0.001	1.707	1.387–2.100*
Hypercholesterol	-0.211	0.164	1.663	1	0.197	0.810	.587–1.116

Note. * Significance level ≤0.05 Multivariable logistic regression was used to determine the strength of association between dementia and each variable and the contribution to the model.

As depicted in Table 8, the logistic coefficient (B) is the expected amount of change in the logit (outcome) for each one unit change in the predictor when all other predictors are held constant (Field, 2009). The closer B is to zero, the lower its predictive value. The Wald statistic has a chi square distribution and an associated *p* value and is used to evaluate whether the logistic coefficient is different than zero. The OR represented the association between dementia and each predictor. Predictors which

increase, have no effect, or decrease the logit (outcome) will have an OR greater than 1.0, 1.0, or less than 1.0, respectively (Field, 2009).

Prediabetes. In the chi-square analysis, PD was not associated with dementia (X^2 (1) = .374, p =.541). In the MLR, the results revealed that PD was not associated with dementia (OR .984, 95% CI=.786-1.233, p = 0.890). None of the risk factors selected a priori as potentially changing the association between PD and dementia based on the dementia literature were found to alter the association between PD and dementia.

Age. In the chi-square analysis, linear age was not associated with dementia (X^2 (2) = 4.328, p =.115) or with PD (X^2 (2) = 2.160, p =.340). When age category was analyzed in the MLR, the results revealed that age did not change the association between PD and dementia; however, a significant and independent association between age category (75–84.9 years) and dementia was found and age (75–84.9) contributed significantly to the model (OR 1.267, 95% CI=1.025 - 1.566, p = 0.028). Age was categorized by decade because dementia risk increases according to advanced age and is most often reported by decade.

Gender. In the chi-square analysis, gender was not associated with dementia (X^2 (1) = .564, p =.453) or with PD (X^2 (1) = 1.665, p =.197). Gender was initially entered into the MLR analysis but because it did not change the OR by at least 10%, it was not retained in the final model.

Race. In the chi-square analysis, race was not associated with dementia (X^2 (2) = 1.950, p =.377) but was associated with PD (X^2 (2) = 14.600, p =.001). Results of the MLR revealed that race did not change the association between PD and dementia and

there was a non-significant association between race and dementia (OR .965, 95% CI=.803-1.160, p = 0.703).

SES. In the chi-square analysis SES was associated with dementia (X^2 (2) = 34.519, p < 0.001) and PD (X^2 (2) = 8.113, p =.017). In the MLR, the results revealed that SES did not change the association between PD and dementia; however, there was a significant and independent association between SES (insurance) and dementia (OR 2.079, 95% CI = 1.519 - 2.843, p = .000), and SES (insurance) contributed significantly to the model.

Atherosclerosis. In the chi-square analysis, atherosclerosis was associated with dementia (X^2 (1) = 8.632, p =.003) but not with PD (X^2 (1) = 1.869, p =.172). In the MLR, the results revealed that atherosclerosis did not change the association between PD and dementia, but there was a significant and independent association between atherosclerosis and dementia (OR 1.806, 95% CI=1.112-2.933, p = 0.017), and atherosclerosis contributed significantly to the model.

BMI. In the chi-square analysis, obesity alone (BMI $\geq$ 30) was associated with dementia (X^2 (1) = 68.914, p =.000) and PD (X^2 (1) = 36.976, p =.000). In the MLR, BMI was categorized according to the defined CDC (2102) BMI categories. The results revealed that BMI did not alter the association between PD and dementia; however, a BMI <18 (underweight) was found to be significantly and independently associated with dementia (OR 2.684, 95% CI=1.356-5.313, p = 0.005), and BMI < 18 contributed significantly to the model. A BMI $\geq$ 25-29.9 (overweight), and a BMI $\geq$ 30 (obesity) were both statistically significantly but weakly and negatively associated with dementia

(OR .719, 95% CI=.579-.894, p=.003) and (OR .263, CI=.195-.355, p=.000), respectively.

Cerebrovascular disease. In the chi-square analysis, CeVD was not associated with dementia (X^2 (1) = 1.484, p =.223) or with PD (X^2 (1) = .000, p =.990). CeVD was initially entered into the MLR analysis but because it did not change the OR by at least 10% it was not retained in the final model.

Dyslipidemia. In the chi-square analysis, hypercholesterolemia was not associated with dementia (X^2 (1) = .367, p =.545) but was associated with PD (X^2 (1) = 34.302, p <0.001). In the MLR, the results revealed that dyslipidemia did not change the association between PD and dementia, and there was a non-significant association between dyslipidemia and dementia (OR .81, 95% CI=.587-1.116, p = 0.197).

Hypertension. In the chi-square analysis, HTN was associated with dementia (X^2 (1) = 27.359, p = .000) and PD (X^2 (1) = 224.483, p =.000). In the MLR, the results revealed that HTN did not change the association between PD and dementia; however, there was a significant and independent association between HTN and dementia (OR 1.707, 95% CI = 1.387 – 2.100, p = 0.000), and HTN contributed significantly to the model.

Stroke. In the chi-square analysis, stroke was not associated with dementia (X^2(1) =.092, p=.762) but was associated with PD (X^2 (1) =5.939, p=.015). Stroke was initially entered into the MLR analysis but because it did not change the OR by at least 10%, it was not retained in the final model.

Results of the MLR were used to answer Research Question 2 (do other risk factors such as age, atherosclerosis, cerebral vascular disease, dyslipidemia, gender, HTN, obesity, race, SES, and stroke alter the association between PD and dementia adults, age 65–95 years?). The association between PD and dementia did not change significantly when controlling for the pre-specified risk factors by adding them to the model. The risk factors that were significantly and independently associated with dementia in this sample population were (a) age category (75-84.9 years), (b) BMI < 18 (underweight), (c) atherosclerosis, (d) HTN and (e) SES (Medicare insurance). There was failure to reject the null hypothesis for Research Question 2; however other risk factors were identified as significantly and independently associated with dementia in adults, age 65–95 years.

Research Question 3

Is there an interaction between certain risk factors for PD?

$H_0$3: Race and SES do not modify the association between PD and dementia in adults with PD, age 65–95 years.

*H*a3: Race and SES modify the association between PD and dementia in adults with PD, age 65–95 years.

Comparing the crude measure of association and the adjusted OR for dementia in those with and without PD provides information on effect modification, and this procedure was used to test the null hypothesis of Research Question 3. Chi square analysis showed no significant unadjusted association between race and dementia or SES and dementia. The adjusted OR's for race and SES were also non-significant (Tables 9

and 10). The unadjusted and adjusted associations for race and SES with dementia were not different indicating there was no effect modification; therefore, there was failure to reject the null hypothesis for Research Question 3.

When no effect modification is present, stratum-specific estimated effects can be pooled to form a summary estimate of effect across strata. This summary estimate represents an adjusted OR, which is an OR adjusted for confounding (Tables 11 and 12). The stratified analyses using the MH test were used to determine whether the effect of PD exposure on dementia varied according to race and SES subgroup. Assumptions of the Mantel Haenszel test included: (a) observations are independent from each other (each observation is unique and randomly selected), and (b) all observations are identically distributed (Field, 2009). The MH null hypothesis was that there is no consistent difference in the distribution of dementia cases across the SES strata (Tables 9, 10, 11, and 12).

The OR for dementia was homogeneous across the strata for SES (insurance) (Table 9); however, the findings were non-significant. The MH OR was 1.020, 95% CI .846 – 1.23, p = .835 (Table 10) meaning that the odds of dementia in those with PD were not altered when stratified by SES.

The OR's for dementia were not homogeneous across the strata for race; however, the results were non-significant for each race (Table 11). The MH OR was 1.025, 95% CI =.850–1.236, p=.798 meaning that the odds of dementia in those with PD were not altered when stratified by race.

Table 9

Chi Square Analysis and Risk Estimate for Dementia by SES Strata in the UHS Sample Population of Elderly Adults

	X^2	df	Sig.	OR	95% CI
Private	0.088	1	0.766	1.098	.592–2.039
Medicare	0.016	1	0.900	1.013	.832–1.233
Medicaid	-	-	-	-	-

Note. Chi Square analysis was conducted producing the OR with corresponding 95% CI. Significance level ≤ 0.05.

Table 10

Mantel Haenszel Test of Independence and Pooled Odds Ratio for SES in the UHS Sample Population of Elderly Adults

	X^2	df	Sig.	OR estimate	95% CI	Sig.
Mantel Haenszel	0.026	1	0.872	1.02	.846-1.23	0.835

Note. Mantel Haenszel analysis was conducted producing the OR with corresponding 95% CI. Significance level ≤0.05

Table 11

Chi Square Analysis and Risk Estimate for Dementia by Race in the UHS Sample Population of Elderly Adults

	X^2	df	Sig.	OR	95% CI
White	0.041	1	0.84	1.02	.839 -1.241
African American	1.435	1	0.231	0.517	.173 - 1.549
Other	2.476	1	0.116	1.891	.844 - 4.237

Note. Chi Square was conducted, producing the OR with 95% CI. Significance level ≤0.05

Table 12

Mantel Haenszel Test of Independence and Pooled Odds Ratio for Race in the UHS Sample Population of Elderly Adults

	X^2	df	Sig.	OR estimate	95% CI	Sig.
Mantel Haenszel	0.043	1	0.835	1.025	.85 - 1.236	0.798

Note. Chi Square analysis was conducted producing the OR with corresponding 95% CI. Significance level ≤0.05

The MH OR for both SES and race were similar to the unadjusted and adjusted OR for dementia in those with PD; all three odds ratios were non-significant. Stratifying by both race and SES did not alter the association between PD and dementia.

Model Summary

The Omnibus test provides information on how well the set of predictors in the model relate to the outcome (dementia). In this study, the Omnibus test result was X^2 (11) = 177.936, $p < .001$ indicating that the set of predictors were significantly related to dementia. The Classification Table provides information on how well the predictors classify participants with dementia (percent correct). The overall classification rate for the final model in this study was 79.3%, which was statistically significant based on the Omnibus test result.

Summary and Transition

There was failure to reject the null hypotheses for Research Questions 1, 2, and 3. Importantly, what emerged from this study were independent risk factors significantly

associated with dementia which included age category (75–84.9 years), atherosclerosis, BMI < 18 (underweight), HTN, and low/average SES (Medicare primary insurance).

In response to Research Question 1, the unadjusted odds of dementia were no greater in those with PD relative to those without PD in this sample population of 65–95 year old ambulatory adults. There was failure to reject the null hypothesis; there is no association between PD and dementia in adults 65–95 years old.

In response to Research Question 2, the adjusted odds of dementia were no greater in those with PD relative to those without PD in this sample population of 65–95 year old ambulatory adults; other risk factors did not alter the association between PD and dementia. There was failure to reject the null hypothesis; other risk factors do not alter the association between PD and dementia. Other risk factors were found to be independently and significantly associated with dementia, however, and contributed significantly to the model for predicting dementia. These risk factors include age category (75–84.9) (OR 1.267, 95% CI=1.025 - 1.566, p = 0.028); atherosclerosis (OR 1.806, 95% CI = 1.112-2.933, p = .017); BMI <18 (underweight) (OR 2.684, 95% CI=1.356-5.313, p = 0.005); HTN (OR .81, 95% CI=.587-1.116, p = 0.197); and low/average SES (OR 2.079, 95% CI=1.519-2.843, p = .000). The variables negatively and weakly associated with dementia were BMI $\geq$ 25-29.9 (overweight), a BMI $\geq$ 30 (obesity) (OR .719, 95% CI=.579-.894, p=.003), and (OR .263, CI=.195-.355, p=.000), respectively.

In response to Research Question 3, the effect of PD on dementia was not modified by race and SES subgroups when the data were stratified using the MH test.

There was failure to reject the null hypothesis; race and SES do not modify the association between PD and dementia in 6595 year old ambulatory adults.

Chapter 5 includes interpretation and discussion of findings from this study, a discussion of the limitations of this study, recommendations for further research, and the implications for social change based on the study findings.

Chapter 5: Discussion, Conclusions, and Recommendations

Introduction

The purpose of this study was to determine whether PD is associated with dementia in ambulatory adults aged 65–95 years and whether the association varies according to race, SES, or other health risk factors. This study was a quantitative, case control design that examined the relationship between the variables. The intent of this study was to provide scientific evidence of those at high risk for dementia and support the allocation of resources for targeted dementia prevention interventions. Dementia risk reduction interventions have the potential to reduce incident dementia and related morbidity, mortality, and healthcare costs.

The questions addressed in this study were: (a) Is PD associated with dementia in prediabetic adults, age 65–95 years, (b) Do other risk factors such as age, atherosclerosis, cerebral vascular disease, dyslipidemia, gender, HTN, obesity, race, SES, and stroke alter the association between PD and dementia in prediabetic adults, age 65–95 years?, and (d) Is the association between PD and dementia differentially altered when stratified by race and SES? The sampling frame for this study was the ambulatory care population of the UHS in Rochester, New York. The UHS dataset was randomly sampled for adults 65–95 years of age with dementia (cases). The IV was PD, and the DV was dementia. Chapter 5 contains an interpretation of the study findings, limitations of the study, recommendations for future research, the implications for social change, and conclusions.

Interpretation of Findings

Data in the literature regarding the relationship between PD and dementia are mixed. This study sought to assess the association between PD and dementia to address a gap in knowledge and contribute to the scientific literature. The final aim of the statistical analysis in this study was the creation of a multivariable model that appropriately accounted for confounding. There was failure to reject the null hypothesis for Research Questions 1, 2, and 3, and Chapter 5 includes a discussion of why these findings may have occurred, the significance and implications of these findings, and the potential for future research.

Research Question 1

Is PD associated with dementia risk in prediabetic adults, age 65–95 years?

The findings from this study for the primary research question did not support a rejection of the null hypothesis; there was no association found between PD and dementia in elderly adults in this sample population (OR 1.067; 95% CI = .867–1.313; p = .541). The findings of the unadjusted OR from this study indicating that PD is not associated with dementia, and these findings support those of Christman et al. (2012), Fuh, Wang, Hwu, and Lu (2007), Rouch et al. (2012), and others but are in contrast to the findings of Craft et al. (2009), Duarte et al. (2013), Kloppenborg et al., (2008), Strachan (2010), Williamson et al. (2013), and others.

Randomized controlled trials that have examined the effect of PD on dementia incidence and found no association are lacking. There are several studies that have examined various measures of PD and cognitive decline or cognitive performance and

found no association. Rouch et al. (2012) conducted the PROOF study (prognostic indicator of cardiovascular and cerebrovascular events), a 2-year study of community dwellers aged 65 years or older without dementia at baseline that included an examination of memory, attention, and executive performance; the investigators did not find a relationship between PD and cognitive decline but found a significant association between T2D and cognitive decline and executive function. The differences between this study and that of Rouch et al. (2012) were that they used a population-based cohort design rather than a case control design, defined PD using fasting glucose only, and the outcome was cognitive decline and not dementia.

Using a matched case-control study design, Fuh et al. (2007) found no association between glucose tolerance status and cognitive performance in a population-based cohort of Taiwanese middle-aged women. The difference between this study and that of Fuh et al. (2007) was that they examined a cohort of middle aged and not elderly subjects; they also studied the range of glucose tolerance (normal, PD, and T2D) and administered various cognitive tests to measure cognitive performance. Fuh et al. (2007) did not examine dementia as an outcome and used a younger cohort to examine cognitive function in relation to glucose status.

Christman et al. (2012) used a large prospective study design entitled the Atherosclerosis Risk in Communities study (ARIC) and did not find evidence that PD increased the risk of dementia. Unlike the case control design used in the dissertation study, these investigators studied people with and without diabetes and examined the spectrum of A1C (normal, PD, and overt diabetes) along with three measures of

cognition over a six year period (Christman et al., 2012). Christman et al. (2012) found that A1Cs in the prediabetic range did not have predictive power for dementia, but A1Cs in the diabetic range did (Christman et al., 2012). This is consistent with the findings of the dissertation study, which did not find an association between PD and dementia, although the study design of Christman et al. (2012) was longitudinal and used only A1C as a measure of PD status.

The studies that have found an association between PD and dementia were generally prospective, longitudinal studies with long duration follow-up (Ohara et al., 2011; Ravona Springera et al., 2012; Yaffe et al., 2006). Yaffe et al. (2006) used a 4-year longitudinal study design and found that for every 1% increase in A1C within the prediabetic range, there was an age-adjusted 50% increased risk for MCI. Another group of investigators did a 15-year follow-up study and found evidence of cognitive decline in nondiabetic, nondemented elderly subjects when A1C increased from the normal range into the PD range (Ravona Springera et al., 2012).

There is strong scientific evidence that dementia is associated with and may be an end-organ disease of T2D (ADI, 2014; Steen et al., 2005). Additionally, diabetes across the life course has a possible causal association with dementia that is mechanistically plausible and strongly associated (ADI, 2014); therefore, there remains great concern for the 86 million Americans who have PD because of the high conversion rate to T2D, placing them at increased risk for dementia (ADI, 2014; Strachan, 2010).

This study did not find an association between PD and dementia, which may be due to several factors. The criteria used to capture those with PD were consistent with the

ADA diagnostic criteria, and there were no missing data; therefore, misclassification of the exposure does not seem likely. Although PD is the prodromal period that precedes T2D, it is plausible that the area under the curve for PD exposure was insufficient to produce a consistent association with dementia. A prospective longitudinal study of many-year duration may be a better study design for assessing dementia incidence in those exposed to PD. This is because the severity of PD most often increases over time, producing a greater area under the curve for PD exposure.

Research Question 2

Do other risk factors such as age, atherosclerosis, cerebral vascular disease, dyslipidemia, gender, HTN, obesity, race, and SES alter the association between PD and dementia in adults, age 65–95 years?

Interpretation of results for Research Question 2 is presented by variable, starting with the demographic variables and continuing with the health risk factor variables. There was no evidence of collinearity in this study between any of the covariates as the variance inflation factor for each variable was at or around 1; therefore, there did not appear to be any confounding based on strong associations between any of the covariates.

Age. Mean age of the sample population was 76.1 years. Age did not change the association between PD and dementia; however, a significant association between age category (75–84.9 years) and dementia was found. Using age category (65–74.9) as the reference, the risk of dementia was higher as age increased to age category (75–84.9) but did not remain significantly associated with dementia when age increased to age category (85–95). This is not fully consistent with the literature which shows that the incidence of

dementia is linearly related to age, doubling approximately every five years between the ages of 65 and 85 years and increases to 50% in adults age 90 or above (Budson & Solomon, 2011; Peters et al., 2008; van der Flier, 2005). Approximately 18% of the sample population and 17% of those with dementia were in the 85–95 years old age group; therefore, there was adequate power to evaluate age and dementia risk.

Gender. Gender was not found to alter the association between PD and dementia and was not associated with dementia. This is consistent with the finding of Ruitenberg, Ott, van Swieten, Hofman, and Breteler (2001) who found no gender differences in the incidence of dementia (RR 1.00; 95% CI: 0.80–1.24); however, it is inconsistent with what is reported by the Alzheimer's Association (2014). They reported that the estimated lifetime risk of developing AD at age 65 is 1 in 6 and nearly 1 in 11 for women and men, respectively. It is speculated that longer life expectancy in women plays a role in the increased risk.

There was an imbalance of females to males in the sample population; the gender distribution was 39.1% males and 60.9% females. This is not an unusual finding for a sample of adults over the age of 65 years. In the past 50 years, the sex ratio for people aged 65 years and above changed from 90 men per 100 women to 72 men per 100 women. For people aged 85 years and over, the ratio has changed from 70 men per 100 women to 46 men per 100 women (CDC, 2013). The dataset for the dissertation study was compiled from the UHS ambulatory care population in those between the ages of 65 and 95 years. There is also evidence that women seek health care more than men do;

therefore, the imbalance can be explained by these facts especially in a nonurgent ambulatory care setting.

Race. Race was not found to be significantly associated with dementia in any of the analyses in this study including the chi square analysis, the MLR, and the stratified analysis using the MH test. This is in contrast to other reports in the literature suggesting increased dementia risk, both AD and VaD in African Americans (Froehlich, Borgardus, & Inouye, 2001). The finding in the dissertation study of no association between race and dementia, specifically Whites and African Americans, but a significant association between SES and dementia, should be considered within the context of the findings presented at the 2013 Alzheimer's Association International Conference (AAIC, 2013). Yaffe et al. (2012) reported that African Americans were 1.5 times more likely to develop dementia than Whites; however, the finding was not statistically significant after adjusting for several SES factors. Yaffe et al. concluded that the excess risk for dementia in African American elderly people may be related to SES rather than genetics (AAIC, 2013).

The racial makeup of the Rochester metropolitan statistical area, (MSA) from which the UHS dataset is compiled, is 83.35% White, 10.73% African American, 1.90% Asian, 0.27% Native American, 0.03% Pacific Islander, 1.99% from other races, and 1.73% from two or more races. Hispanic or Latino of any race was 4.50% of the population (U.S. Census Bureau, 2012). The sample population for this study was somewhat similar to the MSA population and comprised of White (88.8 %), African American (4.1%), and Other (5.9%); however, there was an overrepresentation of White

and an underrepresentation of African American participants. This disparity in the sample population may be due to the difference between Whites and African American in healthcare seeking behavior in an ambulatory care setting (IOM, 2012). African American's may be more likely than Whites to delay seeking healthcare as a result of cultural barriers, mistrust, misunderstanding of healthcare instructions, poor interactions with and lack of knowledge about health care systems, and inadequate access to private physician offices and clinics (IOM, 2012).

SES. In the chi-square analysis, SES was found to be associated with dementia. In the MLR, SES did not change the association between PD and dementia; however, there was a significant association between SES and dementia, and SES contributed significantly to the predictive model. The participant's primary insurance provider was used as the surrogate for SES. The median income of Medicare beneficiaries across the United States in 2013 was $22,502 compared with the median income among those with private insurance, which was $41,086 **(**Bernard, Banthin & Encinosa**,** 2009; Kaiser Family Foundation, 2013). These statistics help justify the use of the health insurance provider as a surrogate for SES. Low SES is associated with low educational attainment, and according to the World Alzheimer's Report 2014, low education in early life is one of the strongest possible causal factors for dementia (ADI, 2014). These facts may help to explain the statistically significant association between low average SES (Medicare insurance) and dementia found in this study.

Atherosclerosis. In the chi-square analysis, atherosclerosis was associated with dementia (X^2 (1) = 8.632, p =.003) but not with PD (X^2 (1) = 1.869, p =.172). In the MLR,

the results revealed that atherosclerosis did not change the association between PD and dementia, but there was a significant and independent association between atherosclerosis and dementia (OR 1.806, 95% CI=1.112, $p = 0.017$), and atherosclerosis contributed significantly to the model. Vascular risk factors including HTN, coronary vessel disease. and atherosclerosis has been implicated in the development of dementia (Solomon et al., 2009). Brain damage associated with AD includes ischemia, which may be caused by cerebral amyloid deposits, cerebral atherosclerosis, and small vessel disease. The findings of the dissertation study showed an 80% increase in dementia risk in those with atherosclerosis and are consistent with the scientific literature.

BMI. A BMI of less than 18 (underweight) was found to be significantly and independently associated with dementia contributing significantly to the predictive model for dementia. A BMI of 25–29.9 (overweight) and a BMI over 30 (obese) were negatively and significantly associated with dementia. This indicates that low body weight is associated with and predictive of dementia, and the categories of overweight and obese are associated with a lower risk for dementia in elderly adults (65–95 year). The findings of this study contradict the findings of others which suggest that obesity increases dementia risk in elderly subjects.

The findings from the dissertation study align with the findings of Burns et al. (2011), which were that normal or low body weight (BMI < 25) is a strong predictor of dementia risk. Burns et al. (2011) found that weight loss may be one of several body changes that occur in AD years before signs of dementia become evident. In their study,

Burns et al. (2011) found amyloid plaques in 85% of those with MCI and a BMI less than 25 compared to 48% in those with MCI who were overweight.

Burns et al. (20011) found that being overweight in middle age is a risk factor for AD, but being overweight or obese later in life is associated with a lower risk for age-related dementia and that low body weight late in life is a predictor of future dementia. The findings from the dissertation study and that of Burns et al. (2011) support the idea that proper weight management across the life-course is critical for lowering dementia risk.

The findings for association between BMI and dementia are in contrast to those of Whitmer et al. (2008), Kivipelto et al. (2005), Loef and Walach (2013) and others. Whitmer et al. (2008) found that in a longitudinal analysis of over 6,000 members of Kaiser Permanente, central obesity in midlife increased the risk of incident dementia nearly three-fold over a 30-year period, and this was independent of T2D and cardiovascular comorbidities.

The findings from the dissertation study also contradict those of Kivipelto et al. (2005) from the Cardiovascular Risk Factors, Aging, and Dementia (CAIDE) study The CAIDE study found up to a six-fold additive effect for the following: midlife obesity, high total cholesterol, and high systolic blood pressure. The researchers concluded that obesity at midlife is associated with an increased risk of dementia and AD later in life, and vascular risk factors increase the risk in an additive manner. Lastly the findings of the dissertation study contradict those of Loef and Walach (2013) who conducted a meta-analysis of observational studies and found that midlife obesity increased the risk of

dementia later in life. Loef and Wallach noted that when obesity is added to predictive models, the prevalence of dementia goes up exponentially.

Cerebrovascular Disease. In the chi-square analysis, CeVD was not associated with dementia (X^2 (1) = 1.484, p =.223). CeVD was initially entered into the MLR analysis, but because it did not change the OR by at least 10% it was not retained in the final model. Cerebrovascular disease is the fourth leading cause of death among all adults in the United States and a leading cause of death among patients with diabetes. CeVD is a group of brain dysfunctions related to blood vessels supplying the brain and is the underlying cause of cerebrovascular accidents (CVA's) or strokes. Although CeVD has been suggested as having an association with dementia, CeVD is a diverse group of disorders that is further classified and subdivided; therefore, an association with dementia may not have been detected in this study.

Dyslipidemia. Dyslipidemia was not associated with dementia in the chi square analysis or the MLR (OR 0.81, 95 % CI = .587–1.116, p = 0.197). Several epidemiologic studies have found a relationship between elevated serum cholesterol levels and dementia, although results have not been consistent (Ramdane & Daoudi-Gueddah, 2011). The dissertation research examined an elderly sample population, and it is possible that dyslipidemia in midlife is related to dementia as suggested by Solomon et al., (2009) but not in late life as suggested by Reed et al. (2014).

Hypertension. In this study, HTN did not change the association between PD and dementia; however, it was a significantly associated with dementia (OR 1.707, 95% CI = 1.387–2.100, p = 0.000), and HTN contributed significantly to the predictive model.

Hypertension (HTN) is associated with dementia (VaD) and is now thought to be in the causative pathway for dementia and play a role in the pathogenesis of dementia (AD) (Craft, 2009; Kivipelto & Solomon, 2008). The *World Alzheimers Report 2014*, reported HTN in midlife as one of four risk factors with the strongest evidence for possible causal association with dementia (ADI, 2014). Although conducted in elderly subjects, the study clearly showed that HTN increased the risk for dementia with an OR of 1.7

Stroke. Stroke, both hemorrhagic and vessel occlusion, can cause morphologic changes in the brain. Stroke is considered a risk factor for dementia, and dementia is reported to be twice as high in those who have had a stroke, with an estimated prevalence of 30% following a stroke (Budson & Solomon, 2011; Gorelick et al., 2011; Williamson et al, 2014). This study did not find an association between stroke and dementia in the chi square analysis, and it did not change the OR for dementia by 10%; therefore, it was not retained in the final model. Although stroke is a hard endpoint and thought to be a risk factor for dementia, it is likely that mini-infarcts in the brain, which are associated with dementia, often are not diagnosed.

Research Question 3

Is there an interaction between certain risk factors for PD?

Race and SES were analyzed as confounders as well as effect modifiers. Identification of mediating variables is important because they can be used for prevention and treatment interventions designed to change the outcome of interest. If the stratum-specific estimates differed from one another, interaction would be present and the association between PD and dementia would be modified by the stratifying factor (race or

SES). Determining whether interaction exists is often difficult, since the stratum-specific estimates often vary secondary to random variation, even when a true effect exists (Field, 2009).

Socioeconomic Status. Results from the stratified analysis using the MH test based on SES subgroups revealed that the effect of PD exposure on dementia did not vary according to SES subgroup (OR 1.020, 95% CI .846–1.23, p = .835 (Table 10). Socioeconomic status was estimated using the participant's primary insurance payer as a surrogate marker of SES. Low educational attainment (LEA) has been shown to increase the risk of dementia, and LEA is more likely in those with lower SES (Gatz et al., 2007). Information on SES based on income, employment, and educational attainment was not available in the UHS dataset; therefore, primary insurance provider was chosen as the surrogate marker for SES. Median income of Medicare beneficiaries in 2013 was $22,502, and median income of those with private insurance was $41,086; therefore, primary insurance provider appeared to be a valid surrogate marker for SES in the study **(**Bernard et al.**,** 2009; Kaiser Family Foundation, 2013).

Stratification assumes that each stratum is homogeneous in relation to the confounding variable (Field, 2009). This assumption depends on the way the strata are defined, with better results achieved and substantial differences detected when the strata are relatively narrow, meaning that those within the subgroup are alike or uniform. Substantial differences in the effect of the exposure on the outcome are not likely to be detected between when the subgroups within each stratum are broad, meaning that there are wide variations within the subgroup. The lack of difference in effect of PD exposure

on dementia across the SES subgroups likely had to do with the definition of the strata; the strata were broad with 82% of participants having Medicare as their primary insurance, indicating a low/average SES. Primary insurance was used as the surrogate marker for SES, and there was likely a great deal of variability in terms of health insurance status within that group; therefore, differences in dementia were not detected when SES was stratified using such a broad definition.

Race. Results of the stratified analysis using the MH test revealed that race did not modify the effect of PD exposure on dementia risk according to race subgroup (OR 1.025, 95% CI = .850–1.236, p = .798). The lack of effect of difference in effect of PD on dementia risk likely had to do with the broad definition of the race subgroups. The UHS dataset did not identify ethnicity; therefore, Hispanic or Latino participants could have been in any of the three racial groups. The other category for race included those participants who did not report or refused to report race, and those of more than one race; therefore, homogeneity was lacking for the subgroups for race, which made detecting an interaction effect for race difficult. Additionally, there was underrepresentation of African Americans in the sample: 4.1% African Americans in the sample versus 10.7% in the population, making the determination of effect modification by race difficult.

The findings of the effect of PD on dementia risk based on stratification by race can be put in context with other study findings. Yaffe et al. (2012) reported that African Americans were 1.5 times more likely to develop dementia than Whites; however, when the data was adjusted for several SES factors, the excess dementia risk in African American participants was not statistically significant (AAIC, 2013). The findings of the

dissertation study are consistent with those of Fitzpatrick et al. (2004) who did not find racial differences in incident dementia between White and African American participants in the Cardiovascular Health Study (CHS). The impact of race and race related factors such as education and SES on dementia risk requires further investigation.

Theoretical Framework. The ecosocial theory was tested in this study by examining PD along with covariates that had either a biological, social, or behavioral relationship to dementia. The ecosocial theory served as the theoretical foundation and deductive framework for the study. The ecosocial theory considers social and ecologic causes of disease and links societal and biologic determinants of disease (Krieger, 2011). The ecosocial theory supports the concept that life-course exposures that may operate at critical periods with varying strength of association observed at different time periods (ADI, 2014). PD was not found to be significantly associated with dementia, perhaps because the life-course exposure to PD or exposure to PD during a critical period was absent or insufficient to produce the outcome.

In the dissertation research, the risk of dementia was associated with social and lifestyle risk factors that were likely experienced over the course of a lifetime. These risk factors included HTN, atherosclerosis, low body weight, and low/average SES (as a marker of low educational attainment). The findings from this study are contextualized with the ecosocial theory and support the concept of cumulative and combined exposure to these specific risk factors that increased the risk of dementia (ADI, 2014; Mangialasche et al., 2012).

The ecosocial theory also helps frame the findings of this study specifically pertaining to race and SES. Race was not found to be associated with dementia; however, the life-course exposures of African Americans may be different resulting in a higher likelihood of HTN, and lower SES, and educational attainment. HTN and low/average SES were found to be significantly associated with dementia. The ecosocial theory helps contextualize and frame the research findings regarding race, SES, and dementia with a life-course perspective (CDC, 2014; U.S. Department of Education, 2014).

Strengths of the Study

A major strength of the dissertation research was the use of a large ambulatory care dataset compiled from many and diverse outpatient health centers and generally representative of the population. The dataset was complete with very little missing data. An additional strength was a thorough review of the dementia literature which led to identifying appropriate potential risk factors for inclusion in the analyses. The case control design allowed for an efficient examination of dementia risk based on PD exposure and assessment of additional risk factors. Additionally, the ecosocial theory was used to frame the study findings and provide context for lifetime social and economic factors that impact presence of disease. The findings of the study corroborate in part the summary of knowledge on dementia and dementia risk factors published in the World Alzheimer's Report 2014 (ADI, 2014).

Limitations of the Study

The results of this research must be viewed with respect to the study limitations. The research was conducted using the UHS dataset as a secondary data source. There are

limitations in secondary data analyses. First, the data was collected by the UHS for a different purpose, and the research questions posed may not have been fully addressed through the analyses. The data was not collected to answer the specific research questions of the study, and the definitions of the variables may not have fit the criteria for the study as well as desired. Specifically, SES and race were not defined in the UHS dataset in a way that best answered the research questions. Race was also self-reported which can lead to misclassification of the variable. Another disadvantage of use of secondary data is that there is limited knowledge of how the data collection process was done, how well it was done, and what the overall response rate was to specific questions regarding health and medical history.

Another limitation is that the dataset was compiled from the ambulatory care population associated with the UHS, which may not represent the general population and potentially could limit the generalizability of the study findings. The UHS ambulatory care dataset contains participants who have access to the health system and may have more health problems than those not in the health system. Additionally, an ambulatory care dataset eliminates those who are institutionalized for dementia or other health issues, which limits the generalizability of the study findings. The UHS dataset also overrepresented Whites and females, and underrepresented African Americans and males, which further limits the generalizability of the study findings.

The World Alzheimer's Report 2014 states that one of the strongest possible causal factors for dementia is smoking (ADI, 2014). Smoking was not assessed in this study because the information was inconsistently collected in the UHS dataset; therefore,

the dataset limited the scope of the study. Smoking, a significant factor for dementia, was not assessed and may have significantly altered the findings of dementia risk.

The case control design was a limitation although it was an efficient way to examine dementia, which is a disease with a very long latency period. The duration of PD was not assessed because of the case control design, which does not account for causality or temporality. In light of the strong scientific evidence linking T2D and dementia, the duration and severity of exposure to PD would be important to determine. Using a longitudinal design would have allowed for an examination of a longer duration of exposure and increasing severity of PD over time, with a greater area under the exposure curve and allow for a more meaningful and valid assessment of the association between PD and dementia. Longitudinal studies take vast resources including years to conduct, making those types of studies more difficult to conduct.

Missing data decreases the statistical power of a study to detect significant effects particularly if the missing data are in patterns associated with any of the variables (Hardy, Allore & Studenski, 2009). For example, the point estimate of the effect as well as p-values and confidence intervals may be distorted. Missing data can, therefore, make the results of a study less generalizable and potentially biased. The dissertation study had little to no missing data. The missing data reports ranged from 0% to less than 5%; therefore, it was appropriate to conduct the analyses by deleting missing cells for the affected variables without great risk of bias (Hardy et al., 2009).

Recommendations for Further Research

The primary research question in this study was whether PD is associated with dementia in adults aged 65–95 years. There was no association found between PD and dementia; however, other risk factors were found to be independently associated with dementia including atherosclerosis, HTN, low body weight, and low/average SES. Further research is needed to determine whether PD is associated with dementia especially because of the overwhelming evidence suggesting a causal link between T2D and dementia and the high conversion rate from PD to T2D (ADI, 2014; Strachan, 2010). Case control studies contribute significantly to epidemiologic research because they are efficient for looking at exposure and disease and can control for many additional risk factors. Case control studies are efficient and can be used to identify associations between an exposure and disease with few resources and limited time; however, there are many unanswered questions and hypotheses regarding the risk factors associated with and causal factors of dementia. More randomized controlled trials (RCT) are needed to examine dementia risk by experimentally manipulating lifestyle and other risk factors over time. These may include smoking, HTN, T2D, physical activity, vascular risk factors, and educational attainment. Socialization and cognitive stimulation may be factors to consider in a RCT as well. If time and resources permit, a longitudinal study design would be best to study incident dementia in those who remain free of PD, those who develop PD, and those who convert from PD to T2D over time.

The impact of race and race related factors such as educational attainment and SES on dementia risk requires further investigation. This study did not find that race was

an independent risk factor for dementia or modified the association between PD and dementia; however, T2D and smoking are more prevalent in low SES and minority populations and both are considered likely causative factors in dementia development (ADI, 2014). PD is the prodromal period preceding T2D; therefore, research needs to focus on low SES and minority groups particularly to examine modifiable risk factors associated with dementia that can be targeted for dementia reduction initiatives and population-based education.

Implications for Social Change

This study was novel and important scientifically and socially because it helps determine that PD in elderly subjects may not be associated with dementia and that other demographic and health risk factors are. This study can serve as a vehicle for social change as it extends the existing body of knowledge about dementia risk factors in elderly people and provides additional scientific evidence for dementia prevention strategies.

The study was important clinically because it provides health care professionals with information about key risk factors for dementia. The risk factors found to be significantly and independently associated with dementia were atherosclerosis, HTN, low body weight, and low/average SES. The dementia risk factors can be discussed with patients as part of a risk reduction strategy. Based on the results of this study, health care professionals may be able to focus patient education and counseling on vascular risk factors for dementia prevention, specifically atherosclerosis and HTN. Additionally, low body weight may be used as a possible early marker of dementia risk in the elderly.

Comprehensive public health campaigns for dementia prevention should focus on vascular risk factor reduction and be targeted toward lower SES subgroups.

The World Alzheimer's Report 2014 includes proposals for the United States and world community to reduce dementia in the population and promote positive social change. The report describes the strong scientific evidence that dementia risk in populations can be modified through reduction in and detection of hypertension and cardiovascular risk factors, and that heart and brain health are linked (ADI, 2014). HTN, atherosclerosis, and low SES were found to be independently associated with dementia, and findings from the dissertation study are consistent with the risk factors described in the World Alzheimer's Report 2014 as likely in the causative pathway of dementia (low education in early life, hypertension in midlife, smoking, and diabetes across the life course). The potential for positive social change from this study includes a reduction of dementia incidence by identification and treatment of patients with independent dementia risk factors, which may include atherosclerosis, HTN, low body weight, and low SES. This study provides scientific evidence of dementia risk factors that potentially will support the allocation of resources for dementia prevention initiatives. The result of these initiatives may be a reduction in incident dementia and dementia-related morbidity, mortality and healthcare costs.

Conclusion

Dementia is a serious public health concern that has reached epidemic proportion in the United States and the world. There is no known prevention or cure for dementia. There is a growing body of evidence that suggests PD is associated with dementia, but

the literature is conflicting. The purpose of the dissertation study was to determine whether PD is associated with dementia in elderly people and whether the association varies according to race, SES, or other health risk factors. The intent of the study was to provide scientific evidence of those at high risk for dementia and support the allocation of resources for targeted dementia prevention interventions. Dementia risk reduction interventions have the potential to reduce incident dementia and related morbidity, mortality, and healthcare costs.

PD and dementia were not found to be significantly associated. The scientific literature on the association between PD and dementia is mixed; therefore, this study is consistent with the findings of others who have not found an association between PD and dementia (Christman et al., 2012; Fuh, Wang, Hwu, & Lu, 2007; Rouch et al., 2012). It is important to note that PD is the prodromal period that precedes T2D, and the World Alzheimer's Report 2014 identified T2D over the life course as one of four risk factors with the strongest scientific evidence for possible causal associations with dementia. The association between PD and dementia warrants further research because diabetes is thought to be in the causal pathway to dementia, and up to 65% of those with PD will convert to T2D within a six year time frame (Duarte et al., 2013; Garber et al., 2008).

Independent and significant associations with dementia were found in this study between atherosclerosis, HTN, low body weight, and low/average SES. Consistent with recommendations from the World Alzheimer's Report 2014, this study provides evidence that improved detection and treatment of vascular risk factors, specifically HTN and atherosclerosis, should be prioritized through targeted dementia prevention programs

(ADI, 2014). This study provides evidence that low BMI may be a marker of dementia risk as well. The findings from this study were framed and contextualized using the ecosocial theory, which supports the concept of cumulative and combined exposure to risk factors such as atherosclerosis, HTN, and low body weight that appear to increase the risk of dementia. Race was not significantly associated with dementia, but SES was significantly associated. The ecosocial theory helped frame the study outcome at it relates to race. In the general population, African Americans have a higher risk of HTN and are more likely to have lower SES and lower educational attainment over the course of their lifetime (CDC, 2014; U.S. Department of Education, 2014). These factors need to be considered when developing targeted dementia prevention initiatives. The dissertation study contributes scientific evidence to support such initiatives.

The results of this study need to be considered within the context of the study limitations. The case control design and use of a secondary dataset limit the assessment of temporality and reduce the generalizability. Further research is needed to determine whether PD is associated with dementia especially because of the overwhelming evidence suggesting a causal link between T2D and dementia and the high conversion rate from PD to T2D.

Dementia is epidemic in the United States and has no known cure; therefore it is important to identify those at high risk so that dementia prevention initiatives can be put in place. Dementia is the sixth leading cause of death in the United States, and the fifth leading cause of death in those over the age of 65 years (Alzheimer's Association, 2014). An estimated 5.2 million people have dementia in the United States. The estimated

annual cost of dementia in the United States was $213 billion in 2013 and is projected to reach $1.2 trillion by 2050 (Alzheimer's Association, 2014). Because of the social and economic burden of dementia, dementia prevention needs to be a national public health priority. This study provides scientific evidence of dementia risk by identifying risk factors significantly and independently associated with dementia: atherosclerosis, HTN, low body weight, and low SES. The findings from this study may help healthcare professionals educate and council patients on specific risk reduction strategies and support dementia reduction initiatives that have the potential to reduce the burden of dementia, save lives, and reduce health care costs significantly.

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Appendix A: Unity Health System IRB

Date: 11/4/2013

Unity Health System

INSTITUTIONAL REVIEW BOARD

Unity Health System

1555 Long Pond Road

Rochester, NY 14626

585.723.7490

Principal Investigator: S. Alford

Title: Dementia and Pre-Diabetes in Older Women. Race Differences Examined.

I reviewed the above referenced study and determined that it does not require continuing review by the Institutional Review Board and is classified as Exempt because the research involves retrospective chart review that will not allow for direct identification of patients.

Please contact the IRB Office at 723-7490 should you have any questions.

George Nasra, MD

Chair

Curriculum Vitae

SUSAN ALFORD

EDUCATION

Walden University, Minneapolis, MN

Doctor of Philosophy Candidate, Public Health November 2014

Syracuse University, Syracuse, New York

Master of Science: Nutrition Science/Human Metabolism May 1990

Bachelor of Science, Clinical Nutrition May 1984

EXPERIENCE

Senior Medical Liaison,
Novo Nordisk Inc. 2009–Present

Exceeds or Outstanding performance rating 3 of 5 years

Regional trainer ONSET trials, Cornerstones for Care consultant, STAR call presenter, facilitator for DUAL 3 Summit, FMA mid-year presenter: HEOR, FiAsp, beta cell physiology.

Co-author of LMS slides on beta cell physiology.

Engaged in mentoring program

Diabetes Care Specialist II,
Novo Nordisk. Inc. 2003–2008

Excellent and consistent sales performance in the endocrine and primary care settings

Circle of Excellence winner, 2004;

Insulin Pump Trainer and Educator, Medtronic Diabetes **2000–2003**

National Certified Pump Trainer participant, Paradigm pump launch, patient education and pump management

Certified Diabetes Educator and Registered Dietitian
Diabetes Care and Resource Center, Rochester, N.Y. **1994–2002**

Distinguished performance evaluations, clinical lead for the Optifast Program for obese and severely obese patients

Adjunct Professor, Biology Department
Monroe Community College, Rochester, NY **1992–1994**

Responsible for classroom didactics and lecturing in Nutrition Science and Consumer Nutrition, student counseling, mentoring and tutoring.

Associate Director, Nutritional Services
Highland Hospital, Rochester, N.Y. **1988–1991**

Managed Department of Nutritional Services, liaison to medical and surgical chiefs, Pharmacy and Therapeutics (P&T) committee member, initiated Employee Weight Loss and Fitness program.

Clinical Dietitian
Crouse Hospital, Syracuse, N.Y. **1985–1987**

Active oncology team member responsible for full nutritional assessments, enteral and parenteral calculations and prescriptions; written commendation of excellence from Chief of Medical ICU

PROFESSIONAL MEMBERSHIPS & AUXILLARY SKILLS

Rochester Area Diabetes Educator group, member/lecturer	Present
American Diabetes Association, marathon runner, fund raiser, Dublin, Ireland.	Oct 2000
Nat'l Certification Exam, Diabetes Educator	1994, 1999, 2004, 2009
Genesee Dietetic Association, Public Relations spokesperson	1994/1995
American Dietetic Association, Registered	1984

Published author, radio/television appearances, professional lecturer