2015

Deleterious Effects Of Hyperglycemia On Cognitive Functioning In The Cardia Study Cohort

Michele Holland Talley
University of Alabama at Birmingham

DELETERIOUS EFFECTS OF HYPERGLYCEMIA ON COGNITIVE FUNCTIONING IN THE CARDIA STUDY COHORT

by

MICHELE LYN HOLLAND TALLEY

DAVID VANCE, COMMITTEE CHAIR
MICHAEL CROWE
SHANNON MORRISON
ERICA PRYOR
VIRGINIA G. WADLEY

A DISSERTATION

Submitted to the graduate faculty of the University of Alabama at Birmingham,
in partial fulfillment of the requirements for the degree of
Doctor of Philosophy

BIRMINGHAM, ALABAMA

2015

DELETERIOUS EFFECTS OF HYPERGLYCEMIA ON COGNITIVE FUNCTIONING IN THE CARDIA STUDY COHORT

MICHELE LYN HOLLAND TALLEY

SCHOOL OF NURSING

ABSTRACT

With an aging society, maintaining cognitive functioning into older age is becoming more important. Because of the impact cognitive functioning has on daily activities, any disruption may inhibit the ability to perform such daily activities successfully. To prevent disruptions, determinants of cognitive functioning must be considered. Such determinants may or may not be modifiable. Some predictors may be demographic, metabolic, or inflammatory in nature. In addition, predictors or determinants may differ based on genetic predisposition to Alzheimer's disease. As part of a three article dissertation, a subset of data from the Coronary Artery Risk Development in Young Adults (CARDIA) Study was used to conduct this dissertation study. The first article focused on a review of literature related to determinants, including hyperglycemia, of cognitive function later in life. The second article focused on the use of hierarchical regression models to determine the predictors (e.g., hyperglycemia) of cognitive functioning in persons with and without genetic predisposition (i.e., the APOE ε4 allele). The third article used structural equation modeling to specify relationships between body habitus, hyperglycemia, inflammatory markers, vascular health, and lipids; which were hypothesized to predict cognitive functioning 5 years later in those with and without APOE ε4.

Keywords: hyperglycemia, cognitive functioning, metabolic predictors, inflammatory predictors

DEDICATION

This dissertation is dedicated in honor of my husband, Matt Talley, for his love, encouragement, and support and my precious daughters, Matilyn, Meghan, and Olivia Talley for lightening my mood when I felt overwhelmed. Their loving support and encouragement enabled me to pursue this dream and complete my dissertation.

ACKNOWLEDGEMENTS

I express the utmost gratitude to Dr. David Vance, my committee chair. He always made time to assist me in working on this dissertation. His feedback was always timely and appreciated. His mentorship and expertise in scholarly work has been instrumental to my success.

I also thank Drs. Pryor, Wadley, Morrison, and Crowe for their tireless dedication in assisting me to reach my educational goal. Dr. Pryor encouraged me throughout my program and assisted me in keeping on my timeline for my doctoral studies. Dr. Wadley always made time to assist me with the CARDIA Study. Her support is greatly appreciated. Dr. Morrison always provided timely feedback and encouragement when I needed it most. Dr. Crowe encouraged me to pursue my interests for this dissertation and provided timely feedback along the way.

I acknowledge my colleagues at the University of Alabama at Birmingham's School of Nursing for their continual support. I appreciate all of the encouragement and mentorship that you have provided to assist me in reaching this goal. My department chair, Dr. Jacqueline Moss, always had time to help direct my career path as I pursued my PhD.

Last but not least, I thank my parents for their encouragement throughout my academic pursuits to always aim higher. My parents and in-laws provided countless meals and childcare throughout my coursework.

TABLE OF CONTENTS

Page

TABLE OF CONTENTS (Continued)

Page

APPENDIX

LIST OF TABLES

Table *Page*

METABOLIC, INFLAMMATORY, AND APOLIPOPROTEIN E VARIATION ON COGNITIVE FUNCTIONING IN MID-LIFE

DIRECT AND INDIRECT EFFECTS OF METABOLIC AND INFLAMMATORY PREDICTORS ON COGNITIVE FUNCTIONING IN MIDDLE-AGED ADULTS WITH AND WITHOUT APOLIPOPROTEIN E ε4: A STRUCTURAL EQUATION MODELING STUDY

LIST OF FIGURES

Figure *Page*

THE PHYSIOLOGICAL MECHANISMS OF DIABETES AND AGING ON BRAIN HEALTH AND COGNITION: IMPLICATIONS FOR NURSING PRACTICE AND RESEARCH

DIRECT AND INDIRECT EFFECTS OF METABOLIC AND INFLAMMATORY PREDICTORS ON COGNITIVE FUNCTIONING IN MIDDLE-AGED ADULTS WITH AND WITHOUT APOLIPOPROTEIN E ε4: A STRUCTURAL EQUATION MODELING STUDY

INTRODUCTION

Background and Significance

According to the National Institutes of Aging, by 2050, adults aged 65 years and older are projected to triple to 1.5 billion, totaling 16% of the world population (U.S. Department of Health and Human Services, 2014). With an aging society, the maintenance of normal cognitive functioning is becoming more important throughout the lifespan. According to Vance and colleagues (2011), perhaps one of the most important components of successful cognitive aging is maintaining normal cognition due to the direct impact it has on day-to-day activities. Even subtle disruptions in cognition can interfere with everyday tasks (e.g., grocery shopping, answering the phone, and driving). The preservation of cognitive functioning in young and middle-aged adults could lessen the deficits later in life.

There are many determinants of cognitive functioning (Rafnsson et al., 2007; Singh-Manoux, Britton, & Marmot, 2003; Strachan, 2011). Some determinants may be modified (e.g., hyperglycemia, inflammatory markers, lipids, and vascular health). Other determinants of cognitive functioning cannot be modified (e.g., genetic expression of the Alzheimer's gene [APOE ε4], age, gender, and race).

Determinants of Cognitive Functioning

Of the determinants of cognitive functioning, hyperglycemia, a hallmark of diabetes, was of particular interest in this dissertation. According to the Centers for

Disease Control and Prevention (CDC, 2014), approximately 29.1 million children and adults in the United States (9.3% of the population) have diabetes. Adults aged 20 years and older represent 28.8 million of these Americans with diabetes, with 15.5 million men and 13.4 million women affected. Among adults with diabetes, 7.6% are White while 13.2% are Black. Among older adults in the United States (i.e., persons 65 years or older), 11.2 million have diabetes. Additionally, patients with diabetes are 1.5 times more likely to have deficits in cognitive functioning compared to patients without diabetes (Cukierman, Gerstein, & Williamson, 2005).

Hyperglycemia (or high blood sugar levels) can occur acutely or chronically. Acute hyperglycemia, chronic hyperglycemia, and insulin resistance are hallmarks of diabetes. These hallmarks are also associated with deficits in cognitive functioning (Cukierman-Yaffe et al., 2009) and can be measured by a vast array of cognitive tests. Researchers from the ACCORD-MIND Trial studied 2,977 participants to define the relationship between cognitive functioning (measured by the Mini Mental Status Exam, Digit Symbol Substitution Test [DSST], Stroop Test, and Rey Auditory Verbal Learning Test [RAVLT]) and chronic hyperglycemia (measured by A1c scores) (Cukierman-Yaffe et al., 2009). These researchers concluded that a 1% higher A1c score was associated with a 0.20-point lower score of the Mini Mental Status Exam (95% CI -0.11 to -0.28; $p < 0.0001$), a 1.75-point lower score on the DSST (95% CI -1.22 to -2.28; $p < 0.0001$), a worse score (0.75 seconds or greater) on the Stroop Test (95% CI 1.31 to 0.19; $p = 0.0094$), and a 0.11-point lower score on the RAVLT (95% CI -0.22 to -0.19, $p < 0.0142$).

Other determinants responsible for cognitive impairment include activation of inflammatory markers, poor lipid control, and poor vascular health (Akiyama et al., 2000; Anstey, Lipnicki, & Low, 2008; Helzner et al., 2009). Chronic activation of inflammatory markers, including interleukin-6 and C-reactive protein, can alter the vasculature supplying major organs such as the brain (Akiyama et al.). Additionally, poor lipid status, more specifically elevated low density lipoprotein (LDL-C) and triglycerides, impact the flow of blood through the vasculature as fatty plaques accumulate in the walls of arteries (Anstey, Lipnicki, & Low, 2008; Helzner et al., 2009). This impairment in blood flow in turn leads to changes in the vasculature, which lead to changes in the functioning of the brain. Patients with diabetes are known to have poor lipid health (Donahue et al., 1996; Marcovina et al., 1993; Pradhan, Manson, Rifai, Buring, & Ridker, 2001). Patients with diabetes are also known to have sustained inflammation (Fujita et al., 2013).

Non-modifiable determinants (e.g., age, gender, and race) of cognition can also impact functioning. Normal healthy aging can lead to changes in cognitive functioning (Administration on Aging, 2012; Koen & Yonelinas, 2014). Gender-related differences, specifically after the age of 65 years, could also impact cognitive functioning (McDougall et al., 2014). McDougall and colleagues reported that episodic memory decline occurred more in men than women.

Combined, the effects of modifiable and non-modifiable determinants can have ill-effects on cognition. The synergistic effects warrant further studies because deficits in cognitive functioning can have devastating effects on individual health and daily activities, as well as the community, due to the social and economic implications. Therefore, if specific determinants are identified and treated appropriately, the social and

economic costs potentially can be reduced. For example, Moghessi and colleagues (2009) noted that control of hyperglycemia not only improves acute and chronic conditions in these patients but also reduces healthcare costs associated with these conditions. According to the CDC (2014), the costs associated with the acute and chronic conditions caused by diabetes are alarming. In 2012, diabetes costs were estimated at $245 billion, which encompasses $176 billion in direct costs (e.g., medical expenditures related to diabetes care or inpatient and outpatient care, medications, and supplies) and $69 billion in indirect costs (e.g., reduced national productivity or loss of work related to diabetes).

The National Institute of Nursing Research (NINR), a department of the National Institute of Health (NIH), is dedicated to the health and health promotion of individuals through the funding of nursing research in several major areas (U.S. Department of Health & Human Services: NINR, 2015). These areas include: building the scientific foundation for clinical practice, preventing disability and disease, improving quality of life and end-of life care, and eliminating or managing symptoms related to illness. Given the areas of NINR interest, the overall focus of this dissertation is to identify significant determinants of cognitive functioning in young to middle-aged adults.

Purpose of the Study

Previous studies have focused on some of the determinants for cognitive functioning; however, such studies either have small sample sizes or lack key variables that are of interest in this dissertation (Arvanitakis, Wilson, Bienias, Evans, & Bennett, 2004; Bruce, Harrington, Foster, & Westerfelt , 2009; Rizzo et al., 2010; Galanina, Surampudi, Ciltea, Singh, & Perlmuter, 2008; Gonder-Frederick et al., 2009; Shimada et

al., 2010). Fortunately, the Coronary Artery Risk Development in Young Adults (CARDIA) Study has a large sample size and many variables thought to contribute to cognitive functioning. Therefore, the purpose of this study was to examine the effects that hyperglycemia and related metabolic, inflammatory, and physiological markers have on cognitive function in those with and without APOE ε4 expression (due to its known association with Alzheimer's disease risk) using records from the CARDIA Study database.

The CARDIA Study enrolled 5,116 men and women who were either White or Black and were 18 to 30 years old (at baseline) in 1985 through 1986 and conducted periodic testing on the cohort over the next 25 years to examine the development of heart disease (Friedman et al., 1988; Hughes et al., 1987). The study took place at four centers: the University of Alabama at Birmingham in Birmingham, Alabama; Northwestern University in Chicago, Illinois; the University of Minnesota in Minneapolis, Minnesota; and Kaiser Permanente in Oakland, California. The participants were asked to participate in follow-up examinations at baseline (year 0), year 2, year 5, year 7, year 10, year 15, year 20, and year 25. Even though the specific aims of each examination varied, data were collected on a variety of determinants thought to be related to heart disease (blood pressure, cholesterol and other lipids, glucose, insulin, weight, and body composition), lifestyle factors (e.g., dietary and exercise patterns), substance use (e.g., alcohol and tobacco), behavioral and psychological variables, and medical and family history. In addition, diagnostic tests such as echocardiography, chest and abdominal computed tomography scans, carotid ultrasonography, and brain magnetic resonance imaging were also performed during some of the examination periods.

Indeed, the synergistic effects of these determinants on cognitive impairment are very similar to the clustering of factors that influence metabolic syndrome (Yaffe et al., 2004). The metabolic syndrome is associated with abnormal lipid levels, blood pressure, glucose, and adiposity to the abdomen. Similar to cognitive impairment, the individual risk factors for metabolic syndrome have been studied intensely, but the clustering effect had not received much attention until the researchers from CARDIA performed their study (Carnethon et al., 2004). In that study, 5,115 participants were studied over time to determine the risk of metabolic syndrome. The researchers noted that the risk increased with age, was higher among African Americans participants, and those with the least amount of education (RR 0.79, 95% CI 0.50 to 1.24). Yet, the associations among age, gender, race, and education, and the development of metabolic syndrome are complex and vary depending on the severity of other risk factors present (i.e., lipid levels, glucose levels, abdominal adiposity, and blood pressure).

Again, the synergistic relationships responsible for the metabolic syndrome are likely similar to the relationships responsible for changes in cognitive functioning. In the CARDIA Study, 2,510 participants were studied at year 25 in order to determine if vascular disease (measured by calcification) in middle-age was associated with cognitive changes later in life. The researchers found that greater amounts of calcification of the vasculature were associated with worse performance on cognitive tests (measured by DSST, Stroop Test, and RAVLT). In addition, the researchers noted that the risk factors associated with vascular disease attenuated the association of calcification to the vasculature (Carnethon et al., 2004).

Research Questions

For this dissertation, a subset of the data gathered from the CARDIA Study was used to determine the effects that diabetes and other related physiological markers have on cognitive function in those with and without the APOE ε4 expression (due to its known impact on Alzheimer's disease risk; Spinney, 2014). Demographic, clinical, and neuropsychological data from the CARDIA Study were used in order to answer the following research questions:

1. Using multiple regression, what model best predicts cognitive function for those regardless of APOE ε4 status, those with APOE ε4, and those without APOE ε4?
2. Using structural equation modeling, what are the relationships between variables that best predict cognitive functioning 5 years later in those with and without APOE ε4?

Description of the Articles

As a part of the dissertation, three articles were prepared for publication. The first article detailed the synergistic effects of diabetes and aging on cognitive impairments with an explanation of the role that insulin plays in the brain. The authors also proposed areas for nursing practice and research such as diet and exercise, blood pressure and cholesterol management, as well as the delivery of intranasal insulin. This article provided a review of literature that was used to identify predictors of cognitive functioning. This article was accepted for publication in the *Journal of Neuroscience Nursing*.

Using the CARDIA Study dataset, the second article detailed the design, methods, analysis, and results using hierarchical multiple regression models to determine the demographic, metabolic, and inflammatory predictors of cognitive functioning in those with and without the APOE ε4 expression. All of the records of participants in the original CARDIA Study were included as long as the record did not have missing data and the participant had denied stroke or transient ischemic attack by self-report. The variables of interest for this analysis included several predictor/independent variables including demographic data (i.e., age, gender, race) gathered at year 0, and measurements of hyperglycemia, lipid status, inflammatory markers, and vascular disease gathered from year 20. In general, these variables were utilized to predict cognitive functioning 5 years later (at year 25) through the use of cognitive tests (i.e., Stroop Test, DSST, and RAVLT). In addition, a composite cognitive score was used to reflect global cognitive functioning because the specific cognitive tests used test specific domains of cognition rather than overall functioning. Next, a series of hierarchical regression analyses was performed to test the best model to predict cognitive functioning after 5 years.

The third article describes the design, methods, results, and conclusions that were used to evaluate how predictor variables (i.e., body habitus, hyperglycemia, vascular health, and lipid status) are interrelated as they contribute to cognitive functioning in the CARDIA Study cohort. The goal was to build structural equation models to determine the relationships between variables that predict cognitive functioning 5 years later in participants with and without APOE ε4 (genetic expression for Alzheimer's disease). Again, all of the records for participants in the original CARDIA study were included as long as participants denied having a stroke or transient ischemic attack and the records

had complete data for the variables of interest. To clean the dataset, listwise deletion was used.

In summary, this dissertation consists of a brief introduction, a review of the literature in article 1, the results of the hierarchical multiple regressions analysis in article 2, the results of a structural equation modeling analysis in article 3, and a brief summary of the dissertation.

THE PHYSIOLOGICAL MECHANISMS OF DIABETES AND AGING ON BRAIN HEALTH AND COGNITION: IMPLICATIONS FOR NURSING PRACTICE AND RESEARCH

by

MICHELE H. TALLEY, ERICA R. PRYOR, VIRGINIA G. WADLEY, MICHAEL CROWE, SHANNON MORRISON, AND DAVID E. VANCE

Journal of Neuroscience Nurses, Vol. 47(5)

Format adapted [and errata corrected] for dissertation

Abstract

A substantial proportion of individuals over age 65 years will experience some degree of cognitive impairment, and older adults with diabetes are at increased risk for these impairments. Such impairments can negatively affect activities of daily living and lead to a decrease in quality of life as well as increase caregiver burden. Cumulatively, the effects of diabetes and aging slowly diminish cognitive function, resulting in various degrees of cognitive impairment including dementia. In fact, older adults with diabetes have a 65% higher chance of developing Alzheimer's disease than those without diabetes. This article reviews the synergistic effects of aging and diabetes on cognitive function. A discussion of the physiologic basis for these effects is included, in particular, the role of insulin in the brain. The final section of the article focuses on intervention strategies that can be used by nurses and allied healthcare providers to mitigate the influence of diabetes and aging so that optimal cognitive performance is maintained. Areas for future research are also discussed.

Keywords: diabetes, aging, cognition, cognitive impairment, risk factors

Synergistic Effects of Diabetes and Aging on Cognition: Implications for Nursing Practice and Research

In 2050, approximately 88.5 million people will be 65 years and older as compared to the 40 million alive in 2010 (U. S. Department of Aging, 2008). Within this group of older individuals, 20% to 56% report a cognitive complaint with memory loss being the most common; such complaints often correspond to objective measures of neuropsychological performance (St. John & Montgomery, 2003). Unfortunately, co-morbidities such as diabetes become more prevalent with advancing age and contribute to

poorer cognition. According to the Centers for Disease Control and Prevention (CDC, 2011), 26.9% (10.9 million) of older Americans have diabetes. Persons with diabetes are 1.5 times more likely to have cognitive impairments than those without diabetes (Cukierman, Gerstein, & Williamson, 2005). Both aging and diabetes have been shown to affect cognition independently. Combined, diabetes and aging represent an increased risk for the development of cognitive impairments and dementia (Lee et al., 2011).

Although the interplay between diabetes and aging does not always mean that frank cognitive impairments will result, the synergy from them may result in poorer cognitive performance when compared to younger adults and individuals free of diabetes. While individuals are likely familiar with the physical signs and symptoms associated with aging and diabetes, many individuals may be less familiar with the cognitive outcomes associated with diabetes and aging, especially in cases where diabetes is poorly controlled (i.e., when there is poor glycemic control). In addition, some individuals and healthcare providers may be unfamiliar with the significance of maintaining optimal cognitive functioning, which is crucial in performing daily activities such as negotiating medication regimens, driving, and managing finances.

The purpose of this article is to inform researchers and healthcare providers about the cognitive outcomes associated with diabetes and aging. Within the context of cognitive reserve, the effects of diabetes on brain health are examined, followed by the effects of aging on brain health. As seen in Figure 1, their combined influence on brain health is synthesized. From this, as seen in Figure 2, intervention strategies may be used to prevent or potentially improve cognitive functioning, or at a minimum, help prevent some cognitive impairment.

Cognitive Reserve

Neuronal connections are necessary for the transmission of signals in the brain; it is from these constant signals that cognition emerges. It is the strength, sophistication, and density of these connections that constitute cognitive reserve. Cognitive reserve refers to an individual's ability to physiologically adapt to insults to neurons and neuronal connections in lieu of pathologic burden and still support the functions necessary for cognition (Stern, 2012; Vance & Wright, 2009). When insults are introduced to the neurons or neuronal connections, new pathways may be formed and such rerouting allows the communication between neurons to still occur. This physiological process parallels the process of collateral flow observed with the heart (Choi et al., 2013). For example, during heart perfusion, arteries will develop new pathways for blood to flow to the heart muscle if a narrowing in the coronary artery occurs, thus allowing normal physiologic function of the heart. Similarly, in the brain, the neurons may have damage or die but communication can still occur as the nerve impulses are rerouted around blocked pathways.

These actual morphological and neurochemical changes that occur in the brain, nervous system, and neurons are known as positive and negative neuroplasticity (Vance et al., 2012). Positive neuroplasticity results when the stimuli, or *presses*, from one's environment encourage the restructuring of neurons to enhance cognitive reserve. Likewise, when one's environment does not have a high press on cognition, meaning the brain can handle environmental demands, cognitive reserve is decreased because atrophy of brain tissue occurs. Such loss is consistent with the "use it or lose it" theory in which

energy needed for these underused systems is actually shifted to those systems that are used more frequently. This loss is known as negative neuroplasticity.

Health behaviors and demands from one's environment affect neuronal health and cognitive reserve (Vance & Wright, 2009). More specifically, more education, physical exercise, social contact, and mental stimulation provide an environment that enriches neuronal health and cognitive reserve. Conversely, inadequate sleep, substance abuse, and co-morbid conditions yield an environment that is not conducive to neuronal health and cognitive reserve. Consequently, these factors determine the occurrence and amount of positive and negative neuroplasticity. For example, Boyke and colleagues (2008) conducted a longitudinal study of older adults (M_{age} = 60) who could not juggle, in order to determine the adaptive changes of the brain and nervous system in response to a new demand, learning to juggle three balls at a time. A total of 25 participants learned to juggle while another 25 participants served as the control group and were not taught to juggle. Next magnetic resonance images (MRI) from the jugglers and the control group were compared. These researchers found significant post-juggling changes in the gray matter of the brain and a decrease in changes in the gray matter over time when this activity ceased. Although slower than the younger brain, Boyke and colleagues noted that the older adult brain is able to maintain its capacity to change in structure so as to meet the environmental demands placed on it by learning (i.e., developing juggling skills). Their findings are similar to others (Brayne et al., 2010; Roe et al., 2008) who suggest that particular activities actually support cognitive reserve and can even delay cognitive impairments and dementia. Therefore, it is within this context of cognitive reserve and

neuroplasticity that impairments associated with diabetes, aging, and the combination thereof are examined.

Diabetes and Cognition

Diabetes has been defined as a condition marked by hyperglycemia (high blood glucose) as a result of the body's inability to properly use blood glucose for energy (American Diabetes Association [ADA], 2014). Diabetes can be diagnosed via four methods: a fasting blood glucose above or equal to 126 mg/dL, a random blood glucose greater than 200 mg/dL (with accompanying complaints of excessive thirst, hunger, and urination), a glycated hemoglobin A1c above 6.5%, or a blood glucose greater than 200 mg/dL 2 hr after an oral glucose tolerance test. Healthcare providers can further classify diabetes as type 1 or type 2. Physiologically, type 1 diabetes and type 2 diabetes differ in several ways but the most pronounced difference is that in type 1 diabetes, no insulin is produced; whereas in type 2 diabetes, insulin is still produced, but it may be insufficient in its action or production.

Insulin is produced by the beta cells in the pancreas; unfortunately, in type 2 diabetes, beta cell function decreases over time. By the time a person is diagnosed with type 2 diabetes, beta cell function has actually declined by approximately 50% with a 3-5% decline in function annually thereafter (U.K. Prospective Diabetes Study, 1995). Regardless of the type of diabetes, acute hyperglycemia, chronic hyperglycemia, and insulin resistance are hallmarks of diabetes and have been associated with cognitive impairments (Cukierman-Yaffe et al., 2009; Euser et al., 2010). Indeed, researchers from the ACCORD-MIND Trial (Cukierman-Yaffe et al., 2009) conducted a study of 2,977

participants in order to determine the relationship between chronic hyperglycemia and cognitive impairment (measured by the Mini Mental Status Exam, Stroop Test, Rey Auditory Verbal Learning Test, and Digit Symbol Substitution Test). These researchers found that a 1% higher A1c score was associated with a 1.75 lower score on the Digit Symbol Substitution Test, a 0.20-point lower score on the Mini Mental Status Exam, a 0.11-point lower score for the Rey Auditory Verbal Learning Test, and a worse score (0.75 seconds or more) on the Stroop Test.

As seen in Figure 1, many physiologic mechanisms have been postulated to explain predictors of diabetes-associated cognitive impairment. It involves either direct damage to the brain and its structures from hyperglycemia (non-vascular damage) and/or increased risk imposed by atherosclerosis on the vasculature from diabetes itself (vascular damage) (McCutchan et al., 2012). Other mechanisms providing insight on diabetes-related cognitive impairment involves insulin, the insulin resistance intrinsic to diabetes, and the by-products of diabetes.

Insulin Resistance

Insulin is a hormone that functions to aid in glucose homeostasis in muscle and adipose tissues. At times, insulin may not be produced (type 1 diabetes) or its production does not meet the demand, or its action is impaired (type 2 diabetes). When insulin is produced but its action in aiding glucose into cells is impaired, this is known as insulin resistance (Bruce & Hanson, 2010; Petersen & Shulman, 2006). When insulin resistance occurs, major dysfunction to its target organs, including the brain, can occur (Petersen & Shulman, 2006). To emphasize the role that insulin resistance plays in cognitive

impairment, in the Diabetic Encephalopathy Trial, Brands and colleagues (2003) found more marked MRI changes in patients with type 2 diabetes versus type 1 diabetes. These results suggest that the development of cognitive impairment hinges on the inherent insulin resistance found in type 2 diabetes rather than just the presence of insulin.

The role of insulin resistance in the brain is of particular importance. Like other tissues in the body, the brain requires oxygen, food, and nutrients to meet its metabolic needs (Hall, 2011). In fact, the brain itself requires about 15% of the body's total metabolism. Most of the metabolism takes place in the neurons; therefore, a constant supply of energy in the form of glucose is required. Unlike other tissues in the body, the brain and neurons do not require insulin to transport glucose into the cell. The glucose can enter the cell directly. Insulin actually crosses the blood brain barrier and is present in the brain. While neurons are not insulin dependent, they are insulin responsive (Petersen & Shulman, 2006).

Since 1955, researchers have known that the brain was relatively insulin-independent (Park & Johnson). Not much emphasis was placed on this scientifically until researchers began noting high densities of insulin receptors in the brains of humans and rats (Havrankova, Roth, & Brownstein, 1978; Potau, Escofet, & Martinez, 1991). These insulin receptors were especially noted in the hippocampal area, a brain structure necessary for memory consolidation (Havrankova, Roth & Brownstein, 1978), and the hypothalamus, a brain structure necessary for many metabolic processes and producing neurotransmitters (e.g., glutamate and Gamma-aminobutyric acid [GABA]) (Zhao, Chen, Quon, & Alkon, 2004).

Insulin in the brain is also known to have an influence on the release and uptake of neurotransmitters. Neurotransmitters are the chemicals in the brain that are responsible for potentiating the action potentials between neurons allowing them to communicate. A careful balance between, for example, glutamate (an excitatory neurotransmitter) and GABA (an inhibitory neurotransmitter), becomes necessary for normal cognition (Zhou & Danbolt, 2013). The effect that insulin has on neurotransmitters has been shown to improve memory (Zhao, Chen, Quon, & Alkon, 2004). When neurons are resistant to insulin, the balance between the neurotransmitters is not maintained, thereby influencing the transmission of signals. Such disturbances in the cerebral insulin signaling pathways have been associated with dementia and the aging brain (Biessels & Kappelle, 2005). In addition, the neurons are also susceptible to damage from chronic states of hyperglycemia.

Neurotoxic Effects of Diabetes

Another mechanism in which diabetes impacts cognition is through its production of several by-products that exert neurotoxic effects (i.e., altered tau and beta-amyloid metabolism and glucose metabolites). These by-products influence the amyloid cascade in the brain; excessive amyloid is neurotoxic (Costa, 2013). Insulin mitigates hippocampal synapse sensitivity to beta-amyloid, inhibits the phosphorylation of tau, and is involved in the regulation of the metabolism of beta-amyloid protein and tau (Biessels & Kappelle, 2005). Beta-amyloid and tau are responsible for amyloid plaques (senile plaques) and neurofibrillary tangles, respectively, which are the hallmark pathological signs of Alzheimer's disease. Such amyloid plaques form when they mix with other

proteins and disturb the normal transmission between neurons. When transmission of signals is disrupted, the functional connectivity of the brain is compromised which obviously results in cognitive impairment (Biessels & Kappelle).

Furthermore, the plaque formation can be lessened through a process involving insulin-degrading enzymes (Biessels & Kappelle, 2005). Insulin-degrading enzymes are found inside cells or on their surface. These enzymes degrade insulin and beta-amyloid protein (Messier & Teutenberg, 2005). Insulin stimulates beta-amyloid to be released. If excessive amounts of insulin are present during states of insulin resistance, then more beta-amyloid is present, potentiating more senile plaque formation. If more insulin-degrading enzymes are released, less insulin is present, and in turn, fewer beta-amyloid proteins are present. Interestingly, the protective nature of these insulin-degrading enzymes is known to be less expressed in those who carry the APOE4 allele for Alzheimer's disease (Cook et al., 2003). Therefore, when neurons are resistant to insulin, the effects can be particularly harmful.

Another mechanism involves the role of toxic glucose metabolites that exist during times of hyperglycemia which can damage the brain through its vasculature (Biessels & Kappelle, 2005). Many studies support an association between both acute and chronic hyperglycemia and cognitive impairment (Bruce et al., 2009; Messier et al., 2010; Rizzo et al., 2010; Shimada et al., 2010; van Elderen et al., 2010). Such hyperglycemia is characteristic of diabetes. Hyperglycemia stimulates inflammatory processes in the vessels. The inflammation potentiates narrowing of arteries that supply tissues, including brain tissue. As a result, when the brain tissue does not receive adequate nutrients (e.g., oxygen, glucose, and water), ischemia occurs. This insufficiency

of vascular flow carrying the necessary nutrients can worsen over time in the presence of atherosclerosis. In addition, as the capillary walls in the vessels in the cerebrum thicken, the exchange of nutrients across the vessels is lessened, leading to even more ischemia (Biessels & Kappelle, 2005). When ischemia occurs, subcortical white matter lesions develop. In turn, these white matter lesions, appearing as hyperintensities on MRIs, are associated with declines in cognitive performance (Maillard et al., 2012).

Cholesterol

Metabolism also plays a key role in cognition (Hall, 2011). Basically, metabolism occurs when fat, protein, and carbohydrates are broken down chemically to provide energy for the cells of the body. In doing so, harmful by-products can result. For example, insulin is needed to enable carbohydrate metabolism to occur. Outside of the brain, insulin is required to allow glucose to enter cells for energy. In patients with diabetes, the lack of adequate insulin actually increases the cholesterol concentration in the blood, mainly due to changes in the activation of specific enzymes responsible for the metabolism of fat. Excessive amounts of specific cholesterol components in the circulatory system cause plaque formation within the vessel walls. The formation of plaques within the vessels lead to narrowing of the arteries, and hence, small vessel disease (microvascular) and large vessel disease (macrovascular) develops. Such diseases prevent adequate blood flow to tissues and organs. When these vessels fail to perfuse the brain sufficiently, cognitive impairments emerge. This reduced vasculature also means waste products are not removed as well which can increase oxidative stress.

Oxidative Stress

Oxidative stress is caused by the imbalance of free radicals and antioxidants in the body. Free radicals, which are a by-product of normal oxygen metabolism, cause death to neurons and prevent the transmission of signals necessary for cognition. Antioxidants bind to free radicals making them inert; thus, they can restore homeostasis to the structures necessary for cognition. Unfortunately, patients with diabetes have greater oxidative stress in their tissues, suggesting that hyperglycemia may disrupt the balance between free radicals and antioxidants (Ziegler, Sohr, & Nourooz-Zadeh, 2004). In addition, a disruption in this balance also results in vessel damage. Therefore, oxidative stress can cause direct damage to neurons as well as damage to vessels leading to microvascular and macrovascular diseases that can also cause cognitive impairment.

Multidimensional Model

Diabetes impacts the brain through several mechanisms, which supports a multi-dimensional model (Figure 1). Mechanisms in this multi-dimensional model are similar to those found for the cluster of conditions known as metabolic syndrome (Biessels, van der Heide, Kamal, Bleys, & Gispen, 2002). Metabolic syndrome is usually characterized by abdominal obesity, insulin resistance, prediabetes, hypertension, hypertriglyceridemia, and low high-density lipoproteins (Reaven, 2004; Yaffe, 2007) or a combination of three to four of these conditions. Metabolic syndrome is also associated with atherosclerotic disease. In fact, some of the same factors noted to potentiate the metabolic syndrome are also factors found to potentiate cognitive impairments. These factors have been identified as independent predictors for dementia, accelerated cognitive impairment, ischemic

stroke, and cardiovascular as well as cerebrovascular diseases (Whitmer, Sidney, Selby, Johnston, & Yaffe, 2005). Additionally, peripheral (or skeletal muscle) insulin resistance may lead to type 2 diabetes, ischemic cerebrovascular disease, and Alzheimer's-type pathology. Any one of these or all three may then lead to cognitive impairment. Studies suggest that people with metabolic syndrome have an increased risk of cognitive impairment when compared to those without the metabolic syndrome (Yaffe et al., 2004). Therefore, the additive effects of these factors may accelerate the mechanisms thought to produce cognitive impairment with aging.

Interestingly, some studies have reported that the actual duration of diabetes is associated with worsening cognitive impairment (Okereke et al., 2008; Tiehuis et al., 2008). Okereke and colleagues conducted a prospective cohort study on 5,907 men in the Physicians' Health Study II and 6,326 women in the Women's Health Study (M_{age} = 74.1 and 71.9, respectively). Of these participants, 553 men and 405 women had diabetes and underwent cognitive testing at baseline and then several years later. Using adjusted linear regression models, these researchers found that participants with diabetes scored significantly lower at baseline on all cognitive outcomes. In addition, longer duration of diabetes was associated with lower scores on global cognitive tests (p-trends <.001). Diabetes may also accelerate the aging process; therefore, the effects of normal aging on cognitive reserve must also be considered.

Aging Contributions to Cognitive Impairment

Age-related cognitive impairment is thought to affect up to 40% of otherwise healthy adults over the age of 60 years (Small, 2002). As people live longer, the number

of those impacted by cognitive impairment will rise as well (Van Guilder et al., 2011). Common health problems such as hypertension and atherosclerosis are known to increase the risk for cognitive impairment in those who are aging. Albeit, genetic influences are important as well.

In a recent prospective study from the Religious Orders Study, Hayden and colleagues (2011) examined 1,049 (M_{age} = 75) Catholic priests, nuns, and brothers to determine the significance of cognitive impairment over a 15-year period. These researchers found that over time, approximately two thirds of participants experienced slow cognitive decline while the other one-third experienced a rapid decline in cognition during the study. Those participants with the fastest rate of impairment in cognition were noted to have a greater frequency of APOE4 allele as well as greater levels of amyloid plaques and neurofibrillary tangles.

In addition, other physiologic processes associated with aging include increased oxidative stress, reduced glucose utilization and metabolism, and abnormal protein synthesis and signaling. These processes negatively impact the health of neurons and their connections. The health of the nerve fiber depends on its insulation, known as myelin sheath. Healthy, insulated nerve fibers transmit signals properly and enhance cognition. Myelin sheaths undergo three phases: myelination (formation of the myelin sheath), demyelination (or degeneration), and remyelination (or restoration). These processes, or phases, begin at birth and continue well into middle-age (Bartzokis et al., 2012). These phases are not necessarily a sequence of events but rather occur simultaneously. Therefore, the formation of myelin sheath occurs while other sheaths are being destroyed, restored, and repaired.

Degeneration of these sheaths results in neuronal mass loss with an actual reduction in the weight of the brain (Eliopoulos, 2014). In Bartzokis and colleagues' (2012) study, white matter MRI changes, consistent with demyelination, influenced the volume of the brain. These volumetric changes followed a U-shaped trajectory wherein the processes of development, degenerative, and repair of myelin sheath occurred in the aging brain. The results support the notion that as one matures, a healthy brain is constantly changing and is driven by development and repair of myelin in order to support function among the neural connections in which optimal cognition is dependent.

Once the sheath is damaged, the healthy tissue may be replaced by protein deposits, amyloid plaques, and neurofibrillary tangles in the process of being restored. These deposits, plaques, and tangles reduce the ability to transmit signals in the white matter of the brain. As a result, signals cannot reach the areas of the brain responsible for long-term memory and other cognitive functions (Hall, 2011). These changes in the microenvironment have been linked to dementia and Alzheimer's disease due to the inhibition of proper signal transmission. Thus, identifying accelerators of the demyelination and remyelination process is of particular interest. Diabetes may be one of these accelerators.

Diabetes, Cognition, and Aging

The underlying pathophysiologic changes that occur in both aging and diabetes are likely contributors to cognitive impairment, yet the exact mechanisms are unknown. In the same Religious Orders Study mentioned above, Arvanitakis and colleagues (2004) followed 824 older nuns, priests, and brothers with similar lifestyles to determine whether

diabetes was associated with the incidence of Alzheimer's disease. These researchers found that those with diabetes experienced a 65% higher chance of Alzheimer's disease compared to those without diabetes. Similarly, in a cross-sectional study of 121 older patients with type 2 diabetes, Rizzo and colleagues (2010) found a significant relationship between acute glucose swings and cognitive impairment. Likewise, when studying a prospective cohort study of 54 male veterans with type 2 diabetes, Galanina and colleagues (2008) noted that patients with higher, rather than lower, glucose values scored poorer on cognitive tests of short-term visual memory, word fluency, attention, mental flexibility, and visuoperceptual processing.

Interestingly, the type of diabetes a patient has may also impact cognitive impairment in older adults (Biessels et al., 2002; Lee et al., 2011). More specifically, type 2 diabetes has been more closely linked with cognitive impairment than type 1 diabetes. Perhaps this association is related to the fact that oxidative stress, the accumulation of by-products of metabolism, and microvascular disease all occur in type 2 diabetes and the aging brain (Reijmer, van den Berg, Ruis, Kapelle, & Biessels, 2010). In addition, patients with type 1 diabetes have a shortened lifespan as compared to patients with type 2 diabetes and are therefore less likely to live to ages at which dementia becomes more common.

This combination of aging and diabetes on brain health becomes more problematic because the self-care behaviors (e.g., compliance with medications and blood glucose monitoring) important in diabetes management tend to worsen with age (Feil, Zhu, & Sultzer, 2012). In a cross-sectional study on 1,398 older adults with diabetes aged 60+, Feil and colleagues found that those participants with greater cognitive impairment

were less likely to adhere to physical exercise and their diet. These results indicate that poorer cognitive function may interfere with self-care behaviors leading to poor glycemic control. Poor glycemic control can ultimately contribute to further neurological insults which slowly decreases cognitive reserve.

Influential Factors for Practice

As seen in Figure 2, aging, diabetes, and cognition are all influenced by multiple factors. Each of these factors can potentiate or lessen the effects of these physiological processes that affect neuronal health and cognition. Factors such as diabetes control, nutrition, physical exercise, social support/stimulation, sleep, substance abuse, polypharmacy, depression, and co-morbid conditions have all been linked with cognition (Vance & Burrage, 2006). Therefore, controlling one or more of these factors could potentially reduce the risk of developing cognitive impairment later in life.

Diabetes Control

Optimal glucose control in those with diabetes has been associated with a lower risk of the development of co-morbid conditions. Although when patients age, the risk associated with tighter glycemic control may outweigh the benefit (e.g., lower risk of co-morbid condition development) due to a higher incidence of hypoglycemia occurrence. As a result, glycemic goals for older adults may be less stringent than younger patients with diabetes (ADA, 2014), leading to an increased risk for developing diabetes-related co-morbidities such as hypertension and stroke, which are also detrimental to brain health.

Healthcare providers can use A1c levels to gauge how adequately glucose is controlled. Typically, in patients with diabetes, A1c levels should remain below 7% (ADA, 2014). If patients with type 1 diabetes are noted with A1c levels greater than 7%, then changes in diet and physical exercise levels should be implemented as well as changes in the insulin regimen. If patients with type 2 diabetes are noted with A1c levels greater than 7%, then changes in diet and physical exercise should also be implemented. If after 3 months the A1c level is still not at goal, then oral medications may be added such as insulin sensitizing agents (e.g., metformin, pioglitazone) (Dominguez, Marschoff, Gonzalez, Repetto, & Serra, 2012). If patients fail to achieve optimal glycemic control despite oral agents or a combination of them, then progression to insulin therapy may be required in patients with type 2 diabetes. If patients are unable to achieve goals within 3-6 months of the initiation of multiple oral agents, introduction of insulin should be initiated, as its use has been associated with reaching therapeutic goals more rapidly (Morris & Burns, 2012). When goals are not achieved, co-morbid conditions occur at an increased frequency.

Co-morbid Conditions

Cardiovascular disease is the major cause of mortality and morbidity among patients with diabetes (ADA, 2014). The United Kingdom Prospective Diabetes Study (1998) estimated that at the time of diagnosis of diabetes, the risk of cardiovascular disease increases by 1.5% per year. Therefore as patients with diabetes age, this risk increases (Stevens, Kothari, Adler, & Stratton, 2001). Proper management of blood pressure, cholesterol levels, and diabetes can drastically reduce the incidence and severity

of cardiovascular co-morbidity. Poor control of these conditions may yield atherosclerosis, which also impacts brain health.

Using the guidelines from the Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (James et al., 2014), nurses and healthcare providers should aim to maintain a blood pressure less than 140/90 mm/Hg in patients with diabetes. Again, diet and physical exercise modifications often are needed initially. Then if blood pressure goals are still not met, pharmacologic agents may be required. Angiotensin-receptor blockers, angiotensin converting enzyme inhibitors, calcium channel blockers, and diuretics have all been found to be helpful in achieving blood pressure goals for patients who also have diabetes (ADA, 2014).

Cholesterol management is also crucial to minimizing co-morbid conditions in patients with diabetes. In a landmark study, 5,102 patients with diabetes were found to have a cardiovascular disease risk that is the same as that of a patient who has sustained a previous cardiovascular event (known as a cardiovascular risk equivalent) (Holman, 2001). Nurses and healthcare providers should aggressively treat older patients with diabetes to maintain low density lipoprotein levels below 100 mg/dL. In order to accomplish this, the Adult Treatment Panel III (U. S. Department of Health and Human Services, 2002) recommends diet and physical exercise modification first. If these modifications fail to achieve the acceptable low density lipoprotein level, then nurses and healthcare providers should add a statin. Statins reduce the incidence of atherosclerosis, thereby reducing the incidence of cognitive impairment from the sequelae of nutrients not reaching the neurons via the arteries supplying the brain. For management of other

elevated lipids, the use of other dyslipidemic medications (e.g., fibrates plus statins) may be necessary (Moretti, Gorini, & Villa, 2011).

Depression

Emotional well-being is an important aspect of many disease processes. Unfortunately, depression affects as many as 20-25% of patients with diabetes (Anderson, Freedland, Clouse, & Lustman, 2001). Kaulgud and colleagues (2013) found that depression occurs significantly more in older adults with diabetes compared to those without diabetes. Additionally, in the ACCORD-MIND Trial, diabetic patients with the greatest cognitive impairment were more likely to have depression (Sullivan et al., 2013). Fortunately, researchers have found that treatment with antidepressants improves cognitive functioning (Greer et al., 2014). Thus, screening for and treating depression in patients with diabetes is also important for cognitive health.

Sleep

Sleep disturbances are common in adults with diabetes (Bopparaju & Surani, 2010), aging adults (Schmidt, Peigneux, & Cajochen, 2012), and among obese adults who are also prone to type 2 diabetes (Gangwisch et al., 2005). Such fragmented sleep can lead to difficulties in cognition (Vance, Heaton, Eaves, & Fazeli, 2011). Sleep disturbances also have been linked to an increased appetite due to the disturbance in hormone release (i.e., leptin) that occurs during sleep (Mesarwi, Polak, Jun, & Polotsky, 2013). With less sleep comes hunger, with hunger comes increased intake, and with increased caloric intake comes weight gain. Weight gain leads to decreased insulin

sensitivity and increased risk for type 2 diabetes. Hence, adequate sleep is necessary to reduce risk for impairments in cognition and prevent worsening in diabetes as a result of increasing insulin resistance.

Nutrition

Disturbances in sleep have been associated with an increased insulin resistance, which leads to an increased appetite (Mesarwi, Polak, Jun, & Polotsky, 2013). With increased appetite, excessive weight gain can occur. Fortunately, the adherence to specific dietary regimens can yield better glycemic control in patients with diabetes. In the Diabetes Prevention Program, researchers noted that early initiation of modifications in diet along with physical exercise leads to a decrease in the progression of prediabetes to diabetes by 58% after 2.8 years (Knowler et al., 2002). Current ADA guidelines recommend that patients with diabetes adhere to a diet with reduced calories and fat but rich in fiber (2014). Also, high fiber diets take longer to metabolize. When metabolism is delayed, a sharp spike in glucose levels does not occur and, as a result, the need for a sharp spike in insulin is prevented. In turn, the body avoids undue burden on the pancreas for insulin production. Likewise, poor nutrition itself, characterized by low fiber and excessive carbohydrate diets, has been associated with cognitive impairments (Ahmed & Haboubi, 2010). Therefore, the role of a healthy diet, especially in those with diabetes, is essential.

Physical Exercise

Physical exercise is important for patients with diabetes, as it has been associated with better health outcomes (e.g., healthy weight, better glycemic control, blood pressure, and cholesterol) (ADA, 2014). In addition, older adults who are physically active tend to perform better cognitively than those who are not (Vance, Wadley, Ball, Roenker, & Rizzo, 2005). In a randomized controlled clinical trial on 33 older adults, Baker and colleagues (2010) noted that certain domains of cognition (e.g., executive functioning) were improved by participation in aerobic physical exercise for 45 min to 60 min a day for at least 4 days a week. Additionally, physical exercise has been found to mitigate heart disease and diabetes (Lewis & Hoeger, 2005). Physical exercise has been shown to reduce A1c levels in individuals with diabetes, and such improved A1c is independent of weight loss (Boule, Haddad, Kenny, Wells, & Sigal, 2001). In addition, many older adults find that exercising with others also promotes social stimulation (Vance et al., 2005).

Social Support/Stimulation

Social stimulation has been purported to stimulate the brain and nervous system, thereby ensuring maintenance of or improvement in cognition. In addition, social support has also been noted to be an important predictor of better glycemic control in those with diabetes (ADA, 2014). Without adequate social support, those aging with diabetes may not have someone to remind them to eat healthily or assist in the management of their diabetes. For example, Gau and colleagues (2013) conducted a study on 274 older adults and found that social support was indirectly related to glycemic control through diabetes

self-care behaviors. Therefore, those patients with greater social support had better diabetes control. Sadly, social support is lacking for many people as they age (Schnittker, 2007; Shaw, Krause, Liang, & Bennett, 2007).

Polypharmacy

Jyrkka and colleagues (2011) conducted a prospective cohort study of 294 older adults and noted that polypharmacy (defined as using more than 10 daily medications) was associated with increased cognitive impairment ($p < .001$) when compared to a non-polypharmacy group (no more than 5 daily medications). Therefore, nurses and healthcare providers should strive to eliminate any unnecessary medications for aging patients with diabetes.

Substance Abuse

Low to moderate alcohol use has been associated with the lowest risk of dementia when compared to abstainers and heavy drinkers (Weyerer et al., 2011). In addition, those aging with diabetes can have problems that arise from abuse of substances like alcohol (Hall, 2011). Alcohol abuse increases the risk of liver disease such as cirrhosis. Liver disease impacts the production of cholesterol which in turn impacts vascular health. With abnormal levels of “bad” cholesterol (e.g., triglycerides and low density lipoproteins), more microvascular and macrovascular disease of the brain results (Hall, 2011). These changes in cholesterol and vascular health are already known co-morbid conditions of diabetes. Therefore, the synergistic effects of aging, diabetes, and alcohol abuse yield negative cognitive consequences. Thus, nurses and healthcare providers must

assess whether aging patients with diabetes are abusing substances that can potentiate cognitive impairment.

Implications for Research

Because cognitive impairment results from either direct damage or indirect damage caused by diabetes, researchers should focus their attention on ways to target these two processes. Interestingly, researchers have identified intranasal insulin as a novel way to locally reduce insulin resistance in just the brain instead of systemically lowering blood glucose levels (Shemesh, Rudich, Harman-Boehm, & Cukierman-Yaffe, 2012). Researchers have noted that in rodents, intranasal insulin actually bypasses the blood-brain-barrier and reaches the brain within 30 min (Thorne, Pronk, Padmanabhan, & Frey, 2004). Researchers have postulated that improved insulin sensitivity in the brain improves cognition. Thus, intranasal insulin reaches the olfactory neural pathways and then reaches the hippocampus relatively quickly. Also when insulin is administered intranasally, the close proximity to the tissues of the brain allow for a rise in central nervous system insulin without a systemic effect. This localized effect allows for enhanced neuronal signal transmission and allows improved cognition, as evidenced by the study performed by Reger and colleagues (2006). They studied 26 participants with impaired memory and 35 participants with normal cognition. The researchers administered intranasal insulin and then performed cognitive testing. Interestingly, participants with Alzheimer's disease had improvement in cognition without experiencing dangerous hypoglycemia. The results suggest that normalizing insulin levels may reduce cognitive impairment. With better understanding of the pathologic processes

involved with diabetes and aging, better treatment options for maintaining or improving cognition should be considered.

Conclusion

As people age, diabetes and other co-morbidities become more prevalent. The combination of such disease processes impact neural health. As neural health deteriorates, poor cognitive functioning often results (e.g., mild cognitive impairment or dementia). Therefore, nurses, healthcare providers, and researchers continue to develop ways to (a) prevent co-morbidities associated with aging and diabetes, (b) decrease the severity of such diseases or co-morbid conditions through effective treatment, (c) enhance cognitive reserve, and (d) avoid cognitive losses. Healthcare providers may choose to focus on the pathophysiology of diabetes and cognitive health and target interventions there. They may also choose to focus on lifestyle interventions shown to improve diabetes or cognitive reserve. Regardless of whether one strategy or multiple strategies are implemented in practice, the ultimate goal should improve diabetes control and cognitive health.

References

Ahmed, T., & Haboubi, N. (2010). Assessment and management of nutrition in older people and its importance to health. *Clinical Interventions in Aging, 5,* 207-216. doi: 10.2147/cia.s9664

American Diabetes Association. (2014). Standards of medical care in diabetes-2014. *Diabetes Care, 37,* supplement 1, s14-s80. doi: 10.2337/dc14-S14.

Anderson, R. J., Freedland, K. E., Clouse, R. E., & Lustman, P. J. (2001). The prevalence of co-morbid depression in adults with diabetes. *Diabetes Care, 24,* 1069-1078.

Arvanitakis, Z., Wilson, R. S., Bienias, J. L., Evans, D. A., & Bennett, D. A. (2004). Diabetes mellitus and risk of Alzheimer's disease and decline in cognitive function. *Archives of Neurology, 61,* 661-666.

Baker, L. D., Frank, L. L., Foster-Schubert, K., Green, P. S., Wilkinson, C. W., McTiernan, A., & Craft, S. (2010). Effects of aerobic exercise on mild cognitive impairment: A controlled study. *Archives of Neurology, 67*(1), 71-79. doi: 10.1001/archneurol.2009.307.

Bartzokis, G., Lu, P. H., Heydari, P., Couvrette, A., Lee, G. J., …Altshuler, L. L. (2012). Multimodal magnetic resonance imaging assessment of white matter aging trajectories over the lifespan of healthy individuals. *Biological Psychiatry, 72,* 1026-1034. doi: 10.1016/j.biopsych.2012.07.010

Biessels, G. J., & Kappelle, L. J. (2005). Increased risk of Alzheimer's disease in type II diabetes: Insulin resistance of the brain or insulin-induced amyloid pathology? *Biochemical Society Transactions, 33*(5), 1041-1044. doi: 10.1042/BST20051041

Biessels, G. J., Van der Heide, L. P., Kamal, A., Bleys, R. L., & Gispen, W. H. (2002). Ageing and diabetes: Implications for brain function. *European Journal of Pharmacology, 441*(1-2), 1-14. doi: 10.1016/S0014-2999(02)01486-3

Bopparaju, S., & Surani, S. (2010). Sleep and diabetes. *International Journal of Endocrinology, 2010,* 1-9. doi: 10.1155/2010/759509

Boulé, N. G., Haddad, E., Kenny, G. P., Wells, G. A., & Sigal, R. J. (2001). Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus: A meta-analysis of controlled clinical trials. *Journal of American Medical Association, 286,* 1218-1227.

Boyke, J., Driemeyer, J., Gaser, C., Buchel, C., & May, A. (2008). Training-induced brain structure changes in the elderly. *Journal of Neuroscience, 28,* 7031-7035. doi: 10.1523/JNEUROSCI.0742-08.2008

Brands, A. M., & Kessels, R. P. (2003). Cognitive decline in type 1 diabetes mellitus. *Journal of International Neuropsychological Society, 9,* 583-584.

Brayne, C., Ince, P. G., Keage, H. A., McKeith, I. G., Matthews, F. E., Povikoski, T., & Sulkava, R. (2010). Education, the brain and dementia: Neuroprotection or compensation? *Brain, 133*(pt.8), 2210-2216. doi: 10.1093/brain/awq185

Bruce, J. M., Harrington, C. J., Foster, S., & Westervelt, H. J. (2009). Common blood laboratory values are associated with cognition among older inpatients referred for neuropsychological testing. *The Clinical Neuropsychologist, 23*, 909-925. doi: 10.1080/13854040902795026

Bruce, K. D., & Hanson, M. A. (2010). The development origins, mechanisms, and implications of metabolic syndrome. *Journal of Nutrition, 140,* 648-652.

Centers for Disease Control and Prevention. (2011). *National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States.* Atlanta, GA.: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. Retrieved on 3/18/2013 from: //www.ndep.nih.gov/media/FS,OlderAdult.pdf

Choi, J. H., Chang, S. A., Choi, J. O., Song, Y. B., Hahn, J. Y., Choi, S. H., … Gwon, H. C. (2013). Frequency of myocardial infarction and its relationship to angiographic collateral flow in territories supplied by chronically occluded coronary arteries. *Circulation, 6,* 703-709. doi: 10.1161/CIRCULATIONAHA.112.092353

Cook, D. G., Leverenz, J. B., McMillan, P. J., Kulstad, J. J., Ericksen, S., Roth, R. A. . . . Craft, S. (2003). *American Journal of Pathology, 162,* 313-319.

Costa, S. (2013). Experts address mechanisms, link between cognitive decline and diabetes. *Endocrine Today, 11*(3), 1, 12-14.

Cukierman, T., Gerstein, H. C., & Williamson, J. C. (2005). Cognitive decline and dementia in diabetes- a systematic overview of prospective observational studies. *Diabetologia, 42,* 2460-2469.

Cukierman-Yaffe, T., Gerstein, H. C., Williamson, J. D., Lazar, R. M., Lovato, L., Miller, M. E., …Launer, L. J. (2009). Relationship between baseline glycemic control and cognitive function in individuals with type 2 diabetes and other cardiovascular risk factors. *Diabetes Care, 32*(2), 221-226. doi: 10.2337/dc08-1153

Domingueuz, R. O., Marschoff, E. R., Gonzalez, S. E., Repetto, M. G., & Serra, J. A. (2012). Type 2 diabetes and/or its treatment leads to less cognitive impairment in Alzheimer's disease patients. *Diabetes Research and Clinical Practice, 98*(1):68-74. doi: 10.1016/j.diabres.2012.05.013

Eliopoulos, C. (2014). Neurologic function. In *Gerontological Nursing (*pp. 349-358). Philadelphia, PA: Wolters Kluwer Health/ Lippincott Williams & Wilkins.

Euser, S. M., Sattar, N., Witteman, J. C., Bollen, E., Sijbrands, E. J., Hofman, A., … Westendorp, R. G. (2010). A prospective analysis of elevated fasting glucose levels and cognitive function in older people: Results from PROSPER and the Rotterdam study. *Diabetes, 59,* 1601-1607. doi: 10.2337/db09-0568

Feil, D. G., Zhu, C. W., & Sultzer, D. (2012). The relationship between cognitive impairment and diabetes self- management in a population-based sample of older adults with Type 2 diabetes. *Journal of Behavioral Medicine, 35*(2), 190-199. doi: 10.1007/s10865-011-9344-6

Galanina, N., Surampudi, V., Ciltea, D., Singh, S. P., & Permuter, L. C. (2008). Blood glucose levels before and after cognitive testing in diabetes mellitus. *Experimental Aging Research, 34,* 152-161. doi: 10.1080/036107307011876979

Gangwisch, J. E., Malaspina, D., Boden-Albala, B., & Heymsfield, S. B. (2005). Inadequate sleep as a risk factor for obesity: Analyses of the NHANES I. *Sleep, 28,* 1289–1296.

Gau, J., Wang, J., Zheng, P., Haardörfer, R., Kegler, M. C., Zhu, Y., & Fu, H. (2013). *Bio Med Central Family Practice, 14*, 66. Retrieved from: http://www.biomedcentral.com/1471-2296/14/66

Greer, T. L., Sunderajan, P., Grannemann, B. D.,Kurian, B. T., & Trivedi, M. H. (2014). Does duloxetine improve cognitive function independently of its antidepressant effect in patients with major depressive disorder and subjective reports of cognitive dysfunction? *Depression Research and Treatment, 2014*, 1-14. doi.org/10.1155/2014/627863

Hall, J. E. (2011). *Guyton and Hall: Textbook of medical physiology*. Philadelphia, PA: Saunders Elsevier.

Havrankova, J., Roth, J., & Brownstein, M. (1978). Insulin receptors are widely distributed in the central nervous system of the rat. *Nature, 272*, 827 – 829. doi: 10.1038/272827a0

Hayden, K. M., Reed, B. R., Manly, J. J., Tommet, D., Pietrzak, R. H., Chelune, G. J. ,…Jones, R. N. (2011). Cognitive decline in the elderly: An analysis of population heterogeneity. *Age and Ageing, 40*, 684-689. doi: 10.1093/ageing/afr101

Holman, R. (2001). The UKPDS: Implications for the dyslipidaemic patient. *Acta Diabetology, 38* (supplement 1), S9-14.

James, P. A., Oparil, S., Carter, B., Cushman, W. C., Dennison-Himmelfarb, C., Handler, J., Lackland, D. T., … Ortiz, E. (2014). 2014 evidence-based guideline for the management of high blood pressure in adults: Report from the panel members appointed to the eighth joint national committee (JNC8). *Journal of the American Medical Association, 311(5)*, 507-520. doi: 10.1001/jama.2013.284427

Jyrkka, J., Enlund, H., Lavikainen, P., Sulkava, R., & Hartikainen, S. (2011). Association of polypharmacy with nutritional status, functional ability and cognitive capacity over a three-year period in an elderly population. Pharmacoepidemiology and Drug Safety, 20, 514–522. doi: 10.1002/pds.2116

Kaulgud, R. S., Nekar, M. S., Sumanth, K. J., Joshi, R. R., Vijayalakshmi, P. B., Desai, S., & Patil, H. (2013). Study of depression in patients with diabetes compared to non diabetics among elderly population and its association with blood sugar, HbA1c values. *International Journal of Biomedical Research, 4*(1), 55-61.

Knowler, W. C., Barrett-Connor, E., Fowler, S. E., Hamman, R. F., Lachin, J. M., Walker, E. A., …The Diabetes Prevention Program Research Group. (2002). Reduction in the incidence of type 2 diabetes with lifestyle intervention or

metformin. *New England Journal of Medicine, 346*(6), 393-403. doi: 10.1056/NEJMoa012512

Lee, S. M., Koh, D., Fun, S. N., & Sum, C. F. (2011). Diabetes management and hyperglycemia in safety sensitive jobs. *Safety and Health at Work, 2*(4), 380-384. doi: 10.5491/shaw.2011.2.4.380

Lewis, V., & Hoeger, K. (2005). Prevention of coronary heart disease: A nonhormonal approach. *Seminars in Reproductive Medicine, 23*(2), 157-166. doi: 10.1055/s-2005-869483

Maillard, P., Carmichael, O., Fletcher, E., Reed, B., Mungas, D., & DeCarli, C. (2012). Coevolution of white matter hyperintensities and cognition in the elderly. *Neurology, 79*(5), 442-448. doi: 10.1212/WNL.0b013e3182617136.

McCutchan, J. A., Marquie-Beck, J. A., FitzSimons, C. A., Letendre, S. L., Ellis, R. J., Heaton, R. K., … Grant, I. (2012). Role of obesity, metabolic variables, and diabetes in HIV-associated neurocognitive disorder. *Neurology, 78*(7), 485-492. doi: 10.1212/WNL.0b013e3182478d64

Mesarwi, O., Polak, J., Jun, J., & Polotsky, V. (2013). Sleep disorders and the development of insulin resistance and obesity. *Endocrinology and Metabolism Clinics 42*(3), 617-634. doi.org/10.1016/j.ecl.2013.05.001

Messier, C., & Teutenberg, K. (2005). The role of insulin, insulin growth factor, and insulin-degrading enzyme in brain aging and Alzheimer's disease. *Neural Plasticity, 12*(4), 311-327.

Messier, C., Tsiakas, M., Gagnon, M., & Desrochers, A. (2010). Effect of age and glucoregulation on cognitive performance. *Journal of Clinical and Experimental Neuropsychology, 32*(8), 809–821. doi: 10.1080/13803390903540323

Moretti, A., Gorini, A., & Villa, R. F. (2011). Pharmacotherapy and prevention of vascular dementia. *CNS & Neurological Disorders Drug Targets, 10*(3), 370-390.

Morris, J. K., & Burns, J. M. (2012). Insulin: an emerging treatment for Alzheimer's disease dementia? *Current Neurology and Neuroscience Reports, 12*(5), 520-7. doi: 10.1007/s11910-012-0297-0

Okereke, O., Kang, J., Cook, N. R., Gaziano, J. M., Manson, J. E., Buring, J. E., & Grodstein, F. (2008). Type 2 diabetes mellitus and cognitive decline in two large cohorts of community-dwelling older adults. *Journal of the American Geriatrics Society, 56,* 1028-1036. doi: 10.1111/j.1532-5415.2008.01686.x

Park, C. R., & Johnson, L. H. (1955). Effect of insulin on transport of glucose and galactose into cells of rat muscle and brain. *American Journal of Physiology, 182*(1), 17-23

Petersen, K. F., & Shulman, G. I. (2006). Etiology of insulin resistance. *American Journal of Medicine, 119,* 510-516.

Potau, N., Escofet, M. A., & Martinez, M. C. (1991). Ontogenesis of insulin receptors in human cerebral cortex. *Journal of Endocrinological Investigation, 14*(1), 53-58.

Reaven, G. (2004). The metabolic syndrome or the insulin resistance syndrome? Different names, different concepts, and different goals. *Endocrinology and Metabolism Clinics of North America, 33,* 283-303. doi: 10.1016/j.ecl.2004.03.002

Reger, M. A., Watson, G. S., Frey, W. H., Baker. L. D., Cholerton, B., Keeling, M. L., …Craft. S. (2006). Effects of intranasal insulin on cognition in memory-impaired older adults: Modulation by APOE genotype. *Neurobiology of Aging, 27*(3), 451-458. doi: 10.1016/j.neurobiolaging.2005.03.016

Reijmer, Y. D., van den Berg, E., Ruis, C., Kapelle, L. J., & Biessels, G. J. (2010). Cognitive dysfunction in patients with type 2 diabetes. *Diabetes/ Metabolism Research and Reviews, 26,* 507–519. doi: 10.1002/dmrr.1112

Rizzo, M. R., Marfella, R., Barbieri, M., Boccardi, V., Vestini, F., Lettieri, B., …Paolisso, G. (2010). Relationship between daily acute glucose fluctuations and cognitive performance among aged type 2 diabetics. *Diabetes Care, 33*(10), 2169-2174. doi:10.2337/dc10-0389

Roe, C. M., Mintun, M. A., D'Angelo, G., Viong, C., Grant, E. A., & Morris, J. C. (2008). Alzheimer disease and cognitive reserve: Variation of education effect with carbon 11-labeled Pittsburg Compound B uptake. Archives in Neurology, 65(11), 1467-1471. doi: 10.1001/archneur.65.11.1467

Schmidt, C., Peigneux, P., & Cajochen, C. (2012). Age-related changes in sleep and circadian rhythms: Impact on cognitive performance and underlying neuroanatomical networks. *Frontiers in Neurology, 3*(118), 1-11. doi: 10.3389/fneur.2012.00118

Schnittker, J. (2007). Look (closely) at all the lonely people: Age and the social psychology of social support. *Journal of Aging and Health, 19*(4), 659-682. doi:10.1177/0898264307301178

Shaw, B. A., Krause, N., Liang, J., & Bennett, J. (2007). Tracking changes in social relations throughout later life. *Journal of Gerontology: Psychological Science and Social Science, 62(*2), S90-S99.

Shemesh, E., Rudich, A., Harman-Boehm, I., & Cukierman-Yaffe, T. (2012). Effect of intranasal insulin on cognitive function: A systematic review. *Journal of Clinical Endocrinology, 97,* 366-376. doi: 10.1210.jc.2011-1802

Shimada, H., Miki, T., Tamura, A., Ataka, S., Emoto, M., & Nishizawa, Y. (2010). Neuropsychological status of elderly patients with diabetes mellitus. *Diabetes Research and Clinical Practice, 87*(2), 224-227. doi: 10.1016/j.diabres.2009.09.026

Small, G. W. (2002). What we need to know about age related memory loss. *British Medical Journal, 324*, 1502–1505.

Stern, Y. (2012). Cognitive reserve in ageing and Alzheimer's disease. *Lancet Neurology, 11*, 1006–1012. doi: 10.1016/S1474-4422(12)70191-6

Stevens, R. J., Kothari, V., Adler, A. I., & Stratton, I. M. (2001). The UKPDS risk engine: a model for the risks of coronary heart disease on Type II diabetes. *Clinical Science, 101*, 671-679.

St. John, P., & Montgomery, P. (2003). Is subjective memory loss correlated with MMSE scores on dementia? *Journal of Geriatric Psychiatry and Neurology, 16*, 80-83.

Sullivan, M. D., Katon, W. J., Lovato, L. C., Miller, M. E., Murray, A. M., Horowitz, K. R., … Launer, L. J. (2013). Association of depression with accelerated cognitive decline among patients with type 2 diabetes in the ACCORD-MIND trial. *Journal of the American Medical Association Psychiatry, 70*(10), 1041-1047. doi: 10.1001/jamapsychiatry.2013.1965.

Thorne, R. G., Pronk, G. J., Padmanabhan, V., & Frey, W. H. (2004). Delivery of insulin-like growth factor-I to the rat brain and spinal cord along olfactory and trigeminal pathways following intranasal administration. *Neuroscience, 127*, 481–496

Tiehuis, A. M., van der Graaf, Y., Visserman, F. L., Vincken, K. L., Biessels, G. J., Appelman, A. P., …Mail, W. P. (2008). Diabetes increases atrophy and vascular lesions on brain MRI in patients with symptomatic arterial disease. *Stroke, 39*, 1600-1603. doi:10.1161/strokeaha.107.506089

United Kingdom Prospective Diabetes Study Group. (1995). Overview of 6 years' therapy of type II diabetes, a progressive disease. *Diabetes, 44(*11), 1249-1258.

United Kingdom Prospective Diabetes Study Group. (1998). Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *British Medical Journal, 317*(7160), 703-713.

United States Department of Aging: United States Bureau of the Census, Population Division. (2008). *Projections of the Population by Age and Sex for the United States: 2010 to 2050* (Publication No. NP2008-T12), Retrieved from http://www.aoa.gov/AoARoot/Aging_Statistics/future_growth/future_growth.aspx#age

United States Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute, National Cholesterol Education Program. (2002). *The Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)* (NIH Publication No. 02-5215). Retrieved from http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3full.pdf

Vance, D. E., & Burrage, J. W. (2006). Promoting successful cognitive aging in adults with HIV: Strategies for intervention. *Journal of Gerontological Nursing, 32*(11), 34-41.

Vance, D. E., Heaton, K., Eaves, Y., & Fazeli, P. L. (2011). Sleep and cognition on everyday functioning in older adults: Implications for nursing practice and research. *Journal of Neuroscience Nursing, 43*(5), 261-273. doi: 10.1097/jnn.0b013e318227efb2

Vance, D. E., Kaur, J., Fazeli, P. L., Talley, M. H., Yuen, H. K., …, Lin, F. (2012). Neuroplasticity and successful cognitive aging: A brief overview for nursing. *Journal of Neuroscience Nursing*, *44*(4), 218-27. doi: 10.1097/JNN.0b013e3182527571

Vance, D. E., Wadley, V. G., Ball, K. K., Roenker, D. L., & Rizzo, M. (2005). The effects of physical activity and sedentary behavior on cognitive health in older adults. *Journal of Aging & Physical Activity*, *13*(3), 294-313.

Vance, D. E., & Wright, M. A. (2009). Positive and negative neuroplasticity: Implications for age-related cognitive declines. *Journal of Gerontological Nursing*, *35*(6), 11-17. doi: 10.3928/00989134-20090428-02

Van Elderen, S. G., de Roos, A., de Craen, A. J., Westendorp, R. G., Blauw, G. J., Jukema, J. W., …van der Grond, J. (2010). Progression of brain atrophy and cognitive decline in diabetes mellitus. *Neurology, 75*(11), 997-1002. doi: 10.1212/WNL.0b013e3181f25f06

Van Guilder, H. D., Farley, J. A., Yan, H., Van Kirk, C. A., Mitschelen, M., … Freeman, W. M. (2011). Hippocampal dysregulation of synaptic plasticity-associated proteins with age-related cognitive decline. *Neurobiology Disorders*, *43*(1), 201-212. doi: 10.1016/j.nbd.2011.03.012.

Weyerer, S., Schaufele, M., Wiese, B., Maier, W., Tebarth, F., van den Bussche, H., … Riedel-Heller, S. G. (2011). Current alcohol consumption and its relationship to incident dementia: results from a 3-year follow-up study among primary care attenders aged 75 and older. *Age Aging, 40*(4), 456-463. doi: 10.1093/ageing/afr007.

Whitmer, R. A., Sidney, S., Selby, J., Johnston, C. S., & Yaffe, C. (2005). Midlife cardiovascular risk factors and risk of dementia in late life. *Neurology, 64*(2), 277-81

Yaffe, K. (2007). Metabolic syndrome and cognitive disorders: Is the sum greater than its parts? *Alzheimer's Disease and Associated Disorders, 21*(2), 167-171. doi: 10.1097/WAD.0b013e318065bfd6

Yaffe, K., Kanaya, A., Lindquist, K., Simonstick, E. M., Harris, T., Shorr, R., …Newman, A. B. (2004). The metabolic syndrome, inflammation, and risk of cognitive decline. *Journal of the American Medical Association, 292*(18), 2237-2242. doi: 10.1001/jama.292.18.2237

Zhao, W. Q., Chen, H., Quon, M. J., & Alkon, D .L. (2004). Insulin and the insulin receptor in experimental models of learning and memory. *European Journal of Pharmacology, 490*, 71–81.

Zhou, Y., & Danbolt, N. C. (2013). GABA and glutamate transporters in the brain. *Frontiers in Endocrinology, 4*(165), 1-14. doi: 10.3389/fendo.2013.00165

Ziegler, D., Sohr, C. G., & Nourooz-Zadeh, J. (2004). Oxidative stress and antioxidant defense in relation to the severity of diabetic polyneuropathy and cardiovascular autonomic neuropathy. *Diabetes Care, 27*(9), 2178-2183. doi: 10.2337/diacare.27.9.2178

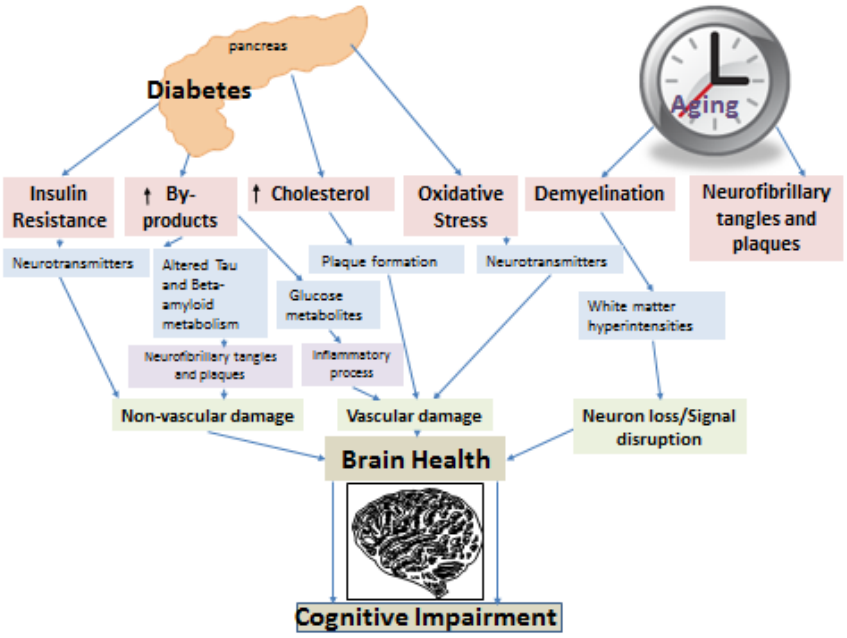

Figure 1. Effects of Diabetes and Aging on Cognitive Impairment.

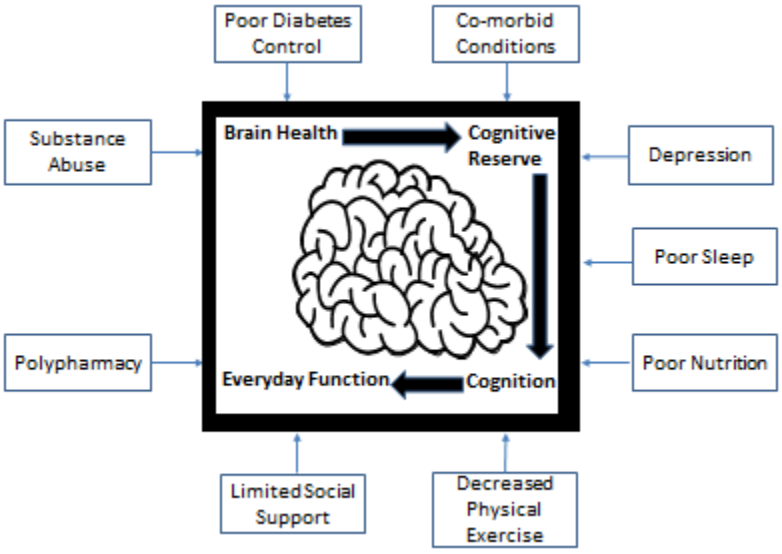

Figure 2. Factors that Influence Diabetes, Cognitive Impairment, and Aging.

METABOLIC, INFLAMMATORY, AND APOLIPOPROTEIN E VARIATION ON COGNITIVE FUNCTIONING IN MID-LIFE

by

MICHELE H. TALLEY, ERICA R. PRYOR, VIRGINIA G. WADLEY, MICHAEL CROWE, SHANNON MORRISON, AND DAVID E. VANCE

Disclaimer: Article 2 has not received final approval from the Coronary Artery Risk Development in Young Adults' (CARDIA) Publication and Presentation Committee and should not be considered the final version. Therefore, the manuscripts and content therein should not be cited or referenced.

Format adapted for dissertation

Abstract

With an aging population, a focus on successful cognitive aging in midlife is warranted. Predictor variables at year 20 were used to determine cognitive functioning 5 years later (i.e., at year 25). The objective of this study was to identify predictors and investigate the relationship between predictors of cognitive functioning among middle-aged adults in the Coronary Artery Risk Development in Young Adults (CARDIA) Study with and without apolipoprotein E epsilon 4 allele (APOE ε4) expression. Hierarchical regression analyses were used to examine predictors of cognitive functioning. After controlling for age, gender, race (Black or White), level of education, and site, hyperglycemia, hyperlipidemia, elevated inflammatory markers, and poor vascular health were added to the model incrementally. Demographic covariates were examined added in step 1 of the model. Step 2 examined hyperglycemia after controlling for demographic covariates. Lipid levels were added in step 3; inflammatory markers in step 4, and vascular health in step 5. These analyses were performed separately for all participants and for participants stratified by APOE ε4 expression. Several hypothesized relationships were suggested. Specifically, lower levels of HbA1c, triglycerides, and interleukin-6 were associated with better cognitive functioning 5 years later for those without APOE ε4 carrier status and for the unstratified group. However, for those participants with APOE ε4 carrier status, only younger age, higher levels of education, and surprisingly, higher LDL-C levels were associated with higher cognitive composite scores. Younger age was associated with better cognitive functioning.

Keywords: cognitive functioning, diabetes, predictors, CARDIA, APOE ε4

Introduction

By 2050, those who are aged 65 years and older are expected to triple to 1.5 billion, representing 16% of the world population (U.S. Department of Health and Human Services, 2014). Therefore, it is important to understand correlates of successful cognitive aging. Successful cognitive aging depends largely on cognitive reserve. Cognitive reserve refers to the amount of insult neurons and their connections can absorb while still functioning and supporting cognition. Normal cognitive functioning is required for engagement in cognitively demanding everyday activities (e.g., driving a car, grocery shopping, taking medications, managing finances and healthcare, etc.). Even modest disruption in cognitive functioning can result in interference with higher-order activities of daily living (McGuire, Ford, & Ajani, 2006; Okonkwo, Griffith, Vance, Marson, Ball, & Wadley, 2009). Determining cognitive functioning at middle-age along with identifying the relationship among metabolic and inflammatory predictors could be of great importance as strides are made to protect cognitive reserve and optimize cognitive functioning later in life. Long-term exposure to such predictors could seemingly increase the risk of developing decline in cognitive functioning. Hence, the importance of identifying significant predictors of cognition in middle-aged adults is crucial to determining the best model that predicts cognitive functioning later in life. Once this has been accomplished, interventions can be implemented during middle-age so that the severity and occurrence of future cognitive impairment may be reduced while the brain is relatively more plastic than in older age (Carmelli, 2014).

Many predictors of coronary artery disease are also predictors for a decline in cognitive functioning in later life (e.g., diabetes, genetic predisposition, calcification in

the arteries, and inflammatory factors) (Feinkohl et al., 2013). Of these predictors, some can be controlled (e.g., diabetes, vascular disease from hyperlipidemia, and inflammatory factors) while others cannot (e.g., race, gender, and the presence of the APOE ε4 allele). Coronary Artery Risk Development in Young Adults (CARDIA), a 25-year cohort study, was designed to evaluate the coronary artery risk development in Black and White adults who were aged 18-30 years at enrollment (Friedman et al., 1988). Cognitive functioning also was assessed in CARDIA.

Demographic, metabolic, and inflammatory processes marker variables are potential predictors of cognitive functioning (Rafnsson et al., 2007; Singh-Manoux, Britton, & Marmot, 2003; Strachan, 2010). By studying each potential predictor, significant associations can be identified and can be used later to determine the best model that predicts cognitive impairment in middle-aged adults. The longitudinal nature of the CARDIA Study provided a unique opportunity to examine these factors in a racially diverse cohort.

Demographic Covariates

Demographic covariates such as age, race, gender, and level of education may prove to be important in determining cognitive functioning through their impact on aging and chronic disease development. Arterial atherosclerotic plaque, which is often calcified, leads to turbulence in blood flow. In addition, Black adults, at least in America, are also more likely to have hypertension and diabetes than White adults (Nasir). This point is important because such medical conditions can impair brain health (Cukierman, Gerstein, & Williamson, 2005; Talley et al., 2015). Specific racial, gender, and

educational differences have been reported in previous studies conducted by the CARDIA researchers. For example, in the CARDIA Study, education levels were higher in White participants; White men had higher levels of triglycerides and low density lipoprotein cholesterol (LDL-C) and triglycerides than Black men; however, lower high density lipoprotein cholesterol (HDL-C) levels were noted in White men when compared to Black men (Norman, Bild, Lewis, Liui, & West, 2003). Additionally, Black and White men along with Black women were noted to have blood cholesterol increase with age (Van Horn et al., 1991); as the cholesterol increases, risk for neurovascular disease may increase and negatively impact cognitive functioning. In addition, higher levels of education have been associated with better cognitive maintenance (Mortamais et al., 2013).

Metabolic and Inflammatory Predictors

Many metabolic and inflammatory predictors may influence cognitive functioning including hyperglycemia, dyslipidemia, inflammatory markers, and loss of vascular health. In the recent Whitehall II Cohort, researchers studied cognitive performance over time in 6,401 adults who were of normal weight, overweight, or obese (Singh-Manoux et al., 2012). These researchers observed that obese participants had the fastest decline in cognition when they also had metabolic abnormalities compared to those without such abnormalities, indicating that while obesity has a link with cognitive functioning, its effects may be strengthened by co-morbid conditions due to metabolic abnormalities. Therefore, metabolic predictors in relation to cognitive functioning should be examined in greater detail.

Hyperglycemia, a hallmark characteristic of diabetes, may also negatively impact cognitive functioning. Diabetes is a metabolic risk factor that becomes more prevalent with advancing age. Indeed, 10.9 million (26.9%) older Americans have diabetes (Centers for Disease Control and Prevention [CDC], 2011). Moreover, based on a systematic review of 25 observational studies (Cukierman et al., 2005), it is estimated that persons with diabetes are 1.5 times more likely to suffer from cognitive impairments than persons without diabetes. While we know that diabetes is related to lower cognitive function and greater risk for declines, it is less clear whether hyperglycemia, even at levels below those found in diabetes, may also negatively influence cognitive functioning. Hyperglycemia affects lipids, inflammatory markers, and vascular health—all factors which plausibly relate to cognitive functioning (Zhang & Wu, 2014).

Dyslipidemia is another syndrome negatively associated with cognitive functioning in older adults (Anstey, Lipnicki, & Low, 2008). More specifically, elevated LDL-C levels are associated with poorer cognitive functioning later in life as a result of vascular damage. In a study conducted by Helzner and colleagues (2009), 156 patients with higher LDL-C levels before the diagnosis of Alzheimer's disease experienced faster decline in cognitive functioning after diagnosis than those without high LDL-C levels. Higher triglyceride levels are associated with a higher risk of cardiovascular disease and death (Liu et al., 2013) while higher HDL-C levels are associated with lower risk of cardiovascular disease and related deaths (Silbernagel et al., 2013). The ratio of LDL-C and HDL-C is what actually determines the amount of plaque and arterial calcifications. Plaques in the arteries result in poorer cardiovascular health and, therefore, negatively

affect neurovascular health which can contribute to poorer cognitive functioning (Alosco et al., 2014).

Inflammatory markers, including interleukin-6 and C-reactive protein, may also contribute to neuroinflammation which hinders cognition (Ownby, 2010). Interleukin-6 is a key cytokine that mediates the acute phase of inflammation. With inflammation, local thrombosis (or clotting) is initiated. Such chronic inflammatory changes can alter the vasculature and might accelerate risk for the development of Alzheimer's disease and associated cognitive changes (Akiyama et al., 2000). C-reactive protein is another indicator of inflammation. Higher levels (greater than 10 mg/L) can indicate acute infection while lower more subtle levels (1-3 mg/L) indicate inflammation. Levels between 3-10 mg/L may indicate inflammatory processes such as cardiovascular disease; hence, monitoring these markers of inflammation in conjunction with cognitive function is warranted.

Measurements of changes in the vasculature can be determined by studying the calcification of the coronary arteries. Calcification of atherosclerotic plaque is typically a head-to-toe occurrence; therefore, coronary artery calcification could correlate with cerebral calcification. Cerebral calcification could in turn alter cognitive functioning because the calcifications limit the amount of blood that can flow to the brain and its structures. Alosco and colleagues (2014) conducted a study on 55 older adults and found that less cerebral blood flow predicted poorer cognitive functioning.

Specific genetic predispositions (i.e., presence of APOE ε 4) also might relate to cognitive functioning (Radwan et al., 2014), although this relationship is equivocal in young and middle-aged adults and likely is age-dependent (Small, Rosnick, Fratiglioni, &

Backman, 2004). Apolipoprotein E is a polymorphic glycoprotein with three alleles (ε2, ε3, and ε4) which are present in the plasma on chylomicrons, namely very low density lipoprotein cholesterol and HDL-C (Radwan et al.). These apolipoproteins serve as a ligand for the LDL receptor and LDL receptor-related protein. Hence, APOE plays a vital role in catabolism triglyceride-rich lipoprotein as well as cholesterol homeostasis (Mortimer, Redgrave, Spangler, Verstuyft, & Rubin, 1994). Additionally, APOE ε3/4, and ε4/4 alleles have been associated with elevated LDL-C levels (Puttonen, Elovainio, Kivimaki, Lehtimaki, & Keltikangas-Jarvinen, 2003). A complex relationship has been noted between LDL-C, genetic expression of APOE, and cognitive functioning (Barres & Smith, 2002).

Purpose

The purpose of this study was to determine the relationship of hyperglycemia to cognitive functioning while controlling for potential metabolic and inflammatory markers. These relationships were examined in those with and without APOE ε4 expression, specifically, to determine whether the relationships differed in those with this genetic predisposition to Alzheimer's disease (Rizzuto, 2013). In the CARDIA Study, 3,485 Black and White men and women were examined to determine APOE phenotypes as well as gender and racial differences in phenotype frequencies (Howard, Gidding, & Liu, 1998). These researchers found that Black men and women had higher frequencies of the ε4 allele than White adults ($p < .005$).

Based upon the literature, hierarchical regression models for predicting the relationship of hyperglycemia to cognitive functioning in middle-aged adults were

constructed. Demographic variables were controlled in all models. Potential confounding metabolic and inflammatory variables were added in a stepwise fashion. Hypothesized relationships appeared in the order in which they were thought to influence one another (i.e., hyperglycemia influenced lipids, inflammatory markers, and vascular health so they were added to the model in that order [Zhang & Wu, 2014]). Therefore, hyperglycemia was introduced in step 2 after the demographic covariates were introduced in step 1. In step 3, lipids were introduced as they influence inflammatory markers and vascular health, which in turn influences cognitive functioning (Donahue et al., 1989). In step 4, inflammatory markers were introduced due to their influence on vascular health and finally cognitive functioning (Umegaki, 2014). In step 5, vascular health was added due to its effect on cognitive functioning. These models were tested first for all participants, using an overall cognitive composite score as the outcome; and then separately in participants with and without the APOE ε4 allele.

Methods

Participants

This study was conducted using records from the participants of the CARDIA Study, a prospective study designed to study the evolution of cardiovascular disease risk over 25 years in a cohort of Black and White women and men who were 18 to 30 years old at enrollment (Friedman et al., 1988). A young population was recruited from four urban areas: University of Alabama at Birmingham (Birmingham, AL), the University of Minnesota (Minneapolis, MN), Northwestern University (Chicago, IL), and Kaiser Permanente (Oakland, CA) (Hughes et al., 1987). Within each of these locations, care

was taken to ensure that equal representation was achieved with regard to race, gender, education, and age. Specific inclusion and exclusion criteria were also instituted for participation. Participants in these cities who were free of disability and long-term diseases that could interfere with the examinations were invited to participate. Participants who were pregnant or up to 3-months postpartum, deaf, blind, mentally challenged, mute, or unable to ambulate on a treadmill were excluded. Initially, CARDIA recruited a total of 5,115 participants, which was approximately 50% of those invited. At year 25 (2010-2011), 3,499 participants were examined (72% of surviving cohort). Of these participants, 233 were excluded for the current study because they had incomplete information on all three tests of cognitive function and 79 were excluded for reporting a prior transient ischemic attack or stroke. After using listwise deletion, a total of 2,229 participants remained; only those participants whose records had complete data for all variables of interest including the cognitive tests at year 25 were included in this study.

Measures

The CARDIA Study collected data at years 0, 2, 5, 7, 10, 20, and 25 post-recruitment. Because each assessment had a different set of aims, not all variables were tested at each follow-up visit. Demographic data (e.g., age, gender, and race) were gathered at year 0; except for level of education, which was garnered from year 25. Apolipoprotein E status was retrieved from year 7. The measures of hyperglycemia, lipid status, inflammatory markers, and vascular disease from year 20 were used. These variables were used as potential predictors of cognitive functioning 5 years later when cognitive tests were administered at year 25.

Demographic Covariates. A sociodemographic questionnaire was used to determine age, gender, race, and level of education. These variables were self-reported. The date of birth (i.e., age in years), gender (women = 0; men = 1), and race (Black = 4; White = 5) were used from year 0 of the study. In addition, site was statistically controlled (Birmingham = 1; Chicago = 2; Minnesota = 3; Oakland = 4). Race and sex were later verified at year 2. The total number of years a participant had completed by year 25 was reported as level of education.

Metabolic and Inflammatory Predictors. Specific laboratory measures were used to study hyperglycemia, lipid levels, inflammatory markers, and coronary artery calcification (CAC). Venous blood sampling was performed after participants had fasted for at least 12 hr. The sample was collected using minimal stasis, divided, stored at -70°C, and then shipped to the central study laboratories (Howard, Gidding, & Liu, 1998). In order to determine whether participants had hyperglycemia, the results from the hemoglobin A1c (HbA1c), a 90 to 120 day average of blood glucose levels, were evaluated. A lipid panel was used to determine the value of LDL-C, HDL-C, and triglycerides.

Specific inflammatory markers, namely C-reactive protein and interleukin-6, were used to determine if inflammation was present. C-reactive protein was assessed using a nephelometry-based high throughput assay. Interleukin-6 was measured using an ELISA assay from R&D Systems with methodology well established in the laboratory. Interleukin-6 is a key cytokine that mediates acute inflammation which then promotes clotting within the vasculature.

Vascular health was determined using coronary artery calcification scores from year 20. The coronary artery calcification was either measured using the GE Lightspeed QX/I (Birmingham), the Imatron C-150 (Chicago and Oakland), or the Siemens S4+ Volume Zoom (Minneapolis). The scanning protocol was developed by a committee of cardiologists, radiologists, and a physicist to ensure that the scans were as uniform as possible when using different technologies (Carr et al., 2005). A central CT reading center at Harbor-UCLA Research and Education Institute, Los Angeles, California was used to coordinate all activities and measurements of the calcified coronary artery plaque. The presence of CAC was defined as a positive, non-zero Agatston score after averaging two scans. For this study, the CAC variable was dichotomized; 0 indicated participants with no coronary artery calcification while 1 indicated the presence of coronary artery calcification.

Presence of the APOE ε4 allele may predict vascular health and dementia risk and, hence, cognitive functioning. Apolipoprotein E status from year 7 was determined from plasma samples obtained from each participant. CARDIA modified the method originally identified by Kamboh et al. (1988). For this study, participants were classified according to APOE phenotype prior to the analysis. Two groups were created - those with APOE ε4 (ε3/4 or ε4/4 alleles) and those without APOE ε4 (ε2/4, any ε2 and ε3 alleles).

Dependent Variable. The dependent variable of interest was cognitive functioning. For this study, cognitive functioning was operationalized as the composite *z*-score derived from scores on three cognitive tests. These tests were administered by

certified cognitive technicians and included the Stroop Test, the Digit Symbol Substitution Test (DSST), and the Rey-Auditory Verbal Learning Test (RAVLT).

Stroop Test. The Stroop Test is a measure of executive function (often attributed to the frontal lobe). Executive function is a conglomerate of skills needed for complex, goal-directed behavior and adaptation to one's environment. The Stroop Test evaluated the participant's ability to view complex visual stimuli and respond to one stimulus while blocking out the processing of other stimuli. Three subtests were utilized for the Stroop Test. In subtest 1, the participants verbalized color words that were written in black ink. In subtest 2, the participants verbalized the colors of colored rectangles. In subtest 3, the participants verbalized the color of ink in which color words were written (i.e., if the word "red" is written in green ink, the correct answer is green) (Reis et al., 2013). An interference score was calculated by subtracting the score on subtest 3 from the score from subtest 2. Interference provided a measure of the additional executive processing needed to respond to subtest 3; higher interference scores indicate worse performance.

Digit Symbol Substitution Test (DSST). The DSST is a subtest of the Wechsler Adult Intelligence Scale, Third Edition, and is a measure of psychomotor speed (Salthouse, 1992). For this test, participants were presented with rows of numbers with empty boxes underneath. A key appeared at the top of the form, and the numbers 1-9 were shown. Each number was paired with a distinct symbol. Participants were asked to fill in the blank boxes below the numbers with their distinct symbols (up to 140 boxes) in a 2-min period. Participants received a point for each correctly drawn symbol. The

obtained range of scores was 0-133; higher scores indicate better cognitive functioning (Reis et al., 2013).

Rey-Auditory Verbal Learning Test (RAVLT). The RAVLT assesses memory as well as verbal learning (Malloy-Diniz, Lasmar, Gazinelli, Fuentes, & Salgado, 2007). More specifically, the test assessed participants' ability to recall a short list of words with immediate, short-term, and long-term recall. A 15-item word list was read to the participants at a rate of one word per second. The list of words was presented five times and participants were asked to immediately recall as many words as possible. A 1-min maximum time limit was allowed per trial for the recall. The cognitive technician checked off all of the words the participants were able to recall. An interference list of words was presented next. Participants were asked to recall these words immediately. Participants were then asked to recall words from the first trial. Then once 10 min had lapsed, the cognitive technician asked the participants to recall as many of the words as possible that were on the first list. Participants were scored according to the total number of words remembered correctly for each trial (Trial 1-5). Five trials were scored but only the long delay score was used for this study. Higher scores indicating better cognitive performance.

Composite Cognitive Score. In order to have a stable global measure of cognition, the scores from each cognitive test (Stroop, DSST, and RAVLT) were transformed into *z*-scores and summed to form a composite cognition score. Higher scores indicate better cognitive functioning.

Data Analysis

When data were missing, listwise deletion was used. The large sample size in this study eliminated the need for pairwise deletion or imputation. Larger sample sizes are typically resistant to violations of assumptions of normality as the larger the sample, the more likely it is to be representative of the population (Polit & Beck, 2008). Parametric correlations (i.e., Pearson's *r*) were conducted for all continuous variables and nonparametric correlations were used for dichotomous data. Threats to multicollinearity were assessed in each of the steps but none were found.

Hierarchical regression analyses were performed to investigate the relationship between predictors of cognitive functioning among middle-aged adults in the CARDIA Study. Demographic variables (i.e., age, gender, race, level of education, and site), hyperglycemia (e.g., HbA1c at year 20), lipids (i.e., LDL-C, HDL-C, and triglycerides at year 20), inflammatory markers (i.e., C-reactive protein and interleukin-6 at year 20), and vascular health (i.e., coronary artery calcification at year 20) were entered to determine their relationships with cognitive functioning (i.e., Stroop, DSST, and RAVLT at year 25). The data were analyzed using hierarchical regression modeling in order to test 3 sets of regression models (one with all participants, a second with only those with APOE ε4 [tested at year 7], and a third for those without APOE ε4 [tested at year7]).

Results

Table 1 provides sample characteristics. At year 25, included participants with APOE ε4 ranged in age from 42 to 56 (M_{age} = 50.14 years) while participants without APOE ε4 ranged in age from 42 to 57(M_{age} = 50.14 years). Fifty-six percent (n = 320) of

the participants with APOE ε4 were women and 52% of participants with APOE ε4 (*n* = 297) were White. Fifty-seven percent (*n* = 949) of the participants without APOE ε4 were women and 63% of participants without APOE ε4 (*n* = 1,050) were White. Significant differences in race, level of education, LDL-C, HDL-C, C-reactive protein, DSST, and RAVLT were noted between groups (with and without APOE ε4). Table 2 shows correlations among study variables. A number of variables had strong associations with the cognitive tests and the cognitive composite. Those variables with moderate or strong associations to the Stroop Test included all variables except sex, triglycerides, and coronary artery calcification scores. Variables with strong to moderate associations to the DSST included all variables except LDL-C. Variables with moderate to strong associations with the RAVLT included all variables except age and LDL-C. Variables with moderate to strong associations with the cognitive composite score included all variables except age and LDL-C.

Results from the hierarchical regression modeling are presented in Table 3. For Model 1, which included all participants (i.e., those with and without APOE ε4), Step 1 explained 33.8% of the variance of the cognitive composite score. With the addition of HbA1c (t = -3.127, p = .002), step 2 explained 34.1% of the variance. With the addition of lipids, step 3 included triglycerides (t = -2.436, p = .015) and explained 34.3% of the variance. With the addition of inflammatory markers, step 4 included interleukin-6 (t = -2.340, p = .019) and explained 34.6% of the variance. Although the addition of coronary artery calcification scores approached significance (t = -1.760, p = .078), step 5 explained 34.7% of the variance in cognitive functioning.

In the final model, higher levels of education were associated with higher cognitive composite scores. Younger age and lower levels of HbA1c, triglyceride, and interleukin-6 were associated with higher cognitive composite scores. Coronary artery calcification scores approached significance as well, with the lack of coronary artery calcification being predictive of better cognitive functioning.

The second multiple regression model was run only on participants with the APOE ε4 allele (n = 573). Step 1 explained 34.7% of the variance in cognitive functioning. With the addition of HbA1c (t = -1.453, p = .147), step 2 explained 35.0% of the variance. With the addition of lipids, step 3 explained 35.5% of the variable but triglycerides (t = -1.068, p = .286), LDL-C (t = 1.937, p = .053), and HDL-C (t = -.017, p = .986) were all non-significant. With the addition of inflammatory markers, step 4 explained 36.0% of the variance and neither C-reactive protein (t = -1.389, p = .165) nor interleukin-6 (t = -1.151, p = .250) were significant. With the addition of coronary artery calcification scores, step 5 explained 36.1% of the variance and coronary artery calcification scores was not significant (t = -.714, p = .476). In the final model, higher levels of education were associated with higher cognitive composite scores. Younger age was associated with better cognitive functioning. Higher LDL-C levels were associated with better cognitive functioning (t = 1.937, p = .049).

The third multiple regression analysis was run on participants without the APOE ε4 allele (n = 1,656). Step 1 explained 33.2% of the variance in cognitive functioning using the cognitive composite score. With the addition of HbA1c (t = -2.836, p = .005), step 2 explained 33.5% of the variance. With the addition of lipids, step 3 included triglycerides (t = -2.123, p = .034) and explained 33.7% of the variance. With the

addition of inflammatory markers, step 4 included interleukin-6 (t = -2.077, p = .038) and explained 34.0% of the variance. Although the addition of coronary artery calcification scores was not statistically significant (t = -1.552, p = .121), step 5 explained 34.1% of the variance in cognitive functioning. In the final model, higher levels of education were associated with higher cognitive composite scores. Younger age was associated with better cognitive functioning as well as lower levels of HbA1c, triglycerides, and interleukin-6.

Discussion

The purpose of this study was to determine which metabolic and inflammatory predictors that were studied at year 20 were associated with cognitive functioning at year 25 among Black and White middle-aged adults. High levels of metabolic and inflammatory markers were significantly associated with worse cognitive functioning 5 years later but they explained little to none of the variance in cognitive functioning between individuals.

Regardless of genetic predisposition to Alzheimer's disease, the first model revealed lower levels of HbA1c, triglycerides, and interleukin-6 were predictive of better cognitive functioning in mid-life. In the second model, those participants with APOE ε4 who had higher levels of LDL-C were noted with better cognitive functioning in mid-life. Interestingly, the ε4 variant of APOE has been identified as the most common genetic risk factor of Alzheimer's disease (Puglielli, Tanzi, & Kovacs, 2003). Therefore, likely a complex relationship exists between LDL-C, genetic expression of APOE alleles, and cognition functioning (Puttonen, Elovainio, Kivimaki, Lehtimaki, & Keltikangas-

Jarvinen, 2003). Such a relationship could be due to an interaction between LDL-C and APOE whereby the APOE polymorphism impacts neural activity (Barres & Smith, 2002). In order to understand this better, it is necessary to understand APOE's role in the transport of cholesterol between cells and around the body (Barres & Smith, 2002). Cholesterol, like LDL-C, is bound to APOE and is released by astrocytes and absorbed by neurons. This cholesterol may promote an increase in the number of synapses. These synapses assist in plasticity. Therefore, if abundant amounts of LDL-C are noted, then perhaps this abundance is protective of cognitive functioning in middle-aged adults. If so, the results noted in this study support this premise.

Yet another explanation for the ambiguous findings of elevated LDL-C levels and better cognitive functioning could be explained by a U-shaped phenomenon, although one was not found, for which LDL-C and cognitive functioning share. Perhaps, in middle age, higher levels of LDL-C are protective to cognitive functioning but then later in life they are detrimental to cognitive functioning. If so, then an age-related component of APOE, LDL-C, and cognitive function also exists. If so, one explanation could be similar to the age-related effects of APOE ε4 on cognitive functioning (Liu et al., 2010). Liu and colleagues noted APOE ε4's effect on one cognitive domain (e.g., memory) becomes more pronounced with aging.

At the time of the study, elevated LDL-C levels were defined as those above 160 mg/dL. Interestingly, only 163 participants out of 2,229 had LDL-C levels greater than 160 mg/dL. The levels of LDL-C ranged from 14-282 mg/dL (M = 111.81). Therefore, one simple explanation for the results may be that those who had "elevated" LDL-C levels were not the majority.

For those participants without the genetic predisposition to Alzheimer's disease, lower levels of HbA1c, triglycerides, and interleukin-6 was associated with better cognitive functioning, mirroring the findings in the full sample. These results are likely possible because only 25% of all participants had the genetic predisposition for Alzheimer's disease. Therefore, the results are similar to the larger group findings (i.e., Tables 3 and 5).

Strengths and Limitations

Several strengths may be noted about this study. This study had a large sample size with diversity of gender, race, and level of education, enhancing generalizability and power. Second, this study examined cognitive functioning in middle-aged rather than older adults. Many studies examine cognitive functioning in older adults; however, studying participants earlier may be useful to identify predictors and the complex relationships among these variables. Third, this study used standardized and acceptable measures at all sites for the collection of data. The cognitive tests in the study focused on three different domains of cognition. These were selected so that a wide range of deficits that one might expect in middle-age were detected. However, for the purposes of evaluating more global cognitive functioning, a composite cognitive score was used.

One limitation of this study was the restricted age range of our sample. Although the range was 18-30 years at onset of the study, the study did not examine anyone over the age of 57 at year 25, making it difficult to analyze the effect of much older age on cognition; by that same token, this is a strength of examining cognitive functioning in mid-life. Additionally, fewer participants with APOE ε4 were noted which results in less

power to detect associations. Many genes are associated with Alzheimer's disease but the current study only looked at one. Yet another limitation in the study was the lack of a direct measure of transient ischemic attacks, stroke, or vascular dementia, although the prevalence or incidence in middle aged adults is low. Participants were asked to report whether they had a previous stroke and transient ischemic attack at year 25 as one of the exclusion criteria. Many limitations exist with self-reported measures. Therefore, FLAIR magnetic resonance imaging could have assessed whether a previous stroke or transient ischemic attack had occurred. This was performed by CARDIA researchers; however, the FLAIR MRI studies results were not available at the time of this analysis. The dichotomous nature of the coronary artery calcification variable (either some or none) may limit the interpretability of these findings. In addition, although the study occurred over 25 years, many measures were repeatedly performed while others were not. This makes it difficult to study predictors at baseline and compare them to predictors at year 25 when cognitive testing was performed. Cognitive testing was also only tested once. Likewise, the assumption is that biologic measures are reflective and accurate "single time measures". However, if assessed over time, these biologic measures could better be examined using individual slopes as predictors. Lastly, three models were run without an alpha correction, which could also be a weakness, as this could have inflated family-wise error rate.

Implications for Practice and Research

This study offers many opportunities to enhance practice and thus promote health. First, as a measure of hyperglycemic and diabetic health, HbA1c should be maintained at

normal levels. Periodic surveillance of this measure should follow the evidence-based guidelines supported by the experts in this field because of the predictive nature HbA1c has on cognitive functioning (Cukierman-Yaffe et al., 2009). Second, this study suggests that low triglyceride levels are associated with better cognitive functioning. Therefore, monitoring triglycerides according to established standards should be implemented with consideration given to the use of dietary and lifestyle modifications, as well as pharmacologic therapies when indicated (Giacco et al., 2014). As noted by Giacco and colleagues, a change as simple as switching from refined sugar based cereals to whole-grain based cereals was noted to reduce high glucose and reduce triglyceride levels. Interventions aimed at reducing the inflammatory process within the body should be considered. This approach may include adding more antioxidants through dietary measures or with the aid of pharmacologic agents when an inflammatory process is present (Scoditti et al., 2012)

Concerning research implications, further determination of the possible age-varying relationships between LDL-C and cognitive function is needed, particularly among carriers of the APOE ε4 allele. It will be of interest to follow the CARDIA cohort into older ages to examine the shape of this relationship more fully. Future research could also extend examination of the relationships identified here to other ethnic and racial groups. Different measures of hyperglycemia could be studied rather than HbA1c, as HbA1c is more a measure of chronic glycemic control rather than hyperglycemia. For example, random blood glucoses could be more sensitive to acute episodes of hyperglycemia. Studies comparing acute versus chronic measures of hyperglycemia and its effect on cognitive functioning could be a target of future studies. In addition, more

studies are needed on LDL-C and cognitive functioning to further determine the nature of their relationship. More specifically, age-related factors related to LDL-C as well as any interaction of APOE ε4 carrier status with LDL-C needs to be studied with cognitive functioning. Inflammatory markers other than C-reactive protein and interleukin-6, such as D-dimer and lipoprotein-associated phospholipase A2, are possible candidates for future research in relation to vascular health and with cognitive functioning.

.

Conclusions

As adults age, many will experience changes in cognitive functioning later in life. Sufficient cognitive functioning is needed in order to negotiate the activities of daily living (Vance, Larsen, Eagerton, & Wright, 2011). Even a subtle impairment in cognition can impact everyday functioning. Cognitive reserve becomes an important focus for middle-aged adults so that cognitive functioning may be preserved (Stern, 2012; Vance & Wright, 2009). Better cognitive functioning may be predicted by lower HbA1c levels, triglycerides, and interleukin-6 levels for all participants regardless of genetic predisposition for Alzheimer's disease. Monitoring the levels of HbA1c, triglycerides, and interleukin-6 in mid-life could assist in maintenance of cognitive functioning in older life.

References

Akiyama, H., Barger, S., Barnum, S., Bradt, B., Bauer, J., Cole, G. M. …Van Muiswinkel. (2000). Inflammation and Alzheimer's disease. *Neurobiology of Aging, 21*(3), 383-421.

Alosco, M. L., Gunstad, J., Beard, C., Xu, X., Clark, U. S., Labbe, D. R., ...Sweet, L. H. (2014). The synergistic effects of anxiety and cerebral hypoperfusion on cognitive dysfunction in older adults with cardiovascular disease. *Journal of Geriatric Psychiatry and Neurology*, available online ahead of print: 0891988714541871.

Anstey, K. J., Lipnicki, D. M., & Low, L. F. (2008). Cholesterol as a risk factor for dementia and cognitive decline: A systematic review of prospective studies with meta-analysis. *American Journal of Geriatric Psychiatry, 16*, 343–54.

Barres, B. A., & Smith, S. J. (2001). Cholesterol- making or breaking the synapse. *Science, 294*, 1296-1297. doi: 10.1126/science.1066724

Carmeli, E. (2014). Aging, neuroplasticity and neuro rehabilitation. *Aging Science, 2*(1), e110. doi: 10.4172/2329-8847.1000e110

Carr, J. J., Nelson, J. C., Wong, N. D., McNitt-Gray, M., Arad, Y., Jacobs Jr, D. R., ... Detrano, R. C. (2005). Calcified coronary artery plaque measurement with cardiac CT in population-based studies: Standardized protocol of multi-ethnic study of atherosclerosis (MESA) and coronary artery risk development in young adults (CARDIA) study 1. *Radiology, 234*(1), 35-43.

Centers for Disease Control and Prevention. (2011). *National diabetes fact sheet: National estimates and general information on diabetes and prediabetes in the United States*. Atlanta, GA.: U. S. Department of Health and Human Services, Center for Disease Control and Prevention. Retrieved on 3/18/2013 from://www.ndep.nih.gov/media/FS, OlderAdult.pdf

Cukierman, T., Gerstein, H. C., & Williamson, J. C. (2005). Cognitive decline and dementia in diabetes: A systematic overview of prospective observational studies. *Diabetologia, 42*, 2460-2469.

Cukierman-Yaffe, T., Gerstein, H. C., Williamson, J. D., Lazar, R. M., Lovato, L., Miller, M. E., … Launer, L. (2009). Relationship between baseline glycemic control and cognitive function in individuals with type 2 diabetes and other cardiovascular risk factors: The Action to Control Cardiovascular Risk in Diabetes- Memory in Diabetes (ACCORD-MIND) trial. *Diabetes Care, 32*, 221-226. doi: 10.2337/dc08-1153

Doherty, T. M., Tang, W., & Detrano, R. C. (1999). Racial differences in the significance of coronary calcium in asymptomatic black and white subjects with coronary risk factors. *Journal of the American College of Cardiology, 34*, 787-94.

Donahue, R. P., Jacobs, D. R., Sidney, S., Wagenknecht, L. E., Albers, J. J., & Hulley, S. B. (1989). Distribution of lipoproteins and apolipoproteins in young adults in the CARDIA Study. *Arteriosclerosis, Thrombosis, and Vascular Biology: Journal of the American Heart Association, 9*, 656-664.

Farbstein, D., Blum, S., Pollak, M., Asaf, R., Viener, H. L., Lache, O., …Levy, A. P. (2011). Vitamin E therapy results in a reduction in HDL function in individuals with diabetes and the haptoglobin 2-1 genotype. *Atherosclerosis, 219*(1), 240–244. doi:10.1016/j.atherosclerosis.2011.06.005

Feinkohl, I., Keller, M., Robertson, C. M., Morling, J. R., Williamson, R. M., Nee, L. D., ... Price, J. F. (2013). Clinical and subclinical macrovascular disease as predictors of cognitive decline in older patients with type 2 diabetes The Edinburgh Type 2 Diabetes Study. *Diabetes Care, 36*(9), 2779-2786. doi: 10.2337/dc12-2241

Friedman, G. D., Cutter, G. R., Donahue, R. P., Hughes, G. H., Hulley, S. B., Jacobs, D. R., …Savage, P. J. (1988). CARDIA: Study design, recruitment, and some characteristics of the examined subjects. *Journal of Clinical Epidemiology, 41*(11), 1105-1116.

Giacco, R., Costabile, G., Della Pepa, G., Anniballi, G., Griffo, E., Mangione, A., ...Riccardi, G. (2014). A whole-grain cereal-based diet lowers postprandial plasma insulin and triglyceride levels in individuals with metabolic syndrome. *Nutrition, Metabolism and Cardiovascular Diseases, 24*(8), 837-844. doi: 10.1016/j.numecd.2014.01.007

Helzner, E. P., Luchsinger, J. A., Scarmeas, N., Cosentino, S., Brickman, A. M., Glymour, M. M., …Stern, Y. (2009). Contribution of vascular risk factors to the progression in Alzheimer disease. *Archives of Neurology, 66*(3), 343-348. doi:10.1001/archneur.66.3.343.

Howard, B. V., Gidding, S. S., & Liu, K. (1998). Association of apolipoprotein E phenotype with plasma lipoproteins in African-American and white young adults the CARDIA Study. *American Journal of Epidemiology, 148*(9), 859-868.

Hughes, G. H., Cutter, G., Donahue, R., Friedman, G. D., Hulley, S. B., Hunkeler, E., …Wagenknecht, L. (1987). Recruitment in the coronary artery disease risk development in young adults (CARDIA) study. *Controlled Clinical Trials, 8,* 68S-73S.

Kamboh, M. I., Ferrell, R. E., & Kottke, B. (1988). Genetic studies of human apolipoproteins. V. A novel rapid procedure to screen apolipoprotein E polymorphism. *Journal of Lipid Research, 29*(11), 1535-1543.

Liu, F., Pardo, L.M., Schuur, M., Sanchez-Juan, P., Isaacs, A., Sleegers, K., …van Duijn, C.M. (2010). The apolipoprotein E gene and its age-specific effects on cognitive function. *Neurobiology of Aging, 31,* 1831-1833. doi: 10.1016/j.neurobiolaging.2008.09.015

Liu, J., Zeng, F.-F., Liu, Z.-M., Zhang, C.-X., Ling, W.-h., & Chen, Y.-M. (2013). Effects of blood triglycerides on cardiovascular and all-cause mortality: A systematic review and meta-analysis of 61 prospective studies. *Lipids in Health and Disease, 12*, 159. doi: 10.1186/1476-511x-12-159

Malloy-Diniz, L. F., Lasmar, V. A., Gazinelli, L. D., Fuentes, D., & Salgado, J. V. (2007). The Rey Auditory-Verbal Learning Test: Applicability for the Brazilian elderly population. *Revista Brasileira de Psiquiatria, 29*(4), 324-329.

McGuire, L. C., Ford, E. S., & Ajani, U. A. (2006). Cognitive functioning as a predictor of functional disability in later life. *The American Journal of Geriatric Psychiatry, 14(*1), 36-42. doi: org/10.1097/01.JGP.0000192502.10692.d6

Mortamais, M., Portlet, F., Brickman, A. M., Provenzano, F.A., Muraskin, J., Akbaraly, T. N., … Artero, S. (2013). Education modulates the impact of white matter lesions on the risks of mild cognitive impairment and dementia. *The American Journal of Geriatric Psychiatry, 22*(11), 1336-1345. doi: 10.1016/j.jagp.2013.06.002.

Mortimer, B. C., Redgrave, T. G., Spangler, E. A., Verstuyft, J. G., & Rubin, E. M. (1994). Effect of human apoE4 on the clearance of chylomicron-like lipid emulsion and atherogenesis in transgenic mice. *Arteriosclerosis, Thrombosis, and Vascular Biology, 14*, 1542-1552.

Nasir, K., Katz, R., Takasu, J., Shavelle, D. M., Detrano, R., Lima, J. A., …Budoff, M. J. (2008). Ethnic differences between extra-coronary measures on cardiac computed tomography: Multi-ethnic study of atherosclerosis (MESA). *Atherosclerosis, 198*(1), 104-114. doi: 10.1016/j.atherosclerosis.2007.09.008

Norman, J. E., Bild, D., Lewis, C. E., Liu, K., & West, D. S. (2003). The impact of weight change on cardiovascular disease risk factors in young black and white adults: the CARDIA study. *International Journal of Obesity, 27*(3), 369-376.

Okonkwo, O. C., Griffith, H. R., Vance, D. E., Marson, D. C., Ball, K. K., & Wadley, V. G. (2009). Awareness of functional difficulties in mild cognitive impairment: A multidomain assessment approach. *Journal of the American Geriatrics Society, 57*(6), 978-984. doi: 10.1111%2Fj.1532-5415.2009.02261.x

Ownby, R. L. (2010). Neuroinflammation and cognitive aging. *Current Psychiatry Reports, 12*(1), 39-45. doi: 10.1007/s11920-009-0082-1

Polit, D. F., & Beck, C. T. (2008). Designing a study to generate evidence for nursing. In Surrena, H., & Kogut, H. (Eds.), *Nursing research: Generating and assessing evidence for nursing practice, 8th ed.* (337-364). Philadelphia: Wolters, Kluwer, Lippincott, Williams, & Wilkins.

Puglielli, L., Tanzi, R. E., & Kovacs, D. M. (2003). Alzheimer's disease: The cholesterol connection. *Nature Neuroscience, 6*(4), 345-351.

Puttonen, S., Elovainio, M., Kivimaki, M., Lehtimaki, T., & Keltikangas-Jarvinen, L. (2003). The combined effects of Apolipoprotein E polymorphism and low-density lipoprotein cholesterol on cognitive performance in young adults. *Neuropsychobiology, 48,* 35-40. doi: 10.1159/000071827

Radwan, Z. H., Wang, X., Waqar, F., Pirim, D., Niemsiri, V., Hokanson, J. E., ...Kamboh, M. I. (2014). Comprehensive evaluation of the association of APOE genetic vVariation with plasma lipoprotein traits in US Whites and African Blacks. *PloS one*, *9*(12), e114618.

Rafnsson, S. B., Deary, I. J., Smith, F. B., Whiteman, M. C., Rumley, A., Lowe, G. D., & Fowkes, G. R. (2007). Cognitive decline and markers of inflammation and hemostasis: The Edinburgh Artery Study. *Journal of the American Geriatric Society, 55,* 700-707. doi: 10.1111/j.1532-5415.2007.01158.x

Reis, J. P., Loria, C. M., Launer, L. J., Sidney, S., Liu, K., Jacobs, D. R., ...Yaffe, K. (2013). Cardiovascular health through young adulthood and cognitive functioning in midlife. *Annals of Neurology, 73*(2), 170-179. doi: 10.1002%2Fana.23836

Rizzuto, D. (2013). Living longer than expected: Protective and risk factors related to human longevity. *Open Archive*.

Salthouse, T. A. (1992). What do adult age differences in the Digit Symbol Substitution Test reflect? *Journal of Gerontology, 47*(3), 121-128.

Scoditti, E., Calabriso, N., Massaro, M., Pellegrino, M., Storelli, C., Martines, G., ...Carluccio, M. A. (2012). Mediterranean diet polyphenols reduce inflammatory angiogenesis through MMP-9 and COX-2 inhibition in human vascular endothelial cells: A potentially protective mechanism in atherosclerotic vascular disease and cancer. *Archives of Biochemistry and Biophysics, 527*(2), 81-89. doi: 10.1016/j.abb.2012.05.003

Silbernagel, G., Schoettker, B., Appelbaum, S., Scharnagl, H., Kleber, M. E., Grammer, T. B., … Maerz, W. (2013). High-density lipoprotein cholesterol, coronary artery disease, and cardiovascular mortality. *European Heart Journal, 34,* 3563-3571. doi: 10.1093/eurheartj/eht343

Singh-Manoux, A., Britton, A., & Marmot, M. (2003). Vascular disease and cognitive function: Evidence from the Whitehall II Study. *Journal of the American Geriatric Society, 51,* 1445-1450.

Singh-Manoux, A., Czernichow, S., Elbaz, A., Dugravot, A., Sabia, S., Hagger-Johnson, G., …Kivimäki, M. (2012). Obesity phenotypes in midlife and cognition in early old age: The Whitehall II Cohort Study. *Neurology. 79*(8), 755-62. doi: 10.1212/WNL.0b013e3182661f63.

Small, B. J., Rosnick, C. B., Fratiglioni, L., & Backman, L. (2004). Apolipoprotein E and cognitive performance: A meta-analysis. *Psychology and Aging, 19*(4), 592-600. doi: 10.1037/0882-7974.19.4.592

Strachan, M. W. (2010). The brain as a target organ in Type 2 diabetes: Exploring the links with cognitive impairment and dementia. *Diabetic Medicine, 28*, 131-147. doi: 10.1111/j.1464-5491.2010.03199.x

United States Department of Health and Human Services. (2014). *Global health and aging.* National Institutes of Health. National Institute of Aging. Retrieved from: http://www.nia.nih.gov/research/publication/global-health-and-aging/humanitys-aging

Umegaki, H. (2014). Type 2 diabetes as a risk factor for cognitive impairment: Current insights. *Clinical Interventions in Aging, 9*, 1011-1019.

Van Horn, L. V., Ballew, C., Liu, K., McDonald, A., Hilner, J. E., Burke, G. L., ...Sidney, S. (1991). Diet, body size, and plasma lipids-lipoproteins in young adults: Differences by race and sex The Coronary Artery Risk Development in Young Adults (CARDIA) Study. *American Journal of Epidemiology, 133*(1), 9-23.

Vance, D. E., Eagerton, G., Harnish, B., McKie, P., & Fazeli, P. (2011). Cognitive prescriptions: A nursing approach to increasing cognitive reserve. *Journal of Gerontological Nursing, 37*(4), 22-31. doi: 10.3928/00989134-20110304-01

Zhang, E., & Wu, Y. (2014). Metabolic memory: Mechanisms and implications for diabetic vasculopathies. *Science China Life Sciences, 57*(8), 845-851.

Table 1

Characteristics of the Sample at Year 25 (N = 2,229)

	With APOE ε4					Without APOE ε4					
Variable	*n*	%	*M*	*SD*	Range	*n*	%	*M*	*SD*	Range	*p* - value
Age, yr	573		50.14	3.62	42 - 56	1656		50.37	3.56	42 - 57	.20
Race											.00†
Black	276	48.2				606	36.6				
White	297	51.8				1050	63.4				
Sex											.54
Men	253	44.2				707	42.7				
Women	320	55.8				949	57.3				
Education, yr	573		14.34	2.23	7 - 20	1656		14.65	2.34	8 - 20	.01†
HbA1c	573		5.68	0.87	4 - 14	1656		5.65	0.94	4 - 15	.54
LDL-C	573		119.39	31.38	34 - 263	1656		109.19	31.67	14 - 282	.00†
HDL-C	573		56.71	17.18	25 - 152	1656		59.25	17.80	24 - 171	.00†
Triglycerides	573		107.28	59.10	24 - 354	1656		108.61	59.40	21 - 399	.64
C-reactive protein	573		2.35	3.68	0 - 27	1656		3.01	4.53	0 - 42	.00†
Interleukin-6	573		2.42	2.46	0 - 22	1656		2.54	3.10	0 - 29	.40
CAC											.15
With	120	20.9				301	18.2				
Without	453	79.1				1355	81.8				
Stroop	573		22.40	10.67	-27 - 74	1656		21.76	9.85	-20 - 127	.19
DSST	573		69.52	15.37	30 - 119	1656		72.00	15.74	8 - 125	.00†
RAVLT	573		8.29	3.27	0 - 15	1656		8.77	3.17	0 - 15	.00†

Note. APOE ε4 = apolipoprotein E 4 allele; APOE ε4 (With = ε 3/4 and ε4/4 and Without = ε2/4 and any ε2 or ε3 alleles);Yr = years; BMI = body mass index; HbA1c = hemoglobin A1c; LDL-C = low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol; CAC = coronary artery calcification scores; DSST = Digit Symbol Substitution Test; RAVLT = Rey-Auditory Verbal Learning Test. †$p < 0.01$

Table 2
Correlation Matrix

Variable	1	2	3	4	5	6	7	8
1. Age[a]	1.00							
2. Race[b]	0.19‡	1.00						
3. Sex[b]	-0.00	-0.09‡	1.00					
4. Education[a]	0.25‡	0.34‡	-0.03	1.00				
5. HbA1c[a]	0.01	-0.23‡	-0.05†	-0.15‡	1.00			
6. LDL-C[a]	0.23	0.03	-0.05†	0.02	-0.02	1.00		
7. HDL-C[a]	0.08‡	0.03	0.37‡	0.09‡	-0.17‡	-0.13‡	1.00	
8. Triglycerides[a]	0.01	0.12‡	-0.19‡	-0.06‡	0.18‡	0.17‡	-0.42‡	1.00
9. C-reactive protein[a]	-0.06‡	-0.22‡	0.17‡	-0.16‡	0.17‡	-0.01	-0.11‡	0.07‡
10. Interleukin-6[a]	-0.05†	-0.15‡	0.06‡	-0.13‡	0.10‡	-0.02	-0.07‡	0.03
11. CAC[b]	0.14‡	0.06‡	-0.24‡	0.00	0.06‡	0.02	-0.13‡	0.12‡
12. Stroop[a]	0.04†	-0.35‡	-0.01	-0.27‡	0.15‡	-0.06‡	-0.05†	0.04
13. DSST[a]	-0.06‡	0.24‡	0.29‡	0.34‡	-0.18‡	0.02	0.15‡	-0.07‡
14. RAVLT[a]	0.03	0.25‡	0.29‡	0.26‡	-0.12‡	-0.03	0.13‡	-0.06‡
15. Cognitive[a]	-0.03	0.22‡	0.41‡	0.38‡	-0.20‡	0.02	0.14‡	-0.08‡
16. APOE ε4[b]	-0.03	-0.10‡	-0.01	-0.06‡	0.01	0.14‡	-0.06‡	-0.01

Note. Correlations are unadjusted. [a] Continuous variable. [b] Dichotomous variable. † $p < 0.05$. ‡ $p < 0.01$. Race (women = 0 and men = 1); Race (Black = 4 and White = 5); Education (total number of years); HbA1c = hemoglobin A1c; LDL-C = low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol; CAC = coronary artery calcification scores; DSST = Digit Symbol Substitution Test; RAVLT = Rey-Auditory Verbal Learning Test; APOE ε4 = apolipoprotein E ε4 allele. APOE ε4 (With = ε3/4 and ε4/4 and Without = ε2/4 and any ε2 or ε3 alleles).

Table 2 (Continued)
Correlation Matrix

Variable	9	10	11	12	13	14	15
1. Age[a]							
2. Race[b]							
3. Sex[b]							
4. Education[a]							
5. HbA1c[a]							
6. LDL-C[a]							
7. HDL-C[a]							
8. Triglycerides[a]							
9. C-reactive protein[a]	1.00						
10. Interleukin-6[a]	0.27‡	1.00					
11. CAC[b]	0.01	0.02	1.00				
12. Stroop[a]	0.11‡	0.12‡	0.04	1.00			
13. DSST[a]	-0.12‡	-0.12‡	-0.12‡	-0.42‡	1.00		
14. RAVLT[a]	-0.05†	-0.05‡	-0.08‡	-0.26‡	0.38‡	1.00	
15. Cognitive[a]	-0.12‡	-0.13‡	-0.10‡	-0.74‡	0.80‡	0.72‡	1.00
16. APOE ε4[b]	-0.07‡	-0.02	0.03	0.03	-0.07‡	-0.07‡	-0.07‡

Note. Correlations are unadjusted. [a] Continuous variable. [b] Dichotomous variable. † $p < 0.05$. ‡ $p < 0.01$. Race (women = 0 and men = 1); Race (Black = 4 and White = 5); Education (total number of years); HbA1c = hemoglobin A1c; LDL-C = low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol; CAC = coronary artery calcification scores; DSST = Digit Symbol Substitution Test; RAVLT = Rey-Auditory Verbal Learning Test; APOE ε4 = apolipoprotein E ε4 allele. APOE ε4 (With = ε 3/4 and ε4/4 and Without = ε2/4 and any ε2 or ε3 alleles).

Table 3

Hierarchical Multiple Regression Examining Predictors of Cognitive Functioning

Model 1	*B*	*SE*	*β*	*p*	*F*	*Adj. R^2*	*Δ R^2*
Step 1: Demographics					162.275	.336	
Age, yrs.	-.038	.004	-.178	.000			
Race	.566	.029	.367	.000			
Gender	.390	.026	.256	.000			
Education	.099	.006	.303	.000			
Step 2:Hyperglycemia					143.774	.339	.002
Age	-.037	.004	-.174	.000			
Race	.548	.030	.355	.000			
Gender	.384	.026	.252	.000			
Education	.097	.006	.298	.000			
HbA1c	-.046	.015	-.056	.002			
Step 3: Lipids					105.441	.340	.002
Age	-.037	.004	-.174	.000			
Race	.561	.030	.364	.000			
Gender	.375	.028	.246	.000			
Education	.096	.006	.293	.000			
HbA1c	-.038	.015	-.046	.012			
LDL-C	.001	.000	.022	.203			
HDL-C	.001	.001	-.002	.932			
Triglycerides	-.001	.000	-.048	.015			
Step 4: Inflammatory Markers					90.257	.342	.003
Age	-.037	.004	-.175	.000			
Race	.548	.031	.355	.000			
Gender	.389	.029	.256	.000			
Education	.094	.006	.288	.000			
HbA1c	-.034	.015	-.041	.025			
LDL-C	.001	.000	.021	.226			
HDL-C	.000	.001	-.008	.693			
Triglycerides	-.001	.000	-.045	.021			
C-reactive protein	-.005	.003	-.028	.143			
Interleukin-6	-.011	.005	-.042	.019			
Step 5: Vascular Health					84.111	.343	.001
Age	-.036	.004	-.170	.000			
Race	.550	.031	.256	.000			
Gender	.379	.030	.249	.000			
Education	.094	.006	.287	.000			
HbA1c	-.033	.015	-.040	.028			
LDL-C	.000	.000	.021	.234			
HDL-C	.000	.001	-.009	.658			
Triglycerides	-.001	.000	-.044	.027			
C-reactive protein	-.005	.003	-.026	.159			
Interleukin-6	-.011	.005	-.041	.022			
CAC	-.061	.035	-.032	.078			

Note. Controlled for site using dummy variables. Yrs. = years; Gender (women = 0 and men = 1); Race (Black = 4 and White = 5); APOE ε4 = apolipoprotein E ε4 allele; APOE ε4 (With = ε 3/4 and ε4/4 and Without = ε2/4 and any ε2 or ε3 alleles); HbA1c = hemoglobin A1c; LDL-C= low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol; CAC = coronary artery calcification scores. Step 1 R^2 = .338; Step 2 R^2 = .341; Step 3 R^2 = .343; Step 4 R^2 = .346; Step 5 R^2 = .347.

Table 4
Hierarchical Multiple Regression Examining Predictors of Cognitive Functioning in Those With APOE ε4

Model 2	*B*	*SE*	*β*	*p*	*F*	*Adj. R^2*	*Δ R^2*
Step 1: Demographics					42.944	.339	
Age, yrs.	-.036	.007	-.174	.000			
Race	.564	.057	.370	.000			
Gender	.384	.053	.250	.000			
Education	.099	.006	.303	.000			
Step 2: Hyperglycemia					37.914	.340	.003
Age, yrs.	-.035	.007	-.169	.000			
Race	.544	.059	.357	.000			
Gender	.376	.053	.246	.000			
Education	.100	.013	.294	.000			
HbA1c	-.045	.031	-.052	.147			
Step 3: Lipids					28.099	.343	.005
Age, yrs.	-.036	.007	-.172	.000			
Race	.556	.060	.365	.000			
Gender	.375	.057	.245	.000			
Education	.100	.013	.292	.000			
HbA1c	-.037	.032	-.042	.250			
LDL-C	.002	.001	.067	.053			
HDL-C	-.001	.002	-.001	.986			
Triglycerides	-.001	.001	-.042	.286			
Step 4: Inflammatory Markers					24.217	.345	.005
Age, yrs.	-.036	.007	-.170	.000			
Race	.536	.061	.352	.000			
Gender	.403	.059	.263	.000			
Education	.098	.013	.288	.000			
HbA1c	-.033	.032	-.037	.309			
LDL-C	.002	.001	.069	.045			
HDL-C	.000	.002	-.010	.814			
Triglycerides	.000	.001	-.038	.332			
C-reactive protein	-.011	.008	-.051	.165			
Interleukin-6	-.013	.011	-.042	.250			
Step 5: Vascular Health					22.504	.345	.001
Age, yrs.	-.035	.008	-.166	.000			
Race	.536	.061	.352	.000			
Gender	.395	.060	.258	.000			
Education	.098	.013	.287	.000			
HbA1c	-.031	.032	-.035	.338			
LDL-C	.002	.001	.068	.049			
HDL-C	.000	.002	-.011	.787			
Triglycerides	-.000	.001	-.034	.382			
C-reactive protein	-.011	.008	-.051	.168			
Interleukin-6	-.013	.011	-.041	.258			
CAC	-.048	.068	-.026	.476			

Note. Controlled for site using dummy variables. Yrs. = years. Gender (women = 0 and men = 1); Race (Black = 4 and White = 5); APOE ε4 = apolipoprotein E ε4 allele; APOE ε4 (With = ε 3/4 and ε4/4 and Without = ε2/4 and any ε2 or ε3 alleles); HbA1c = hemoglobin A1c; LDL-C = low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol; CAC = coronary artery calcification scores. Step 1 R^2 = .347; Step 2 R^2 = .350; Step 3 R^2 = .355; Step 4 R^2 = .360; Step 5 R^2 = .361.

Table 5

Hierarchical Multiple Regression Examining Predictors of Cognitive Functioning in Those Without APOE ε4

Model 3	*B*	*SE*	*β*	*p*	*F*	*Adj. R^2*	*Δ R^2*
Step 1: Demographics					116.922	.329	
Age, yrs.	-.038	.004	-.180	.000			
Race	.566	.034	.364	.000			
Gender	.390	.031	.258	.000			
Education	.098	.007	.306	.000			
Step 2: Hyperglycemia					103.749	.332	.003
Age, yrs.	-.037	.004	-.175	.000			
Race	.548	.035	.352	.000			
Gender	.384	.031	.254	.000			
Education	.096	.007	.299	.000			
HbA1c	-.047	.017	-.059	.005			
Step 3: Lipids					75.979	.333	.002
Age, yrs.	-.037	.004	-.175	.000			
Race	.561	.035	.360	.000			
Gender	.375	.033	.248	.000			
Education	.095	.007	.296	.000			
HbA1c	-.040	.017	-.050	.021			
LDL-C	.000	.000	.010	.642			
HDL-C	.000	.001	-.004	.854			
Triglycerides	-.001	.000	-.049	.034			
Step 4: Inflammatory Markers					64.972	.334	.003
Age, yrs.	-.037	.004	-.176	.000			
Race	.548	.036	.352	.000			
Gender	.387	.034	.255	.000			
Education	.093	.007	.290	.000			
HbA1c	-.036	.017	-.044	.039			
LDL-C	.000	.000	.009	.675			
HDL-C	.000	.001	-.010	.664			
Triglycerides	-.001	.000	-.047	.042			
C-reactive protein	-.004	.004	-.023	.295			
Interleukin-6	-.011	.005	-.044	.038			
Step 5: Vascular Health					60.555	.335	.001
Age, yrs.	-.036	.004	-.172	.000			
Race	.551	.036	.354	.000			
Gender	.376	.034	.248	.000			
Education	.093	.007	.289	.000			
HbA1c	-.035	.017	-.044	.041			
LDL-C	.000	.000	.009	.673			
HDL-C	.000	.001	-.011	.647			
Triglycerides	-.001	.000	-.046	.046			
C-reactive protein	-.004	.004	-.022	.330			
Interleukin-6	-.010	.005	-.043	.043			
CAC	-.063	.041	-.032	.121			

Note. Controlled for site using dummy variables. Yrs. = years; Gender (women = 0 and men = 1); Race (Black = 4 and White = 5); APOE ε4 = apolipoprotein E ε4 allele; APOE ε4 (With = ε3/4 and ε4/4 and Without = ε2/4 and any ε2 or ε3 alleles); HbA1c = hemoglobin A1c; LDL-C = low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol; CAC = calcification scores. Step 1 R^2 = .332; Step 2 R^2 = .335; Step 3 R^2 = .337; Step 4 R^2 = .340; Step 5 R^2 = .341.

DIRECT AND INDIRECT EFFECTS OF METABOLIC AND INFLAMMATORY PREDICTORS ON COGNITIVE FUNCTIONING IN MIDDLE-AGED ADULTS WITH AND WITHOUT APOLIPOPROTEIN E ε4: A STRUCTURAL EQUATION MODELING STUDY

by

MICHELE H. TALLEY, ERICA R. PRYOR, VIRGINIA G. WADLEY, MICHAEL CROWE, SHANNON MORRISON, AND DAVID E. VANCE

Disclaimer: Article 3 has not received final approval from the Coronary Artery Risk Development in Young Adults' (CARDIA) Publication and Presentation Committee and should not be considered the final version. Therefore, the manuscripts and content therein should not be cited or referenced.

Format adapted for dissertation

Abstract

Using structural equation modeling, the investigators examined causal models of cognitive functioning in a sample of 1,911 middle-aged adults from the Coronary Artery Risk Development in Young Adults (CARDIA) Study. Prior studies suggest that body habitus, hyperglycemia, inflammatory processes, vascular health, lipid status, and expression of apolipoprotein E ε4 predict cognitive functioning in older adults; however, it is unclear whether such predictors of cognition have value in middle-aged adults when a great deal of cognitive reserve remains. Based on the literature, a model of how these different predictors influence each other to affect cognitive functioning was hypothesized. The model was tested using physiological measures to determine predictors of cognitive functioning after 5 years. Several direct and indirect effects were noted. More specifically, for those participants with apolipoprotein E ε4, no direct effects were noted on cognitive functioning. However, for those without apolipoprotein E ε4, lower levels of inflammatory marker levels were predictive of better cognitive functioning.

Key words: body habitus, hyperglycemia, inflammatory processes, cognitive functioning, vascular health, lipid status, and APOE ε4

Introduction

With a rapidly aging society, it becomes necessary to focus earlier on maintaining normal cognitive functioning over the lifespan. Within the United States, the number of people 65 years and older continues to grow, with expectations of the population doubling to 79 million by 2040, therefore constituting 20% of the population

(Administration on Aging, 2012). Nonpathological, healthy aging can still result in a decline in cognition functioning (Administration of Ageing, 2012). This decline is unfortunate because the maintenance of normal cognition functioning is a highly important component of successful aging due to its direct relationship with everyday functioning and health promotion (Vance, Eagerton, Harnish, McKie, & Fazeli, 2011). Even moderate disruption in cognitive functioning, without dementia, has been found to interfere with everyday tasks such as driving a car, taking medications, managing healthcare and finances, grocery shopping, and using the telephone (McGuire, Ford, & Ajani, 2006; Okonkwo et al., 2009).

Several mechanisms may affect cognitive functioning including: genetic predisposition (apolipoprotein E ε4, or APOE ε4, the allele associated with Alzheimer's disease), hyperglycemia, vascular disease, inflammatory factors, and others (Strachan, 2010). Of these mechanisms, some can be controlled (e.g., hyperglycemia, inflammatory factors, and vascular disease resulting from dyslipidemia), while others cannot (e.g., gender, race, and genetic predisposition). Thus, understanding the significant mechanisms responsible for cognitive functioning can allow healthcare providers and researchers to focus on controllable risk factors in hopes of maintaining normal cognitive functioning with age.

Predictors of coronary artery disease are very similar to predictors for changes in cognitive functioning. For that reason, some of the variables of interest in the Coronary Artery Risk Development in Young Adults (CARDIA) Study can be evaluated for their effects on cognitive functioning. The CARDIA Study, a 25-year longitudinal cohort study, was designed to explore the evolution of risk factors associated with coronary

heart disease in 18-30 year old White and Black women and men (Friedman et al., 1988). Understanding the causal nature of changes in cognitive functioning might also provide areas for healthcare providers to target for prevention.

Many metabolic and inflammatory predictors may influence cognitive functioning including body habitus (measured by waist circumference and BMI), hyperglycemia, lipids, inflammatory markers, and vascular health. A large body habitus, known as obesity, is one such modifiable mechanism that could affect cognitive functioning. In fact, the CARDIA Study researchers have noted that over time young adults participating in their study have significantly increased their weight (Burke et al., 1996). Such weight gain may cause an individual to be diagnosed with obesity. Researchers in the Whitehall II Study found that in 6,401 participants, those with the fastest cognitive decline were also those who were obese and had metabolic abnormalities (Singh-Manoux et al., 2012). Unfortunately, obesity is becoming an epidemic in the United States and has been linked to declines in cognitive functioning across the lifespan (Launer et al., 2000; Launer, 2005; Whitmer et al., 2005; Yaffe et al., 2007). Unfortunately, obesity is linked to other co-morbidities, including diabetes.

Hyperglycemia, a hallmark of diabetes, is one of the modifiable mechanisms of particular interest. According to the Centers for Disease Control and Prevention (CDC, 2011), diabetes affects 10.9 million, or 26% of the population 65 years and older. Unfortunately, people with diabetes are 1.5 times more likely than those without diabetes to experience deficits in cognitive functioning (Cukierman et al., 2005). In fact, several studies link both diabetes with poorer cognitive functioning (Arvanitakis, Wilson, Bienias, Evans, & Bennett, 2004; Bruce, Harrington, Foster, & Westerfelt , 2009;

Galanina, Surampudi, Ciltea, Singh, & Perlmuter, 2008; Gonder-Frederick et al., 2009; Rizzo et al., 2010; Shimada et al., 2009).

In addition to diabetes (Gregg et al., 2000; Grodstein, Chen, Wilson, & Manson, 2001; Kanaya, Barrett-Connor, Gildengorin, & Yaffe, 2004), dyslipidemia (elevated high density lipoproteins, elevated low density lipoproteins, and elevated triglycerides) has also been reported to affect vascular health which in turn negatively impacts cognitive functioning (Evans et al., 2000; Moroney et al., 1999; Yaffe, Barrett-Connor, Lin, & Grady, 2002). Even in early to middle-aged adults in the CARDIA Study, dyslipidemia was already present in many of the participants (Donahue et al., 1989; Marcovina et al., 1993). Studies have linked diabetes and dyslipidemia to underlying inflammation (Pradhan, Manson, Rifai, Buring, & Ridker, 2001), which potentiates the processes involved in vascular disease (Barzilay et al., 2001; Ridker, Buring, Shih, Matias, & Hennekens, 2003). More specially, elevated interleukin-6 and C-reactive protein, both inflammatory markers, are associated with an increased risk of developing diabetes, vascular disease (i.e., atherosclerosis measured by coronary artery calcification), Alzheimer's disease, as well as other complications (Umegaki, 2014). In the CARDIA Study, 9.6% of the participants had coronary artery calcification (M_{age} = 40-42 years old) noted after 15 years (Loria et al., 2007). When considering that coronary artery calcification is associated with head-to-toe vascular disease, the risk of developing neurovascular-related cognitive impairment in early to middle-aged adults is of some concern. The concern for vascular disease generates even more emphasis on detrimental cognitive functioning over time.

Further, the APOE ε4 allele may predict vascular health and eventually cognitive functioning. As noted by Rizzuto (2013), the APOE phenotypes have been noted to be determinants of cardiovascular disease, cerebrovascular disease, and dementia. Apolipoprotein E, a polymorphic glycoprotein, can be found in the plasma on certain chylomicrons and serves as a binder for the LDL receptor and LDL receptor-related protein. It can be expressed in 3 different alleles, ε2, ε3, and ε4. In the CARDIA Study, Howard and colleagues (1998) studied 3,485 White and Black men and women in order to determine APOE phenotypes as well as gender and racial differences. These researchers found that Black men and women had higher frequencies of the ε4 allele than Whites ($p < 0.005$) indicating a racial predisposition on genotype.

Overall, the larger one's body habitus, the worse one's hyperglycemia, vascular health, and lipid status, and the higher one's inflammatory markers, then the higher the risk for worsening cognitive functioning (Talley et al., in press). Although all of the predictors discussed here have been implicated in worsening cognitive functioning, the manner in which they all contribute to cognitive functioning is not well understood. The purpose of this study was to examine how such predictors are interrelated as they contribute to cognitive functioning over time.

The goal of this study was to test structural equation models that specified relationships between the latent variables (i.e., body habitus, hyperglycemia, inflammatory markers, vascular health, and lipids) hypothesized to predict cognitive functioning after 5 years. Structural equation models were created to determine which paths were most salient in predicting subclinical changes in cognitive functioning in middle-aged participants with and without the APOE ε4 allele (U. S. Department of

Health and Human Services, 2014). Based on the literature, direct paths were identified between latent variables known to be associated with cognitive functioning. Hypothesized paths are displayed in Figure 1. Paths were specified with a direct path from body habitus to hyperglycemia, lipids, inflammatory markers, vascular health, and cognitive functioning (Talley et al., in press). The order in which the variables were added to the model was based on the causal relationship observed between hyperglycemia and dyslipidemia to underlying inflammation (Pradhan et al., 2001), further potentiating vascular disease (Barzilay et al., 2001; Ridker et al., 2003). Going downstream from the exogenous to the endogenous latent variables, direct paths from inflammatory markers were specified to vascular health and cognitive functioning; hyperglycemia to inflammatory markers, lipids, vascular health, and cognitive functioning were specified; direct paths from lipids were specified to inflammatory markers and vascular health; finally, a direct path from vascular health to cognitive functioning was specified.

Methods

Participants

Recruitment for the CARDIA Study was conducted using a stratified random sampling method from four urban areas: University of Alabama at Birmingham (Birmingham, AL), the University of Minnesota (Minneapolis, MN), Northwestern University (Chicago, IL), and Kaiser Permanente (Oakland, CA) (Hughes et al., 1987). Eligible participants were at least 18 years old but younger than 30 years of age and either White or Black. Only participants who were free of disability and long-term

diseases (those that would interfere with the examinations) were invited to participate. Participants were not eligible if they were pregnant, 3 months postpartum, mute, deaf, blind, mentally challenged, or unable to ambulate on a treadmill. Additionally, participants who self-reported stroke and who did not complete the neurocognitive tests at year 25 were excluded from the present analyses. A total of 5,116 participants were included in the original CARDIA Study. In addition to the physical exam performed at entry into the study, participants were asked to undergo follow-up examinations over 25 years. All participants gave informed consent. The study design, data collection, and analyses were approved by the institutional review boards where the participants were recruited. For this study, only those records from participants with complete data for each of the variables were included. Thus, using such a listwise deletion approach, a total of 1,911 records remained for analysis.

Measures

The CARDIA Study collected data at year 0, 2, 5, 7, 10, 15, 20, and 25 post-recruitment. Each year had a different set of aims; therefore, not all variables were tested at each interval. Demographic data (age, gender, race, and site) were collected at year 0. Self-reported education level at year 25 was also used for this study. The measurement of body habitus, hyperglycemia, lipids, inflammatory markers, and vascular health from year 20 were used. The results from cognitive tests were collected from year 25. Measurements for age, body habitus, hyperglycemia, lipids, inflammatory markers, and cognitive tests were continuous variables while gender, race, site, and vascular health were dichotomous or categorical variables.

Waist Circumference. Waist circumference was measured using the *Gulick II Plus* anthropometric tape which was applied horizontally at a lateral level midway between the iliac crest, the lowest lateral area of the rib cage, and anteriorly midway between the xiphoid process and the umbilicus (Scientific Resources Section, 2005). For the purposes of this study, the average of the two measurements of waist circumference were used since they were highly correlated with one another (*Pearson's* correlation = 0.999).

Body Habitus. Body mass index (BMI) is a measure commonly used to objectively measure obesity. Measures of height and weight of the participants were used to calculate BMI (kg/m^2).

Hyperglycemia. Hyperglycemia was measured by hemoglobin A1c (HbA1c), oral glucose tolerance tests, and fasting blood glucoses. Hemoglobin A1c was used as an average for blood glucoses over the last 90-120 days and was converted to a percentage for evaluation. Oral glucose tolerance tests, which were used to test a glucose challenge after a long fasting period, were measured using the hexokinase ultraviolet method to assess glycemia 2 hr after the glucose challenge. Fasting blood glucose was measured using the hexokinase ultraviolet method (Scientific Resources Section, 2005).

Lipids. A lipid panel was used to determine the value of low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), and triglycerides. LDL cholesterol was calculated using the Friedewald equation (Scientific Resources

Section, 2005). HDL cholesterol by trinder-type method was determined enzymatically after the precipitation of dextran sulfate-magnesium on the Abbot Spectrum. Triglycerides were determined by ultraviolet method which was again determined enzymatically on the Abbot Spectrum (using Hitachi 917 – R1Buffer/4-Chloropheno/Enzymes).

Inflammatory Markers. The inflammatory markers, C-reactive protein and interleukin-6, were used to determine if inflammation was present. C-reactive protein was gauged using a nephelometry-based high throughput assay (Scientific Resources Section, 2005). Interleukin-6 was assessed using an ELISA assay from R&D Systems with methodology well established in the laboratory. Interleukin-6 is a key cytokine that mediates the acute phase of inflammation, promotes local thrombosis (or clotting), and over time can alter vasculature.

Vascular Health. Coronary calcification scores from year 20 were used to determine if vascular disease was present. The coronary calcification was measured with different scanners; the Birmingham field center used the GE Lightspeed QX/I, the Chicago site used the Imatron C-150, the Minneapolis site used the Siemens S4+ Volume Zoom, and the Oakland site used the Imatron C-150 (Scientific Resources Section, 2005). The same scanning protocol was developed and used by all sites to ensure uniformity of the scans because different technologies were used. The presence of coronary calcification was defined as having a positive, non-zero Agatston score using the average of two scans. Those participants with higher coronary artery calcification scores have

greater plaque burden and a greater risk of having cardiac events related to poor vascular health. This variable was dichotomized with a score of 0 indicating the absence of calcification in the coronary arteries and therefore a low likelihood that these participants would have cardiac events related to poor vascular health.

Cognitive Functioning. Three different neurocognitive tests were used to evaluate cognitive functioning in the participants. Cognitive functioning was measured using the: Rey-Auditory Verbal Learning Test (RAVLT), Digit Symbol Substitution Test (DSST), and Stroop Test. Neurocognitive technicians all used the same protocol in order to perform the tests and ensure inter-rater reliability.

Stroop Test. The Stroop Test is a measure of executive function (a function attributed to the frontal lobe). To assess this, the Stroop Test was used to evaluate the participants' ability to view complex visual stimuli, respond to one stimulus, while purposefully ignoring the processing of the other dimension. The Stroop Test consists of three subtests. In subtest 1, participants read aloud color words that are written with black ink. In subtest 2, participants stated the colors of colored rectangles. In subtest 3, participants read aloud the color of ink that color words are written (i.e., if the word "green" is written in red ink, the correct answer is red) (Reis et al., 2013). Next, an interference score was calculated by subtracting the score on subtest 3 from the score from subtest 2. Interference provided a measure of the additional executive processing needed to respond to subtest 3. For scoring purposes, higher interference scores indicate worse cognitive functioning.

Digit Symbol Substitution Test (DSST). The DSST, a subtest of the Wechsler Adult Intelligence Scale, Third Edition, is a measure of psychomotor speed (Salthouse, 1992). For this test, participants were presented with rows of numbers with empty boxes underneath and a key appeared above the rows where the numbers 1-9 were shown. Each number was paired with a distinct symbol. For this test, participants were asked to fill-in the blank boxes with their distinct symbol (up to 140 boxes) in a 2-min period. The participants received a point for each correctly drawn symbol. The range of scores is 0-133, with lower scores indicating poorer cognitive functioning (Reis et al., 2013).

Rey-Auditory Verbal Learning Test (RAVLT). The RAVLT is a well-known test of memory and verbal learning (Malloy-Diniz, Lasmar, Gazinelli, Fuentes, & Salgado, 2007). More specifically, this test was used to evaluate the participants' ability to recall a short list of words with immediate, short-term, and long-term recall. A 15-item word list was read to the participants (a rate of one word per second). The list of words was presented five times and then the participants were asked to immediately recall as many words as possible in one minute's time. The neurocognitive technician checked off all of the words the participants were able to recall. An interference list of words was presented next and the participants were asked to recall these words immediately followed by recall of the words from the first trial. After about 10 min had lapsed, the neurocognitive technician asked the participants to recall as many of the words that were in the first trial. The long delay score for the RAVLT was used for this study.

Data Analysis

From the entire data set of 5,115 participants, listwise deletion was used to eliminate participants with incomplete data leaving 1,912 participants. Violations of multivariate normality were explored using bivariate graphs, Cook's distance, and Mahalanobis distance. Body mass index had one outlier (136.64 kg/m^2; *z*-score = 16.75) that was highly aberrant and was eliminated from the dataset because the observed value was not trusted. After this elimination, a total of 1,911 participants remained.

Correlations among study variables were analyzed using SPSS 11.5 (Norusis, 1993) and LISREL (Jöreskog & Sörbom, 1993). A partial correlation matrix was created and latent variables were extracted for body habitus (BMI and waist circumference), hyperglycemia (fasting blood glucose, oral glucose tolerance test, and HbA1c), lipids (LDL-C, HDL-C, and triglycerides), inflammatory markers (C-reactive protein and interleukin-6), vascular health (coronary calcification), and cognitive functioning (RAVLT, DSST, and the Stroop Test).

A causal model was constructed to determine the effects of body habitus, hyperglycemia, lipids, inflammatory markers, and vascular health on cognitive functioning (Figure 1). Standard fit indices were used to compare the fit of the models. Standard absolute fit indices included the adjusted goodness-of-fit index and the goodness-of-fit index; these compare the models to a saturated model instead of a nested model. The chi-square test was used as the conventional overall test of fit. The chi-square is overly sensitive because it provides a value of the difference between the sample and the fitted partial correlation matrix controlling for age, gender, race, level of education, and site.

To trim the model, *t*-tests of the significance of each estimated path were evaluated, and non-significant paths were fixed to zero so as to improve parsimony and model fit and then rerun. Finally, modification indices were examined to identify paths that could be added that would improve the overall fit of the model. The above procedure was conducted for participants with and without the APOE ε4 allele.

Results

Demographic and Cognitive Associations

Table 1 compares the descriptive statistics for the demographic variables at year 25 for participants with and without APOE ε4. Of the 1,911 participants who had complete data for analysis, 489 (25.6%) participants had the APOE ε4 allele. Participants with APOE ε4 ranged in age from 42 to 56 (M_{age} = 50.10 years). Women comprised 55% of these participants and 55% were White (*n* = 269). These participants had completed 7-20 years of school (*M* = 14.68 years). The mean HbA1c for those with APOE ε4 was 5.54% and ranged from 4 to 14%. The average levels of LDL-C, HDL-C, and triglycerides were noted to be 120.56 mg/dL, 56.75 mg/dL, and 104.55 mg/dL, respectively.

Conversely, a total of 1,422 (74.4%) did not have the APOE ε4 allele. Of those without APOE ε4, their age ranged from 42 to 57 (M_{age} = 50.35 years). Women comprised 56% of these participants and 66% were White (*n* = 936). These participants had completed 8 to 20 years of school (*M* = 14.76 years). The mean HbA1c for those without APOE ε4 was 5.51% and ranged from 4 to 15%. The average levels of LDL-C, HDL-C, and triglycerides were noted to be 111.03 mg/dL, 59.50 mg/dL, and 107.28

mg/dL, respectively. Significant differences between those with and without APOE ε4 were noted for race, level of education, LDL-C, HDL-C, C-reactive protein, DSST, and RAVLT.

Table 2 included the partial correlations for the variables of interest after controlling for age, race, sex, level of education, and site. Because LISREL does not create *p* values for individual correlations, significance levels were determined in SPSS. For those with APOE ε4, strong correlations were noted between: waist circumference with BMI ($r = .91$, $p < .01$); oral glucose tolerance test with fasting blood glucose ($r = .70$, $p < .01$) and HbA1c ($r = .62$, $p < .01$); and fasting blood glucose with HbA1c ($r = .77$, $p < .01$). Moderate correlations were noted between: waist circumference with fasting blood glucose ($r = .26$, $p < .01$), C-reactive protein ($r = .33$, $p < .01$), triglycerides ($r = .30$, $p < .01$), and HDL-C ($r = -.39$, $p < .01$); BMI with C-reactive protein ($r = .35$, $p < .01$) and HDL-C ($r = -.34$, $p < .01$); oral glucose tolerance test with triglycerides ($r = .27$, $p < .01$); HDL-C with triglycerides ($r = -.38$, $p < .01$); and DSST with Stroop ($r = -.27$, $p < .01$).

For those without APOE ε4, strong correlations were noted between: BMI with waist circumference ($r = .90$. $p < .01$); fasting blood glucose with oral glucose tolerance test ($r = .74$, $p < .01$); HbA1c with oral glucose tolerance test ($r = .64$, $p < .01$) and fasting blood glucose ($r = .76$, $p < .01$); as well as DSST with RAVLT ($r = -.74$, $p < .01$). Moderate correlations were noted for waist circumference with C-reactive protein ($r = .35$, $p < .01$); interleukin-6 with waist circumference ($r = .25$, $p < .01$) and BMI ($r = .25$, $p < .01$); triglycerides with oral glucose tolerance test ($r = .28$, $p < .01$); HDL-C with waist

circumference (r = -.37, p < .01), BMI (r = -.31, p < .01), oral glucose tolerance test (r = -.25, p < .01), and triglyceride (r = -.44, p < .01).

For structural equation modeling, Anderson and Gerbing (1988) suggested following a procedure whereby models are compared in a sequential, logical manner. Thus, for this analysis, a baseline model was constructed first using six conceptual or latent variables (body habitus, hyperglycemia, lipids, inflammatory markers, vascular health, and cognitive functioning). This baseline model was constructed to check the validity of the latent variables. Waist circumference and BMI served as the observed variables for body habitus. Oral glucose tolerance test, fasting blood glucose, and HbA1c served as the observed variables for hyperglycemia. Low density lipoprotein cholesterol, triglycerides, and HDL-C served as observed variables for lipids. C-reactive protein and interleukin-6 served as indicator variables for inflammatory markers. A dummy latent variable was created for vascular health since it only had one observed variable (coronary artery calcification). Reference variables were identified and specified to help in interpreting the valence of the model (i.e., triglycerides for lipids and RAVLT for cognitive functioning); therefore, higher scores indicated higher levels of the construct. Next, a causal model was specified whereby all of the proposed paths were added, regardless of significance. Lastly, in an iterative process, the trimmed model was constructed by eliminating the least nonsignificant paths one at a time until only all significant paths remained. Data were then interpreted from this trimmed model.

Analysis with APOE ε4 Sample

For those participants with APOE ε4, first, the independence model tested the hypothesis that all variables are not correlated, this model was rejected, X^2 (91, n = 489) = 2058.47, $p < .001$. The baseline model was then tested, and fit was significant (X^2 [63, n = 489] = 94.86, $p < .001$). A chi-square difference test indicated significant improvement in fit between the independence model and the baseline model, X^2_{diff} (28, n = 489) = 1,963.61, $p < .001$. The full model was specified next. Many of the model predicted paths were not significant; therefore, the trimmed model was developed by sequentially removing nonsignificant paths (based on the lowest *t*-value) one at a time and then recalculating the model estimates. This respecification process was continued until only significant paths remained in the model ($p < .05$).

Figure 2 shows the fully trimmed model along with the path coefficients with standardized solutions. As noted in Table 3, the standard fit indices (e.g., *GFI* = 0.97, *AGFI* = 0.96) for the trimmed model provided excellent fit to the observed data, X^2 (71, n = 489) = 105.64, $p < .001$. Ullman (1996) suggests running a correlation between the baseline model and the trimmed model estimates after performing post hoc model modification. Therefore, a very high correlation was observed (r = .96; p < .01) which is indicative of stable parameter estimates for the statistically significant paths after removal of all nonsignificant paths.

Interestingly, the fully trimmed model for the APOE ε4 sample shows that none of the latent causal variables (body habitus, hyperglycemia, lipids, inflammatory markers, and vascular health) directly affected cognitive functioning in those with APOE ε4. However, body habitus predicted hyperglycemia (standardized coefficient = 0.19),

inflammatory markers (standardized coefficient = 0.54), lipids (standardized coefficient = 0.41), and vascular health (standardized coefficient = 0.23); thus, the larger the body habitus the worse the hyperglycemia, inflammatory markers, lipids, and vascular health. Hyperglycemia predicted inflammatory markers (standardized coefficient = 0.20) and lipids (standardized coefficient = 0.22); thus, worse hyperglycemia predicted higher inflammatory markers and lipid levels.

Several significant indirect paths were noted in the trimmed model. More specifically, larger body habitus predicted worse hyperglycemia which predicted higher levels of inflammatory markers (R^2 = .04, p < .01). In addition, larger body habitus predicted worse lipid status (R^2 = .04, p < .01).

Analysis without APOE ε4 Sample

For those participants without APOE ε4, first, the independence model tested the hypothesis that all variables are not correlated, this model was rejected, X^2 (91, n = 1,422) = 5,999.67, p < .01. The baseline model was then tested, and fit was significant (X^2 [63, n = 1,422] = 184.90, p < .01). In fact, a chi-square difference test indicated a significant improvement in fit between the independence model and the baseline model, X^2_{diff} (28, n = 1,422) = 5,814.77, p < .01. The full model was specified next. Many of the model predicted paths were not significant; therefore, the trimmed model was developed.

Figure 3 shows the fully trimmed model including path coefficients with standardized solutions. As noted in Table 3, the standard fit indices (e.g., *GFI* = 0.98, *AGFI* = 0.97) for the trimmed model provided excellent fit to the observed data, X^2 (71, n = 1,422) = 197.43, p < .01. Because Ullman (1996) suggests running a correlation

between the baseline model and the trimmed model estimates after performing post hoc model modification, a correlation analysis was conducted. A very high correlation was observed (r = .99; p < .01) and indicates that stable parameter estimates exist for the statistically significant paths after removal of all nonsignificant paths.

In contrast to the final model for those with APOE ε4, the final model for those without APOE ε4 showed one latent causal variable, inflammatory markers, had a direct effect on cognitive functioning. Inflammatory markers affected cognitive functioning in an inverse way (standardized coefficient = -0.15). Albeit, body habitus affected hyperglycemia (standardized coefficient = 0.27), inflammatory markers (standardized coefficient = 0.54), lipids (standardized coefficient = 0.54), and vascular health (standardized coefficient = 0.13). Hyperglycemia affected inflammatory markers (standardized coefficient = 0.27) and lipids (standardized coefficient = 0.36).

Several significant indirect paths were noted in the trimmed model. Larger body habitus predicted worse lipid status (R^2 = .06, p <.01). Larger body habitus also predicted worse hyperglycemia which predicted higher inflammatory markers and eventually worse cognitive functioning (R^2 = -.08, p < .01). In addition, larger body habitus predicted higher inflammatory markers and, in turn, predicted worse cognitive functioning.

Discussion

The purpose of this study was to examine the possible influence that several metabolic and inflammatory predictors have on cognitive functioning with middle-aged adults with and without APOE ε4. With the use of structural equation modeling analyses, both the independent contributions and the common contributions on cognitive

functioning were investigated. The trimmed model for those without APOE ε4 produced only one direct path; lower levels of inflammatory markers predict better cognitive functioning in 5 years. Yet, several indirect effects were noted. Body habitus was noted to predict cognitive functioning as larger body habitus predicted hyperglycemia, higher levels of hyperglycemia predicted higher levels inflammatory markers, and higher levels of inflammatory markers predicted poorer cognitive functioning. In addition, larger body habitus predicted higher levels of inflammatory markers and lipids as well as worse vascular health. These findings are consistent with previous studies (e.g., Launer et al., 2000; Launer, 2005; Singh-Manoux et al., 2012; Whitmer et al. 2005; Yaffe et al., 2007).

Unfortunately, the trimmed model for those with APOE ε4 revealed that the variables of interest did not have any direct effects on cognitive functioning. Some indirect effects were found in the trimmed model. More specifically, body habitus predicted both worse lipid status and higher levels of inflammatory markers and also indirectly through hyperglycemia. The indirect effects that were noted predicted vascular health. Perhaps poor vascular health results in poor performance of the heart; therefore, cognitive functioning may be dependent on blood pressure. When the blood pressure is low, there is poor perfusion to organs such as the brain. When the brain lacks perfusion, it cannot function properly and cognitive functioning is impaired.

Third, the inability to find a predictive relationship directly on cognitive functioning in those with APOE ε4 at first seems surprising but may be due to the restricted age of the study. These results are likely due to studying middle-aged adults rather than an older population as subtle changes in cognitive functioning may not be detected as much in middle-aged adults as it is in older adults. If the participants had been

older at the beginning of the study, perhaps more direct effects on cognitive functioning may have been found.

Clearly, middle-aged adults with and without APOE ε4 have differences inherently that predict cognitive functioning over time. Thus, many unexplored predictive explanations for the difference in cognitive functioning exist for those with and without APOE ε4 as evident by only 2-5% of the variance of the cognitive measure being explained in the trimmed models. For example, midlife systolic blood pressure may predict late-life cognitive functioning as in the Honolulu-Asia Aging Study (Peila et al., 2001).

Strengths and Limitations

This study has several strengths. First, a large sample size with diverse gender, race, and level of education was used. Such a sample size allows for higher power and a greater ability to generalize its findings to the general population. Second, this study focused on middle-aged adults rather than older adults in order to determine the synergistic effects that metabolic and inflammatory predictors had on cognitive functioning. Finally, cognition was studied using more than one domain of cognition enabling a more global evaluation of cognitive functioning. The tests and measures within the study were performed using standardized measures at each site.

One limitation of this study is the age range; only adults from age 42 to 57 years old were in the study. This middle-aged sample did not allow the effects of older age on cognitive functioning. In addition, there were fewer participants in the APOE ε4 group which could account for less power in the detection of associations. There are also many

genes associated with Alzheimer's disease and this study only looked at one. This study also lacked a direct measurement of transient ischemic attacks and stroke. Instead, the participants reported whether or not they had experienced either transient ischemic attacks or stroke. A more direct way to measure previous transient ischemic attack or stroke could have included FLAIR imaging via magnetic resonance imaging, therefore, allowing the exclusion of these participants in a more reliable way. However, the results of the FLAIR imaging were not available at the time of this study. In addition, this study measured coronary artery calcification as either being present or not being present. Again, a more precise measurement of coronary calcification could yield even richer results. Indeed, CARDIA had a quantitative measurement of coronary artery calcification that could have been used. Because some the measures in this study were only measured once, the effects that they have over time could be better studied through the use of repeated measures. For example, interleukin-6 and cognitive measures were only conducted once. If some of the variables of interest had been studied at baseline and repeated at another time, change in cognition could be studied in more detail. In particular, with one measure of interleukin-6, it is difficult to determine whether the inflammation is occurring acutely or chronically.

Implications for Practice and Research

Based on the direct and indirect paths noted from the trimmed model for those with and without APOE ε4, a few implications for future practice and research can be gleaned. For those with APOE ε4, certainly there are multiple factors effecting cognitive functioning as noted by some of the strong correlations and the GFI for the trimmed

model. However, since this trimmed model explained such little variance, more exploratory research would need to be performed to explain cognitive functioning before practice changes could be made.

For those without APOE ε4, because direct paths from body habitus to hyperglycemia to inflammatory markers to cognitive functioning were noted, a few practice implications may be suggested. The measurement of body habitus via BMI and waist circumference should be considered. Then evidence based dietary and lifestyle modification plans can be taught and recommended in this patient population. Next, a focus on evidence based modifications of glycemia via diet, exercise, monitoring, and medications should be encouraged for patients. Additionally, measuring inflammatory markers periodically over time may be valuable in risk reduction in this patient population in efforts to maintain cognitive functioning (Talley et al., in press).

Further research for both those with and without APOE ε4 is necessary. First, this study could be replicated on other genes associated with Alzheimer's disease risk. Additionally, this study could be repeated on an older sample to determine if the results are age-related. Furthermore, other potential predictors of cognitive functioning still need to be explored, such as blood pressure (Cukierman-Yaffe et al., 2009). Repeating the measures of several metabolic and inflammatory predictors could also be useful with an older population to determine the change over time that may affect cognitive functioning.

References

Administration on Aging. (2012). *A profile of older Americans,* Vol. June 18. United States Department of Health and Human Services.

Anderson, J. C., & Gerbing, D. W. (1988). Structural equation modeling in practice: A review and recommended two-step approach. *Psychology Bulletin, 103,* 411-423.

Arvanitakis, Z., Wilson, R. S., Bienias, J. L., Evans, D. A., & Bennett, D. A. (2004). Diabetes mellitus and risk of Alzheimer disease and decline in cognitive function. *Archives of Neurology, 61,* 661-666.

Barzilay, J. L., Abraham, L., Heckbert, S. R., Cushman, M., Kuller, L. H., Resnick, H. E., & Tracy, R. P. (2001). The relation of markers of inflammation to the development of glucose disorders in the elderly: The Cardiovascular Health Study. *Diabetes, 50,* 2384-2389.

Bruce, J. M., Harrington, C. J., Foster, S., & Westervelt, H. J. (2009). Common blood laboratory values are associated with cognition among older inpatients referred for neuropsychological testing. *The Clinical Neuropsychologist, 23*, 909-925. doi: 10.1080/13854040902795026

Burke, G. L., Bild, D. E., Hilner, J. E., Folsom, A. R., Wagenknecht, L. E., & Sidney, S. (1996). Differences in weight gain in relation to race, gender, age and education in young adults: The CARDIA Study. Coronary Artery Risk Development in Young Adults. *Ethnicity and Health, 1(*4), 327-335.

Centers for Disease Control and Prevention. (2011). *National diabetes fact sheet: National estimates and general information on diabetes and prediabetes in the United States*. Atlanta, GA.: U. S. Department of Health and Human Services, Center for Disease Control and Prevention. Retrieved on 3/18/2013 from://www.ndep.nih.gov/media/FS, OlderAdult.pdf

Cukierman, T., Gerstein, H. C., & Williamson, J. C. (2005). Cognitive decline and dementia in diabetes: a systematic overview of prospective observational studies. *Diabetologia, 42*, 2460-2469. doi: 10.1007/s00125-005-0023-4

Cukierman-Yaffe, T., Gerstein, H. C., Williamson, J. D., Lazar, R. M., Lovato, L., Miller, M. E., … Launer, L. (2009). Relationship between baseline glycemic control and cognitive function in individuals with type 2 diabetes and other cardiovascular risk factors: The Action to Control Cardiovascular Risk in Diabetes- Memory in Diabetes (ACCORD-MIND) trial. *Diabetes Care, 32*, 221-226. doi: 10.2337/dc08-1153

Donahue, R. P., Jacobs, D. R., Sidney, S., Wagenknecht, L. E., Albers, J. J., & Hulley, S. B. (1989). Distribution of lipoproteins and aplipoproteins in young adults in the CARDIA Study. *Arteriosclerosis, Thrombosis, and Vascular Biology: Journal of the American Heart Association, 9*, 656-664.

Evans, R. M., Emsley, C. L., Gao, S., Sahota, A., Hall, K. S., Farlow, M. R., & Hendrie, H. (2000). Serum cholesterol, APOE genotype, and the risk of Alzheimer's disease: A population based study of African Americans. *Neurology, 54*, 240-242.

Friedman, G. D., Cutter, G. R., Donahue, R. P., Hughes, G. H., Hulley, S. B., Jacobs, D. R., …Savage, P. J. (1988). CARDIA: Study design, recruitment, and some characteristics of the examined subjects. *Journal of Clinical Epidemiology, 41*(11), 1105-1116.

Galanina, N., Surampudi, V., Ciltea, D., Singh, S. P., & Permuter, L. C. (2008). Blood glucose levels before and after cognitive testing in diabetes mellitus. *Experimental Aging Research, 34*, 152-161. doi: 10.1080/036107307011876979

Gregg, E. W., Yaffe, K., Cauley, J. A., Rolka, D. B., Blackwell, T. L., Narayan, K. M., & Cummings, S. R. (2000). Is diabetes associated with cognitive impairment and cognitive decline among older women? Study of Osteoporotic Fractures Research Group. *Archives of Internal Medicine, 160,* 174-180.

Gonder-Frederick, L. A., Zrebiec, J. F., Bauchowitz, A. U., Ritterband, L. M., Magef, J.,C., Cox, D. J., & Clarke, W. L. (2009). Cognitive function is disrupted by both hypo- and hyperglycemia in school-aged children with type 1 diabetes mellitus: A field study. *Diabetes Care, 32*(6), 1001-1006. doi: 10.2337/dc08-1722

Grodstein, F., Chen, J., Wilson, R. S., & Manson, J. E. (2001). Type 2 diabetes and cognitive function in community-dwelling elderly women. *Diabetes Care, 24*, 1060-1065.

Howard, B. V., Gidding, S. S., & Liu, K. (1998). Association of apolipoprotein E phenotype with plasma lipoproteins in African-American and white young adults the CARDIA Study. *American Journal of Epidemiology, 148*(9), 859-868.

Hughes, G. H., Cutter, G., Donahue, R., Friedman, G. D., Hulley, S. B., Hunkeler, E., …Wagenknecht, L. (1987). Recruitment in the coronary artery disease risk development in young adults (CARDIA) study. *Controlled Clinical Trials, 8,* 68S-73S.

Jöreskog, K. G., & Sörbom, D. (1993). *LISREL 8: The SIMPLIS command language*. SPSS, Chicago, IL.

Kanaya, A. M., Barrett-Connor, E., Gildengorin, G., & Yaffe, K. (2004). Change in cognitive function by glucose tolerance status among older adults: A 4-year prospective study of the Rancho Bernardo Study Cohort. *Archives of Internal Medicine, 164*, 1327-1333. doi:10.1001/archinte.164.12.1327

Launer, L. J. (2005). Diabetes and brain aging: Epidemiologic evidence. *Current Diabetes Report, 5,* 59-63. doi: 10.1007/s11892-005-0069-1

Launer, L. J., Ross, G. W., Petrovitch, H., Masaki, K., Foley, D., White, L. R., & Havlik, R. J. (2000). Midlife blood pressure and dementia: The Honolulu-Asia Aging Study. *Neurobiology of Aging, 21*, 49-55.

Loria, C. M., Liu, K., Lewis, C. E., Hulley, S. B., Sidney, S., Schreiner, P. J., …Detrano, R. (2007). Early adult risk factor levels and subsequent coronary artery calcification: The CARDIA Study. *Journal of the American College of Cardiology, 49*(20), 2013-2020. doi: 10.1016/j.jacc.2007.03.009

Malloy-Diniz, L. F., Lasmar, V. A., Gazinelli, L. D., Fuentes, D., & Salgado, J. V. (2007). The Rey Auditory-Verbal Learning Test: Applicability for the Brazilian elderly population. *Revista Brasileira de Psiquiatria, 29*(4), 324-329.

Marcovina, S. M., Albers, J. J., Jacobs, D. R., Perkins, L. L., Lewis, C. E., Howard, B. V., & Savage, P. (1993). Lipoprotein[a] concentrations and apolipoprotein[a] phenotypes in Caucasians and African Americans. The CARDIA Study. *Arteriosclerosis, Thrombosis, and Vascular Biology: Journal of the American Heart Association, 13*, 1037-1045.

McGuire, L. C., Ford, E. S., & Ajani, U. A. (2006). Cognitive functioning as a predictor of functional disability in later life. *The American Journal of Geriatric Psychiatry, 14(*1), 36-42. doi: 10.1097/01.JGP.0000192502.10692.d6

Moroney, J. T., Tang, M. X., Berglund, L., Small, S., Merchant, C., Bell, K., …Mayeux, R. (1999). Low density lipoprotein cholesterol and the risk of dementia with stroke. *Journal of the American Medical Association, 282*, 254-260.

Norusis, M. J. (1993). *SPSS: SPSS for windows based systems user's guide, release 6.0*. SPSS, Chicago, IL.

Okonkwo, O. C., Griffith, H. R., Vance, D. E., Marson, D. C., Ball, K. K., & Wadley, V. G. (2009). Awareness of functional difficulties in mild cognitive impairment: A multidomain assessment approach. *Journal of the Geriatric Society, 57*, 978-984. doi: 10.1111/j.1532-5415.2009.02261.x.

Peila, R., White, L. R., Petrovich, H., Masaki, K., Ross, G. W., Havlik, R. J., …Launer, L. J. (2001). Joint effect of the APOE gene and midlife systolic blood pressure on late-life cognitive functioning: The Honolulu-Asia Aging Study. *Stroke, 32*, 2882-2889.

Pradhan, A. D., Manson, J. E., Rifai, N., Buring, J. E., & Ridker, P. M. (2001). C-reactive protein, interleukin 6, and the risk of developing type 2 diabetes mellitus. *Journal of the American Medical Association, 286*, 327-334.

Reis, J. P., Loria, C. M., Launer, L. J., Sidney, S., Liu, K., Jacobs, D. R., ...Yaffe, K. (2013). Cardiovascular health through young adulthood and cognitive functioning in midlife. *Annals of Neurology, 73*(2), 170-179. doi: 10.1002%2Fana.23836

Ridker, P. M., Buring, J. E., Shih, J., Matias, M., & Hennekens, C. H. (1998). Prospective study of C-reactive protein and the risk of future cardiovascular events among apparently healthy women. *Circulation, 98*, 731-733.

Rizzo, M. R., Marfella, R., Barbieri, M., Boccardi, V., Vestini, F., Lettieri, B., …Paolisso, G. (2010). Relationships between daily acute glucose fluctuations and cognitive performance among aged type 2 diabetics. *Diabetes Care, 33*(10), 2169-2174. doi: 10.2337%2Fdc10-0389

Salthouse, T. A. (1992). What do adult age differences in the Digit Symbol Substitution Test reflect? *Journal of Gerontology, 47*(3), 121-128.

Scientific Resources Section. [ca.2005]. *Protocols*. (Year 20, 2005-2006). Retrieved from CARDIA website: http://www.cardia.dopm.uab/edu/exammaterials2/protocol

Shimada, H., Miki, T., Tamura, A, Ataka, S., Emoto, M., & Nishizawa, Y. (2010). Neuropsychological status of elderly patients with diabetes mellitus. *Diabetes Research and Clinical Practice, 87*(2), 224-227. doi: 10.1016/j.diabres.2009.09.026

Singh-Manoux, A., Czernichow, S., Elbaz, A., Dugravot, A., Sabia, S., Hagger-Johnson, G., …Kivimäki, M. (2012). Obesity phenotypes in midlife and cognition in early old age: The Whitehall II Cohort Study. *Neurology. 79*(8):755-62. doi: 10.1212/WNL.0b013e3182661f63.

Strachan, M. W. (2010). The brain as a target organ in type 2 diabetes: Exploring the links with cognitive impairment and dementia. *Diabetic Medicine, 28*, 131-147. doi: 10.1111/j.1464-5491.2010.03199.x

Talley, M. H., Morrison, S., Crowe, M., Pryor, E., Wadley, V., & Vance, D. (in press). The physiological mechanisms of diabetes and aging on brain health and cognition: Implications for nursing practice and research. *Journal of Neuroscience Nursing*

Ullman, J. B. (1996). Structural equation modeling. In: Tabachnick, B. G., Fidell, L. S., editors. *Using Multivariate Statistics*. (pp. 709-811). Harper Collins: New York.

Umegaki, H. (2014). Type 2 diabetes as a risk factor for cognitive impairment: Current insights. *Clinical Interventions in Aging, 9*, 1011-1019.

United States Department of Health and Human Services. National Institute of Health. Alzheimer's Disease Education and Referral Center; A Service of the National Institute on Aging. (2011). *Alzheimer's disease fact sheet.* (pp. 1-8). NIH publication 11-6423.

Vance, D., Eagerton, G., Harnish, B., McKie, P., & Fazeli, P. (2011). Cognitive prescriptions: A nursing approach to increasing cognitive reserve. *Journal of Gerontological Nursing, 37*(4), 22-31. doi: 10.3928/00989134-20110304-01

Vance, D., Webb, N. M., Marceaux, J. C., Viamonte, S. M., Foote, A., & Ball, K. (2008). Mental stimulation, neural plasticity, and aging: Directions for nursing research and practice. *Journal of Neuroscience Nursing, 40*(4), 241-249.

Whitmer, R. A., Gunderson, E. P., Barrett-Connor, E., Quesenberry, C. P., & Yaffe, K. (2005). Obesity in middle age and future risk of dementia: A 27 year longitudinal population based study. *British Medical Journal, 330*, 1360-1365.

Yaffe, K., Barrett-Connor, E., Lin, F., & Grady, D. (2002). Serum lipoprotein levels, statin use, and cognitive function in older women. *Archives of Neurology, 59*, 378-384. doi: 10.1001/archneur.59.3.378.

Yaffe, K., Haan, M., Blackwell, T., Cherkasova, E., Whitmer, R. A., & West, N. (2007). Metabolic syndrome and cognitive decline in elderly Latinos: Findings from the Sacramento Area Latino Study of Aging study. *Journal of the American Geriatric Society, 55*, 758-762.

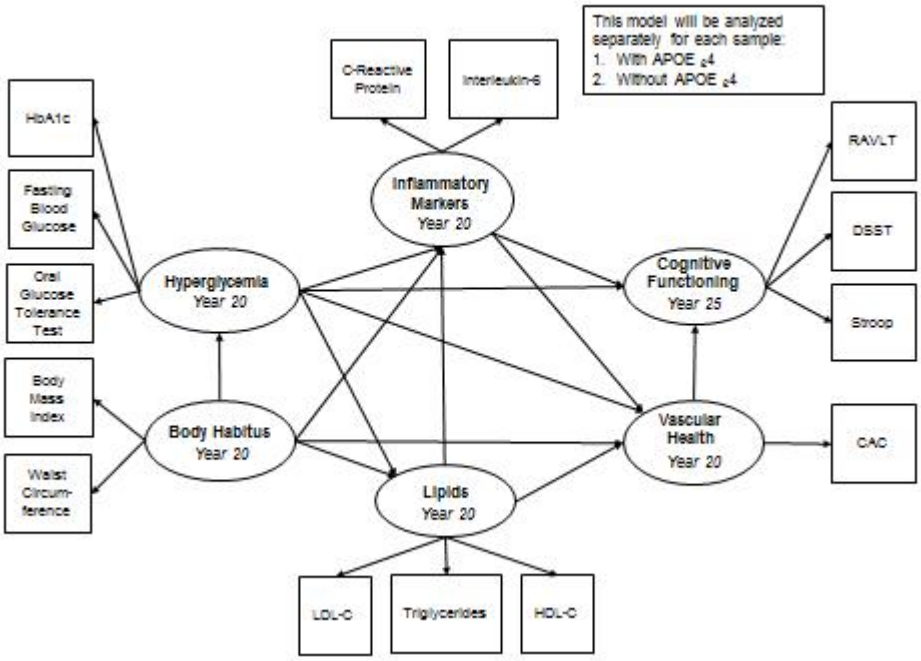

Figure 1. Proposed Causal Model of Cognitive Functioning. APOE ε4 = Apolipoprotein E 4 allele. HbA1c = hemoglobin A1c; LDL-C = low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol; CAC = coronary artery calcification; DSST = Digit Symbol Substitution Test; RAVLT = Rey Auditory Verbal Learning Test.

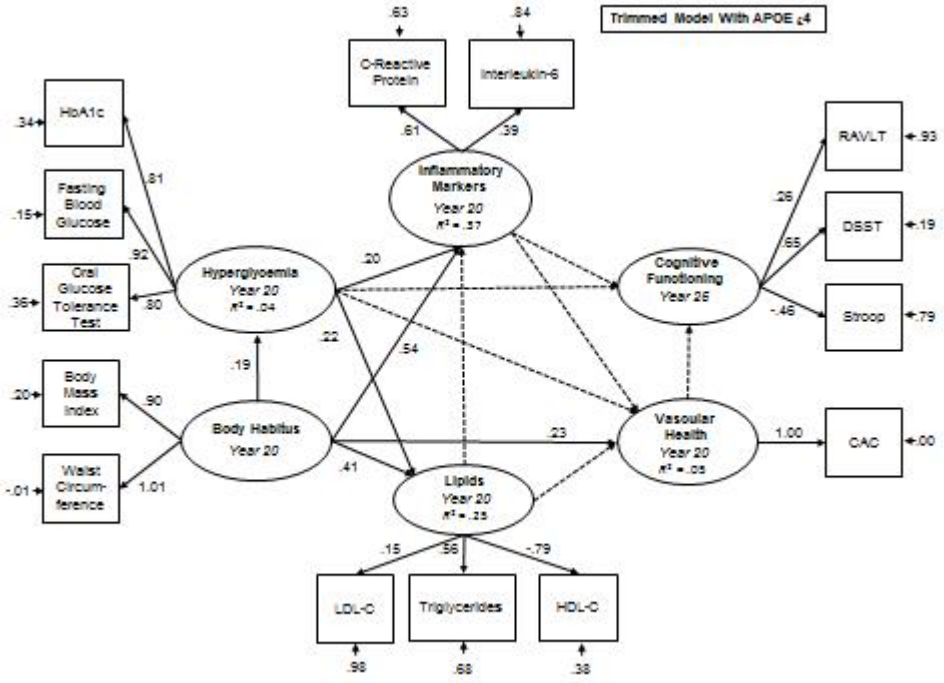

Figure 2. Trimmed Causal Model of Cognitive Functioning with APOE ε4. APOE ε4 = Apolipoprotein E 4 allele. HbA1c = hemoglobin A1c; LDL-C = low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol; CAC = coronary artery calcification; DSST = Digit Symbol Substitution Test; RAVLT = Rey Auditory Verbal Learning Test. All solid lines represent significant effects ($p < 0.05$); broken lines indicate proposed nonsignificant paths. A partial correlation matrix was used to control for age, gender, race, level of education, and site.

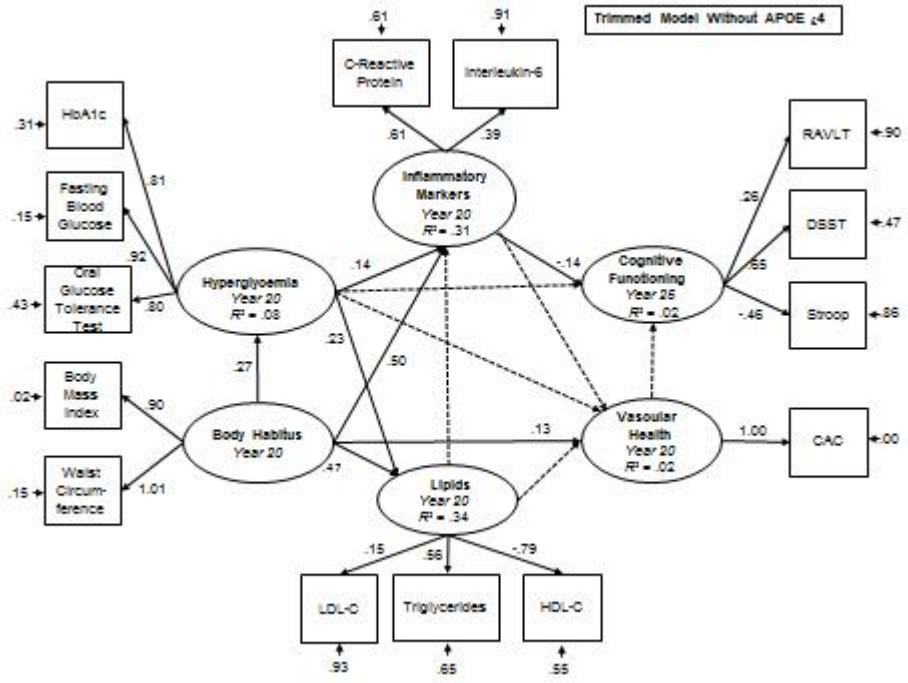

Figure 3. Trimmed Causal Model of Cognitive Functioning without APOE ε4. APOE ε4 = Apolipoprotein E 4 allele. HbA1c = hemoglobin A1c; LDL-C = low density lipoprotein; HDL-C = high density lipoprotein cholesterol; CAC = coronary artery calcification; DSST = Digit Symbol Substitution Test; RAVLT = Rey Auditory Verbal Learning Test. All solid lines represent significant effects ($p < 0.05$); broken lines indicate proposed nonsignificant paths. A partial correlation matrix was used to control for age, gender, race, level of education, and site.

Table 1

Characteristics of the Sample at Year 25 (N = 1,911)

	With APOE ε4					Without APOE ε4					
Variable	*n*	%	*M*	*SD*	Range	*n*	%	*M*	*SD*	Range	*p* - value
Age, yr	489	25.6	50.10	3.63	42 - 56	1,422	74.4	50.35	3.55	42 - 57	.18
Race											.00†
Black	220	45.0				486	34.2				
White	269	55.0				936	65.8				
Sex											.65
Men	220	45.0				623	43.8				
Women	269	55.0				799	56.2				
Education, yr	489		14.43	2.24	7 - 20	1,422		14.76	2.33	8 - 20	.01†
Waist Circumference	489		90.39	13.57	61 - 134	1,422		90.02	13.72	60 - 140	.60
BMI	489		28.76	5.71	17 - 54	1,422		28.43	6.04	18 - 57	.29
Oral Glucose Tolerance Test	489		108.23	41.32	23 - 477	1,422		110.12	41.46	25 - 499	.38
Fasting Blood Glucose	489		94.93	17.40	67 - 285	1,422		95.25	17.14	48 - 367	.72
HbA1c	489		5.54	.61	4 - 14	1,422		5.51	.60	4 - 15	.28
LDL-C	489		120.56	29.85	34 - 263	1,422		111.03	31.24	14 - 282	.00†
HDL-C	489		56.75	16.18	25 - 123	1,422		59.50	17.93	24 - 171	.00†
Triglycerides	489		104.55	56.80	24 - 354	1,422		107.28	58.29	21 - 399	.37
C-reactive protein	489		2.27	3.65	0 - 27	1,422		2.86	4.17	0 - 33	.01†
Interleukin-6	489		2.31	2.38	0 - 22	1,422		2.40	3.01	0 - 29	.54
CAC											.47
With	91	18.6				244	17.2				
Without	398	81.4				1,178	82.8				
Stroop	489		21.77	9.79	5 - 74	1,422		21.29	9.18	-20 - 74	.33
DSST	489		70.57	15.38	30 - 119	1,422		72.86	15.57	8 - 125	.01†
RAVLT	489		8.40	3.32	0 - 15	1,422		8.90	3.16	0 - 15	.00†

Note. APOE ε4 = apolipoprotein E 4 allele; APOE ε4 (With = ε 3/4 and ε4/4 and Without = ε2/4 and any ε2 or ε3 alleles);Yr = years; BMI = body mass index; HbgA1c = hemoglobin A1c; LDL-C = low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol; CAC = coronary artery calcification scores; DSST = Digit Symbol Substitution Test; RAVLT = Rey-Auditory Verbal Learning Test. †$p < 0.01$

Table 2

Partial Correlation Matrix for Participants with and without the APOE ε4 Allele

Variable	1	2	3	4	5	6	7
1. Waist Circumference[a]	1.00	0.91‡	0.24‡	0.26‡	0.19‡	0.33‡	0.17‡
2. BMI[a]	0.90‡	1.00	0.21‡	0.23‡	0.19‡	0.35‡	0.17‡
3. Oral Glucose Tolerance Test[a]	0.22‡	0.19‡	1.00	0.70‡	0.62‡	0.19‡	0.03
4. Fasting Glucose[a]	0.17‡	0.15‡	0.74‡	1.00	0.77‡	0.14‡	0.05†
5. HbA1c[a]	0.10†	0.08	0.64‡	0.76‡	1.00	0.16‡	0.07†
6. C-reactive protein[a]	0.35‡	0.36	0.22‡	0.18‡	0.16‡	1.00	0.20‡
7. Interleukin-6	0.25‡	0.25‡	0.07	0.06	0.03	0.24‡	1.00
8. LDL-C[a]	0.03	0.03	0.10†	0.08	0.07	0.04	0.01
9. Triglyceride[a]	0.23‡	0.18‡	0.28‡	0.18‡	0.11†	0.12‡	0.05
10. HDL-C[a]	-0.37†	-0.31‡	-0.25‡	-0.18‡	-0.13‡	-0.18‡	-0.07
11. CAC[b]	0.23‡	0.16‡	0.05	0.02	0.02	0.05	0.06
12. RAVLT[a]	0.06	0.09	0.02	0.01	0.03	-0.03	0.01
13. DSST[a]	-0.05	0.01	-0.03	-0.03	-0.05	-0.12‡	-0.17
14. Stroop[a]	-0.05	0.07	0.01	-0.03	0.01	0.04	0.06

Note. Controlled for age, sex, race, level of education, and site. Values above the diagonal represent those with apolipoprotein E ε4 allele (APOE ε4) and those below the diagonal are from those without APOE ε4. [a]Continuous variable. [b] Dichotomous variable. †$p < 0.05$. ‡$p < 0$ .01. BMI = body mass index; HbA1c = hemoglobin A1c; LDL-C = low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol; CAC = coronary artery calcification scores; DSST = Digit Symbol Substitution Test; RAVLT = Rey-Auditory Verbal Learning Test.

Table 2 (Continued)

Partial Correlation Matrix for Participants with and without the APOE ε4 Allele

Variable	8	9	10	11	12	13	14
1. Waist Circumference[a]	0.07‡	0.30‡	-0.39‡	0.13‡	0.01	-0.04	0.05†
2. BMI[a]	0.05	0.23‡	-0.34‡	0.13‡	-0.00	-0.04	0.05
3. Oral Glucose Tolerance Test[a]	0.04	0.27‡	-0.20‡	0.01	-0.07‡	-0.07†	0.03
4. Fasting Glucose[a]	0.07‡	0.22‡	-0.19‡	-0.01	-0.01	-0.06†	0.01
5. HbA1c[a]	0.09‡	0.20‡	-0.18‡	0.01	-0.03	-0.08‡	0.05
6. C-reactive protein[a]	0.03	0.14‡	-0.20‡	0.08‡	-0.02	-0.07‡	0.02
7. Interleukin-6	0.01	0.04	-0.08‡	0.03	-0.02	-0.03	0.05
8. LDL-C[a]	1.00	0.23‡	-0.18‡	0.02	-0.03	-0.01	-0.02
9. Triglyceride[a]	0.12‡	1.00	-0.38‡	0.02	-0.03	-0.03	0.06†
10. HDL-C[a]	-0.11‡	-0.44‡	1.00	-0.03	0.00	0.04	-0.03
11. CAC[b]	-0.01	0.14‡	-0.14‡	1.00	-0.01	-0.00	0.03
12. RAVLT[a]	0.00	0.01	-0.04	-0.08‡	1.00	0.23	-0.12‡
13. DSST[a]	0.08	-0.06	0.01	-0.10‡	-0.74‡	1.00	-0.27‡
14. Stroop[a]	0.02	-0.08	0.02	0.03	0.03	-0.07‡	1.00

Note. Controlled for age, sex, race, level of education, and site. Values above the diagonal represent those with apolipoprotein E ε4 allele (APOE ε4) and those below the diagonal are from those without APOE ε4. [a]Continuous variable. [b] Dichotomous variable. †$p < 0.05$. ‡$p < 0$ .01. BMI = body mass index; HbA1c = hemoglobin A1c; LDL-C = low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol; CAC = coronary artery calcification scores; DSST = Digit Symbol Substitution Test; RAVLT = Rey-Auditory Verbal Learning Test.

Table 3
Fit Measures of Baseline, Causal, and Trimmed Models

	With APOE ε4							
	X^2 (df)	*GFI*	*AGFI*	*PGFI*	*RMR*	*RMSEA*	*NFI*	*PNFI*	*RFI*
Baseline model	94.855 (63)	0.974	0.957	0.584	0.035	0.032	0.954	0.660	0.933
Full model	96.131(64)	0.974	0.957	0.593	0.036	0.032	0.953	0.670	0.933
Trimmed model	105.639 (71)	0.971	0.957	0.657	0.038	0.032	0.949	0.740	0.934
	Without APOE ε4							
	X^2 (df)	*GFI*	*AGFI*	*PGFI*	*RMR*	*RMSEA*	*NFI*	*PNFI*	*RFI*
Baseline model	184.902 (63)	0.982	0.970	0.589	0.025	0.037	0.969	0.671	0.955
Full model	185.951 (64)	0.982	0.970	0.598	0.025	0.037	0.969	0.681	0.956
Trimmed model	197.426 (71)	0.981	0.971	0.663	0.028	0.036	0.967	0.755	0.958

Note. GFI = goodness-of-fit index; AGFI = adjusted goodness-of-fit index; PGFI = parsimony goodness-of-fit; RMR = root-mean residual; RMSEA = root-mean-square-error of approximation; NFI = normed fit index; PNFI = parsimony normed fit index; RFI = relative fit index.

CONCLUSIONS

With an aging society, maintaining cognitive functioning throughout the lifespan is becoming more important so that normal day-to-day activities can continue to be performed (Vance et al., 2011). Many determinants of cognitive functioning exist; some are modifiable (e.g., level of education, body habitus, hyperglycemia, inflammatory markers, lipids, and vascular health) while others are not (age, gender, race, and the genetic expression of Alzheimer's disease) (Talley et al., in press). The synergistic effects of these determinants can have detrimental effects on cognitive functioning. This dissertation project was designed to use a subset of data in order to determine the best model that predicted cognitive functioning for all participants of the CARDIA Study and then also those with APOE ε4, and those without APOE ε4 using multiple regression modeling. In addition, SEM was used to determine significant predictors of cognitive functioning 5 years later for those with and without APOE ε4.

As a part of the dissertation, the first manuscript was submitted for publication while the second and third manuscripts were generated with permission of the CARDIA Publication and Presentation Committee. Final approval by this committee will be required prior to submission of these manuscripts for publication. The first article was a literature review that explored the synergistic effects of diabetes and aging on cognitive functioning. Literature supported the notion that diabetes caused insulin resistance, increased by-products, increased cholesterol levels, and oxidative stress while aging

caused demyelination and the formation of neurofibrillary tangles and plaques. The combined, synergistic effects impacted brain health and ultimately cognitive functioning. The impact that insulin plays in the brain and potential methods of delivery of insulin, such as intranasal delivery, was also explored. Implications for practice and research were also outlined and included changes in diet, exercise, blood pressure, and cholesterol management.

The second article included the design, methods, analysis, and results of hierarchical regression models to identify significant demographic, metabolic, and inflammatory predictors of cognitive functioning among the CARDIA Study participants. These analyses were conducted on records from 2,229 participants and stratified by APOE ε4 status. The results of the study indicated that among all participants, regardless of APOE ε4 status, lower levels of HbA1c, triglycerides, and interleukin-6 were predictive of better cognitive functioning among Black and White middle-aged participants; although, the amount of variance explained in predicting cognitive functioning was small.

For those participants with APOE ε4, higher levels of LDL-C were noted with better cognitive functioning in mid-life. This result is consistent with the notion that a complex relationship likely exists between LDL-C cholesterol, genetic expression of APOE alleles, and cognition functioning (Puttonen, Elovainio, Kivimaki, Lehtimaki, & Keltikangas-Jarvinen, 2003). This relationship may be due to an interaction between LDL-C and APOE whereby the APOE polymorphism impacts neural activity (Barres & Smith, 2002). Higher LDL-C may actually facilitate more synapses; these synapses assist in plasticity. This plasticity is neuroprotective in middle-aged adults but as aging occurs,

perhaps this neuroprotective mechanism decreases. As the protective nature diminishes, the high levels become detrimental to cognitive functioning due to the negative impact LDL-C has on vascular health. This relationship is similar to the age-related effects that APOE ε4 status has on cognitive functioning (Liu et al., 2010) whereby APOE ε4 tends to have a more pronounced effect as aging occurs. When considering that APOE ε4 is a major component of LDL-C, genetic variations of APOE ε4 may likely impact LDL-C as well. Those participants without the APOE ε4 had lower levels of HbA1c, triglycerides, and interleukin-6, which resulted in better cognitive functioning. These results are similar to the results found by the first model whereby all participants, regardless of APOE ε4 status, were studied.

The third article used structural equation modeling to determine the relationships between variables that predict cognitive functioning 5 years later in those middle-aged participants with and without APOE ε4 from the CARDIA Study. Interestingly, the fully trimmed model for the APOE ε4 sample revealed that none of the latent causal variables (body habitus, hyperglycemia, lipids, inflammatory markers, and vascular health) had a direct effect on predicting cognitive function. In contrast to the trimmed model for those with APOE ε4, the trimmed model for those without APOE ε4 revealed that one latent causal variable, inflammatory markers, had a significant and direct effect on cognitive functioning. Lower levels of inflammatory markers predicted better cognitive functioning. However, several other indirect paths were noted and include: larger body habitus predicted worse hyperglycemia, inflammatory markers, lipids, and vascular health. In addition, worse hyperglycemia predicted higher levels of inflammatory markers and lipids.

The review of literature and statistical analyses performed for this dissertation provided implications for future practice and research. There has been a growing consensus on the need to identify the pathogenic processes that lead to dementia in middle-aged adults or even sooner (Sperling et al., 2011), which could yield both practice changes and research possibilites. Practice changes for those at risk for changes in cognitive functioning later in life should be managed using the best evidence provided by research studies in order to preserve cognition. Based on the findings of this study, the measurement of body habitus via BMI or waist circumference should be monitored by health care providers. Dietary and lifestyle modifications can then be prescribed, if the body habitus is excessive. In addition, glycemic control may be tested. In those who have uncontrolled hyperglycemia, diet, exercise, frequent monitoring, and medication regimens could be individually tailored to improve control. The measurement of lipid status and inflammatory markers may also be implemented to identify those at risk for decline in cognitive functioning. Once identified, health care providers may adhere to evidence-based standards of care for the treatment of abnormal findings.

Another implication from this dissertaton, is that further research is needed among persons with and without a genetic predisposition for Alzheimer's disease. Clearly, additional predictors should be studied as well as the ways in which those with and without a genetic predisposition to Alzheimer's disease differ in regard to clinically relevant variables. Future efforts in research should be aimed at replicating the findings from this study with an older population and a more racially diverse population. In order to determine the age-related changes on specific metabolic and inflammatory predictors, researchers need to conduct studies with repeated measures of these key variables to

determine the change over time that may affect cognitive functioning. In addition, identifying the synergistic effects that metabolic and inflammatory predictors have on cognitive reserve should also be explored.

GENERAL LIST OF REFERENCES

Administration on Aging. (2012). *A profile of older Americans*, Vol. June 18. Department of Health and Human Services.

Akiyama, H., Barger, S., Barnum, S., Bradt, B., Bauer, J., Cole, G. M. …Van Muiswinkel. (2000). Inflammation and Alzheimer's disease. *Neurobiology of Aging, 21*(3), 383-421.

American Diabetes Association. (2008). Economic costs of diabetes in the U.S. in 2007. *Diabetes Care, 31*(3), 596-615.

Anstey, K. J., Lipnicki, D. M., & Low, L. F. (2008). Cholesterol as a risk factor for dementia and cognitive decline: A systematic review of prospective studies with meta-analysis. *American Journal of Geriatric Psychiatry, 16*, 343–54. doi: 10.1097/01.JGP.0000310778.20870.ae

Arvanitakis, Z., Wilson, R. S., Bienias, J. L., Evans, D. A., & Bennett, D. A. (2004). Diabetes mellitus and risk of Alzheimer disease and decline in cognitive function. *Archives of Neurology, 61*, 661-666.

Barres, B. A., & Smith, S. J. (2001). Cholesterol- Making or breaking the synapse. *Science, 294*, 1296-1297. doi: 10.1126/science.1066724

Bruce, J. M., Harrington, C. J., Foster, S., & Westervelt, H. J. (2009). Common blood laboratory values are associated with cognition among older inpatients referred for neuropsychological testing. *The Clinical Neuropsychologist, 23*, 909-925. doi: 10.1080/13854040902795026

Carnethon, M. R., Loroa, C. M., Hill, J. O., Sidney, S., Savage, P. J., & Liu, K. (2004). Risk factors for the metabolic syndrome: The coronary artery risk development in young adults (CARDIA) study, 1985-2001. *Diabetes Care, 27*(11), 2707-2715.

Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion Division of Diabetes Translation. (2014). *National diabetes statistics report*. Atlanta, GA; Retrieved from http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf

Cukierman, T., Gerstein, H. C., & Williamson, J. C. (2005). Cognitive decline and dementia in diabetes: a systematic overview of prospective observational studies. *Diabetologia, 42*, 2460-2469. doi: 10.1007/s00125-005-0023-4

Cukierman-Yaffe, T., Gerstein, H. C., Williamson, J. D., Lazar, R. M., Lovato, L., Miller, M., …Launer, L. J. (2009). Relationship between baseline glycemic control and cognitive function in individuals with type 2 diabetes and other cardiovascular risk factors. *Diabetes Care, 32*(2), 221-226. doi: 10.2337/dc08-1153

Donahue, R. P., Jacobs, D. R., Sidney, S., Wagenknecht, L. E., Albers, J. J., & Hulley, S. B. (1989). Distribution of lipoproteins and aplipoproteins in young adults in the CARDIA Study. *Arteriosclerosis, Thrombosis, and Vascular Biology: Journal of the American Heart Association, 9*, 656-664

Friedman, G. D., Cutter, G. R., Donahue, R. P., Hughes, G. H., Hulley, S. B., Jacobs, D. R., …Savage, P. J. (1988). CARDIA: Study design, recruitment, and some characteristics of the examined subjects. *Journal of Clinical Epidemiology, 41*(11), 1105-1116.

Fujita, T., Hemmi, S., Kajiwara, M., Yabuki, M., Fuke, Y., Satomura, A., & Soma, M. (2013). Complement-mediated chronic inflammation is associated with diabetic microvascular complication. *Diabetes/Metabolism Research and Reviews, 29*(3), 220-226.doi: 10.1002/dmrr.2380

Galanina, N., Surampudi, V., Ciltea, D., Singh, S. P., & Permuter, L. C. (2008). Blood glucose levels before and after cognitive testing in diabetes mellitus. *Experimental Aging Research, 34*, 152-161. doi: 10.1080/036107307011876979

Gonder-Frederick, L. A., Zrebiec, J. F., Bauchowitz, A. U., Ritterband, L. M., Magef, J. C., Cox, D. J., & Clarke, W. L. (2009). Cognitive function is disrupted by both hypo- and hyperglycemia in school-aged children with type 1 diabetes mellitus: A field study. *Diabetes Care, 32*(6), 1001-1006. doi: 10.2337/dc08-1722

Helzner, E. P., Luchsinger, J. A., Scarmeas, N., Cosentino, S., Brickman, A. M., Glymour, M. M., …Stern, Y. (2009). Contribution of vascular risk factors to the progression in Alzheimer disease. *Archives of Neurology, 66*(3), 343-348. doi:10.1001/archneur.66.3.343.

Hughes, G. H., Cutter, G., Donahue, R., Friedman, G. D., Hulley, S., Hunkeler, E., … Wagenknecht, L. (1987). Recruitment in the coronary artery disease risk development in young adults (CARDIA) study. *Controlled Clinical Trials, 8*, 68S-73S.

Koen, J. D., & Yonelinas, A. P. (2014). The effects of healthy aging, amnestic mild cognitive impairment, and Alzheimer's disease on recollection and familiarity: a meta-analytic review. *Neuropsychology Review*, *24*(3), 332-354. doi: 10.1007/s11065-014-9266-5

Marcovina, S. M., Albers, J. J., Jacobs, D. R., Perkins, L. L., Lewis, C. E., Howard, B. V., & Savage, P. (1993). Lipoprotein[a] concentrations and apolipoprotein[a] phenotypes in Caucasians and African Americans. The CARDIA Study.

Arteriosclerosis, Thrombosis, and Vascular Biology: Journal of the American Heart Association, 13, 1037-1045.

McDougall, G. J., Pituch, K. A., Stanton, M. P., & Chang, W. (2014). Memory performance and affect: Are there gender differences in community-residing older adults? *Issues in Mental Health Nursing, 35*(8), 620-627. doi: 10.3109/01612840.2014.895071

Moghissi, E. S., Korytkowski, M. T., DiNardo, M., Einhorn, D., Hellman, R., Hirsch, I. B.,... Umpierrez, G. E. (2009). American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. *Diabetes Care, 32*(6), 1119-1131. doi: 10.2337%2Fdc09-9029

Palmer, E. C., David, A. S., & Fleming, S. M. (2014). Effects of age on metacognitive efficiency. *Consciousness and cognition, 28*, 151-160. doi: 10.1016/j.concog.2014.06.007

Pradhan, A. D., Manson, J. E., Rifai, N., Buring, J. E., & Ridker, P. M. (2001). C-reactive protein, interleukin 6, and the risk of developing type 2 diabetes mellitus. *Journal of the American Medical Association, 286*, 327-334.

Puttonen, S., Elovainio, M., Kivimaki, M., Lehtimaki, T., & Keltikangas-Jarvinen, L. (2003). The combined effects of Apolipoprotein E polymorphism and low-density lipoprotein cholesterol on cognitive performance in young adults. *Neuropsychobiology, 48*, 35-40. doi: 10.1159/000071827

Rafnsson, S. B., Deary, I. J., Smith, F. B., Whiteman, M. C., Rumley, A., Lowe, G. D., & Fowkes, G. R. (2007). Cognitive decline and markers of inflammation and hemostasis: The Edinburgh Artery Study. *Journal of the American Geriatric Society, 55*, 700-707. doi: 10.1111/j.1532-5415.2007.01158.x

Rizzo, M. R., Marfella, R., Barbieri, M., Boccardi, V., Vestini, F., Lettieri, B.,…Paolisso, G. (2010). Relationships between daily acute glucose fluctuations and cognitive performance among aged type 2 diabetics. *Diabetes Care, 33*(10), 2169-2174.

Shimada, H., Miki, T., Tamura, A, Ataka, S., Emoto, M., & Nishizawa, Y. (2010). Neuropsychological status of elderly patients with diabetes mellitus. *Diabetes Research and Clinical Practice, 87*(2), 224-227. doi: 10.1016/j.diabres.2009.09.026

Singh-Manoux, A., Britton, A., & Marmot, M. (2003). Vascular disease and cognitive function: Evidence from the Whitehall II Study. *Journal of the American Geriatric Society, 51*, 1445-1450.

Sperling, R. A., Aisen, P. S., Beckett, L. A., Bennett, D. A., Craft, S., Fagan, A. M., ... Phelps, C. H. (2011). Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia, 7*(3), 280-292.

Spinney, L. (2014). Alzheimer's gene: The forgetting gene. *Nature, 510*(7503), 26-28. doi: 10.1038/510026a

Strachan, M. W. (2011). The brain as a target organ in Type 2 diabetes: Exploring the links with cognitive impairment and dementia. *Diabetic Medicine, 28,* 131-147. doi: 10.1111/j.1464-5491.2010.03199.x

Talley, M. H., Pryor, E., Wadley, V., Crowe, M., Morrison, S., & Vance, D. E. (in press). The physiological mechanisms of diabetes and aging on brain health and cognition: Implications for nursing practice and research. *Journal of Neuroscience Nursing*

United States Department of Health and Human Services. (2014). *Global health and aging.* National Institutes of Health. National Institute of Aging. Retrieved from: http://www.nia.nih.gov/research/publication/global-health-and-aging/humanitys-aging

Unite States Department of Health and Human Services: National Institute of Nursing Research. (2015). *Building the scientific foundation for clinical practice: What is nursing research?* Retrieved from: http://www.ninr.nih.gov/

Vance, D. E., Eagerton, G., Harnish, B., McKie, P., & Fazeli, P. (2011). Cognitive prescriptions: A nursing approach to increasing cognitive reserve. *Journal of Gerontological Nursing, 37*(4), 22-31. doi: 10.3928/00989134-20110304-01

Vance, D., Webb, N. M., Marceaux, J. C., Viamonte, S. M., Foote, A., & Ball, K.(2008). Mental stimulation, neural plasticity, and aging: Directions for nursing research and practice. *Journal of Neuroscience Nursing, 40*(4), 241-249.

Yaffe, K., Kanaya, A., Lindquist, K., Simonsick, E. M., Harris, T., Shorr, R. L.,…Newman, A. B. (2004). The metabolic syndrome, inflammation, and cognitive decline. *Journal of the American Medical Association, 292*(18), 2237-2242. doi: 10.1001/jama292.18.2237

APPENDIX A

INSTITUITIONAL REVIEW BOARD APPROVAL FORM

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Institutional Review Board for Human Use

Form 4: IRB Approval Form
Identification and Certification of Research
Projects Involving Human Subjects

UAB's Institutional Review Boards for Human Use (IRBs) have an approved Federalwide Assurance with the Office for Human Research Protections (OHRP). The Assurance number is FWA00005960 and it expires on January 24, 2017. The UAB IRBs are also in compliance with 21 CFR Parts 50 and 56.

Principal Investigator:	TALLEY, MICHELE H
Co-Investigator(s):	BRADLEY, VIRGINIA GRISSOM LEWIS, CORA ELIZABETH
Protocol Number:	**E131204005**
Protocol Title:	*The Effects of Hyperglycemia and Related Physiological Markers on Cognitive Functioning in Those with and without the APOE4 Allele*

The above project was reviewed on 12-20-13. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services. This project qualifies as an exemption as defined in 45CF46.101, paragraph 4.

This project received EXEMPT review.

IRB Approval Date: 12-20-13

Date IRB Approval Issued: 12-20-13

Marilyn Doss

Marilyn Doss, M.A.
Vice Chair of the Institutional Review
Board for Human Use (IRB)

Investigators please note:

IRB approval is given for one year unless otherwise noted. For projects subject to annual review research activities may not continue past the one year anniversary of the IRB approval date.

Any modifications in the study methodology, protocol and/or consent form must be submitted for review and approval to the IRB prior to implementation.

Adverse Events and/or unanticipated risks to subjects or others at UAB or other participating institutions must be reported promptly to the IRB.

470 Administration Building
701 20th Street South
205.934.3789
Fax 205.934.1301
irb@uab.edu

The University of
Alabama at Birmingham
Mailing Address:
AB 470
1720 2ND AVE S
BIRMINGHAM AL 35294-0104

APPENDIX B

CORONARY ARTERY RISK DEVELOPMENT IN YOUNG ADULTS (CARDIA) STUDY APPROVAL

UAB SCHOOL

OF MEDICINE

Department of Medicine
Division of Preventive Medicine
CARDIA Coordinating Center
Sept.17, 2013

MEMORANDUM

TO: Dr. Michele Talley

FROM: Ms. Linda Sellers

RE: **Approved manuscript proposal #810**

Congratulations! Your manuscript proposal entitled **"The Effects of Hyperglycemia and Related Physiological Markers on Cognitive Functioning in Those with and without the APOE4 Allele**" was approved by the CARDIA Publications and Presentations Committee on the **September 11, 2013** call and assigned **#810** for use on all correspondence. We ask that you review this memo as it details information important to the completion of your writing project and direct inquiries to us upon receipt of this communication.

Rachel Whitmer, David Jacobs, Lenore Launer, Kristine Yaffe and Deb Levine were added as co-authors.

The first item required is the completion of the Certificate of Confidentiality (C-Cert). The PI of the CARDIA Center for which you are affiliated should sign as the Center PI. If you are not affiliated with a CARDIA Center, the Coordinating Center (CC) PI will sign the form. This form is sent to Linda Sellers via e-mail: lsellers@uabmc.edu and the CC PI signature will be obtained for you.

To request analytic data sets from the Coordinating Center, it will require completion of the Data and Materials Distribution Agreement (DMDA) and the Data Set Request-Intent to Analyze Form (DSR). It is required by the Study that the signed DMDA be on file prior to the release of the data. Also, page 1 of the DSR is a checklist / instructions for organizing an "Original" and an "Additional" data request. We request that you review these instructions prior to compiling your data request, complete the checklist and return with the data request.

For your convenience, the Publications Policy, as well as, other documents and forms are available on the CARDIA Public Web Site:http://www.cardia.dopm.uab.edu/publications-2/publications-documents.
All documents and forms, *except the DMDA and C-Cert which are a PDF*, are word files and may be downloaded, completed and e-mailed to the CC for processing.

The documents and forms posted to the CARDIA Public Web site are as listed below. Direct these to
Linda Sellers @ **lsellers@uabmc.edu** or as instructed.

A. CARDIA Data Analysis and Publications Policies
B. Manuscript Proposal Form
C. Confidentiality Certification Form (PDF - print, sign and obtain signature and e-mail to the CC)
D. Distributed Materials and Data Agreement (DMDA)
E. How to Complete a Distributed Materials and Data Agreement
F. Data Set Request & Notice of Intent to Analyze (DSR)
G. Manuscript Submission Instructions – to P&P Committee
H. Chief Reviewer's Role
I. Statement of Author's Form
J. Verification Submission Instructions
K. CARDIA Investigators for Ancillary Studies and Publications_Areas of Interest

The Coordinating Center recommends that the dataset verification be performed early in the development of the manuscript. The data set verification allows the data set to be examined for problem areas prior to the completion of the manuscript. The data set verification process is detailed in the Manuscript Verification Submission Instructions. Data verification and questions should be directed to Lucia Juarez via email: ljuarez@dopm.uab.edu.

A final manuscript must go through two simultaneous approval processes. (1) CARDIA Publications & Presentations Committee (P&P) review and approval, and (2) Verification of the data by the CC. NHLBI approval may be required (email: ebpdocs@nhlbi.nih.gov); this applies if an author is a staff member of NHLBI.

The *Instructions for Submitting a Manuscript* to the P&P Committee and the *Statement of Authors (SoA) form* are also posted to the CARDIA Public Web site. The SoA should be sent to the CC (lsellers@uabmc.edu) with the final manuscript when requesting a Chief Reviewer.

Thank you for your interest in the CARDIA Study and if there are any questions feel free to contact the Coordinating Center at: 205-934-0786.