12-2018

The Role of Type 2 Diabetes and Metformin Use in Cognitive Decline

Kelley R. Chilson

The Role of Type 2 Diabetes and Metformin Use in Cognitive Decline

by

Kelley R. Chilson

A doctoral research project submitted to the College of Psychology and Liberal Arts of
Florida Institute of Technology
in partial fulfillment of the requirements
for the degree of

Doctor
of
Psychology

Melbourne, Florida
December 2018

We the undersigned committee hereby approve the attached doctoral research project, "The Role of Type 2 Diabetes and Metformin Use in Cognitive Decline" by Kelley R. Chilson.

_____

Frank Webbe, Ph.D.
Committee Chair
Professor, School of Psychology

_____

Vida Tyc, Ph.D.
Committee Member
Professor, School of Psychology

_____

Julia Grimwade, Ph.D.
Committee Member
Professor, Department of Biomedical and Chemical Engineering and Science

_____

Lisa Steelman, Ph.D.
Professor/ Dean
College of Psychology and Liberal Arts

Abstract

Title: The Role of Type 2 Diabetes and Metformin Use in Cognitive Decline

Author: Kelley R. Chilson, M.S.

Major Advisor: Frank Webbe, Ph.D.

Objectives: Primary objectives of the present study include exploring the role of both A1C values and the anti-diabetic medication, metformin, on cognitive decline through measured by a brief neuropsychological exam (BNE) and the Montreal Cognitive Assessment (MoCA).

Method: Eleven years of archival cognitive testing and medical information from a total of 479 East Central Florida Memory Disorder Clinic patients (52.8 % female, 88.5% Caucasian, M_{age} = 78.79 years) was utilized for the present study. Participants were placed into two groups: Type 2 diabetes (n = 239) and a control group (n = 240). Cognitive testing data were collected via MoCA screening tests and BNE's that assessed six cognitive domains: language, attention, executive functioning, motor and processing speed, visuospatial skills, and learning and memory. Patients diagnosed with Type 2 diabetes were identified from patient electronic medical records (EMR) searched via Health First Information Technology (IT).

Results: There was no significant difference in total BNE scores between the Type 2 diabetes group (M = 12.22, SD = 3.83) and the control group (M = 11.80, SD = 3.98; t (477) = 1.17, p = .24, two-tailed). However, a slight difference in domain

scores was detected between groups as revealed by a one-way between-groups multivariate analysis of variance (MANOVA), Wilks' $\lambda = .97$; F (6, 468) = 2.45, p = .024; partial eta squared = .03, with a significant difference for visuospatial domain, F (1, 473) = 5.49, p = .02, partial eta squared = .01. With regard to metformin use, a significant difference in the learning and memory domain scores for participants on metformin (M = 1.90, SD = .81) compared to participants on other medication classes (M = 1.69, SD = .77; t (237) = -1.95, p = .05 was found, suggesting participants taking metformin demonstrated slightly better performance on learning and memory measures. Lastly, a significant difference in MoCA scores between participants taking the drug metformin (M = 20.26, SD = 4.19) compared to participants taking drugs from other classes of anti-diabetes medications (M = 18.67, SD = 5.05; t (229) = -2.31, p = .02), suggesting participants taking metformin performed significantly better on this measure compared to participants taking other anti-diabetes medications.

Conclusions: On cognitive measures of the BNE, participants demonstrated a higher level of homogeneity than hypothesized, with only slight differences in cognitive domain scores. The most important findings of the present study were the differences in cognitive performance between participants taking metformin versus other anti-diabetic medications. Results support previous literature suggesting a neuroprotective effect of metformin, as opposed to newer studies that suggest a cognitive-impairing role of metformin.

Table of Contents

Abstract iii
List of Figures vii
List of Tables viii
Acknowledgement ix
Introduction 1
Literature Review 3
Type 2 Diabetes 3
Epidemiology 3
Etiology 4
Risk Factors 5
Complications 6
Hemoglobin A1C Values 7
Cognitive Decline 9
Epidemiology 9
Type 2 Diabetes and Cognitive Decline 11
Psychophysiology of Cognitive Decline and Diabetes Relationship 15
Metformin 18
Metformin and Cognition 21
Statement of Purpose 25
Hypotheses 25
Method 26
Participants 26
Setting 27
Materials and Measures 27

Assessment of Diabetes 27
Neuropsychological Exam 28
Montreal Cognitive Assessment 28
Quick Exit 29
Controlled Oral Word Association Test 29
Mack SF4 29
Supraspan Serial Word List 30
Symbol Digits Modalities Test 30
Trailmaking Test part A and B 31
Victoria Stroop Test 31
Clock Drawing Test 32
Rey Complex Figure Test 32
Geriatric Depression Scale 33
Geriatric Anxiety Inventory 33
Brief Symptom Inventory 34
Procedure 34
Statistical Methods 35
Results 36
Hypothesis 1 37
Hypothesis 2 38
Post – hoc Analyses 41
Cognitive Diagnosis 41
Differences in test scores 42
Discussion 43
Limitations 47
Future directions 49
Conclusions 50
References 51

List of Figures

Figure 1- Composition of anti-diabetic medications in Type 2 diabetes group 39

Figure 2- Frequency of patient diagnosis in control and Type 2 diabetes group.....42

List of Tables

Table 1- Results of *t* tests and descriptive statistics of BNE domain scores by medication.....40

Table 2 - Results of *t* tests and descriptive statistics of test scores by group.....43

Acknowledgement

I would like to express the deepest gratitude to my committee chair, Dr. Frank Webbe. Thank you for supporting me endlessly throughout this rewarding process through your expertise, patience, and humor. I am so appreciative for your guidance in developing a unique project that required great persistence, flexibility, and creativity in light of many challenges. I would also like to extend my gratitude to Dr. Vida Tyc and Dr. Julia Grimwade for their interest and dedication to this project. I truly appreciate your time, distinctive perspectives, and recommendations.

I also extend an incredible amount of gratitude to Sandra Stauffer and Dr. Visa Srinivasan at the East Central Memory Disorder Clinic for their contributions to this project. Your endless support and patience did not go unnoticed and this project would not have occurred without your assistance and knowledge.

Finally, I would like to acknowledge my family and boyfriend's role in my educational experience and successes. It is only with your support, kind words, and love that I could have accomplished what I have. I thank my parents for instilling the strong values of perseverance, patience, and hard work within me and never doubting how far I could go. Lastly, I would like to thank one of my biggest supporters, Kenny Kane, for supporting me consistently throughout my education with your unconditional love, care, understanding, and necessary humor. Knowing I had so many wonderful people behind me during trying times made all the difference. I am forever grateful.

Introduction

Diabetes is a leading cause of death in the United States and the prevalence of Type 2 diabetes has tripled in the previous four decades (Center for Disease Control and Prevention [CDC], 2011). A vast line of previous research demonstrated that individuals diagnosed with Type 2 diabetes display accelerated levels of cognitive decline compared to individuals without the disease across various cognitive domains (Awad, Gagnon, & Messier, 2004; McCrimmon, Ryan, & Frier, 2012; Yeung & Fischer, 2009); however, examining differences in cognitive decline across varying levels of diabetes self-management as indicated by A1C values has not been widely explored. A line of research exploring the relationship between the medication metformin for the treatment of Type 2 diabetes and its impact on cognitive decline has been developed recently. Results of these studies yielded inconsistent findings ranging from a neuroprotective role of metformin against particular brain changes in rat samples (Asadbegi, Yaghmaei, Salehi, Ebrahim-Habibi, & Komaki, 2016; Chung et al., 2014) and human subjects (Hsu, Wahlqvist, Lee, & Tsai, 2010; Herath, Cherbuin, Eramudugolla, & Anstey, 2016) to an association between metformin and an increased risk of the development of various neurodegenerative diseases in human subjects (Chen et al., 2008; Imfeld, Bodmer, Jick, & Meier, 2012; Yung-Cheng et al., 2014). Discrepancies identified in this line of research warrant further exploration that will be provided by the current study.

The overall aims of this research study were twofold. First, this study seeks to examine the role of Type 2 diabetes self- management (as measured by A1C values) on levels of domain-specific cognitive decline in older adults. The second aim is to determine whether or not older adults taking the medication metformin to manage Type 2 diabetes experience differences in cognitive decline compared to those not taking the medication. The aforementioned aims were studied through utilizing eleven years of archival neuropsychological testing data of 479 older adults. The following topics will be reviewed:

- The etiology and epidemiology of Type 2 diabetes
- The role of hemoglobin A1C and its use as an indicator of Type 2 diabetes self-management
- Previous literature examining the relationship between Type 2 diabetes and cognitive decline
- Metformin use for the treatment of Type 2 diabetes
- Previous literature examining the relationship between metformin use and cognition in older adults.

Results from the present study indicate no significant difference in total BNE scores between the Type 2 diabetes and control group, with a slight difference in domain scores. Specifically, statistical analyses revealed a significant difference in the visuospatial domain, suggesting slightly worse performance on visuospatial tasks by participants in the Type 2 diabetes group. With regard to metformin use, two noteworthy findings were found. Firstly, a significant difference in learning

and memory scores for participants on metformin were found compared to participants taking other anti-diabetic medications, suggesting better performance by participants taking metformin. Secondly, an unexpected finding related to the Montreal Cognitive Assessment (MoCA) was revealed as participants taking metformin performed better on this multi-domain measure of cognitive functioning than those taking other anti-diabetic medications.

Review of Literature

Type 2 Diabetes

Epidemiology

Diabetes is estimated to be the 7th leading cause of death in the United States (CDC, 2017). Type 2 diabetes accounts for approximately 90- 95% of all diagnosed cases of diabetes, with Type 1 diabetes accounting for the remaining 5% (CDC, 2017). Approximately 30 million people in the United States (9.4% of the entire population) have been diagnosed with diabetes and it is estimated 25% of those with diabetes are unaware they have the disease. Furthermore, approximately 86 million adults in the United States suffer from a condition termed prediabetes, a health condition that increases a person's risk of developing Type 2 diabetes, but has not met the threshold to warrant a full diagnosis. Approximately 90% of this group is unaware they have the condition (CDC, 2017). An estimated 366 million individuals are predicted to develop the disease worldwide by 2030, which is

significantly increased from 171 million in 2000 (Wild, Roglic, Green, Sicree, & King, 2004).

The prevalence of Type 2 diabetes is highest among American Indians/Alaskan natives (14.9%), non-Hispanic blacks (12.7%) and Hispanics (12.1%) (CDC, 2017). Among the Hispanic population, the highest prevalence occurred in Mexicans (13.8%), followed by Puerto Ricans (12.0%), Cubans (9.0%), and Central/South Americans (8.5%). Diabetes affects men slightly more than women (15.3 vs. 14.9 million). It has been found that education significantly related to the prevalence of diabetes in the United States. Specifically, 12.6% of adults with less than a high school education has been diagnosed with diabetes compared to 9.5% of those with a high school education and 7.2% of those with education beyond high school (CDC, 2017).

Etiology

Diabetes is defined as a group of diseases characterized by high levels of glucose in the blood (i.e. hyperglycemia) as a result of the malfunctioning action of insulin (CDC, 2016). Insulin is a hormone produced by the beta cells of the pancreas that facilitates the proper use and storage of glucose obtained from carbohydrates during the process of digestion (American Diabetes Association [ADA], 2015). As digestion occurs, the beta cells of the pancreas secrete insulin to aid in transferring glucose from the blood into the muscle, fat, and liver cells, making it available to use for energy. As glucose enters the cells, the amount of insulin released by the beta cells of the pancreas decreases. For long-term energy

use, excess glucose that is not transferred to muscle cells is stored in the liver as glycogen. Lower insulin levels communicate to the liver that glycogen should be released to sustain energy levels throughout the day (National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK], 2009).

Type 2 diabetes occurs when the human body cells are unable to use insulin properly. Specifically, a complication termed insulin resistance develops, which is characterized by cells' inability to respond to insulin; therefore, causing hyperglycemia (CDC, 2016). Insulin resistance furthermore leads to an excess of insulin levels in the blood as an attempt to compensate for high blood glucose levels. As this pattern reoccurs over time, the pancreas is unable to produce enough insulin to address the chronic high glucose levels. High levels of both glucose and insulin in the blood has been found to be damaging to the human body in a variety of ways including nerve and blood vessel damage, leading to heart disease, stroke, kidney failure, blindness and neuropathy (NIDDK, 2009).

Risk Factors

Multiple risk factors that contribute to the development of Type 2 diabetes have been identified. It has been found that a family history of Type 2 diabetes serves as a significant predictor of the development of the disease, and the relationships is stronger relationship for Type 2 diabetes compared to Type 1 (Meigs, Cupples & Wilson, 2000; Van 't Riet et al., 2010; Scott et al., 2013). Being overweight, being over 45 years old, not engaging in physical activity at least three times a week, and ever having gestational diabetes or giving birth to a baby who

weighed more than nine pounds are considered to be prominent risk factors. Additional risk factors include belonging to the racial categories of African American, Alaskan Native, American Indian, Asian American, Hispanic/Latino, Native Hawaiian or Pacific Islander (NIDDK, 2016).

Many of the most prominent risk factors for the development of Type 2 diabetes are part of a group of conditions known broadly as metabolic syndrome. Metabolic syndrome is defined as a constellation of conditions that increase the risk of developing an array of disorders including heart disease, stroke and diabetes. Conditions that characterize metabolic syndrome include hypertension, hyperglycemia, excess body fat accumulation around the waist and hip area, and elevated triglyceride levels in the blood. A relationship between metabolic syndrome and inactivity, obesity and insulin resistance has been established. Furthermore, as metabolic syndrome persists without proper management such as medication implementation and lifestyle changes, the risk of the development of diabetes increases due to poor management of the factors contributing to insulin resistance. Importantly, one's risk of developing Type 2 diabetes is not increased solely by a diagnosis of metabolic syndrome, but is increased as the individual conditions that comprise metabolic syndrome become present (ADA, 2014).

Complications

Type 2 diabetes is related to multiple, debilitating health complications. These complications include heart disease, cerebrovascular disease, strokes, high blood pressure, neuropathy, kidney damage, eye damage and blindness, skin

conditions, dental disease and limb amputation. Furthermore, diabetes has been found to be the leading cause of lower-limb amputations, kidney failure and adult onset blindness (CDC, 2017). Unfortunately, treatment of diabetes is highly expensive. The total direct and indirect cost of diabetes in the United States in 2012 was $245 billion. Furthermore, the average annual expenditures for diabetic individuals is estimated to be approximately $13,7000 (ADA, 2013).

Hemoglobin A1C Values: An indication of Type 2 Diabetes Self-Management

Management of Type 2 diabetes involves adherence to an established set of guidelines for the purpose of controlling the symptoms related to the diagnosis. A primary goal related to Type 2 diabetes management is increasing longevity, as well as encouraging a better quality of life despite the presence of various adverse symptoms that often make daily life activities difficult. Furthermore, accurate measurements of one's ability to manage his or her success in diabetes management is important. A primary means of accurate diabetes management measurement is discussed in this section.

Hemoglobin is a protein found in red blood cells that functions to carry oxygen from the lungs to all cells in the human body. As glucose enters the blood stream and red blood cells, a subtype of hemoglobin (i.e., A1C) links to the glucose through a process called glycation. As blood glucose levels rise, the more the hemoglobin A1C becomes glycated and the number of hemoglobin A1C molecules that attach to a molecule of glucose is directly proportional to level of glucose in the blood (NIDDK, 2009).

The hemoglobin A1C test is a blood test utilized to help diagnose Type 2 diabetes through providing information regarding an individual's average blood glucose level over the past three months (NIDDK, 2009). The test specifically allows for measuring the percentage of hemoglobin A1C molecules that have glucose attached (ADA, 2013). The American Diabetes Association Standards of Care identifies a hemoglobin A1C value of 5.7% and less as normal, 5.7-6.4% as prediabetes and 6.5% or higher as diabetes (ADA, 2014). Although the ability of the hemoglobin A1C to monitor average blood glucose over time is considered to be a strength of the test, its inability to detect fluctuations of very low and high blood glucose levels is considered a notable weakness (Ryan, Duinkerken & Rosano, 2016).

Hemoglobin A1C values serve as a measure of diabetes self-management and its value can be altered by a variety of lifestyle behavior changes and medication (Kitabchi, 2005). The ADA recommends a reduction in time spent being sedentary, increased moderate physical exercise, weight management, a balanced and nutrient-dense diet, and taking prescribed medications properly as part of proper diabetes management program (ADA, 2017). Research demonstrates incorporation of the aforementioned lifestyle behaviors result in decreased A1C values in conjunction with improvement to various Type 2 diabetes precursors including being overweight and an increase in beta cell function and insulin sensitivity (Kitabchi, 2005; Sjöström et al., 2004). Furthermore, weight loss in diabetic patients has been found to reduce significantly the associated symptoms of

high LDL cholesterol and triglyceride levels when compared with a control group after two and 10 years (Sjöström et al., 2004)). Diabetes self-management has also been found to be highly effective in individuals with prediabetes. Individuals diagnosed with prediabetes who adhered to recommended lifestyle changes decreased their risk of developing type 2 diabetes by approximately 58% (CDC, 2017).

Cognitive Decline

Epidemiology

Dementia is a progressive neurodegenerative disease that negatively impacts multiple cognitive domains including language, attention and concentration, executive functioning, motor and processing speed, visuospatial skills and learning and memory abilities. Furthermore, dementia often affects an individual's personality and behavior. Alzheimer's disease is the most common form of dementia and accounts for approximately 60-80 % of all cases of dementia (Alzheimer's Association, 2017). Additionally, it is the 6th leading cause of death in the United States and an estimated 5.7 million individuals are living with the disease at the current time in the United States. Other less commonly diagnosed forms of dementia include vascular dementia, dementia with Lewy bodies (DLB), mixed dementia and fronto-temporal lobar degeneration (FTLD) (Alzheimer's Association, 2017).

Vascular dementia is the second most commonly diagnosed form of dementia and accounts for approximately 10% of all cases. Importantly, vascular

dementia commonly presents as part of a diagnosis of mixed dementia and occurs in this manner more often than in isolation. Vascular dementia is characterized predominately by initial deficits in executive functioning (i.e., planning, organizing, and decision making) in comparison with Alzheimer's disease, which is characterized by significant deficits in memory and learning (Alzheimer's Association, 2017).

Mild Cognitive Impairment (MCI) is defined as a condition in which an individual displays mild, but measurable decline in cognitive function that have not met the diagnostic criteria of dementia. Individuals diagnosed with MCI often demonstrate cognitive changes that are noticeable to family and friends, but do not interfere with their ability to carry out normal, daily activities. It has been found that approximately 30-40% of individuals diagnosed with MCI develop Alzheimer's disease within five years (Mattsson et al., 2009; Visser et al., 2009) however, not all individuals diagnosed with MCI will later develop a form of dementia. In some cases, MCI has been found to return to a state of normal cognitive functioning or remain stable over time, demonstrating that MCI need not be a pre-dementia condition. MCI can be subdivided into two categories: non-amnestic and amnestic MCI. Non-amnestic MCI is characterized by impairments in cognitive domains other than memory, while amnestic MCI is predominately characterized by impairment in the domain of memory and learning. The two subtypes are further divided into single and multidomain depending on the number of cognitive domains affected (Csukly et al., 2016).

Type 2 Diabetes and Cognitive Decline

A vast line of research demonstrates both Type 1 and Type 2 diabetes are associated with an increased risk of cognitive decline in older adults. (McCrimmon, Ryan, & Frier, 2012; Hassling et al., 2004). The National Institutes of Health (NIH) Diabetes Mellitus Interagency Coordinating Committee identified in 2010 that cognition is one of the primary priorities for diabetes research at the present time and in the following decade (National Institute of Health, 2011). A notable challenge related to exploring the relationship between Type 2 diabetes and cognitive decline is determining whether the cognitive changes related to Type 2 diabetes occur independently as a part of diabetes that begins at the onset of the diagnosis, or as a result of comorbid diseases and old age. Not only has an association been established between a diagnosis of diabetes and changes in cognition of older adults, a vast line of research also demonstrates observable brain abnormalities detected via brain imaging compared to individuals without diabetes (Yau et al., 2010; Hsu et al., 2012; Falvey et al., 2013; McCrimmon, Ryan, & Frier, 2012; Brundel, Kappelle and Biessels 2014).

Studies exploring the relationships between Type 2 diabetes and cognitive decline have found deficits in multiple cognitive domains in individuals with diabetes that are not present in healthy controls. Yeung, Fischer and Roger (2009) found that individuals with mild Type 2 diabetes performed significantly worse on measures of executive functioning and semantic speed than healthy controls. Specifically, significant group differences in both domains were detected in tasks

that commonly relied on speed, inhibition, and cognitive set shifting. Individuals with diabetes scored approximately 12% lower on inhibition tasks and 14% lower on shifting tasks than healthy controls. Importantly, these finding were present in varying age groups (i.e., young-old, age 53-70 years and old-old, age 71-90 years) in the sample, demonstrating that the findings are not likely to be a result of increasing age. Similarly, a key meta-analysis with the aim of comparing effect sizes for cognitive decline in adults with Type 2 diabetes compared to healthy controls found that the largest effect sizes were in the domains of motor function and information processing, while the smallest was found in the domain of attention and concentration (Palta, Schneider, Biessels, Touradji & Hill-Briggs, 2014). The researchers warned, however, that the relationship between decreased motor function in the Type 2 diabetes group should be interpreted with caution as it may be at least partially related to neuropathy.

In addition to the previous findings that reported cognitive decline in particular domains, evidence also exists that Type 2 diabetes is related to the diagnoses of MCI, vascular dementia and Alzheimer's disease. A longitudinal study conducted by Roberts et al. (2014) utilized a sample of older adults with and without a diagnosis of Type 2 Diabetes. It was found that Type 2 diabetes was associated with an increased risk of amnestic MCI, multidomain amnestic MCI, and multidomain non-amnestic MCI. It was found that each of these relationships were stronger in men than women, with the risk of multidomain non-amnestic MCI twice as strong in men than in women. Moreover, a significant relationship was

also found between single domain non-amnestic MCI in women only. Furthermore, diabetes severity as measured by during of the disease, presence of complications, type of treatment and glycemic control, was positively related to a greater risk of MCI.

It has been found additionally that Type 2 diabetes and prediabetes increase the risk of progression from non- amnestic and amnestic MCI to Alzheimer's disease (Cooper et al., 2015). Multiple studies have demonstrated a relationship between Type 2 diabetes and Alzheimer's disease through meta-analyses and longitudinal studies. Studies have consistently found that the development of both Type 1 and Type 2 diabetes is related to an increased risk of developing Alzheimer's disease (Cheng, Nobel, Tang, Schupf, Mayeux, & Luchsinger, 2011; Wang et al., 2012; Crane et al., 2013), especially in women (Wang et al., 2012). Specifically, it has been found that a diagnosis of Type 2 diabetes increases the risk of developing Alzheimer's disease as much as 50 to 100% (Wang et al., 2013; Biessels, Staekenborg, Brunner, Brayne, & Scheltens, 2006).

A significant relationship has also been established between vascular dementia and a diagnosis of Type 2 diabetes. It has been found that a diagnosis of Type 2 diabetes increases the risk of developing vascular dementia by approximately 100 to 150% (Biessels, Staekenborg, Brunner, Brayne, & Scheltens, 2006; Ahtiluoto et al., 2010). Furthermore, the relationship between vascular dementia and diabetes is particularly strong among individuals aged 75 years and older (Xu, Qiu, Wahlin, Winblad, & Fratiglioni, 2004).

Studies have also yielded findings that suggest the occurrence of cognitive decline in individuals that do not yet meet diagnostic criteria for Type 2 diabetes (Van den Berg et al., 2008; Hassenstab, Sweat, Bruehl and Convit, 2010; Yates, Sweat, Yau, Turchiano & Convit, 2012). A study conducted by Van den Berg et al. (2008) compared participants diagnosed with Type 2 diabetes, metabolic syndrome, and a control group on cognitive functioning. It was found participants diagnosed with both Type 2 diabetes and metabolic syndrome performed significantly worse on measures of information processing speed compared to healthy controls. It was also revealed that individuals with only Type 2 diabetes demonstrated significantly worse performance than healthy controls on measures of executive functioning and attention. Overall, however, the cognitive profiles of individuals in the Type 2 diabetes and metabolic syndrome group did not differ significantly from one another. The absence of significant differences in information processing speed between individuals in the Type 2 diabetes and metabolic syndrome group in combination with similar cognitive profiles of individuals in the Type 2 diabetes and metabolic syndrome group yields important information about the association between diabetes and cognitive decline. Specifically, it provides evidence that cognitive decline in particular domains occurs before an individual meets diagnostic criteria for Type 2 diabetes. Furthermore, a study conducted by Hassenstab, Sweat, Bruehl and Convit (2010) found participants diagnosed with metabolic syndrome performed significantly worse on measures of learning and recall in comparison to control groups. The researchers additionally discovered that

of all the conditions that comprise metabolic syndrome, only insulin resistance was found to be a significant predictor of the learning and recall deficits.

A longitudinal study conducted by Sanz, Hanaire, Vellas, Sinclair and Andrieu (2012) yielded findings that extend beyond the aforementioned studies by demonstrating the cognitive changes related to a diagnosis of diabetes in older adults exacerbates functional impairment in those diagnosed with Alzheimer's disease. Functional impairment was measured using the Activities of Daily Living (ADL) scale over a four-year period. Specifically, diabetes was found not only to be related to an increase in functional impairment at baseline measurements, but also shown to be associated with an increased progression of functional impairment in patients with a recent diagnosis of Alzheimer's disease (i.e., within 12 months). As expected, it was found additionally that patients with a diagnosis of Alzheimer's disease for longer than one year demonstrated more severe dementia than those diagnosed within one year.

Pathophysiology of Cognitive Decline and Diabetes Relationship

The exact etiology that accounts for the relationship between diabetes and cognitive decline remains unclear at the present time, however various factors related to the adverse impacts diabetes has on the brain are widely considered to play a prominent role. One of these factors is cerebrovascular disease (McCrimmon, Ryan, & Frier). As discussed previously, glucose serves as a primary source of energy for all cells in the human body, including neurons. The brain consists of approximately 100 billion neurons, making it the most energy

demanding organ in the human body. The brain's ability to perform cognitive functions properly across all domains relies on glucose as a source of fuel. Plausibly, the dysregulation of glucose levels that characterizes diabetes is likely to have a significant impact on the brain's ability to operate properly.

The literature demonstrates several primary, however not independent, areas of change that underlie the relationship between cognitive dysfunction and Type 2 diabetes. These areas include molecular, micro (i.e., white matter and vascular) and macro-structural changes, as well as brain volumetric changes. Each of these changes will be reviewed in the following section.

The risk factors that accompany and contribute to Type 2 diabetes including hyperglycemia, hypertension and elevated triglyceride levels have been found to trigger an overproduction of a reactive oxygen species that in turn, reduces the availability of a crucial vasodilator, nitric oxide, which initiates vascular inflammation. Compounding this event is the presence of hyperglycemia, which increases the body's cellular response to the vasoconstrictor, endothelin-1. It has been found this process, in combination with abnormal insulin levels may lead to a calcium accumulation that tends to result in increased clotting of the blood. These occurrences in combination with elevated triglycerides increase the risk for arteriosclerosis, or stiffening of the artery walls (Bertram, Brixius, & Brinkmann, 2016).

Diabetes has not only been found to affect the peripheral nervous system, but also the central nervous system. An additional molecular factor hypothesized to

contribute to cognitive decline in those diagnosed with Type 2 diabetes relates to abnormal insulin levels in the brain. (van der Heide, Ramakers, & Smidt, 2006). It is thought that insulin increases the action of GLUT4 (a glucose transporter), which is present in the brain. Because of this, disruption of insulin secretion that is characteristic of Type 2 diabetes reduces insulin levels in the brain and may affect this mechanism thus leading to glucose dysregulation (Umegaki et al., 2013). Insulin receptors in the brain and are particularly localized at synapses in the hippocampus (Abbott et al., 1999). Insulin has been found to play a role in neuron survival and death via two different pathways in the brain and studies have found that insulin has the ability to inhibit neuron death. Research in this area demonstrates that Type 2 diabetes influences a reduction in insulin and its receptors in the brain, therefore reducing its ability to inhibit neuron death (van der Heide, Ramakers, & Smidt, 2006).

Consistent with the aforementioned finding of information processing deficits in individuals diagnosed with Type 2 diabetes, evidence exists that microstructural abnormities occur that are related to myelination changes in white matter. These changes are hypothesized to slow processing speed given the knowledge of the role of myelination in speed of information conduction. Furthermore, this finding has been established across various age groups (i.e., adolescence, middle adulthood and older adulthood), lending evidence that the finding is not simply related to the aging process (Yau et al., 2010; Hsu et al., 2012; Falvey et al., 2013). Furthermore, an innovative study utilizing a 3-Tesla diffusion-

weighted MRI scan and a detailed cognitive assessment followed by an analysis of white matter tractology in the entire brain found adults with Type 2 diabetes showed significantly less brain region white matter connectivity in the unicate fasciculus, superior longitudinal fasciculus, inferior longitudinal fasciculus and the splenium of the corpus callosum compared to healthy controls. Furthermore, it was found that the lack of connectivity in all brain lobes was associated with information processing speed slowing that was independent of age (Reijmer et al., 2013).

A meta-analysis conducted by Brundel, Kappelle and Biessels (2014) demonstrated significant reductions in total brain volume reduction in participants diagnosed with Type 2 diabetes compared to healthy controls. Across all studies examined, higher hemoglobin A1C values in combination with high blood pressure and a longer duration of the diagnosis were the strongest predictors of total brain volume reduction. Likewise, a study conducted by Brundel, van den Heuvel, de Bresser, Kappelle and Biessels (2010) found reductions in cerebral cortical thickness predominately in the right temporal lobe of those diagnosed with Type 2 diabetes in comparison to healthy controls. Specifically, the most atrophy was detected in the hippocampal region.

Metformin

Metformin, or commercially known as Glucophage®, Glumetza® , Riomet®, or Fortamet® is an orally administered medication commonly used to treat Type 2 diabetes. Metformin is widely considered to be the first-line

pharmacological treatment for Type 2 diabetes and is a treatment modality that has been reported to be highly effective, safe, and inexpensive (ADA, 2017). Metformin is classified as a biguanide, a term categorizing the medication based on the manner in which it operates. Metformin is the only medication in the class of biguanides. Metformin operates in multiple ways by decreasing glucose production and absorption in the small intestine while simultaneously increasing the sensitivity bodily cells to insulin, without actually stimulating insulin secretion (Rojas & Gomez, 2013). Secondary benefits of the medication that help to manage conditions related to Type 2 diabetes include lowering blood cholesterol and triglyceride levels (Yung-Cheng et al., 2014).

Metformin operates in the liver by reducing glucose output and achieves its widespread effects through its ability to target the enzyme, adenosine monophosphate-activated protein kinase (AMPK). Activation of this enzyme results in glucose uptake and modulation of insulin secretion by the beta cells in the pancreas among numerous other effects, including inhibition of cholesterol and triglyceride synthesis. It has also been found that the medication has the ability to cross the blood-brain barrier, which makes exploring the effects of metformin on the brain and cognitive functioning of particular interest (Łabuzek et al., 2010).

A large meta-analysis conducted by Palmer et al. (2016) explored the efficacy and safety of multiple glucose-lowering medications commonly prescribed for the treatment of Type 2 diabetes. The meta-analysis was conducted by utilizing data obtained from 301 clinical trials. When comparing hemoglobin A1C values

for patients taking metformin versus other medications used to treat Type 2 diabetes (i.e. Sulfonylurea, thiazolidinedione, dipeptidyl peptidase (DPP-4) inhibitor and α-glucosidase inhibitor), significantly lower hemoglobin A1C levels were found in patients taking metformin. Furthermore, this finding was established without evidence of metformin being related to hypoglycemia or weight gain. Large reductions in A1C values were additionally found for dual therapy (the addition of other of drug classes to metformin), beyond the reduction achieved by metformin alone.

Similar to Palmer et al. (2016), a meta-analysis conducted by Bennett et al. (2011) also sought to summarize the costs and benefits associated with multiple medications used to treat Type 2 diabetes including metformin, sulfonylureas, thiazolidinediones, meglitinides, DPP-4 inhibitors, and glucagon-like peptide-1 receptor agonists. It was found the aforementioned medications reduced patient A1C levels by approximately one percent while metformin was found to be significantly more effective than DPP-4 inhibitors. Furthermore, metformin reduced LDL cholesterol at a higher level than other medications while sulfonylureas were found to have a 4-fold higher risk for mild or moderate hypoglycemia than metformin alone. Together, these studies lend support to the ADA's claim that metformin is an appropriate first-line pharmacological treatment for Type 2 diabetes.

Metformin and Cognition

With consideration of the aforementioned benefits of metformin, and the reviewed literature related to the negative impact of insulin resistance on cognitive functioning, it is plausible to posit that diabetes management using this metformin would slow cognitive decline in older adults with diabetes. At the current time, however, the literature related to this area demonstrates the medication is related to both improvement and decline in cognition, leaving the relationship between the two variables unclear.

Various lines of evidence demonstrate metformin has a neuroprotective and positive impact on cognitive functioning (Hsu, Wahlqvist, Lee, & Tsai, 2010; Herath, Cherbuin, Eramudugolla, & Anstey, 2016). Studies have shown that taking metformin for the treatment of diabetes is related to a significant reduction in the risk for dementia in patients with Type 2 diabetes and this relationship is even stronger when combined with sulfonylureas (Hsu, Wahlqvist, Lee, & Tsai, 2010). Specifically, a Taiwanese study conducted by Hsu, Wahlqvist, Lee, and Tsai (2010) found that together, the two medications decreased the risk of dementia by approximately 35% over a span of eight years. Furthermore, a more recent large, longitudinal study conducted by Herath, Cherbuin, Eramudugolla, and Anstey (2016) examined the effect of various diabetes treatment types on change in measures of cognitive domains over four years. Patients who took metformin only demonstrated better cognitive performance in the domains of verbal learning, working memory, and executive functioning at baseline measurement compared to

participants in all other treatment types (i.e. insulin, controlled diet, exercise, other oral medications and metformin in addition to other oral medications). Importantly, this finding remained significant after adjusting for the effects of physical exercise, smoking, hypertension and Body Mass Index (BMI). Longitudinally, however, the only significant difference related to metformin in comparison with the other groups was found for psychomotor speed. This study appears to be the only one of its kind that explored the effect of metformin on specific cognitive domains.

The neuroprotective effect of metformin was also found in a study utilizing a rat sample (Mostafa, Ismail, & Ghareeb, 2016). By implementing an experimental design, the researchers induced learning and memory deficits in the rat sample via the utilization of a pharmacological model of cognitive impairment, scopolamine injection. Scopolamine exerts its effects by inducing dysregulation of cholinergic and memory pathways in the brain. In this study, scopolamine was administered on 14 consecutive days. Following the final injection of scopolamine, one group of the rats were treated with metformin at 2 different doses (i.e., 100 mg/day and 300 mg/day). A water maze and a passive avoidance task was used to test the rats' memory abilities and the composition of various brain chemicals related to memory loss were also measured (i.e., inflammatory markers, nitric oxide, Akt, and phospho-tau). It was found that 100 mg of metformin served as a protective mechanism against learning and memory deficits as measured by both the water maze and passive avoidance tasks. Moreover, this dose of metformin was also found to be related to a significant reduction in inflammation and Akt. A decrease

in Akt is of particular relevance because it serves as a primary regulator of tau biology by affecting both the tau kinases and tau protein quality (Dickey et al., 2008) which are closely associated with the development of Alzheimer's disease. Rats administered the 300-mg dose of metformin's performance was not significantly different from those treated with scopolamine on both the water maze and passive avoidance tasks.

In contrast, results from multiple studies indicate metformin has a harmful impact on the brain and cognitive functioning (Chen et al. 2008; Imfeld, Bodmer, Jick, & Meier, 2012; Yung-Cheng et al., 2014). In a study examining the relationship between various antidiabetic drugs, including metformin, and the risk of developing Alzheimer's disease in a large population- based case-control analysis, it was found that long-term metformin use (i.e. greater than 60 prescriptions) was related to a higher risk of developing Alzheimer's disease (Imfeld, Bodmer, Jick, & Meier, 2012). When comparing the risk of developing Alzheimer's disease while taking metformin with other long-term use of antidiabetic medications (i.e., sulfonylureas and thiazolidinediones) the risk of developing the disease was not significantly higher for those using sulfonylureas and thiazolidinediones. Furthermore, a study conducted by Chen et al. (2008). The researchers aimed to determine whether metformin had an impact on various cellular processes that contribute to the development of Alzheimer's disease including amyloid precursor protein (APP) metabolism and production of the Aβ42 amyloid protein. It is well established that the Aβ42 protein is highly detrimental to

a neuron's ability to function properly, and an accumulation of the proteins are thought to be a beginning factor in the development of Alzheimer's disease. Results demonstrated that metformin led to a significant increase in intracellular and extracellular Aβ42 protein levels. Moreover, the researchers discovered the relationship between metformin and increased Aβ42 levels appeared to be partially dependent on the aforementioned AMPK activation that this medication targets.

Changes in brain structure have also been identified in relation to metformin use (Yung-Cheng et al., 2014). A study conducted by Yung-Chen et al. (2014) that compared the effect of metformin on brain metabolic activity utilizing FDG positron emission tomography. They found metformin use was associated with increased metabolic activity in the white matter located in the right temporal, right frontal and left occipital lobes in patients taking metformin in comparison to two other groups (i.e., patients in metformin withdrawal and patients not taking metformin). In contrast, decreased metabolic activity in the memory system (i.e., the hippocampus, left fusiform gyrus and the ventromedial prefrontal cortex) was found in patients taking metformin. The researchers posited the increase in metabolic activity in white matter may be a result of metformin-induced inflammation of the neurons in these areas. Furthermore, the researchers found that the impact of metformin on white matter may be related to how long it has been since the patients stopped taking the medication. Specifically, a significant negative correlation was found between how long it has been since the patients stopped taking metformin and metabolic activity in white matter. This finding in particular

provides evidence that the potentially damaging effects of metformin may be reversible upon discontinuation of the medication.

Statement of Purpose

The present study is novel in that at the current time, few studies have examined the role of A1C values on levels of domain-specific cognitive decline (i.e., lower A1C values being related to better cognitive performance while higher A1C values are related to worse cognitive performance). Instead, studies often explore the relationship between a diagnosis of Type 2 diabetes and developing a neurodegenerative disease like Alzheimer's disease. Furthermore, few studies have utilized a large battery of neuropsychological tests to examine the relationship between cognitive decline and diabetes. The more comprehensive approach of the present study was designed to contribute to resolving some of the mixed patterns of results across the reviewed studies varying in cognitive domains and measures utilized.

The reviewed literature also indicated inconsistent results for the relationship between the use of metformin for the treatment of Type 2 diabetes and cognitive functioning. Varying results warrant further study in this area. Also making this relationship an important area of focus for the present study is the wide use of the medication for the treatment of Type 2 diabetes and the research demonstrating its safety and utility for the treatment of Type 2 diabetes.

Hypotheses

Based on the reviewed literature, the hypotheses of this study were as follows:

1. Participants with higher A1C values will have significantly lower BNE scores (i.e., more domains within the "borderline" or "impaired" range) as compared to participants with A1C values within the normal range.
2. The medication metformin will impact cognitive performance as measured by the BNE.

Method

Participants

Archival participant data from the Health First Aging Institute and the East Central Florida Memory Disorder Clinic (ECFMDC) were utilized for this study. Participants were selected from patients who had been assessed for cognitive abnormalities using a brief neuropsychological evaluation (BNE) at the ECFMDC. Participants consented to the use of their testing data after being informed of the ECFMDC's research aspects prior to commencement of their testing session. For patients who were not competent to consent to the use of their data, consent was obtained from his or her durable power of attorney. This research has been approved by the Florida Institute of Technology's Institutional Review Board.

The sample utilized for this study consisted of 479 male and female ECFMDC patients who had undergone a full BNE. The sample consisted of 279 females (58.2%) and 200 males. Age of participants ranged from 46 to 95 years (M = 78.79, SD= 7.74). A large majority of the sample was Caucasian/White (88.5%), with 2.7% identifying as Hispanic, 8.4% identifying as African American, .8% identifying as Asian and .6% identifying as Native American. Additionally, .8% of

participants identified their race as “other”, while .8% provided no response. Participant years of education ranged from 3 to 24 years (M = 13.45, SD = 2.86). To establish the Type 2 diabetes group (n = 239), all participants from the ECFMDC research database were used who were diagnosed with Type 2 diabetes and had at least one documented A1C measurement in their medical chart. Participants who were not diagnosed with Type 2 diabetes were selected randomly from the ECFMDC research database to establish the control group (n = 240). A random number generator selected 240 numbers from a total of 2,274 patients that corresponded to the number of patients who did not have a diagnosis of Type 2 diabetes.

Setting

BNE’s were carried out on weekdays between 8:00 a.m. and 5:00 p.m. Each BNE took place in a small, neutral colored, examination room at the East Central Florida Memory Clinic in Melbourne, Florida. Within the room was a desk with two chairs, and a computer and keyboard placed to the far right or left side of the desk surface. Examination rooms also included a small file cabinet in a corner of the room. For all tests, the participant and the psychometrist sat facing each other across a three-foot-wide table. Pencils needed for the examination were placed to the side of testing materials.

Materials and Measures

Assessment of Diabetes. Participants in the diabetes group were diagnosed with diabetes based on a physician diagnosis or the use of diabetes medications.

Furthermore, a determination of a Type 2 diabetes diagnosis was further confirmed by a history of A1C value measurements in his or her medical record. These factors serve as a safeguard against participants misreporting the diagnosis.

Neuropsychological Exam. Each participant underwent a brief battery of neuropsychological assessments that included the Montreal Cognitive Assessment (MoCA) the Quick Exit, Controlled Oral Word Association Test (COWAT), MACK SF4, a Supraspan Serial Word List, Symbol Digit Modalities Test (SDMT), Trailmaking Test (TMT) parts A and B, the Victoria Stroop test (VST), a Clock Drawing Test (CDT), and the Rey Complex Figure Test. The neuropsychological measurements were used to assess the domains of attention and concentration, memory (learning and delayed recall), executive functioning, motor processing speed and visuo-spatial performance. Furthermore, three tests were given to assess the presence and severity of psychological difficulties including the Geriatric Depression Scale (GDS), the General Anxiety Index (GAI) and the Brief Symptom Inventory (BSI).

Montreal Cognitive Assessment (MoCA). The MoCA (Nasreddine et al., 2005) is a cognitive screening tool designed to assist in the detection of mild cognitive impairment. The examiner administers a variety of tasks which measures visuo-spatial, executive functioning, naming, language, memory, attention, delayed recall, abstraction, and orientation. The MoCA is scored by the examiner for a total of 30 possible points. A cut off score of 26 is used to suggest less than normal cognitive functioning, while a score of 26 or greater is classified as normal. Level

of education is also adjusted by adding one point to a patient's total score for those with equivalent to or less than twelve years of education.

Quick EXIT. The Quick Exit (Larson & Heinemann, 2010) is a short, 14-item abbreviated version of the original EXIT-25 (Stockholm et al., 2005). The test was developed to measure executive functioning ability through a variety of tasks that focus on participants' levels of perseveration, apathy, intrusions, disinhibition, utilization and imitation behavior, motor impersistence and concentration. Test items consist of number-letter sequencing, design fluency, sentence repetition, thematic perception, memory with a distraction task, interference inhibition, Luria hand sequence, motor perseveration, counting and serial-order reversal, and imitation behavior. The Quick EXIT is scored on a scale of 0-28, with higher scores indicating greater executive functioning deficits. Possible item scores range from zero to two.

Controlled Oral Word Association Test (COWAT). The COWAT (Benton, Hamsher & Siven, 1983) is a phonemic and semantic verbal fluency test that measures the participants' ability to spontaneously produce words that belong to particular categories designated by a letter of the alphabet (i.e., C, F and L) or to particular semantic categories (i.e., animals, fruit and vegetables). Individuals are allowed one minute to names as many words possible that begin with the designated letter or that represent the semantic category.

Mack SF4. The Mack SF4 (Mack et al., 1992) is a short form of the 60 item Boston Naming Test and consists of 15 items that assess visual naming ability by

utilizing a series of 15 black and white drawing of common objects (e.g., house, octopus, bench, stethoscope or palette). The examiner presented the various objects, one at a time, and records the patient's ability to identify the objects. The test was discontinued after eight consecutive failures. Phonemic and semantic cues are provided by the examiner following patients' difficulty in naming the object. Reliability of the test is weaker than the full Boston Naming Test, ranging from .49 to .84; however, the validity of the Mack SF4 is strong, ranging from .62 to .98.

Supraspan serial word list. This test was designed by the East Central Florida Memory Disorder Clinic and measures auditory-verbal learning and memory. The examiner read a list of 10 single-syllable words over each of five trials. Following each reading, the participant was asked to immediately recall the words in the list each time. Without notice, the patient was then prompted to recall the words from the list after a delay of five to ten minutes. Following the recall, the examiner records the number of words correctly recalled and any intrusions and/ or repetitions. The score is determined by percentage of words learned over the trials, with the best trial score and delay trial recorded. A recognition trial was also presented to the patient that consists of a list of the 10 previously remembered words among various distractor words. The number of patient word recognitions, commissions and omissions are recorded.

Symbol Digit Modalities Test (SDMT). The SDMT (Smith, 1982) is a test that assesses participants' divided attention, visual scanning, tracking and motor

speed. The participant is allotted 90 seconds to fill in numbers that correspond to particular symbols according to the way in which they are paired in a key above.

Trailmaking Test (TMT) part A and part B. The TMT (Partington & Leiter, 1949; Reitan, 1955) is a test comprised of two parts; Part A and Part B. Part A is designed to measure one's visual tracking, scanning and sequencing abilities. The patient was provided with a sheet of paper numbered one through 25 and asked to connect each number in ascending order. The score is calculated from the time the patient takes to complete the task. Each error is corrected immediately by the examiner. Part B of the Trailmaking Test measures one's set shifting and cognitive flexibility. The patient was presented with a sheet of paper with both numbers and letters enclosed in circles and instructed to alternate between a number and letter in ascending order. The score is calculated as the time the patient takes to complete the task. The patient was allotted a maximum of five minutes to complete the task.

Victoria Stroop Test (VST). The VST (Regard, 1981) measures selective attention and cognitive flexibility. The test has 3 components consisting of 23 items each. The first component (Part D) of the test consists of 24 colored (i.e., blue, green, red and yellow) dots arranged in rows. The Participant was asked to name the colors of the dots as quickly as he or she can. The second component (Part W) is similar to Part D, but the dots are replaced by common words and serves as a control task. The participant was prompted to name the color of the words while ignoring the verbal content. In the third and most difficult component of the test (Part C), the common words are replaced by the names of colors (i.e., blue, green,

red and yellow) that do not correspond to the printed color (e.g., blue is written in green ink). The participant was prompted to name the color of the print and not read the word, which is the automatic response. The errors in naming are corrected by the examiner each time it occurs and the total errors and the time it took to complete each part is recorded. Following the task, an interference score is calculated to determine the amount of extra time needed to name the colors in Part C.

***Clock Drawing Test (CDT*).** The CDT (Mendez et al., 1992) is a test that assesses participants' visual-spatial, constructional and executive abilities through drawing an analogical clock face on a piece of paper. Following the completion of the drawing, the patient was asked to set the time to 10 after 11. The participant's response is then scored based on his or her ability to correctly draw the contour of the clock, place the numbers in the correct location and order, and set the clock hands to the correct time.

Rey Complex Figure Test (ROCF). The ROCF (Rey, 1941; Osterrieth, 1944) is a test that assesses the examinee's visual-spatial constructional ability and visual memory. The test is comprised of 3 conditions, all of which relate to the examinee's ability to copy and later remember multiple details of a complex figure. In the first condition, the examinee was provided with an image of the complex design and is prompted to copy the design on an 8 ½ by 11-inch blank sheet of paper with a pencil. The examinee was given five minutes to complete the task. In the second condition, the examiner removed the image of the design, provided a

clean sheet of paper, and prompted the examinee to reproduce the complex design from memory within five minutes. After a 30-minute delay period that is filled with interfering, non-constructional tasks in the testing battery, the examinee is again prompted to reproduce the design from memory. Condition three is an incidental learning test, therefore there was no warning there would be a delayed recall condition. Following the 3 conditions each condition is scored based on accuracy and quality of the drawings.

Geriatric Depression Scale (GDS). The GDS (Yesavage et al., 1983) is a 30-item self-administered mood assessment scale used to screen the elderly for depression. The examiner presented the questionnaire to the examinee that consists of 30 yes/no items that address changes in mood based on how the patient is feeling at the time. The test takes approximately five to ten minutes to complete. GDS scores range from zero to thirty. Scores of 0-9 indicate no depression, 10-14 indicate mild depression, 15-19 indicate moderate depression, and 20-30 indicate severe depression.

Geriatric Anxiety Inventory (GAI). The GAI (Pachana et al., 2007) is a 20-item self-administered mood assessment scale used to screen for typical symptoms of anxiety and is comprised of agree/disagree statements only. The questions are tailored to fit the common symptoms of anxiety in the elderly with only including a limited number of somatic symptom-related questions to avoid confusion between somatic complaints related to anxiety and general medical conditions.

Brief Symptom Inventory (BAI). The BAI (Derogatis, 1993) is a 53-item self-report instrument that assesses psychological distress and symptoms of psychiatric disorders. The patient was prompted to rate their experience with the symptoms over the past 7 days, including today, on a five-point Likert scale. The BSI consists of nine primary dimensions (somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, paranoid ideation, and psychoticism). It also includes three global indices of psychological distress (Global Severity Index, Positive Symptom Distress Index, and Positive Symptom Total).

Procedure

A trained psychometrist administered and scored the brief neuropsychological assessment (BNE). An interdisciplinary professional team consisting of a geriatrician, social worker, neuropsychologist, neurologist, geriatric psychologist, and clinical psychology doctoral students formed a case review panel and collaboratively determined the appropriate diagnosis and treatment for each participant. The results of a complete medical examination, laboratory tests including MRI, and a psychosocial interview were used in forming an accurate diagnosis. Each patient was later informed of their diagnosis, given a treatment plan, and recommended for future neuropsychological assessment depending on the diagnosis given. A patient's cognitive performance scores from the brief neuropsychological battery were separated into appropriate domains and then labeled with the impairment categories accordingly with "Within Normal Limits",

"Borderline", or "Impaired". Data from the BNE was later entered into a database by a trained psychometrist for research purposes at the East Central Florida Memory Disorder clinic.

The study consisted of an archival investigation that began by the primary researcher combining patient cognitive testing data from the ECFMDC database with data retrieved from Health First's information technology (IT) department. Data from IT provided information from patients' medical charts including a diagnosis of Type 2 diabetes, A1C values and their corresponding dates of measurement, and patient's history of anti-diabetic and anti-dementia medications. A final database pertaining both sources of information combined was used to conduct statistical analyses.

Statistical Methods

All data were analyzed using SPSS version 25. Descriptive and frequency summary data were calculated to obtain the demographic information for the sample used for this study, as well as for characterizing the anti-diabetic drugs in the Type 2 diabetes group and the cognitive diagnoses across both groups. To test the role of A1C values on cognitive performance, both a multivariate analysis of variance (MANOVA) and a Pearson product-moment correlation coefficient were utilized. The effect of the medication metformin on cognitive performance as measured by the BNE was explored by a variety of statistical methods including multiple independent samples *t*-tests. These were conducted to compare BNE cognitive domain scores for participants taking metformin with participants taking

any other class of anti-diabetic medications. Independent samples *t*-tests were also used to compare cognitive performance by total BNE score and MoCA scores between participants taking metformin with participants taking other medication classes. Finally, as part of post-hoc analyses, 2 areas outside of the originally proposed hypotheses were explored. Specifically, 1) differences in cognitive diagnoses across the Type 2 diabetes and control groups were investigated by conducting a chi square test for independence, and 2) differences in BNE subtest scores across the Type 2 diabetes and Control group were explored. This was achieved by comparing group means via conducting independent samples *t*-tests.

Results

Prior to tests of hypotheses, group make up by gender, age, race and ethnicity was examined. The control group was comprised of 64.2% females, 95% Caucasian with 92.1% identifying as Non-Hispanic. Control group patients' ages ranged from 48 to 95 years (M=79.63, SD = 7.4) with years of education ranging from 8 to 21 years (M =13.66, SD = 2.7). The Type 2 diabetes group was comprised of 52.3% females, 82% Caucasian with 89% identifying as Non-Hispanic. The Type 2 diabetes group ages ranged from 46 to 95 years (M = 77.94, SD = 8.0) with years of education ranging from 3 to 24 years (M =13.66, SD = 3.0). Groups did not differ from one another in level of education as determined with an independent samples *t*-test, t (473) = 2.37, p = .12. Groups significantly differed from one another on age as determined with an independent samples *t*-test, t (471) = 2.37, p = .02. Cross tabulated frequencies also indicated a significant difference

in gender composition across groups, χ^2 (1, n = 479) = 6.5, p = < .05, *phi* = .12.

Hypothesis 1

This study hypothesized participants with higher A1C values will have significantly lower BNE scores (i.e., more domains within the "borderline" or "impaired" range) than participants with A1C values within the normal range. This hypothesis was tested with relational and comparative statistics.

The relationship between cognitive performance (as measured by both the total BNE score and the MoCA score) and A1C scores was investigated using a Pearson product-moment correlation coefficient. Preliminary analyses were conducted to ensure no violation of the assumptions of normality, linearity and homoscedasticity. All correlations were found to be statistically insignificant.

Secondly a one-way between-groups multivariate analysis of variance (MANOVA) was performed to investigate group differences in BNE domain scores. Six dependent variables were used: language, attention, executive functioning, motor and processing speed, visuospatial skills, and learning and memory scores. The independent variable was group (i.e. Type 2 diabetes or control). Preliminary assumption testing was conducted to check for normality, linearity, univariate and multivariate outliers, homogeneity of variances, with no serious violations noted. There was a statistically significant difference between the Type 2 diabetes and control group on the combined dependent variables, Wilks' λ = .97; F (6, 468) = 2.45, p = .024; partial eta squared = .03, demonstrating a small effect size. When results from the dependent variables were considered separately,

the only one to reach statistical significance was the visuospatial domain, F (1, 473) = 5.49, p = .02, partial eta squared = .01, demonstrating a small effect size. An inspection of mean scores indicated that the Type 2 diabetes group obtained slightly lower visuospatial scores (M = 2.17, SD = .79) than the control group (M = 2.00, SD = .82).

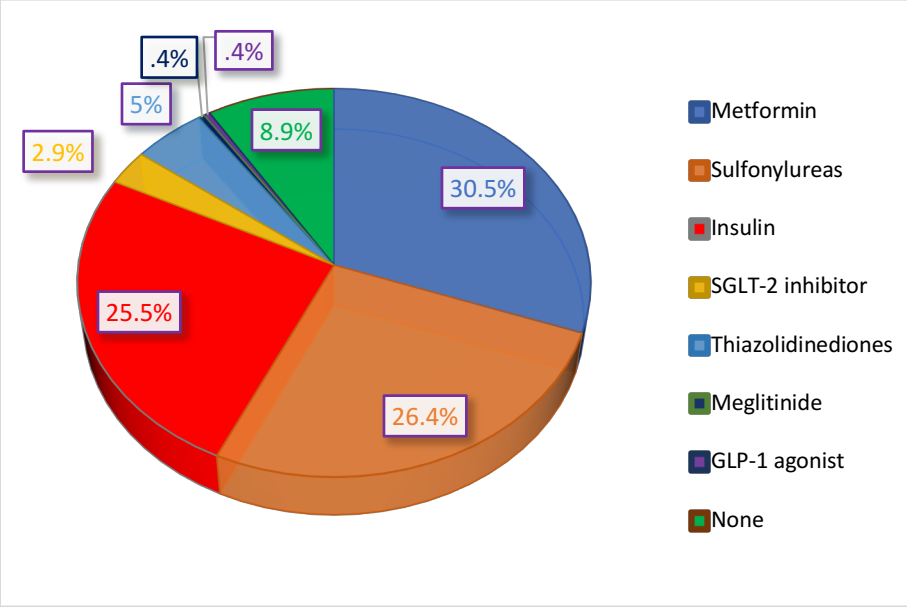
Two independent-samples t-tests were conducted to compare cognitive performance (as measured by both the total BNE scores and MoCA scores) for the Type 2 diabetes and control group. There was no significant difference total BNE scores between the Type 2 diabetes group (M = 12.22, SD = 3.83) and the control group (M = 11.80, SD = 3.98; t (477) = 1.17, p = .24, two-tailed). The was also no significant difference in MoCA scores between the Type 2 diabetes group (M = 19.14, SD = 4.90) and the control group (M = 18.86, SD = 4.70; t (467) = -.65, p = .52, two-tailed).

Hypothesis 2

This study also hypothesized the medication metformin would impact cognitive performance as measured by the BNE. Participants in the Type 2 diabetes group in this study were on a variety of classes of anti-diabetic medications including metformin, sulfonylureas, meglitinides, thiazolidinediones, sodium-glucose cotransporter-2 (SGLT2) inhibitors, glucagon-like peptide (GLP-1) agonists and insulin. Out of the 239 participants in the Type 2 diabetes group, 218 participants were taking an anti-diabetic medication. Seventy-three participants were taking metformin (30.5%), 63 participants were taking a sulfonylurea

(25.4%), 61 participants were on insulin (25.5%), 12 participants were taking thiazolidinediones (5%), 7 participants were taking a SGLT-2 inhibitor (2.9%), while only 1 participant was taking a meglitinide (0.4%) or a GLP-1 agonist (0.4%). Additionally, 21 participants were not indicated as taking any anti-diabetic medications (8.9%).

Figure 1. Composition of anti-diabetic medications in Type 2 diabetes group



To explore the impact of metformin on cognitive performance, independent-samples *t*-tests were conducted to compare BNE cognitive domain scores for participants taking metformin with participants taking all other classes of anti-diabetic medications. There was a marginally significant difference in the learning and memory domain scores for participants on metformin ($M = 1.90$, $SD = .81$) compared to participants on other medication classes ($M = 1.69$, $SD = .77$; $t(237) = -1.95$, $p = .053$. This suggests participants taking metformin demonstrated

slightly better performance on learning and memory measures. All other comparisons were statistically insignificant. Comparison results are reported below in Table 1.

Table 1. Results of *t* tests and descriptive statistics of BNE domain scores by medication

	Metformin Scores		Other Medication Scores		*t*-test	*p*-value
	M	SD	M	SD		
Learning and Memory	1.90	.81	1.69	.77	-1.95	.05*
Language	2.25	.73	2.13	.77	-.1.19	.24
Attention	2.22	.81	2.05	.85	-1.47	.14
Executive Functioning	2.07	.83	1.93	.83	1.16	.25
Motor Processing	2.10	.77	2.08	.85	1.11	.91
Visuospatial	2.15	.80	2.18	.79	.25	.80

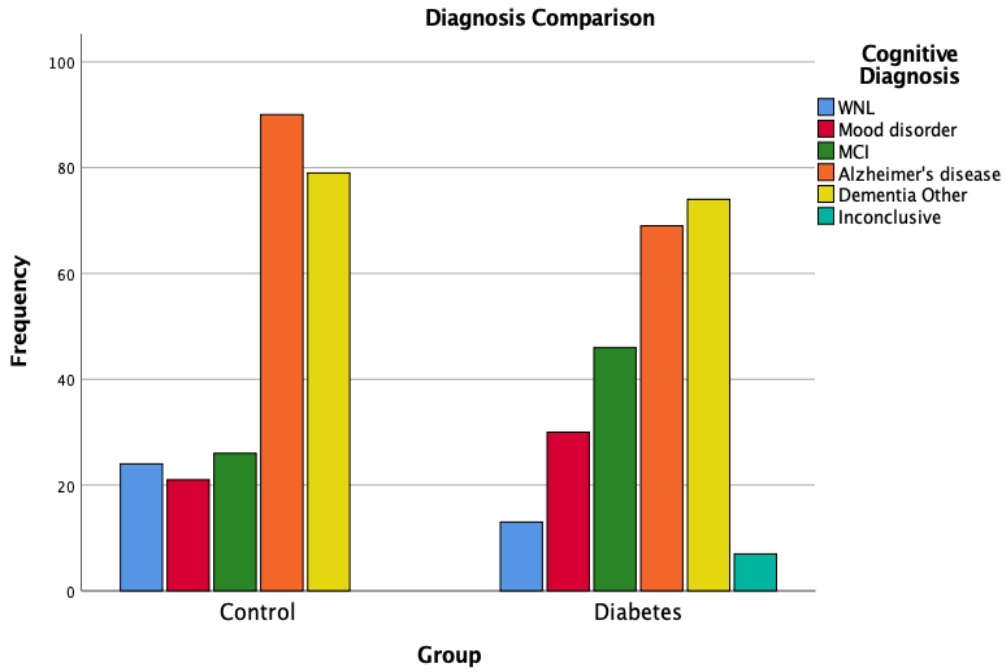
Further independent- sample *t*-tests were conducted to compare cognitive performance by total BNE score and MoCA scores between participants taking metformin with participants taking other medication classes. There was no significant difference in total BNE scores for participants on metformin (M = 12.67, SD = 3.57) compared to participants on other medication classes (M = 12.02, SD = 3.93; t (237) = -1.19, p = .23). There was, however, a significant difference in MoCA scores between participants on metformin (M = 20.26, SD = 4.19) compared

to participants on other medication classes (M = 18.67, SD = 5.05; t (229) = -2.31, p = .02), suggesting participants taking metformin performed significantly better on this measure compared to participants taking other anti-diabetic medications.

Post-hoc analyses

Cognitive diagnosis. Sample participants were diagnosed with a wide variety of dementia diagnoses. These diagnoses include no cognitive impairment, mild cognitive impairment (MCI), Alzheimer's disease, vascular dementia, Lewy body dementia, frontotemporal dementia, mixed dementia, cognitive disorder not otherwise specified, and unspecified cognitive disorder. Due to low participant frequencies in the diagnostic categories of vascular dementia, Lewy body dementia, frontotemporal dementia, mixed dementia, cognitive disorder not otherwise specified, and unspecified cognitive disorder, a category termed "dementia other" was created to capture these diagnoses to allow for further analyses. Participants also were diagnosed with a mood disorder diagnosis if mood difficulties were detected throughout the testing process. The control group had 24 participants within normal limits (WNL) (10%), 21 mood disorder (8.8%), 26 MCI (10.8%), 90 Alzheimer's disease (37.5%), and 79 dementia other (32.9%). For the Type 2 diabetes group, 13 participants were within normal limits (WNL) (5.4%), 30 mood disorder (12.6%), 46 MCI (19.2%), 69 Alzheimer's disease (28.9%), and 74 dementia other (31.0%). Furthermore, 7 participants in this group's testing results were deemed inconclusive (2.9%) and a diagnosis was not provided.

Figure 2. Frequency of patient diagnosis in control and Type 2 diabetes group



To determine whether or not there were statistically significant differences between the Type 2 diabetes and control group in cognitive diagnosis, a chi square test for independence was conducted. Results indicated a significant association between group and cognitive diagnosis, χ^2 (5, n = 479) = 20.35, p = < .01, *phi* = .2.

Differences in test scores. To explore the impact of group on cognitive performance on specific subtests within the BNE, independent- samples *t*-tests were conducted. All comparisons were insignificant, as displayed in Table 2, with the exception of performance on the Clock Drawing Test. Specifically, participants in the Type 2 diabetes group (M = 7.37, SD = 2.63) performed significantly better on the Clock Drawing Test than participants in the control group (M = 6.74, SD = 2.93; t (465) = -2.45, p = .02).

Table 2. Results of *t* tests and descriptive statistics of test scores by group

	Control Group Scores		Type 2 Diabetes Scores		*t*-test	*p*-value
	M	SD	M	SD		
Brief Exit	8.38	4.37	8.25	4.09	.32	.75
COWAT Phonemic	8.48	2.97	8.36	3.06	.43	.67
COWAT Semantic	6.62	2.93	6.92	3.00	-1.06	.29
MackSF4	11.55	2.70	11.55	2.91	.01	1.00
Trails A	7.15	3.62	7.15	3.58	-.03	.98
Trails B	4.99	4.23	5.65	4.11	-1.66	.10
Clock Drawing Test	6.74	2.93	7.37	2.63	-2.45	.02*
Supraspan Best	6.57	1.88	6.65	1.77	-.46	.64
Supraspan Delay	2.90	2.90	3.34	2.67	-1.65	.10

Discussion

Previous research indicated that individuals diagnosed with Type 2 diabetes displayed accelerated levels of cognitive decline compared to individuals without the disease across various cognitive domains (Awad, Gagnon, & Messier, 2004; McCrimmon, Ryan, & Frier, 2012; Yeung & Fischer, 2009). Although this area has been heavily studied, less research exists that investigates differences in cognitive decline across varying levels of diabetes self-management as indicated by A1C values. Secondly, a recent area of research exploring the relationship between the

medication metformin for the treatment of Type 2 diabetes and its impact on cognitive decline has yielded mixed results, with some studies demonstrating a neuroprotective effect (Asadbegi, Yaghmaei, Salehi, Ebrahim-Habibi, & Komaki, 2016; Chung et al., 2014) and others demonstrating an increased risk of the development of various neurodegenerative diseases (Chen et al., 2008; Imfeld, Bodmer, Jick, & Meier, 2012; Yung-Cheng et al., 2014).

With a goal of a making a unique contribution to the aforementioned lines of research, the present study investigated the role of Type 2 diabetes self-management (as measured by A1C values) on levels of domain-specific cognitive decline in older adults. A second aim of the present study was to determine whether or not older adults taking the medication metformin to manage Type 2 diabetes experienced differences in cognitive decline compared to those taking other medications. Based on the review of literature in these areas, it was hypothesized participants with higher A1C values would have significantly worse BNE scores (i.e., more domains within the "borderline" or "impaired" range) as compared to participants with A1C values within the normal range. The second hypothesis of this study was exploratory and posited that the medication metformin would impact cognitive performance as measured by the BNE.

Results of the current study do not support the first hypothesis that participants with higher A1C values would be associated with lower BNE scores. Specifically, this relationship was investigated using a Pearson product-moment correlation coefficient and all correlations were found to be statistically

insignificant. This lack of relationship may be explained in part by a significant limitation of the current study regarding a lack of accurate dates of A1C measures in patient medical records. Specifically, throughout data compilation, it was determined there may have been delays in entering A1C values in patient medical charts; therefore, the date of cognitive testing data and A1C values could not be accurately matched with confidence. Furthermore, patient A1C values often did not coincide with BNE testing dates, further adding to difficulty in matching A1C dates with cognitive data. At the very least, this limitation added variance to the analysis that may prevented a true effect from emerging.

The primary hypothesis of the present study was investigated further by examining differences in BNE domain scores between the Type 2 diabetes and control group. MANOVA results revealed a statistically significant difference between the Type 2 diabetes and control group on BNE domain scores, specifically regarding the visuospatial domain. An inspection of mean scores indicated that the Type 2 diabetes group obtained slightly lower visuospatial scores. This finding is rather unique from the reviewed literature as previous studies suggest domain deficits to primarily occur in the executive functioning and motor processing speed domains (Yeung, Fischer and Roger, 2009; Palta, Schneider, Biessels, Touradji & Hill-Briggs, 2014). Although unique, this finding should be interpreted with caution and the effect size of this finding was small and is overall incongruent with the previous investigations of domain-specific cognitive deficits in Type 2 diabetes samples.

In addressing the exploratory hypothesis of the present study that the medication metformin would impact cognitive performance as measured by the BNE, BNE cognitive domain scores were compared for participants taking metformin with participants taking all other classes of anti-diabetic medications. A significant difference in the learning and memory domain scores was detected, which suggests individuals who were taking metformin performed slightly better on memory and learning measures. This finding is in line with an important study conducted by Herath, Cherbuin, Eramudugolla, and Anstey (2016) that found participants who took metformin demonstrated better cognitive performance in the various areas of learning and memory.

The most important findings of this study emerged with regard to MoCA score comparisons between the metformin and other medication group. It was found participants on metformin performed significantly better on the MoCA than participants on other anti-diabetic medications. This finding is important as the MoCA is a well-established multi-domain measure of cognitive functioning. Furthermore, this finding is rather unique as the reviewed literature did not indicate previous studies utilizing the MoCA to explore cognitive decline in diabetic participants.

Various analyses were conducted outside of the two primary hypotheses of the present study. The aim of these post- hoc analyses were 1) to explore differences in cognitive diagnosis amongst the Type 2 diabetes and control group and 2) to explore potential differences in BNE subtests between the two groups.

Statistically significant differences were found in the cognitive diagnoses between the Type 2 diabetes and control group. By exploring these differences closer, within the Type 2 diabetes group, there were less participants with normal cognitive functioning, and more participants with mood disorder and Mild Cognitive impairment. Furthermore, more participants diagnosed with Alzheimer's disease were present in the control group. Although the investigation of mood disorders in the Type 2 diabetes group was not an aim of the present study, a well-established body of research exists that links depression to diabetes. Specifically, the relationship between diabetes and depression appears to be bi-directional, suggesting diabetes increases the risk of depression, while depression also increases the risk of diabetes (Gonzalez, Peyrot, Collins, Mimiaga & Safren, 2008) Furthermore, stress and anxiety have also been linked to diabetes (Lloyd, Smith & Weinger, 2005; Smith, Bèland, Clyde, Gariépy, Pagé, Badawi et al., 2013). The higher frequency of mood disorders in the Type 2 diabetes group of the present study appears to be in line with these findings. This study did not examine the specific frequencies of specific mood disorders within the Type 2 diabetes group, which may be an interesting future investigation.

Limitations

There are several limitations of the current study, most of which are related to the Electronic Medical Record (EMR) System that was the source of the medical data. The EMR utilized negatively affected data collection and analysis in multiple ways. First, data received from the information technology professionals (IT) was

displayed in a format that made it difficult to organize and convert into a format that could be used for data analysis. A significant amount of time was spent re-organizing and properly formatting the data into a research-friendly format to prepare for statistical analyses. Secondly, the patient data obtained from the EMR had many shortcomings, the worst of which was the lack of accuracy in the dates assigned to various patient information including A1C value measurements, medication prescriptions, and the dates diagnoses were made. After discussion with multiple medical professionals at the ECFMDC, it was determined that there was often a significant delay in entry of medical information into patients' charts after changes and updates have been made, thus rendering the dates associated with this information rather inaccurate. Being able to accurately link dates of medical data in patients' charts with the ECFMDC cognitive testing data was important for being able to draw conclusions about patterns of cognitive decline related to both A1C and anti-diabetic medications. As mentioned previously, it is likely the lack of correlational findings between A1C and BNE cognitive domain scores are accounted for by errors in BNE date and A1C date.

Potential inaccuracy of EMR date information significantly impacted the statistical analyses related to anti-diabetic medications and cognition. Similar to the previously discussed difficulties with linking A1C values and testing data, the same challenges were present in linking medication dates with cognitive testing data. Specifically, information obtained related to patient medication history lacked crucial elements including information about compliance, when a medication was

discontinued or added, and whether or not the medication documented was the first instance the patient took the medication. Likewise, potentially important patient medication information regarding the medications a patient may have took prior to becoming a patient of Health First or at the ECFMDC were not present. Despite request for multiple draws of data from the EMR system to address these shortcomings, information to correct these limitations could not be obtained. To account for these limitations, areas of this research project that relied less heavily on dates were also explored.

Lastly, a notable limitation of the present study was the lack of racial and ethnic diversity since the sample was predominately Caucasian (88.5%) and non-Hispanic. This limitation restricts the ability to generalize findings of the present study to other, more diverse, samples.

Future Directions

Research exploring the role of anti-diabetic medications on Type 2 diabetes will generate the clearest results when conducted within a medical environment where the variables of interest are collected and documented in a structured and experimenter-friendly IT environment. These characteristics allow the researcher to maintain control of many factors that influence the outcomes of this line of research including the collection of crucial information related to A1C values, medication compliance, and medication history. If it is necessary to utilize archival data, it should be ensured data is being extracted from a database that allows for the collecting of comprehensive and accurate data. Furthermore, based on the findings

of the present study, an interesting area for future research may be exploring the use of the MoCA for detecting cognitive decline in the diabetic population.

Conclusions

Although further research is necessary to gain an understanding of the role of A1C values and metformin use on domain-specific cognitive decline, the investigations of the current study revealed interesting findings. In contrast to the reviewed literature on domain-specific cognitive decline in a diabetic sample, this study demonstrated more homogeneity between the control and Type 2 diabetes group than expected. Specifically, few differences in cognitive domain scores were found across groups. This possibly suggests that other important factors may be influencing patterns of cognitive decline more heavily, including the specific cognitive diagnosis and age. The strongest findings of this study were related to metformin use. These suggest a neuroprotective effect of metformin, specifically with regard to learning and memory skills. Moreover, this study also demonstrated significant differences in cognition on the MoCA, a well-established multi-domain measure of cognition, suggesting better performance for participants taking metformin compared other anti-diabetic medications. Overall, these findings make an important contribution to the mixed literature on the impact of metformin on cognitive functioning in diabetic patients.

References

Abbott, M. A., Wells, D. G., & Fallon, J. R. (1999). The insulin receptor tyrosine kinase substrate p58/53 and the insulin receptor are components of CNS synapses. *Journal of Neuroscience*, *19*(17), 7300-7308. Retrieved from http://www.jneurosci.org/content/19/17/7300.long

Ahtiluoto, S., Polvikoski, T., Peltonen, M., Solomon, A., Tuomilehto, J., Winblad, B., ...& Kivipelto, M. (2010). Diabetes, Alzheimer disease, and vascular dementia: A population-based neuropathologic study. *Neurology*, *75*(13), 1195-1202. doi:10.1212/WNL.0b013e3181f4d7f8

Alagiakrishnan, K., Sankaralingam, S., Ghosh, M., Mereu, L., & Senior, P. (2013). Antidiabetic drugs and their potential role in treating mild cognitive Impairment and Alzheimer's disease. *Discovery Medicine, 16*(90), 277-286.

American Diabetes Association. (2013). Economic costs of diabetes in the US in 2012. *Diabetes care*, *36*(4), 1033-1046. doi:10.2337/dc12-2625

American Diabetes Association (2017) Lifestyle Management. In Standards of Medical Care in Diabetes 2017. *Diabetes Care*, 40, S33-S43. doi:10.2337/dc17-S007.

American Diabetes Association. (2015, October 27). Facts about type 2. *In Diabetes basics.* Retrieved from http://www.diabetes.org/diabetes-basics/type-2/facts-about-type-2.html

American Diabetes Association. (2014, December 9). Diagnosing diabetes and learning about prediabetes. In *Are you at risk?* Retrieved from http://www.diabetes.org/are-you-at-risk/prediabetes/

American Diabetes Association. (2013, February). Meet your A1C. In *Diabetes Forecast: the healthy living magazine.* Retrieved from http://www.diabetesforecast.org/2013/feb/meet-your-a1c.html

Asadbegi, M., Yaghmaei, P., Salehi, I., Ebrahim-Habibi, A., & Komaki, A. (2016). Neuroprotective effects of metformin against Aβ-mediated inhibition of long-term potentiation in rats fed a high-fat diet. *Brain Research Bulletin, 121*, 178-185. doi:10.1016/j.brainresbull.2016.02.005

Awad, N., Gagnon, M., & Messier, C. (2004). The relationship between impaired glucose tolerance, type 2 diabetes, and cognitive function. *Journal of Clinical and Experimental Neuropsychology, 26*(8), 1044-1080. doi:10.1080/13803390490514875.

Bennett, W. L., Maruthur, N. M., Singh, S., Segal, J. B., Wilson, L. M., Chatterjee, R., ...& Nicholson, W. K. (2011). Comparative effectiveness and safety of medications for type 2 diabetes: an update including new drugs and 2-drug combinations. *Annals of internal medicine*, *154*(9), 602-613. doi:10.7326/0003-4819-154-9-201105030-00336.

Benton, A. L., de Hamsher, S. K., & Sivan, A. B. Iowa City: AJA Associates; 1983. *Multilingual Aplasia Examination, ed*, *2*.

Bertram, S., Brixius, K., & Brinkmann, C. (2016). Exercise for the diabetic brain: How physical training may help prevent dementia and Alzheimer's disease in T2DM patients. *Endocrine, 53*(2), 350-363. doi:10.1007/s12020-016-0976-8

Biessels, G. J., Staekenborg, S., Brunner, E., Brayne, C., & Scheltens, P. (2006). Risk of dementia in diabetes mellitus: A systematic review. *The Lancet Neurology, 5*(1), 64-74. Retrieved from https://search-proquest-com.portal.lib.fit.edu/docview/201475888?accountid=27313

Centers for Disease Control and Prevention. *National diabetes fact sheet: National estimates and general information on diabetes and prediabetes in the United States.* Atlanta, GA: Centers for Disease Control and Prevention; 2011.

Centers for Disease Control and Prevention. *National diabetes statistics report: Estimates of diabetes and its burden in the United States.* Atlanta, GA: Centers for Disease Control and Prevention; 2017.

Centers for Disease Control and Prevention. *At a glance 2016. Diabetes: Working to reverse the U.S. epidemic.* Atlanta, GA: Centers for Disease Control and Prevention; 2016.

Chen, Y., Zhou, K., Wang, R., Liu, Y., Kwak, Y., Ma, T., . . . Liao, F. (2009). Antidiabetic drug metformin (GlucophageR) increases biogenesis of Alzheimer's amyloid peptides via up-regulating BACE1 transcription. *Proceedings of the National Academy of Sciences of the United States of America, 106*(10), 3907-3912. doi:10.1073/pnas.0807991106

Cheng, D., Noble, J., Tang, M. X., Schupf, N., Mayeux, R., & Luchsinger, J. A. (2011). Type 2 diabetes and late-onset Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders, 31*(6), 424-30. doi:10.1159/000324134

Cooper, C., Sommerlad, A., Lyketsos, C. G., & Livingston, G. (2015). Modifiable predictors of dementia in mild cognitive impairment: A systematic review and meta-analysis. *The American Journal of Psychiatry, 172*(4), 323-334. doi:10.1176/appi.ajp.2014.14070878

Crane, Paul K,M.D., M.P.H., Walker, R., M.S., Hubbard, R. A., PhD., Li, Ge,M.D., PhD., Nathan, D. M., M.D., Zheng, H., PhD., . . . Larson, Eric B,M.D., M.P.H. (2013). Glucose levels and risk of dementia. *The New England Journal of Medicine, 369*(6), 540-8. doi:10.1056/NEJMoa1215740

Csukly, G., Sirály, E., Fodor, Z., Horváth, A., Salacz, P., Hidasi, Z., ... & Szabó, Á. (2016). The differentiation of amnestic type MCI from the non-amnestic types by structural MRI. *Frontiers in aging neuroscience*, *8*. doi:10.3389/fnagi.2016.00052

Dickey, C. A., Koren, J., Zhang, Y., Xu, Y., Jinwal, U. K., Birnbaum, M. J., . . . Petrucelli, L. (2008). Akt and CHIP coregulate tau degradation through coordinated interactions. *Proceedings of the National Academy of Sciences of the United States of America, 105*(9), 3622. doi: 10.1073 pnas.0709180105

Gonzalez, J. S., Peyrot, M., McCarl, L. A., Collins, E. M., Serpa, L., Mimiaga, M. J., & Safren, S.A. (2008). Depression and diabetes treatment nonadherence: a meta-analysis. *Diabetes care*, *31*(12), 2398-2403. doi: https://doi.org/10.2337/dc08-1341

Gorelick, P. B., Scuteri, A., Black, S. E., Decarli, C., Greenberg, S. M., Iadecola, C., . . . Seshadri, S. (2011). American Heart Association Stroke Council, Council on Epidemiology and Prevention, Council on Cardiovascular Nursing, Council on Cardiovascular Radiology and Intervention, and Council on Cardiovascular Surgery, and Anesthesia. Vascular contributions to cognitive impairment and dementia: A statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke, 42*(9), 2672-2713. doi:10.1161/STR.0b013e3182299496

Hassenstab, J. J., Sweat, V., Bruehl, H., & Convit, A. (2010). Metabolic syndrome is associated with learning and recall impairment in middle age. *Dementia and geriatric cognitive disorders*, *29*(4), 356-362. doi:10.1159/000296071

Hassing, L. B., Hofer, S. M., Nilsson, S. E., Berg, S., Pedersen, N. L., McClearn, G., & Johansson, B. (2004). Comorbid type 2 diabetes mellitus and hypertension exacerbates cognitive decline: Evidence from a longitudinal study. *Age and Ageing, 33*(4), 355-61. doi:10.1093/ageing/afh100

Hsu, C., Wahlqvist, M. L., Lee, M., & Tsai, H. (2011). Incidence of dementia is increased in type 2 diabetes and reduced by the use of sulfonylureas and metformin. *Journal of Alzheimer's Disease, 24*(3), 485-493. doi: 10.3233/JAD-2011-101524

Imfeld, P., Bodmer, M., Jick, S. S., & Meier, C. R. (2012). Metformin, other antidiabetic drugs, and risk of Alzheimer's disease: A population-based case–control study. *Journal of the American Geriatrics Society, 60*(5), 916-921. doi:10.1111/j.1532-5415.2012.03916.x

Kitabchi, A. E. (2005). Role of insulin secretion and sensitivity in the evolution of type 2 diabetes in the diabetes prevention program: Effects of lifestyle intervention and metformin. *Diabetes, 54*(8), 2404-14. Retrieved from https://search-proquest-com.portal.lib.fit.edu/docview/216484427?accountid=27313

Kuan, Y., Huang, K., Lin, C., Hu, C., & Kao, C. (2017). Effects of metformin exposure on neurodegenerative diseases in elderly patients with type 2 diabetes mellitus. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 79*, 77-83. doi:10.1016/j.pnpbp.2017.06.002

Łabuzek, K., Suchy, D., Gabryel, B., Bielecka, A., Liber, S., & Okopień, B. (2010). Quantification of metformin by the HPLC method in brain regions, cerebrospinal fluid and plasma of rats treated with lipopolysaccharide. *Pharmacological Reports: PR, 62*(5), 956-965.

Larson, E. B., & Heinemann, A. W. (2010). Rasch analysis of the Executive Interview (the EXIT-25) and introduction of an abridged version (the Quick EXIT). *Archives of physical medicine and rehabilitation*, *91*(3), 389-394. doi: 10.1016/j.apmr.2009.11.015

Lloyd, C., Smith, J., & Weinger, K. (2005). Stress and diabetes: a review of the links. *Diabetes spectrum*, *18*(2), 121-127. doi: https://doi.org/10.2337/diaspect.18.2.121

Mack, W., Freed, D., Williams, B.W., & Henderson, V. (1992). Boston Naming Test: Shortened versions for use in Alzheimer's disease. *Journal of Gerontology: Psychological Sciences, 47 (3)*, P154-P158.

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., . . . Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society, 53*(4), 695-699. doi:10.1111/j.1532-5415.2005.53221.x

Mattsson, N., Zetterberg, H., Hansson, O., Andreasen, N., Parnetti, L., Jonsson, M., ... & Rich, K. (2009). CSF biomarkers and incipient Alzheimer disease in patients with mild cognitive impairment. *Jama*, *302*(4), 385-393. doi: 10.1001/jama.2009.1064

McCrimmon, R. J., Ryan, C. M., & Frier, B. M. (2012). Diabetes 2: Diabetes and cognitive dysfunction. *The Lancet, 379*(9833), 2291-9. doi:10.1016/S0140-6736(12)60360-2

Meigs, J. B., Cupples, L. A., & Wilson, P. W. F. (2000). Parental transmission of type 2 diabetes: The Framingham offspring study. *Diabetes, 49*(12), 2201-7. Retrieved from https://search-proquest-com.portal.lib.fit.edu/docview/216484179?accountid=27313

Mendez, M. F., Ala, T., & Underwood, K. L. (1992). Development of scoring criteria for the clock drawing task in Alzheimer's disease. *Journal of the American Geriatrics Society, 40,* 1095–1099.

Mostafa, D. K., Ismail, C. A., & Ghareeb, D. A. (2016). Differential metformin dose-dependent effects on cognition in rats: Role of akt. *Psychopharmacology, 233*(13), 2513-2524. doi:10.1007/s00213-016-4301-2

National Institute of Diabetes and Digestive and Kidney Diseases. (2009, August). Prediabetes and insulin resistance. In *What is Diabetes?*. Retrieved from https://www.niddk.nih.gov/health-information/diabetes/overview/what-is-diabetes/prediabetes-insulin-resistance

National Institutes of Health (2011). *Advances and emerging opportunities in diabetes research: A strategic planning report of the Diabetes Mellitus Interagency Coordinating Committee*. Bethesda, MD: National Institutes of Health.

Osterrieth, P. A. (1944). Le test de copie d'une figure complex: Contribution a l'étude de la perception et de la mémoire. *Archives de Psychologie, 30,* 286–356.

Ott, A., Stolk, R. P., Van Harskamp, F., Pols, H. A. P., Hofman, A., & Breteler, M. M. B. (1999). Diabetes mellitus and the risk of dementia The Rotterdam Study. *Neurology*, *53*(9), 1937-1937. Retrieved from http://www.neurology.org/content/53/9/1937.short

Pachana, N. A., Byrne, G. J., Siddle, H., Koloski, N., Harley, E., & Arnold, E. (2007). Development and validation of the Geriatric Anxiety Inventory. *International Psychogeriatrics*, *19*(1), 103-114. doi:10.1017/S1041610206003504.

Palmer, S. C., PhD., Mavridis, D., PhD., Nicolucci, A., M.D., Johnson, D. W., PhD., Tonelli, M., M.D., Craig, J. C., PhD., . . . Strippoli, G. F. M., PhD. (2016). Comparison of clinical outcomes and adverse events associated with glucose-lowering drugs in patients with type 2 diabetes: A meta-analysis. *Jama, 316*(3), 313. doi:10.1001/jama.2016.9400

Palta, P., Schneider, A. L., Biessels, G. J., Touradji, P., & Hill-Briggs, F. (2014). Magnitude of cognitive dysfunction in adults with type 2 diabetes: A meta-analysis of six cognitive domains and the most frequently reported neuropsychological tests within domains. *Journal of the International Neuropsychological Society*, *20*(3), 278-291. doi:10.1017/S1355617713001483

Partington, J. E., & Leiter, R. G. (1949). Partington's Pathway Test. *The Psychological Service Center Bulletin, 1,* 9–20.

Regard, M. (1981). *Cognitive rigidity and flexibility: A neuropsychological study.* Unpublished Ph.D. dissertation, University of Victoria.

Reijmer, Y. D., P.H.D., Brundel, M., M.D., de Bresser, J., MD, Kappelle, L. J., Leemans, A., P.H.D., & Biessels, G. J., M.D. (2013). Microstructural white matter abnormalities and cognitive functioning in type 2 diabetes: A diffusion tensor imaging study. *Diabetes Care, 36*(1), 137-44. doi:10.2337/dc12-0493

Reitan, R. M. (1955). The relation of the trail making test to organic brain damage. *Journal of Consulting Psychology, 19,* 393–394.

Rey, A. (1941). L'examen psychologique dans les cas d'encephalopathie traumatique. *Archives de Psychologie, 28,* 286–340.

Roberts, R. O., Knopman, D. S., Geda, Y. E., Cha, R. H., Pankratz, V. S., Baertlein, L., ... & Petersen, R. C. (2014). Association of diabetes with amnestic and nonamnestic mild cognitive impairment. *Alzheimer's & Dementia*, *10*(1), 18-26. doi: 10.1016/j.jalz.2013.01.001

Rojas, L. B. A., & Gomes, M. B. (2013). Metformin: An old but still the best treatment for type 2 diabetes. *Diabetology & Metabolic Syndrome, 5.* doi:10.1186/1758-5996-5-6

Ryan, C. M., van Duinkerken, E., & Rosano, C. (2016). Neurocognitive consequences of diabetes. *American Psychologist*, *71*(7), 563. doi:10.1037/a0040455

Sanz, C. M., Hanaire, H., Vellas, B. J., Sinclair, A. J., & Andrieu, S. (2012). Diabetes mellitus as a modulator of functional impairment and decline in Alzheimer's disease. the real.FR cohort. *Diabetic Medicine, 29*(4), 541-548. doi: doi:10.1111/j.1464-5491.2011.03445.x

Schuur, M., Henneman, P., Van Swieten, J. C., Zillikens, M. C., de Koning, I., Janssens, A. C. J. W., ... & van Dijk, K. W. (2010). Insulin-resistance and metabolic syndrome are related to executive function in women in a large family-based study. *European journal of epidemiology*, *25*(8), 561-568. doi:10.1007/s10654-010-9476-y

Scott, R., Langenberg, C., Sharp, S., Franks, P., Rolandsson, O., Drogan, D., … Wareham, N. (2013). The link between family history and risk of type 2 diabetes is not explained by anthropometric, lifestyle or genetic risk factors: the EPIC-InterAct Study. *Diabetologia*, *56*(1), 60–69. doi:10.1007/s00125-012-2715-x

Sjöström, L., Lindroos, A., Peltonen, M., Torgerson, J., Bouchard, C., Carlsson, B., . . . Swedish Obese Subjects Study, Scientific Group. (2004). Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. *The New England Journal of Medicine, 351*(26), 2683-2693. Retrieved from https://search-proquest-com.portal.lib.fit.edu/docview/67188465?accountid=27313

Smith, A. (1991). *Symbol Digit Modalities Test.* Los Angeles, CA: Western Psychological Services.

Smith, K. J., Béland, M., Clyde, M., Gariépy, G., Pagé, V., Badawi, G., ... & Schmitz, N. (2013). Association of diabetes with anxiety: a systematic review and meta-analysis. *Journal of psychosomatic research*, *74*(2), 89-99. doi: 10.1016/j.jpsychores.2012.11.013

Stokholm, J., Vogel, A., Gade, A., & Waldemar, G. (2005). The executive interview as a screening test for executive dysfunction in patients with mild dementia. *Journal of the American Geriatrics Society, 53*(9), 1577-1581. doi:10.1111/j.1532-5415.2005.53470.x

Umegaki, H., Hayashi, T., Nomura, H., Yanagawa, M., Nonogaki, Z., Nakshima, H., & Kuzuya, M. (2013). Cognitive dysfunction: an emerging concept of a new diabetic complication in the elderly. *Geriatrics & gerontology international*, *13*(1), 28-34. doi:10.1111/j.1447-0594.2012.00922.x

Van, D. B., Dekker, J. M., Nijpels, G., Kessels, R. P. C., Kappelle, L. J., De Haan, E.,H.F., . . . Biessels, G. J. (2008). Cognitive functioning in elderly persons with type 2 diabetes and metabolic syndrome: The hoorn study. *Dementia and Geriatric Cognitive Disorders, 26*(3), 261-9. doi:10.1159/000160959

Van der Heide, L.,P., Ramakers, G. M. J., & Smidt, M. P. (2006). Insulin signaling in the central nervous system: Learning to survive. *Progress in Neurobiology, 79*(4), 205-221. doi:10.1016/j.pneurobio.2006.06.003

Van ’t Riet, E., Dekker, J. M., Sun, Q., Nijpels, G., Hu, F. B., & van Dam, R. M. (2010). Role of Adiposity and Lifestyle in the Relationship Between Family History of Diabetes and 20-Year Incidence of Type 2 Diabetes in U.S. Women. *Diabetes Care*, *33*(4), 763–767. doi:10.2337/dc09-1586

Visser, P. J., Verhey, F., Knol, D. L., Scheltens, P., Wahlund, L. O., Freund-Levi, Y., ... & Bürger, K. (2009). Prevalence and prognostic value of CSF markers of Alzheimer's disease pathology in patients with subjective cognitive impairment or mild cognitive impairment in the DESCRIPA study: a prospective cohort study. *The Lancet Neurology*, *8*(7), 619-627. doi:10.1016/S1474- 4422(09)70139-5

Wang, K., Woung, L., Tsai, M., Liu, C., Su, Y., & Li, C. (2012). Risk of Alzheimer's disease in relation to diabetes: A population-based cohort study. *Neuroepidemiology, 38*(4), 237-244. doi:10.1159/000337428

Wild, S., Roglic, G., Green, A., Sicree, R., & King, H. (2004). Global prevalence of diabetes: Estimates for the year 2000 and projections for 2030. *Diabetes Care, 27*(5), 1047-53. Retrieved from https://search-proquest-com.portal.lib.fit.edu/docview/223068629?accountid=27313

Xu, W. L., Qiu, C. X., Wahlin, Å., Winblad, B., & Fratiglioni, L. (2004). Diabetes mellitus and risk of dementia in the Kungsholmen project A 6-year follow-up study. *Neurology*, *63*(7), 1181-1186.

Yates, K. F., Sweat, V., Yau, P. L., Turchiano, M. M., & Convit, A. (2012). Impact of metabolic syndrome on cognition and brain. *Arteriosclerosis, thrombosis, and vascular biology*, *32*(9), 2060-2067. doi:10.1161/ATVBAHA.112.252759

Yesavage, J. A., Brink, T. L., Rose, T. L., Lum, O., Huang, V., Adey, M. B., & Leirer, V. O. (1983). Development and validation of a geriatric depression rating scale: A preliminary report. *Journal of Psychiatric Research, 17,* 37–49.

Yeung, S. E., Fischer, A. L., & Dixon, R. A. (2009). Exploring effects of type 2 diabetes on cognitive functioning in older adults. *Neuropsychology, 23*(1), 1-9. doi:10.1037/a0013849

Yung-Cheng, H., Chien-Chin, H., Wei-Che, L., Tang-Kai, Y., Chi-Wei, H., Pei-Wen, W., . . . Chiu, N. (2014). Effects of metformin on the cerebral metabolic changes in type 2 diabetic patients. *The Scientific World Journal.* doi:10.1155/2014/694326