Spring 5-2021

The Relationship Between Kidney Function and Cognitive Function in Type II Diabetes

Erika Pacheco

THE RELATIONSHIP BETWEEN KIDNEY FUNCTION AND COGNITIVE

FUNCTION IN TYPE II DIABETICS

by

Erika Pacheco

A Thesis Submitted in Partial Fulfillment
of the Requirements for a Degree with Honors
(Zoology)

The Honors College

University of Maine

May 2021

Advisory Committee:
    Fayeza Ahmed, Ph.D. Assistant Professor of Psychology, Co-advisor
    Michael Robbins, Research Associate Professor of Psychology, Co-advisor
    Mark Haggerty, Rezendes Preceptor for Civic Engagement in the Honors College
    Leonard Kass, Associate Professor of Biological Sciences
    Benjamin King, Assistant Professor of Bioinformatics

ABSTRACT

Individuals who are diagnosed with Type II Diabetes Mellitus (T2DM) have shown decline in proper kidney function, ultimately leading to a form of chronic kidney disease (CKD) in about one- third of T2DM cases. Even though these are alarming rates of both diseases, these conditions are rarely studied concurrently. The general focus for this research is to identify whether or not kidney function in individuals with T2DM relates to their cognitive function. Specifically, is albuminuria in individuals with T2DM a risk for poorer cognitive performance? Maine Syracuse Longitudinal Study (MSLS) data for the 121 participants with T2DM was analyzed through correlational analysis and a series of hierarchical multiple regression analyses. Data analysis showed no evidence to support albuminuria as a risk factor for cognitive decline in T2DM. Evidence was found to support GFR as a risk factor for working memory and executive function decline.

Keywords: diabetes kidney function, cognitive function, albumin, GFR

DEDICATION

I dedicate this to my parents, Evan, Mimi, and Boopy.

ACKNOWLEDGMENTS

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

INTRODUCTION

Roughly 7%, 23 million, United States residents are diagnosed with Type II Diabetes Mellitus (T2DM). About 40,000 of those diagnosed lose their battle each year ("Diabetes Statistics", n.d.). According to the National Institutes of Health, kidney disease is another illness that has a considerable prevalence of about 30 million people in the United States ("Kidney disease statistics for the United States", n.d.). Individuals who are diagnosed with T2DM have shown decline in proper kidney function, ultimately leading to a form of chronic kidney disease (CKD). In most cases, CKD is a result of poorly managed diabetes (Rowley et al. 2017 and "Diabetic Kidney Disease", n.d.). Approximately one-third of those diagnosed with T2DM also have a form of kidney disease ("Diabetic Kidney Disease," n.d.). Even though these are alarming rates of both diabetes and kidney disease, these conditions are rarely studied concurrently. Based on the correlation between the two illnesses, CKD and T2DM should be researched in conjunction with one another to further our understanding of both conditions.

<u>Importance</u>

Many different illnesses take a toll on the cognitive ability of the human brain, however there is a gap in some research on the specific disease processes that cause these cognitive deficits. Therefore, it is important to keep researching different organ systems and how they impact brain health. Organs such as the kidneys and pancreas are very

important to keep the body functioning, but the brain is what makes a person an individual through cognitive processes, making it a very significant subject to research.

Although this thesis will focus primarily on the organ systems that contain the kidney and the brain, it is important to note at the outset that cognitive performance is best addressed from a comprehensive perspective that includes psychological and sociocultural systems. A biopsychosocial approach is useful in medical research because it combines three natural influences and helps us to conceptualize how issues occur, leading to preventive care. The sections that follow provide background information on the focal organ systems and variables used to index other relevant systems featured in this study.

<u>Kidney Structure and Function</u>

Kidneys are composed of about one million nephrons which are functional units of the kidneys. Nephrons consist of a tubule in the outer layer of the kidney and they eventually empty into the ureter. The tubule begins with the bowman's capsule, where water and solutes enter the nephron from the blood (filtration). The water and solutes then move to the proximal tubule in the outer cortex of the kidney which is the reabsorption site. Then, the tubule goes into the loop of Henle which passes through the center of the kidney and back (cortex). The loop of Henle is for reabsorption of more solutes than water. Then, the fluids go through the distal tubule (cortex) and are utilized for reabsorption and secretion to maintain homeostasis. Then with the collecting duct, multiple tubules join and descend to the ureter to empty into the bladder. The collecting duct also serves as a last stop for reabsorption of water (Radi et al., 2019).

In the human body, the kidneys consist of two organs on either side of the retroperitoneal space behind the abdomen. Waste excretion (filtration), regulation of pH, osmolarity, ion concentration, and secretion of hormones are just some of the functions kidneys are utilized for. The kidneys are responsible for maintaining water and electrolyte balance (homeostasis) in the body ("What is Chronic Kidney Disease?," n.d.).

<div align="center">Biomarkers of Proper Kidney Function</div>

Kidney function is measured through biomarker testing. A biomarker is defined as a detectable molecule that is present in specific functions. Biomarker testing has become more popular in recent years. By using blood and urine biomarkers in conjunction, the area of concern can be discovered in the nephron and be determined if it is a structural or functional issue (Menez et al., 2019). The three biomarkers of normal kidney function are glomerular filtration rate, creatinine, and albumin. Glomerular filtration rate (GFR) and creatinine is a blood test to see if the kidneys are working properly and is common in routine testing. GFR is generally estimated through creatinine levels. Creatinine is a waste product that comes from the blood and is excreted through the kidneys. Thus, the more creatinine in the blood, the less is excreted, indicating poor renal function. GFR is dependent on creatinine because it measures how creatinine is filtered out. Albumin is a protein in the liver that functions to keep fluids in the bloodstream and not allow fluids to leak into surrounding tissues (*Albuminuria*). It can also transport hormones and vitamins throughout the body and has been associated with insulin resistance (Bae et al., 2013). Detection of albumin in the kidneys can indicate insufficient blood flow to the brain ("What is albuminuria", n.d.).

Albumin. Albumin, the least researched biomarker of kidney function, is one of the major proteins synthesized in the liver. Its involvement in the bloodstream is crucial to transport necessary hormones and fluids around the body. Reduced levels of serum albumin is linked to malnutrition, risk of coronary artery disease, and cardiovascular issues. On the other hand, elevated albumin levels are associated with metabolic syndrome and obesity. As mentioned prior, insulin resistance is linked to the development of diabetes mellitus. That association may occur through oxidative stress and chronic inflammation which can adversely affect albumin, leading to insulin resistance (Bae et al., 2013).

Biomarker Levels. For GFR, the normal range is anything above 60 mL/min. A result below 60 mL/min can suggest kidney disease while anything below 15 mL/min is considered renal failure ("Explaining your kidney test results: A tool for clinical use.", n.d.) Creatinine levels vary depending on the weight and muscle mass of the individual. For the average adult woman a normal creatinine range is 0.6 to 1.1 mg/dL and the average adult male has a range of 0.9 to 1.3 mg/dL. If the test yields results higher than the normal range then kidney disease, diabetes, or heart failure may be the cause. If the values are low, liver failure is the most common cause ("Creatinine (Blood)", n.d.). GFR is determine through a formula that controls for age, gender, ethnicity, and creatinine levels. The equation is as follows;

GFR

$$= 141 \; x \min(\frac{S_{cr}}{k} \; 1)^a x \; max(\frac{S_{cr}}{k}, 1)^{-1.209} x 0.993^{Age} x 1.018 [if \; female] x 1.159 [if \; African \; American]$$

S_{cr} is serum creatinine level, k is 0.7 for females and 0.9 for males, and a is -0.329 for females and -0.411 for males (*Estimating glomerular filtration rate,* n.d.).

Serum albumin is measured through a blood test and normal results yield 3.4 to 5.4 g/dL, and an albumin urine test result of any amount of albumin below 30 mg/g is within normal limits ("Albumin (Blood)", n.d., & "What is albuminuria", n.d.). Albuminuria is when albumin detected is above the normal range, meaning there is an elevated amount of albumin in urine and can be used to diagnose CKD ("What is albuminuria", n.d.).

Blood Glucose

Glucose enters the body through carbohydrates in food. It travels through blood to cells that require it for energy. Thus, glucose is what gives the body energy and is regulated by the hormone insulin. Insulin is involved in transporting glucose in and out of cells. When there is an increase or decrease of blood glucose, issues occur. Hyperglycemia, increase of blood glucose levels, is caused by type I and type II diabetes mellitus. Altered mental status, excessive urination, dehydration, orthostatic hypotension, and motor coordination issues are responses that can occur from some hyperglycemia cases because of the high plasma osmolarity it causes. On the other hand, hypoglycemia is when there are low blood glucose levels. Usually caused by fasting or excessive exercise, hypoglycemia can lead to coma, loss of consciousness, altered mental status, and anxiety (McMillin et al., 1990; Hantzidiamantis et al., 2020).

Insulin Resistance. Insulin resistance in diabetics and non-diabetics is detrimental to physical health. Hypertension, oxidative stress, chronic inflammation, dyslipidemia and, if not already diagnosed, T2DM are a result from insulin resistance (Kosmas et al.,

2018). Nonetheless, T2DM individuals are more at risk for health deficits because insulin resistance is a leading cause of their lower cognitive performance (Stanford, 2014). Imbalance in the glucose metabolism is what turns insulin resistance into T2DM. The decrease in insulin response to glucose uptake targets the sensitive tissues of skeletal muscle and adipose tissue, leaning towards chronic inflammation (Kosmas et al., 2018).

Insulin Resistance and Comorbidities. CKD is categorized as an insulin resistance state where their risk for developing cardiovascular disease increases to almost 100% (Kosmas et al., 2018). When someone has unknown hypertension or does not properly treat it, insulin resistance is typically the outcome if not the cause. That is due to the impaired glucose uptake because hypertension disturbs the delivery of insulin and glucose to skeletal muscles. Vasoconstriction and activation of the sympathetic nervous system is also a major contributor to the development of cardiovascular disease because it results in structural changes and increase of fast twitch fibers (Salvetti et al., 1993). Cholesterol is another risk factor for cardiovascular disease that has a role with insulin resistance. Insulin resistance increases cholesterol synthesis and decreases cholesterol absorption (Gylling et al., 2010).

Diabetes Mellitus: Type I and II

Type I Diabetes Mellitus is generally diagnosed in adolescence or soon after. There is an issue with how the body produces insulin, so issues with blood glucose arise. The immune system attacks the pancreas and the cells that create insulin so the body stops producing it. Without the hormone insulin, glucose in the blood is not regulated and

leaves the body in a hyperglycemic state. To prevent this, insulin is taken regularly by those diagnosed. T2DM is when blood glucose is too high because there is not enough insulin in the body, or improper function of insulin. Insulin resistance is a leading cause of T2DM. Diet is a huge factor in blood glucose levels. The majority of those diagnosed with the condition are overweight or obese (Rowley et al., 2017).

Pre-Diabetes. The majority of individuals who are diagnosed with T2DM had a period of time prior to the diagnosis considered a "pre-diabetic" stage. During that time, there are hints of kidney disease from their biomarker levels. Usually that is detected by a slightly higher than 60 mL/min GFR test and slightly elevated creatinine. Albumin testing is not common in routine testing, but because of the abnormal results of creatinine and GFR, albumin would be the next step for proper diagnosis of diabetes or kidney disease. Early detection of pre-diabetes tends to slow the progression of T2DM which contributes to the popularity of biomarker testing (Dabla., 2010).

Cognition

Cognition refers to thinking processes, such as the ability to remember, think, and learn and is important for performing everyday tasks. Cognitive decline refers to a decrease in previous levels of functioning. Functional ability refers to the ability to perform everyday tasks ("Cognitive Health and Older Adults," n.d.). Examples of cognitive disorders are cognitive decline or impairment, vascular dementia, Alzheimer's disease, Huntington's disease, Parkinson's disease, and aphasia (Vascular dementia and vascular cognitive impairment, n.d.)

<u>Cognitive Domains</u>

Cognitive domains are the various types of cognitive functions (Harvey, 2019).

<u>Attention</u>. Attention refers to how an individual responds to and processes certain stimuli. An individual can have different attentional capacities to certain stimuli, and capacities differ from person to person. Attention can be altered from one stimulus to another, whether focused or selective, and is commonly known as concentration. The time a person can maintain concentration is referred to their sustained attention. If concentration can be split between different stimuli, it is considered divided. The most common mental issues associated with brain damage are issues with attention and concentration (Leclercq, Deloche, and Rousseaux, 2002; Lezak, 1995).

<u>Working Memory</u>. Working Memory holds information for a short period of time. Some researchers suggest that there are two subsets of working memory; language and visuospatial skills. Working memory is an extremely important memory system to have working properly since it aids in internalizing information and guiding behavior without the need for clues. Language is useful for working memory because of the phonological loop. Processing the words we hear and being able to repeat them aloud is helpful for retaining the information.

<u>Learning and Memory</u>. Memory is the process of encoding, storing, and retrieving information. There are multiple types of memory such as sensory, short term, and long term memory and different memory systems such as declarative and nondeclarative. Each

category is uniquely different and holds and encodes different amounts of information (Zlotnik et al., 2019). Learning is broadly defined as changes in behavior as a result of experience in the organism's environment. A person remembers an experience and uses that to react to other situations or for higher order processing such as abstraction (De Houwer et al., 2013).

The Declarative Memory System. The declarative memory system is divided into semantic and episodic memory. Semantic refers to fact based knowledge while episodic refers to the memory of individual-specific experiences, also known as autobiographical memory. Therefore requiring this memory system to be the ability to learn and remember information (Lezak, 1995).

The Nondeclarative Memory System. The nondeclarative memory system consists primarily of implicit memory. Nondeclarative memory involves unconscious remembering (i.e., buttoning a shirt). This mostly includes reactions to previous experiences and remembering how you felt towards them. This differs from episodic memory since it is not recalling the specific events of the situation, but the unconscious thoughts and reaction to it (Lezak, 1995).

Sensory memory. Sensory memory includes the information that is encountered throughout everyday life. It is what is captured through the senses: sight, taste, hearing, smell, and touch. Most of it is discarded and never kept in long-term memory (Camina et al., 2017).

Short-term memory. Short-term memory is a step above sensory memory in regard to storage. It holds on to a small amount of information, but not for an extended period of time. Sensory memories that are processed are moved onto short-term to be encoded by working memory. Short-term memory is extremely important because it allows for learning, reasoning, and understanding to occur because our memories can change based on new information. Retrieval and rehearsing information is useful to ensure that it can be processed and held onto in long-term memory from short- term memory. Overall, short-term memory is a temporary storage unit for learned information (Camina et al., 2017).

Long-term memory. Long-term memory is essentially unlimited. It is where information can get recalled and hold unconscious and conscious information encoded by short-term memory (Camina et al., 2017). The mechanisms of long-term memory are more at the molecular and cellular level than other parts of the brain. Neurochemical alterations at the synapse and neurons account for the differences in amount of neurotransmitters released or reuptaken when remembering long-term stored information. There is not one part of the brain responsible for long-term memory (Lezak, 1995).

Language. This is the ability to understand, process, and produce verbal functions. Learning and memory are major contributors to language since recall is needed to remember the name of an object that you once learned about. Typically, material learned in childhood (i,e., alphabet, numbers, months) that is repeated throughout life is known as automatism. In order to test for issues with language acquisition, word list learning tests

are typically used since this engages short-term memory and learning capacities. That is, immediate recall testing is insufficient because many older people (typical cognitive study participants) do have the same immediate memory span as young adults. Thus, simple tests such as digit sequence learning are inadequate (Lezak, 1995).

Visuospatial Skills. Visuospatial skills is defined as the ability to imagine and visualize objects and identify differences between similar objects. It is how we visually interact with the world (Possin, 2010). Visuospatial skills use working memory to visually remember an experience and play it back to complete different tasks and actions (Valler et al., 2002). Drawing construct objects such as trees or flowers is an example of a visuospatial skill (Mervis et al., 1999). Impairment in visuospatial skills are one of the first symptoms in neurodegenerative diseases (Possin, 2010).

Executive Function. This domain encompasses the several higher-order processes involved in planning, monitoring, and implementing complex, multi-step tasks. Executive function is broadly defined with various definitions, but core functions include set-shifting (unconscious switching of attention between tasks), response inhibition (suppressing inappropriate actions), planning and problem-solving (Mostofsky et al., 2008). If executive function is lost, it is more obvious to notice cognitive function deteriorating since they have issues socially and completing tasks that were natural to them prior. Usually, family members and friends are the first to notice. However, if there is cognitive decline but executive function is intact, there can be a considerable amount of impairment until daily functioning is disrupted (Lezak, 1982)

Emotion. Emotion is a conscious awareness of a mood perceived from an experience. There are seven emotions: anger, disgust, contempt, happiness, sadness, surprise, and fear. Memory, attention, reasoning, learning, abstraction, and perception are all influenced by emotion. It can serve as a motivator for motor functions as well. Typically, physical and behavioral changes are a response to a change of emotion (Lezak, 1995).

Abstraction and Reasoning. Abstraction is a distinct characteristic of human beings. It is the ability to concentrate and reason on a higher level without the need for concrete information. For example, interpreting statistical results uses abstraction ("On the cognitive process of abstraction," 2016).

Processing Speed. Processing speed refers to the time it takes to complete a mental task. It is dependent on attention, memory, language, and visuospatial skills. A slower processing speed is common in older adults, diagnosed autism, injury, or cognitive decline or impairment (Holdnack et al., 2016). However, the processing speed decline in older adults is not the same as impaired processing speed from injuries or neurological disorders. For healthy adults, the processing ability is still there, but the performance is poorer. While for injuries or neurological disorders, there is a mechanism that is not functioning correctly, leading to the slower processing speed.

Motor Function. Motor function and coordination occurs anterior to the precentral area in the brain (Damasio et al., 2003; Eslinger et al., 2001; Kolb et al., 1996).

Damage to that area results in incoordination, strength, or discontinuous movements, but does not completely inhibit the motor action from occurring (Jason., 1990; Mesulam., 2000). Motor function can be separated into fine and gross functions. Gross motor function implies a large muscle group working to complete a task (i.e. walking) while fine motor movement involves small muscle groups (i.e. writing with a pencil).

<center>Theories of Cognitive Aging</center>

The brain has been shown to change structurally and functionally as it ages. The connectivity between the anatomical structures of the brain is recorded to decrease throughout the years, resulting in changes to functional connectivity which relates to cognitive decline. Those alterations have been shown to decline linearly in regard to the number of connections and total fiber count (Betzel et al., 2014). Research has shown that brain function is dependent on the path length and connected nodes. The increase in neural pathways leads to the increases in connectivity between structures.. In older adults, there fewer are higher order connections between networks than compared to younger adults (Betzel et al., 2014). The loss of some connected networks or reduced white matter integrity is also a result of cognitive decline from aging (Krechner et al., 2012).

The hemispheric asymmetry reduction in older adults (HAROLD) model of cognitive aging states that cognitive performance is less lateralized in older adults than younger adults, reorganizing functional ability when needed. Neural networks and circuits are developed to create more pathways of function to complete given cognitive

tasks. Episodic, semantic, and working memory are the cognitive domains that are highlighted in the HAROLD model (Cabeza, 2002).

Another theory of cognitive aging is known as the Compensation-Related Utilization of Neural Circuits Hypothesis (CRUNCH) model. This model is complementary to the HAROLD model. That hypothesis suggests that as a person ages, more neural circuits are needed to complete a task compared to a younger adult. That was supported by areas of the brain being activated during a task in older adults and not in younger adults. This finding leads to the conclusion that older brains function differently than younger ones. Those active sites are also considered to be overactivating or compensating more than they should in order to complete the tasks due to cognitive decline (Reuter-Lorenz et al., 2008).

The scaffolding theory of aging (STAC) is similar to the CRUNCH model. They both suggest that as the brain ages, it begins to function differently. Scaffolding, which is present throughout life, is the creation of alternative neural circuits to complete a cognitive task. Research suggests that without the development of new neural connections, the brain will decline more rapidly and deteriorate, but it is strengthened by cognitive engagement and exercise (Park et al., 2009).

<center>Lifestyle Factors and Cognition</center>

Mediterranean Diet

The Mediterranean Diet (MedDiet) has recently gained popularity in the last 20 years due to the health benefits it provides (Lăcătușu et al., 2019). In the 1960s, the

MedDiet was first defined and practiced in Greece and Italy mostl, giving the diet it's name since those countries are off of the Mediterranean Sea (Davis et al., 2015 & Lăcătușu et al., 2019). The MedDiet mainly consists of vegetables, legumes, nuts, seeds and fruits with olive oil being the main fat and seafood being moderately consumed. Dairy and alcohol are also not prohibited, but are not a focal point in the diet (Lăcătușu et al., 2019).

Health Benefits of the Mediterranean Diet. Ancel Keys was the first to acknowledge the importance of the Mediterranean diet. He was studying starvation's effect on the human body after World War II and noticed that places that had diets that did not follow the typical high-fat and high-protein standards had significantly less heart issues. Famine may have been the cause for the switch in diets, but it was evident that the diet was effective for avoiding cardiovascular casualties because places without a famine did not show a difference from before the war (Lăcătușu et al., 2019).

The Seven Countries Study was created by Keys to investigate his observation and produce a cause- effect relationship. When followed, MedDiet showed that there was a decreased risk in developing cardiovascular disease (Lăcătușu et al., 2019).

Cognitive Health Benefits of the Mediterranean Diet. Besides the cardiovascular health benefits, researchers suggest that when an individual commits to a strict following to the MedDiet, they are less susceptible to cognitive issues and decline at a lower pace compared to individuals who do not follow the diet. There are also claims that the MedDiet can improve cognitive performance over time (Féart et al., 2010). The cereals,

dietary antioxidants, wine, and macronutrients involved in the MedDiet are the most protective against cognitive decline (Panza et al., 2004).

Mediterranean Diet and Kidney Function. The MedDiet was shown to be associated with kidney function and those who followed it had reduced eGFR compared to those who did not follow the diet. Yielding that the diet is protective over the kidneys and can be beneficial for CKD patients as well in terms of survival (Khatri et al., 2014 &). However, due to the recent discovery of the MedDiet, there is not much research on its impact outside of cardiovascular health. Therefore, the research done in this study will hopefully help shed light on the impact on MedDiet on CKD and T2DM.

Mediterranean Diet and Type II Diabetes. Adhering to a MedDiet has been shown to lower the risk of developing T2DM by about 20% compared to other diets such as DASH. The American Diabetes Association described the MedDiet as beneficial because it also promotes an overall healthy lifestyle which reduces the risk of hypertension, a risk factor for T2DM (Martín-Peláez et al., 2020).

Physical Activity

A healthy diet is not the only factor that controls physical health, physical activity and exercise is crucial for staying healthy. Better performance is shown on cognitive testing from individuals who intentionally make exercise a part of their daily routine than those who do not (Clare et al., 2003). Besides physical health, exercise and physical activity has been shown to alleviate many mental health issues. Low self esteem, anti-

socialism, and insomnia are some of the most common issues that seem to resolve once exercise is incorporated into daily life (Sharma et al., 2006).

Socioeconomic Status

Education. Less education is related to earlier and more severe cognitive decline. Higher education has shown to hold a positive correlation with cognitive function compared to individuals with less education when doing activities (Park et al., 2018). One theory that a lot of researchers support is that higher education leads to better health choices. For example, more education on physical health (i.e. doctors and nurses) may lead to better eating and exercise habits which ultimately lead to better brain health. Higher education may also hide mild cognitive deficits more easily than those without higher education (Lee et al., 2003).

Household Income. Lower income has been associated with numerous mental health issues. When exposed to low income for over twenty years, the effects can be detrimental and irreversible. For example, lower income is related to higher levels of stress which can heavily impact physical health which leads to further cognitive issues. Evidence suggests that processing speed is the cognitive measure that is the most impacted by low income (Zeki AlHazzouri et al., 2016).

Social Activity. Relationships and social activity are beneficial for slowing or preventing cognitive decline. Support, control, and comfort of others reduces stress and reduces physical health issues (Umberson et al., 2010).

Cognitive Performance with Type II Diabetes

Per multiple literature review articles, cognitive measures of recall, trail making, word associations, and sequencing were the areas where the differences between patients with CKD or T2DM scored lower compared to their controls (Li et al. 2018., Passos et al., 2018, Pei et al., 2018, Sacre et al., 2019, & Småbrekke et al, 2019).With insulin resistance, metabolic syndrome and cardiovascular disease follow along with the development of T2DM (Kendall et al., 2002). Researchers suggest that the metabolic and vascular issues that arise with T2DM is the source for cognitive decline in that community (Karvani et al., 2019). Hypertension, insulin resistance, vascular inflammation, lipid disorders, hypoglycemia and hyperglycemia are examples of metabolic and vascular issues that can result from T2DM. Glucose intolerance is a direct result from insulin resistance, impairing glucose uptake in the body, leading to more metabolic issues such as obesity. (Kendall et al., 2002, Zilliox et al., 2016). In patients with and without diabetes comorbid with cardiovascular disease, insulin resistance is related to their lower cognitive performance and cognitive decline (Lutski et al., 2017).

Cognitive Performance with Kidney Disease

Chronic Kidney Disease is a high risk factor for lowered cognitive performance. The decline in cognition is more apparent in those with end-stage renal disease. Cerebrovascular disease is also more apparent in those with CKD which can increase cognitive decline. (Torres et al., 2017). Although cognitive deficits can prompt dementia, CKD often leads to a mild form of decline (Elias et al., 2013). Diminished white matter integrity in CKD patients promotes cognitive decline.

Cognitive Performance with Type II Diabetes and Kidney Disease

   Zhang and colleagues (2016) investigated kidney function in a T2DM sample with known cognitive impairment and discovered that elevated albumin and creatinine levels in urine were higher in those with cognitive impairment compared to those without (Zhang et al., 2016). In the cognitive domains of processing speed, memory, attention and executive function, participants with diagnosed T2DM performed less well. Also, they showed brain atrophy, lower total white and gray matter compared to non-diabetics (Moheet et al., 2015).

Mechanisms Proposed for Associations

   One area for which research on T2DM and CKD comorbidity is important is with regard to cognitive performance. Therefore, the brain, where cognitive processing occurs will be included in the focus of this research. Because of the T2DM and CKD prevalence, it is important to emphasize the significance those conditions have on the human brain. When the kidneys and the brain are initially considered, they may not necessarily seem complementary, but evidence suggests a direct relationship (Sacre et al., 2019). When one of these organ systems is damaged, multiple organ dysfunction syndrome occurs leaving detrimental effects on the human body. Adverse reactions from damage highly target the hippocampus because of alterations to the blood brain barrier from ischemic renal injury or CKD (Malek, 2018). Albuminuria has also been correlated to the breakdown of the blood brain barrier (Burns et al., 2018). Dementia diagnoses are increased in the CKD population compared to those without any stage of kidney disease (Dotiwala et al., 2020).

The blood-brain-barrier is a tight boundary made of endothelial cells , membranes, and astrocytes that keeps the fluid of the brain in the brain while keeping out cerebral capillary blood and while regulating the cerebrospinal fluid. Due to its anatomy, only select molecules can advance through the tight junctions between the cells. However, damage can weaken the barrier and allow for unwanted molecules to pass through and damage the brain (Dotiwala et al., 2020).

In addition to T2DM, CKD is known to have a negative effect on cognitive performance (Torres et al., 2017). Torres (2017) states that chronic kidney disease is a high risk factor for lower cognitive performance compared to those without chronic kidney disease and is more apparent in individuals with end stage renal disease (ESRD) (Torres et al., 2017). However, not all stages of kidney disease and all those diagnosed with T2DM show decline on cognitive testing. Typically, those who are diagnosed with either illness, CKD and T2DM, perform worse on memory, processing speed and recall cognitive testing compared to their undiagnosed counterparts. Some researchers attribute the cognitive decline in T2DM to insulin resistance and metabolic syndrome (Bae et al., 2013). Other studies have concluded that lower cognitive performance in patients with kidney disease may be from deficient blood flow to the brain secondary to albuminuria (Sacre et al., 2019). Some researchers infer that because of the similar vasculature of the kidney and brain, the two should be studied as a direct and unified pathway. However, other researchers suggest the two organs are indirectly linked such that if the kidneys are not properly functioning, there is a decreased blood flow rate to the brain, resulting in possible cognitive decline (Sacre et al., 2019).

<u>Albuminuria</u>

Those with Albuminuria scored worse on cognitive testing, especially in memory and processing speed (Sacre et al., 2019; Passos et al., 2018). Albuminuria was deemed a dementia risk factor due to its prevalence in those who performed less well on cognitive tests. (Deckers et al., 2017; Wei et al., 2017). Albumin levels were almost double in those with cognitive impairment than those without. Cerebrovascular lesions from CKD can correlate to the higher risk of cognitive disorder development (Wei et al., 2017). Breakdown of the blood brain barrier is also a concern with albuminuria due to its association with vascular endothelial function. If that occurs, cognitive changes may be a result along with white matter changes which can be noted on a brain MRI (Burns et al., 2018).

<u>Knowledge Gap and Aims</u>

There are two major knowledge gaps: the relationship between kidney and cognitive function and why cognitive processing is affected by kidney disease in T2DM. By keeping focus on one population, T2DM, and researching their kidney and cognitive functioning, answers may derive. The connection of the brain and the kidney will be investigated through kidney biomarkers, specifically albumin, and cognitive domains with a focus on visual spatial, working memory, verbal memory and scanning and tracking composites of the MSLS. Finding a relationship will help fill knowledge gaps where kidney health directly impacts cognitive function in an at risk community T2DM. The general focus for this research is to identify whether or not kidney function in T2DM relates to their cognitive performance. Specifically, the hope is to determine if

albuminuria in T2DM is a risk for poorer cognitive performance.

METHODS

Maine- Syracuse Longitudinal Study

For this research, the Maine-Syracuse Longitudinal Study (MSLS) provided the data and the cognitive domains. The domains of interest include composites of working memory, scanning and tracking, verbal memory and executive function.

The Maine- Syracuse Longitudinal Study (MSLS) is a study of aging, cardiovascular disease, and cognitive performance. Dr. Merrill F. Elias and Dr. David H. P. Streeten began the study in 1974 with a focus on hypertension and cognitive performance by collecting data with medical examination, cognitive test batteries and questionnaires from participants in central New York. Since 1976, the MSLS has been a part of the Department of Psychology at the University of Maine with co-directors Dr. Elias and Dr. Michael Robbins. Dr. Fayeza Ahmed has been a part of the MSLS team as an associate director since 2018 (Elias, 2016).

Participants

The MSLS archive holds a collection of data from thousands of individuals from Central New York from when they began the study, at any age above 18. If participants chose to keep participating, data collection continued through their adult years (Elias 2016). The MSLS is a very useful tool when studying cognitive function because it has data on individuals as they age through multiple data collections. An individual's cognitive performance can be compared to an earlier data set to see if there is decline in an area.

There were seven waves of data collection making up a rich database for cross-sectional and longitudinal analyses. There are over 2000 community participants, of whom over 1000 provided longitudinal data. The last two waves of MSLS, waves 6 and 7, have the most information on diabetes, strokes, physical activity, nutrition, APOE-e4 genotype, obesity, smoking, and homocysteine and are also the two bigger datasets. For this research Wave 6 data was analyzed cross-sectionally and T2DM participants were categorized based on serum albumin levels. Because of the limited number of T2DM participants at Wave 6 and the number of them lost to attrition at Wave 7, was not be examined longitudinally.

	1975		1981		1986		1991		1996		2001		2006
	W1		**W2**		**W3**		**W4**		**W5**		**W6**		**W7**
C1	E1	→	E2	→	E3	→	E4	→	E5	→	E6	→	E7
C2			E1	→	E2	→	E3	→	E4	→	E5	→	E6
C3					E1	→	E2	→	E3	→	E4	→	E5
C4							E1	→	E2	→	E3	→	E4
C5									E1	→	E2	→	E3

Figure 2: MSLS seven waves.
This figure represents the seven waves of data collection for MSLS. On the left side of the figure there are sections labeled C1 to C5 and those stand for the recruitment cohorts, so the time that community participants were recruited to participate in the study. The Ws on the top in bold stand for the different waves, there were seven and correspond with funding periods from NIH. The Es represent the examination number for a given cohort and given wave.

Covariates and Measurements

With the specific aim of this research being finding evidence to support albuminuria as a risk factor for poorer cognitive performance in T2DM, variables were separated into predictor variables, outcome variables, and covariates.

Outcome variables were composite indices of cognitive function: i.e., Working

Memory, Visual Spatial Organization, Executive Function, Scanning and Tracking, and

Verbal Memory, determined through factor analysis (Elias et al., 2006). Each of the

composites had specific cognitive measures to determine performance (Figure 2) and for

each composite higher values indicate better performance. For Scanning and Tracking,

cognitive measures included the Trail Making Test, parts A and B, digital symbol

substitution, and symbol search. The Verbal Memory composite included logical memory

(immediate and delayed recall) and the Hopkins Verbal Learning Test. The Visual

Spatial Organization composite included measures of visual reproductions (immediate

and delayed recall), matrix reasoning, block design, object assembly, and Hooper visual

organization. Working memory was assessed through measures of digit span forward and

backward, letter-number sequence, and controlled oral word associations (Figure 2).

Executive function was assessed through clock drawing tasks and Controlled Oral Word

Association Test (COWA).

Visual Spatial Organization Composite

Visual Reproduction- Immediate Recall
Visual Reproduction- Delayed Recall
Matrix Reasoning
Block Design
Object Assembly
Hooper Visual Organization

Verbal Memory Composite

Logical Memory- Immediate Recall
Logical Memory- Delayed Recall
Hopkins Verbal Learning Test

Working memory Composite

Digit Span Forward
Digit Span Backward
Letter- Number Sequence
Controlled Oral Word Associations

Scanning and Tracking Composite

Trail Making A
Trail Making B
Digit Symbol Substitution
Symbol Search

Similarities

MMSE

Figure 3: MSLS Outline of cognitive composites.
Outline of the cognitive composites used for MSLS data analyses. For this research, the composites of interest are highlighted in the gold box. The measures used to determine cognitive function are listed under each composite.

Demographic variables used in the study were age (in years), education (in years), gender (0 = male; 1 = female) and ethnicity (African American = 1; other = 0). The biomarkers of kidney function, estimated GFR, creatinine (mg/dl) and albumin (G/DL), were the predictor variables. The eGFR was estimated using the four-variable (serum creatinine, age, sex, ethnicity) Modification of Diet in Renal Disease (MDRD) study formula (mL/min/1.73 m^2) (Levey et al, 1999; Rule, et al., 2004).

The covariates included hypertension, body mass index (BMI) (kg/m^2), and low density lipid (LDL) cholesterol (mg/dl). Hypertension was defined as systolic blood pressure $\geq$ 140 mmHg and/or diastolic blood pressure $\geq$ 90 mmHg and/or anti-

hypertensive medications, and coded as 0 = no and 1 = yes. Systolic and diastolic blood pressure values were averaged from 5 assessments each while recumbent, standing and sitting.

Those variables were chosen because they have a known effect on either cognitive ability or diabetes and kidney function.

Test Procedures at Wave 6

Participants were mailed psychological inventories to complete and bring to their examination at the study center. They were admitted to the study center following a fast from midnight. A blood sample was drawn by a licensed phlebotomist, and a light breakfast, including decaffeinated coffee or tea, was served. Breakfast was followed by a physical examination, including a detailed medical history, measurement of weight and height, and blood pressure assessment. This was followed by administration of the cognitive test battery by a psychological examiner (Elias et al., 2006).

The fasting blood samples were collected in serum separator tubes (gel and clot activator) for serum determinations. All blood samples were immediately sent on ice to Centrex Clinical Laboratories, Syracuse, NY, for processing and determination of the lipid profile (including Low Density Lipid (LDL) cholesterol), glucose, and creatinine. Serum creatinine was determined using a 2-point rate test type on a Johnson and Johnson Vitros Instrument. Coefficients of variation for these procedures were less than 5.0%. Serum samples used for determination of albumin were stored at - 40°C prior to batch shipment on dry ice to Quest Diagnostics, Pittsburgh, PA for analysis at the end of wave 6.

<u>Statistical Analysis</u>

Descriptive statistics were examined for all of the variables used in the study. In order to assess bivariate associations between variables, correlation coefficients were computed comparing demographic information, predictor variables, covariates, and outcome variables. Where bivariate correlations between predictor and outcome variables were statistically significant, a series of hierarchical multiple regression models was used to determine whether the significant associations remained with adjustment for demographic variables and covariates.

RESULTS

Demographic Information

Table 1: *Demographic Information*

	Frequency	Minimum	Maximum	Mean	Standard Deviation
Age (In years)		38	93	64.04	11.09
Gender					
Male	58				
Female	63				
Ethnicity					
African American	21				
Other	100				
Education (in years)		8	20	13.74	2.67
Albumin		3.30	5.00	4.145	.30
Creatinine		53	203	92.01	30.42
GFR		33	137	75.41	22.53
>60	27				
[a] BMI		20	66	33.27	7.44
Cholesterol		95	367	189.80	45.58
Hypertension					
No diagnosis	17				
Diagnosis	104				
GFR		33	137	75.41	22.53

Notes: $N = 121$
[a] BMI = Body Mass Index

    There were a total of 121 T2DM participants in this analysis. Demographic information is presented in Table 1. The minimum age recorded was 38 and the maximum was 93, the average being 64.04 and median being 65. There were 58 males and 63 females. For ethnicity, 100 participants identified as "Other" and 21 identified as "African American". The mean education, in years, was 13.7 with 8 being the minimum and 20 being the maximum. Albumin levels were in the normal range for all participants. The minimum level of albumin recorded was 3.30 and the maximum recorded was 5.00, averaging at 4.14. Creatinine ranged from 53 to 203, with a mean

of 92.01 and standard deviation of 30.42. GFR ranged from 33 to 137, with a mean of 75.4 and standard deviation of 22.5. BMI had a minimum of 20 and maximum of 66 while averaging at 33.27. LDL Cholesterol ranged from 95 to 367 with a mean of 189.80. Out of the 121 participants, only 17 did not have a diagnosis of hypertension.

Bivariate Correlations

Four separate bivariate correlation analyses were run in this study. One analysis related demographic variables, predictor variables and covariates (Table 2). Predictor variables had significant correlations with several of the demographic variables and covariates. Albumin was significantly and negatively correlated with gender (males), ethnicity(non-African Americans), and lower BMI. Creatinine was significantly and negatively correlated with gender and positively correlated with hypertension. GFR was significantly and negatively correlated with creatinine, gender, and age.

There were also significant correlations among demographics variables and covariates. Age showed significant negative correlations with ethnicity, BMI, and cholesterol while holding a significant positive correlation with diagnosed hypertension. Gender had a significant positive correlation with cholesterol, and ethnicity had significant positive correlations with education and BMI.

The second bivariate correlation analysis was between the demographic and cognitive outcome variables (Table 3). Each of the five cognitive outcome variables was significantly and positively correlated with years of education. Visual Spatial Organization was also significantly but negatively correlated with age, gender and ethnicity. Verbal Memory was significantly and negatively correlated with age only. Working Memory was significantly and negatively correlated with ethnicity only.

30

Scanning Tacking and Executive function were both significantly and negatively correlated to age and ethnicity.

The third bivariate correlation analysis related predictor variables to covariates (Table 4). Albumin was significantly and negatively correlated to BMI. Creatinine and GFR were strongly negatively correlated and, respectively, held significant positive and negative correlations to diagnosed hypertension.

The last bivariate correlation analysis related predictor variables to the cognitive outcome variables (Table 5). Neither Verbal Memory nor Scanning Tracking showed significance in relation to any of the predictor variables. Visual Spatial Organization was significantly and positively correlated to albumin and GFR. Both Working Memory and Executive Function showed significant negative correlations to creatinine, but positive correlations to GFR.

Table 2
Pearson Correlation Coefficients: Demographic Variables with Predictors and Covariates

	Albumin	Creatinine	GFR	Age	Gender	Ethnicity	Education	BMI	Cholesterol	Hypertensi
Albumin		-.12	.15	-.06	-.21*	-.20*	.08	-.25**	.09	-.03
Creatinine			-.83**	.09	-.34**	.09	.05	.10	-.14	.19*
GFR				-.31**	-.02	.09	-.09	-.05	.13	-.23*
Age					.04	-.33**	-.08	-.31**	-.22*	.18*
Gender						.18	-.09	.11	.19*	-.06
Ethnicity							-.19*	.43**	.01	.06
Education								.02	-.12	-.10
BMI [a]									-.01	.13
Cholesterol [b]										-.13
Hypertension [c]										

Notes: $N = 121$ for all variables.
[a] BMI = Body Mass Index, measured by kg/m^2
[b] Cholesterol was measured by mg/dL
[c] Hypertension was measured by diagnosis
*p < .05; ** p< .01

Table 3
Pearson Correlation Coefficients: Demographic Variables with Cognitive Variables

	Visual Spatial	Verbal Memory	Working Memory	Scanning Tracking	Executive Function
Age	-.48**	-.32**	-.12	-.44**	-.31**
Gender	-.25**	-.05	-.08	-.09	-.17
Ethnicity	-.25**	-.09	-.29**	-.27**	-.30**
Education	.43**	.30**	.27**	.40**	.34**

*p < .05; ** p< .01

Table 4
Pearson Correlation Coefficients: Predictors with Covariates

	Albumin	Creatinine	GFR	BMI	Cholesterol	Hypertension
Albumin		-.12	.15	-.25**	.09	-.03
Creatinine			-.83**	.10	-.14	.19*
GFR				-.05	.13	-.23*
BMI					-.11	-.13
Cholesterol						.13
Hypertension						

*p < .05; ** p< .01

Table 5
Pearson Correlation Coefficients: Predictor with Cognitive Variables

	Albumin	Creatinine	GFR	Visual Spatial	Verbal Memory	Working Memory	Scanning Tracking	Executive Function
Albumin		-.12	.15	.21*	.05	.09	.15	.09
Creatinine			-.83**	-.08	-.04	-.19*	-.14	-.22*
GFR				.22*	.09	.18*	.17	.25**

*p < .05; ** p< .01

Hierarchical Multiple Regressions

There were six hierarchical regression models used for this research, with the cognitive variables that were significantly correlated with kidney function variables used separately as an outcome variable in each model. For the first four hierarchical models (Tables 6-9), demographic variables were entered in the first step of the model. The

second step added either albumin values or GFR values. The first model related albumin to the Visual Spatial Organization domain, but albumin was not significantly associated with visual spatial scores after accounting for variance from the demographic variables (Table 6). The next three regression models related GFR to Visual Spatial Organization, Working Memory, and Executive Function, respectively. GFR remained a significant predictor for the domains of Working Memory (β=.18, t=2.03 (114), p<.05) and Executive Function (β=.19, t=2.42 (114), p<.05), but not for Visual Spatial Organization (Tables 7-9). In order to examine whether other important health variables (BMI, cholesterol, and hypertension) influenced the relationship we found between GFR and the two cognitive domains (Working Memory and Executive Function), two additional hierarchical regression analyses were run with demographic variables entered into the first step, health variables entered into the second step, and GFR added to the last step (Tables 10-11). For Working Memory, GFR continued to account for significant variance (β=.21, t= 2.31 (111), p<.05; Table 10). For Executive Function, GFR also continued to account for significant variance (β=.19, t=2.38 (111), p<.05: Table 11).

Most of the correlations have relatively small strengths of association, but age and education did show strong associations, particularly to the Visual Spatial (R^2 =.23, R^2 =.18) and scanning tracking (R^2 =.19, R^2 = .16) cognitive domains. Rounding, age and education had about 20% common variance with these cognitive variables (Table 3). For the adjusted R^2 in the hierarchical multiple regression of executive function, covariates, and GFR, the model is accounting for one-third (adjusted R^2 = .33) of the variability in executive function scores (Table 11).

Table 6

Hierarchical Multiple Regression of Visual Spatial and Albumin

Note: N = 120. Step 1: R = .73. R^2 = .530. Adjusted R^2 = .513. standard error of estimate = .80. p < 0.01.
Step 2: R = .730. R^2 = .533. Adjusted R^2 = .512. standard error of estimate = .80. p < 0.01.

Table 7

Hierarchical Multiple Regression of Visual Spatial and GFR

	Step	β	t	p
1	Age	-.57	-8.28	< .01
	Education	.31	4.75	< .01
	Gender	-.13	-2.03	< .05
	Ethnicity	-.35	-4.97	< .01
2	Age	-.54	-7.42	< .01
	Education	.33	4.93	< .01
	Gender	-.13	-2.02	< .05
	Ethnicity	-.35	-4.94	< .01
	GFR	.11	1.57	> .05

Note: N = 120. Step 1: R = .73. R^2 = .530. Adjusted R^2 = .51. standard error of estimate = .80. p < .05. Step 2: R = .74. R^2 = .54. Adjusted R^2 = .52. standard error of estimate = .79. p < .05.

Table 8

Hierarchical Multiple Regression of Working Memory and GFR

	Step	β	t	p
1	Age	-.21	-2.22	< .05
	Education	.18	2.04	< .05
	Gender	.00	.00	> .05
	Ethnicity	-.32	-3.39	< .01
2	Age	-.14	-1.50	> .05
	Education	.20	2.29	< .05
	Gender	.002	.02	> .05
	Ethnicity	-.31	-3.35	< .01
	GFR	.18	2.03	< .05*

Note: N = 120. Step 1: R = .40. R^2 = .160. Adjusted R^2 = .131. standard error of estimate = .97. p < 0.05.
Step 2: R = .44. R^2 = .190. Adjusted R^2 = .15. standard error of estimate = .95. p < .05.

	Step	β	t	p
1	Age	-.57	-8.28	< .01
	Education	.31	4.75	< .01
	Gender	-.13	-2.03	< .05
	Ethnicity	-.35	-4.97	< .01
2	Age	-.56	-8.12	< .01
	Education	.31	4.73	< .01
	Gender	-.12	-1.85	> .05
	Ethnicity	-.34	-4.71	< .01
	Albumin	.06	.90	> .05

Table 9

Hierarchical Multiple Regression of Executive Function and GFR

	Step	β	t	p

Step		β	t	p
1	Age	-.41	-4.98	< .01
	Education	.22	2.76	< .01
	Gender	-.07	-.82	> .05
	Ethnicity	-.38	-4.43	< .01
2	Age	-.35	-4.06	< .01
	Education	.24	3.09	< .01
	Gender	-.06	-.81	> .05
	Ethnicity	-.370	-4.42	< .01
	GFR	.19	2.42	< .05*

Note: N = 120. Step 1: R = .57. R^2 = .32 Adjusted R^2 = .295. standard error of estimate = .89. p < 0.05. Step 2: R = .59. R^2 = .35. Adjusted R^2 = .32. standard error of estimate = .87. p < .05.

Table 10
Hierarchical Multiple Regression of Working Memory, Covariates, and GFR

	Step	β	t	p
1	Age	-.21	-2.22	< .05
	Education	.00	.00	> .05
	Gender	-.32	-3.40	< .01
	Ethnicity	.18	2.04	< .05
2	Age	-.23	-2.23	< .05
	Education	.02	.22	> .05
	Gender	-.37	-3.61	< .01
	Ethnicity	.16	1.74	> .05
	BMI	.08	.84	> .05
	Cholesterol	-.11	-1.24	> .05
	Hypertension	.001	.01	> .05
3	Age	-.16	-1.52	> .05
	Education	.03	.28	> .05
	Gender	-.38	-3.75	< .01
	Ethnicity	.18	2.02	< .05
	BMI	.11	1.14	> .05
	Cholesterol	-.12	-1.33	> .05
	Hypertension	.04	.40	> .05
	GFR	.21	2.31	< .05*

Note: N = 120. Step 1: R = .400. R^2 = .16. Adjusted R^2 = .13. standard error of estimate = .97. p < 0.05. Step 2: R = .42. R^2 = .18. Adjusted R^2 = .13. standard error of estimate = .97. p < .05. Step 3: R = .46. R^2 = .22. Adjusted R^2 = .16. standard error of estimate = .95. p < .05.

Table 11
Hierarchical Multiple Regression of Executive Function, Covariates, and GFR

	Step	β	t	p
1	Age	-.41	-4.98	< .01
	Education	-.07	-.82	> .05
	Gender	-.38	-4.43	< .01
	Ethnicity	.22	2.76	> .05
2	Age	-.45	-4.99	< .01

	Variable	B	t	p
	Education	-.04	-.439	> .05
	Gender	-.39	-4.21	< .01
	Ethnicity	.20	2.44	< .05
	BMI	-.02	-.20	> .05
	Cholesterol	-.16	-1.89	> .05
	Hypertension	-.07	-.92	> .05
3	Age	-.38	-4.20	< .01
	Education	-.03	-.39	> .05
	Gender	-.39	-4.36	< .01
	Ethnicity	.22	2.74	< .01
	BMI	.01	.11	> .05
	Cholesterol	-.16	-1.99	< .05
	Hypertension	-.04	-.52	> .05
	GFR	.19	2.38	< .05*

Note: $N = 120$. Step 1: $R = .57$. $R^2 = .32$. Adjusted $R^2 = .30$. standard error of estimate = .89. $p < .01$. Step 2: $R = .59$. $R^2 = .344$. Adjusted $R^2 = .30$. standard error of estimate = .88. $p < .01$. Step 3: $R = .61$. $R^2 = .38$. Adjusted $R^2 = .33$. standard error of estimate = .86. $p < .01$.

DISCUSSION

The relationship between kidney and cognitive function, specifically why cognitive processing is affected by kidney disease in T2DM, is an ongoing focus in research. Typically, the variables of interest are creatinine and GFR since they are a clearer depiction of proper kidney function and common in routine testing (*Albuminuria*). The research in this study, however, focused on albumin because of its known effect on brain function relative to kidney function (Bae et al., 2013). Albumin is a protein in the liver that functions to transport hormones and fluids through the bloodstream. Albuminuria is associated with obesity and metabolic syndrome, and can eventually lead to insulin resistance. That raises concern because insulin resistance is a leading cause of T2DM. In conjunction with other risk factors such as obesity, hypertension, or high cholesterol, albuminuria can cause significant decline in cognitive function (Deckers et al., 2017; Wei et al., 2017). Albumin levels were found to be significantly higher in those with severe cognitive impairment (Wei et al., 2017). With evidence from previous literature review articles, the next step in evaluating kidney and cognitive function in regards to albuminuria was to research a specific group of people. In this case, T2DM participants from the MSLS dataset were chosen to analyze the association between albuminuria and cognitive function. This is an important area of research due to the prevalence of individuals affected by T2DM and CKD. Due to the increasing life span of the affected population, the T2DM and cognitive dysfunction relationship could pose a public health crisis in the near future (Moheet et al., 2015).

There are many direct relationships between organ systems, such as circulatory and respiratory and many indirect ones such as the urinary and nervous, which need to be researched more. The general aim of this study was to find a relationship between kidney and cognitive function in T2DM, specifically aiming to determine albuminuria as a risk factor cognitive decline. As more information is gathered on kidney biomarker function, further research can delve into proper treatment for these conditions when diagnosed concurrently.

To investigate the general and specific aims of this study, bivariate correlation and hierarchical multiple regressions were conducted from the MSLS dataset. The MSLS dataset provided information on kidney information, cognitive function, diabetes, strokes, physical activity, nutrition, APOE-e4 genotype, obesity, smoking, and homocysteine on each of the participants in the last two waves of the dataset. Also, being able to control for T2DM while comparing kidney and cognitive function allowed for a specific aim.

Notably, there were no cases of albuminuria. Thus, the specific aim for this study was impacted, as there was a restricted range of albumin values. Albuminuria is an increase in albumin in urine and a normal range falls between 3.4 to 5.4 g/dL ("Albumin (Blood"), n.d., & "What is albuminuria", n.d.). The participants had a range between 3.3 and 5.0, falling perfectly within normal limits (Table 1). However, the investigation with albumin was not ceased after this information was noted. Rather, bivariate correlation coefficients were computed to relate the distribution of albumin values to cognitive performance. Albumin values were significantly correlated to performance in the visual spatial cognitive domain only (Table 5), with higher albumin values relating to higher cognitive scores. Therefore, to further investigate this association, a hierarchical linear

regression analysis was conducted to evaluate the variance in Visual Spatial Organization scores that was accounted for by albumin, above and beyond demographic variables. Albumin did not remain a significant predictor in this model (Table 6).

Because GFR was so highly correlated with creatinine (r = -.84), its major constituent variable, it was the significant correlations of GFR with the cognitive domains of visual spatial, working memory and executive function that were followed up with hierarchical multiple regression analyses. For two of these cognitive domains, working memory and executive function, GFR remained a significant predictor with adjustment for the demographic variables (Table 7-9) as well as for the influence of other health variables (BMI cholesterol, and hypertension; Tables 10-11).

Compared to literature review articles about kidney function, the results in this research shared similar results. Zammit and colleagues compared cognitive function in older adults with diagnosed CKD. In their study and this research, GFR did not show significance when correlated with visuospatial abilities, but showed significance to working memory and executive function. The results are consistent with the ones above, but the difference is that the article did not control for diabetes. (Zammit et alk., 2017). Another study that compared cognitive function and CKD resulted in a relationship between poor executive function and low GFR (Silinin et al., 2011). Executive function was also deemed impaired when CKD patients were compared to a similar yet healthy population, but stated hemodialysis served as improvement for that observation (Murthy et al., 2020). A study that solely focused on diagnosed diabetes mellitus individuals yielded claims that executive function is impaired with the diagnoses (Thabit et al., 2012). There are not many credible sources to support both CKD and T2DM in regards to

working memory and executive function cognitive domains. Thus, this research is one of very few that relate the two conditions together.

As mentioned previously, this study included physical health covariates of BMI, cholesterol, and hypertension due to their known relationship with both CKD and T2DM. BMI was significantly correlated with albumin, age, ethnicity, and education. Cholesterol was associated with age and gender. Hypertension held significance with age, creatinine, and GFR.

BMI was included as a covariate to reflect obesity, a known impact on T2DM. If a BMI is recorded as 30.0 or higher, it falls within the obesity range (Nuttall., 2015). The average for the participant group was just over 33.0 (Table 1).

Hypertension was a useful covariate to include because it often is the result of insulin resistance. The chronic increase in blood pressure, hypertension, disturbs the normal uptake of glucose and insulin delivered throughout the body, leading to cardiovascular issues, diabetic issues, and kidney impairment (Salvetti et al., 1993). From the vasoconstriction produced by hypertension, blood flow is reduced, leading to weakness throughout the body. The kidneys are in an extremely vascular area in the body, so any weakening in the blood vessels lead to significant decline of proper function or impairment ("High Blood Pressure & Kidney Disease," n.d.). Thus, they are unable to properly excrete waste, which leads to the significant correlations with hypertension and creatinine and GFR. Cholesterol is also a known risk factor for cardiovascular disease because it is known to be related to insulin resistance. Insulin resistance decreases cholesterol absorption while increasing cholesterol synthesis (Gylling et al., 2010).

Strengths, Limitations and Future Directions

Several limitations occurred throughout the process of this study. One limitation was that the impact of lifestyle factors was not analyzed. However, that gives a clear direction for what should be included in future studies using this database. The database did not include a large sample of T2DM, just over 100 participants, which is on the smaller end of sample sizes for statistical power. Another limitation is that the dataset was not very diverse, the option for ethnicity was either "African American" or "Other".

Despite the limitations, this research holds a considerable amount of strengths. Because these analyses were done on a dataset that was completed years ago, variables were chosen purely based on interest. There was no worry of data collection and the aims were chosen based on the given information. With that, more advanced statistical analyses were completed. Thus, an explicit aim was used to answer specific questions, leaving less room for error, ambiguity, and general claims. The size of the sample in the datasets are quite large, which allowed for the ability to only consider T2DM participants to specifically look for cognitive changes. Also, the participants were community based and reached a large population of individuals in terms of education, ethnicity, and education. Overall, the strength that was the most beneficial is the amount of cognitive domains and neurocognitive tests that were used to collect the data from the participants, allowing for a comprehensive view of cognitive function.

In the future, I would suggest a larger sample size of participants with T2DM and diagnosed albuminuria to investigate the original aim of this study. There, albumin could be investigated more thoroughly to determine whether it is a credible risk factor for cognitive decline. Another recommendation would be to set the population to be

participants with albuminuria and participants without and compare in terms of kidney and cognitive function. With those additions and incorporation of lifestyle factors that affect cognition, the results produced may be stronger and could lead to albuminuria being a risk factor and more evidence to support a healthier lifestyle.

Conclusions

Overall, this study supports a relationship between kidney and cognitive function in T2DM. Although results did not support the original claim of albuminuria being a risk factor for poorer cognitive performance, GFR was significantly associated with compared to working memory and executive function cognitive domains.

REFERENCES

Albumin (Blood)—Health encyclopedia—University of rochester medical center. (n.d.). Retrieved February 7, 2021, from https://www.urmc.rochester.edu/encyclopedia/content.aspx?contenttypeid=167&contentid=albumin_blood#:~:text=Results%20are%20given%20in%20grams,disease%20or%20an%20inflammatory%20disease.

Albuminuria: Albumin in the urine | niddk. (n.d.). National Institute of Diabetes and Digestive and Kidney Diseases. Retrieved September 29, 2020, from https://www.niddk.nih.gov/health-information/kidney-disease/chronic-kidney-disease-ckd/tests-diagnosis/albuminuria-albumin-urine

Bae, J. C., Seo, S. H., Hur, K. Y., Kim, J. H., Lee, M. S., Lee, M. K., Lee, W. Y., Rhee, E. J., & Oh, K. W. (2013). Association between Serum Albumin, Insulin Resistance, and Incident Diabetes in Nondiabetic Subjects. *Endocrinology and metabolism (Seoul, Korea)*, *28*(1), 26–32. https://doi.org/10.3803/EnM.2013.28.1.26

Betzel, R. F., Byrge, L., He, Y., Goñi, J., Zuo, X.-N., & Sporns, O. (2014). Changes in structural and functional connectivity among resting-state networks across the human lifespan. *NeuroImage*, *102*, 345–357. https://doi.org/10.1016/j.neuroimage.2014.07.067

Burns, C. M., Knopman, D. S., Tupper, D. E., Davey, C. S., Slinin, Y. M., Lakshminarayan, K., Rossom, R. C., Pederson, S. L., Gilbertson, D. T., & Murray, A. M. (2018). Prevalence and Risk of Severe Cognitive Impairment in Advanced Chronic Kidney Disease. *The journals of gerontology. Series A, Biological sciences and medical sciences*, *73*(3), 393–399. https://doi.org/10.1093/gerona/glx241

Cabeza R. (2002). Hemispheric asymmetry reduction in older adults: the HAROLD model. *Psychology and aging*, *17*(1), 85–100. https://doi.org/10.1037//0882-7974.17.1.85

Camina, E., & Güell, F. (2017). The Neuroanatomical, Neurophysiological and Psychological Basis of Memory: Current Models and Their Origins. *Frontiers in pharmacology*, *8*, 438. https://doi.org/10.3389/fphar.2017.00438

Cognitive health and older adults. (n.d.). National Institute on Aging. Retrieved January 3, 2021, from http://www.nia.nih.gov/health/cognitive-health-and-older-adults

Creatinine (Blood)—Health encyclopedia—University of rochester medical center. (n.d.). Retrieved February 7, 2021, from https://www.urmc.rochester.edu/encyclopedia/content.aspx?ContentTypeID=167&ContentID=creatinine_serum

Dabla P. K. (2010). Renal function in diabetic nephropathy. *World journal of diabetes*, *1*(2), 48–56. https://doi.org/10.4239/wjd.v1.i2.48

Davis, C., Bryan, J., Hodgson, J., & Murphy, K. (2015). Definition of the Mediterranean Diet; a Literature Review. *Nutrients*, *7*(11), 9139–9153. https://doi.org/10.3390/nu7115459

De Houwer, J., Barnes-Holmes, D. & Moors, A. What is learning? On the nature and

merits of a functional definition of learning. *Psychon Bull Rev* 20, 631–642 (2013). https://doi.org/10.3758/s13423-013-0386-3

Deckers, K., Camerino, I., van Boxtel, M. P., Verhey, F. R., Irving, K., Brayne, C., Kivipelto, M., Starr, J. M., Yaffe, K., de Leeuw, P. W., & Köhler, S. (2017). Dementia risk in renal dysfunction: A systematic review and meta-analysis of prospective studies. *Neurology*, *88*(2), 198–208. https://doi.org/10.1212/WNL.0000000000003482

Diabetes statistics | niddk. (n.d.). National Institute of Diabetes and Digestive and Kidney Diseases. Retrieved January 3, 2021, from https://www.niddk.nih.gov/health-information/health-statistics/diabetes-statistics

Diabetic kidney disease | niddk. (n.d.). National Institute of Diabetes and Digestive and Kidney Diseases. Retrieved January 3, 2021, from https://www.niddk.nih.gov/health-information/diabetes/overview/preventing-problems/diabetic-kidney-disease

Dotiwala AK, McCausland C, Samra NS. Anatomy, Head and Neck, Blood Brain Barrier. [Updated 2020 Sep 17]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK519556/

Elias, M. F., Dore, G. A., & Davey, A. (2013). Kidney disease and cognitive function. *Contributions to nephrology*, *179*, 42–57. https://doi.org/10.1159/000346722

Estimating glomerular filtration rate | niddk. (n.d.). National Institute of Diabetes and Digestive and Kidney Diseases. Retrieved May 18, 2021, from https://www.niddk.nih.gov/health-information/professionals/clinical-tools-patient-management/kidney-disease/laboratory-evaluation/glomerular-filtration-rate/estimating

Explaining your kidney test results: A tool for clinical use | niddk. (n.d.). National Institute of Diabetes and Digestive and Kidney Diseases. Retrieved February 7, 2021, from https://www.niddk.nih.gov/health-information/professionals/advanced-search/explain-kidney-test-results

Féart, C., Samieri, C., & Barberger-Gateau, P. (2010). Mediterranean diet and cognitive function in older adults. *Current opinion in clinical nutrition and metabolic care*, *13*(1), 14–18. https://doi.org/10.1097/MCO.0b013e3283331fe4

Gylling, H., Hallikainen, M., Pihlajamäki, J., Simonen, P., Kuusisto, J., Laakso, M., & Miettinen, T. A. (2010). Insulin sensitivity regulates cholesterol metabolism to a greater extent than obesity: lessons from the METSIM Study. *Journal of lipid research*, *51*(8), 2422–2427. https://doi.org/10.1194/jlr.P006619

Hantzidiamantis PJ, Lappin SL. Physiology, Glucose. [Updated 2020 Sep 22]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK545201/

Harvey P. D. (2019). Domains of cognition and their assessment . *Dialogues in clinical neuroscience*, *21*(3), 227–237. https://doi.org/10.31887/DCNS.2019.21.3/pharvey

High blood pressure & kidney disease | niddk. (n.d.). National Institute of Diabetes and Digestive and Kidney Diseases. Retrieved April 7, 2021, from https://www.niddk.nih.gov/health-information/kidney-disease/high-blood-pressure

Holdnack, J. A., Prifitera, A., Weiss, L. G., & Saklofske, D. H. (2016). Chapter 12—

Wisc-v and the personalized assessment approach. In L. G. Weiss, D. H. Saklofske, J. A. Holdnack, & A. Prifitera (Eds.), *WISC-V Assessment and Interpretation* (pp. 373–413). Academic Press. https://doi.org/10.1016/B978-0-12-404697-9.00012-1

Huang, X., Jiménez-Moleón, J. J., Lindholm, B., Cederholm, T., Arnlöv, J., Risérus, U., Sjögren, P., & Carrero, J. J. (2013). Mediterranean diet, kidney function, and mortality in men with CKD. *Clinical journal of the American Society of Nephrology : CJASN*, *8*(9), 1548–1555. https://doi.org/10.2215/CJN.01780213

Jason, G.W. (1990) Disorders of motor function following cortical lesions: Review and theoretical considerations. In G.R. Hammon (ed.) Cerebral control of speech and limb movements. Amsterdam: Elsevier.

Karvani, M., Simos, P., Stavrakaki, S. *et al.* Neurocognitive impairment in type 2 diabetes mellitus. *Hormones* 18, 523–534 (2019). https://doi.org/10.1007/s42000-019-00128-2

Kidney disease statistics for the united states | niddk. (n.d.). National Institute of Diabetes and Digestive and Kidney Diseases. Retrieved January 3, 2021, from https://www.niddk.nih.gov/health-information/health-statistics/kidney-disease

Kendall, D. M., & Harmel, A. P. (2002). The metabolic syndrome, type 2 diabetes, and cardiovascular disease: understanding the role of insulin resistance. *The American journal of managed care*, *8*(20 Suppl), S635–S657.

Kerchner, G. A., Racine, C. A., Hale, S., Wilheim, R., Laluz, V., Miller, B. L., & Kramer, J. H. (2012). Cognitive processing   speed in older adults: relationship with white matter integrity. *PloS one*, *7*(11), e50425. https://doi.org/10.1371/journal.pone.0050425

Khatri, M., Moon, Y. P., Scarmeas, N., Gu, Y., Gardener, H., Cheung, K., Wright, C. B., Sacco, R. L., Nickolas, T. L., & Elkind, M. S. (2014). The association between a Mediterranean-style diet and kidney function in the Northern Manhattan Study cohort. *Clinical journal of the American Society of Nephrology : CJASN*, *9*(11), 1868–1875. https://doi.org/10.2215/CJN.01080114

Kosmas, C. E., Silverio, D., Tsomidou, C., Salcedo, M. D., Montan, P. D., & Guzman, E. (2018). The Impact of Insulin Resistance and Chronic Kidney Disease on Inflammation and Cardiovascular Disease. *Clinical medicine insights. Endocrinology and diabetes*, *11*, 1179551418792257. https://doi.org/10.1177/1179551418792257

Lăcătușu, C. M., Grigorescu, E. D., Floria, M., Onofriescu, A., & Mihai, B. M. (2019). The Mediterranean Diet: From an Environment-Driven Food Culture to an Emerging Medical Prescription. *International journal of environmental research and public health*, *16*(6), 942. https://doi.org/10.3390/ijerph16060942

Lee, S., Kawachi, I., Berkman, L. F., & Grodstein, F. (2003). Education, other socioeconomic indicators, and cognitive function. *American journal of epidemiology*, *157*(8), 712–720. https://doi.org/10.1093/aje/kwg042

Lezak, M. D. (1995). Neuropsychological assessment (3rd ed). Oxford University Press. Levey AS, Stevens LA, Schmid CH et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009; 150: 604–612

Lutski, M., Weinstein, G., Goldbourt, U., & Tanne, D. (2017). Insulin Resistance and Future Cognitive Performance and Cognitive Decline in Elderly Patients with

Cardiovascular Disease. *Journal of Alzheimer's disease : JAD*, *57*(2), 633–643. https://doi.org/10.3233/JAD-161016

Malek M. (2018). Brain consequences of acute kidney injury: Focusing on the hippocampus. *Kidney research and clinical practice*, *37*(4), 315–322. https://doi.org/10.23876/j.krcp.18.0056

Martín-Peláez, S., Fito, M., & Castaner, O. (2020). Mediterranean Diet Effects on Type 2 Diabetes Prevention, Disease Progression, and Related Mechanisms. A Review. *Nutrients*, *12*(8), 2236. https://doi.org/10.3390/nu12082236

Mesulam, M. (2000). Aging, Alzheimer's disease, and dementia. Clinical and neurobiological perspectives. Principles of behavioral cognitive neurology. New York: Oxford University Press.

Menez, S., & Parikh, C. R. (2019). Assessing the health of the nephron in acute kidney injury: biomarkers of kidney function and injury. *Current opinion in nephrology and hypertension*, *28*(6), 560–566. https://doi.org/10.1097/MNH.0000000000000538

McMillin JM. Blood Glucose. In: Walker HK, Hall WD, Hurst JW, editors. Clinical Methods: The History, Physical, and Laboratory Examinations. 3rd edition. Boston: Butterworths; 1990. Chapter 141. Available from: https://www.ncbi.nlm.nih.gov/books/NBK248/

Moheet, A., Mangia, S., & Seaquist, E. R. (2015). Impact of diabetes on cognitive function and brain structure. *Annals of the New York Academy of Sciences*, *1353*, 60–71. https://doi.org/10.1111/nyas.12807

Mostofsky, S. H., & Simmonds, D. J. (2008). Response inhibition and response selection: two sides of the same coin. *Journal of cognitive neuroscience*, *20*(5), 751–761. https://doi.org/10.1162/jocn.2008.20500

Murthy, V. S., & Shukla, V. S. (2020). A Study of Executive Function in Patients with Chronic Kidney Disease before and after a Single Session of Hemodialysis. *Journal of neurosciences in rural practice*, *11*(2), 250–255. https://doi.org/10.1055/s-0040-1703961

Nuttall F. Q. (2015). Body Mass Index: Obesity, BMI, and Health: A Critical Review. *Nutrition today*, *50*(3), 117–128. https://doi.org/10.1097/NT.0000000000000092

On the cognitive process of abstraction. (2016). *Procedia Computer Science*, *89*, 243–252. https://doi.org/10.1016/j.procs.2016.06.051

Panza, F., Solfrizzi, V., Colacicco, A. M., D'Introno, A., Capurso, C., Torres, F., Del Parigi, A., Capurso, S., & Capurso, A. (2004). Mediterranean diet and cognitive decline. *Public health nutrition*, *7*(7), 959–963. https://doi.org/10.1079/phn2004561

Passos, V., Ladeira, R. M., Souza, C., Santos, I. S., & Barreto, S. M. (2018). First stages chronic kidney disease have mild effects on cognitive performance. Results of a 15,105 brazilian adult baseline cohort. *Jornal brasileiro de nefrologia : 'orgao oficial de Sociedades Brasileira e Latino-Americana de Nefrologia*, *40*(1), 18–25. https://doi.org/10.1590/1678-4685-JBN-3889

Park, D. C., & Reuter-Lorenz, P. (2009). The adaptive brain: aging and neurocognitive scaffolding. *Annual review of psychology*, *60*, 173–196. https://doi.org/10.1146/annurev.psych.59.103006.093656

Park, S., Choi, B., Choi, C., Kang, J. M., & Lee, J. Y. (2019). Relationship between

education, leisure activities, and cognitive functions in older adults. *Aging & mental health*, *23*(12), 1651–1660. https://doi.org/10.1080/13607863.2018.1512083

Pei, X., Lai, S., He, X., Masembe, N. P., Yuan, H., Yong, Z., Zhu, B., Wu, J., & Zhao, W. (2018). Mild cognitive impairment in maintenance hemodialysis patients: a cross-sectional survey and cohort study. *Clinical interventions in aging*, *14*, 27–32. https://doi.org/10.2147/CIA.S178854

Possin K. L. (2010). Visual spatial cognition in neurodegenerative disease. *Neurocase*, *16*(6), 466–487. https://doi.org/10.1080/13554791003730600

Radi Z. A. (2019). Kidney Pathophysiology, Toxicology, and Drug-Induced Injury in Drug Development. *International journal of toxicology*, *38*(3), 215–227. https://doi.org/10.1177/1091581819831701

Robbins T. W. (2011). Cognition: the ultimate brain function. *Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology*, *36*(1), 1–2. https://doi.org/10.1038/npp.2010.171

Rowley, W. R., Bezold, C., Arikan, Y., Byrne, E., & Krohe, S. (2017). Diabetes 2030: Insights from Yesterday, Today, and Future Trends. *Population health management*, *20*(1), 6–12. https://doi.org/10.1089/pop.2015.0181

Reuter-Lorenz, Patricia & Cappell, Katherine. (2008). Neurocognitive Aging and the Compensation Hypothesis. Current Directions in Psychological Science - CURR DIRECTIONS PSYCHOL SCI. 17. 177-182. 10.1111/j.1467-8721.2008.00570.x.

Rule AD, Gussak HM, Pond GR et al. Measured and estimated GFR in healthy potential kidney donors. Am J Kidney Dis 2004; 43: 112–119

Sacre, J. W., Magliano, D. J., Zimmet, P. Z., Polkinghorne, K. R., Chadban, S. J., Anstey, K. J., & Shaw, J. E. (2019). Associations of Chronic Kidney Disease Markers with Cognitive Function: A 12-Year Follow-Up Study. *Journal of Alzheimer's disease : JAD*, *70*(s1), S19–S30. https://doi.org/10.3233/JAD-180498

Salvetti A, Brogi G, Di Legge V, Bernini GP. The inter-relationship between insulin resistance and hypertension. Drugs. 1993;46 Suppl 2:149-59. doi: 10.2165/00003495-199300462-00024. PMID: 7512468.

Slinin, Y., Paudel, M. L., Ishani, A., Taylor, B. C., Yaffe, K., Murray, A. M., Fink, H. A., Orwoll, E. S., Cummings, S. R., Barrett-Connor, E., Jassal, S., Ensrud, K. E., & Osteoporotic Fractures in Men Study Group (2008). Kidney function and cognitive performance and decline in older men. *Journal of the American Geriatrics Society*, *56*(11), 2082–2088. https://doi.org/10.1111/j.1532-5415.2008.01936.x

Thabit, H., Kyaw Tun, T., McDermott, J., & Sreenan, S. (2012). Executive function and diabetes mellitus--a stone left unturned?. Current diabetes reviews, 8(2), 109–115. https://doi.org/10.2174/157339912799424555

Torres, R. V., Elias, M. F., Seliger, S., Davey, A., & Robbins, M. A. (2017). Risk for cognitive impairment across 22 measures of cognitive ability in early-stage chronic kidney disease. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association*, *32*(2), 299–306. https://doi.org/10.1093/ndt/gfw005

Umberson, D., & Montez, J. K. (2010). Social relationships and health: a flashpoint for health policy. *Journal of health and social behavior*, *51 Suppl*(Suppl), S54–S66. https://doi.org/10.1177/0022146510383501

Vascular dementia and vascular cognitive impairment: A resource list. (n.d.). National Institute on Aging. Retrieved January 25, 2021, from http://www.nia.nih.gov/health/vascular-dementia-and-vascular-cognitive-impairment-resource-list

What is albuminuria? (n.d.). Retrieved February 7, 2021, from https://www.kidney.org/atoz/content/albuminuria

What is chronic kidney disease? | niddk. (n.d.). National Institute of Diabetes and Digestive and Kidney Diseases. Retrieved January 3, 2021, from https://www.niddk.nih.gov/health-information/kidney-disease/chronic-kidney-disease-ckd/what-is-chronic-kidney-disease

Wei, Y., Wei, Y. K., & Zhu, J. (2017). Early markers of kidney dysfunction and cognitive impairment among older adults. *Journal of the neurological sciences*, *375*, 209–214. https://doi.org/10.1016/j.jns.2017.01.071

Zammit, A. R., Katz, M. J., Bitzer, M., & Lipton, R. B. (2016). Cognitive Impairment and Dementia in Older Adults With Chronic Kidney Disease: A Review. *Alzheimer disease and associated disorders*, *30*(4), 357–366. https://doi.org/10.1097/WAD.0000000000000178

Zeki Al Hazzouri, A., Elfassy, T., Sidney, S., Jacobs, D., Pérez Stable, E. J., & Yaffe, K. (2017). Sustained Economic Hardship and Cognitive Function: The Coronary Artery Risk Development in Young Adults Study. *American journal of preventive medicine*, *52*(1), 1–9. https://doi.org/10.1016/j.amepre.2016.08.009

Zilliox LA, Chadrasekaran K, Kwan JY, Russell JW. Diabetes and Cognitive Impairment. Curr Diab Rep. 2016 Sep;16(9):87. doi: 10.1007/s11892-016-0775-x. PMID: 27491830; PMCID: PMC5528145.

Zimmermann, J., Ritter, P., Shen, K., Rothmeier, S., Schirner, M., McIntosh, A.R., 2016. Structural architecture supports functional organization in the human aging brain at a region wise and network level. Human brain mapping n/a–n/a. doi:10.1002/hbm.23200.

Zlotnik, G., & Vansintjan, A. (2019). Memory: An Extended Definition. *Frontiers in psychology*,*10*, 2523. https://doi.org/10.3389/fpsyg.2019.02523

Author's Bibliography

Erika Lyn Pacheco was born in Boston, Massachusetts on December 9th, 1998. Erika lived in Bridgewater, MA until she was 17 then moved the town over to Raynham, MA where she still resides. She graduated from the University of Maine in May of 2021 with a Bachelor of Science in Zoology and minors in neuroscience and psychology. Erika plans to continue her education through Optometry school.