Cognitive Function, Self-Care, and Glycemic Control in Rural Adults with Type 2 Diabetes

By

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DEDICATION

Those we love never die, for as long as we live and remember, they are with us.

This dissertation is dedicated to the memory of my father Henry Seidel and beloved Dominick

Cianfarani.

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ABSTRACT

The prevalence of type 2 diabetes mellitus (DM) has increased dramatically over the past two decades, particularly among adults living in rural communities. Related health complications include structural brain changes and decreased cognitive function. Cognitive decline associated with DM may influence one's ability to perform self-care and affect glycemic control. In turn, poor glycemic control contributes to increased complications associated with DM. Although one's ability to maintain glycemic control may be highly dependent on cognitive abilities, there is limited understanding about the relationship between cognitive function, self-care, and glycemic control in rural adults with DM.

Specific aims of this study were to: 1) examine the relationships between cognitive function, glycemic control, and contributing factors (age, years with DM, education category, cardiovascular (CV) risk, level of depression) in rural adults with DM; 2) examine whether cognitive function predicts glycemic control in rural adults with DM; 3) examine the relationship between cognitive function, self-care, and contributing factors (age, years with DM, education category, everyday problem-solving, and level of depression) in rural adults with DM; and, 4) examine whether cognitive function predicts self-care in rural adults with DM.

This descriptive study included a convenience sample of (N=56) rural adults with DM. A face-to-face interview was conducted with each participant, where performance of the cognitive processes of attention, executive function, mental processing speed, and verbal episodic memory was

measured with neuropsychological tests. Frequencies of performing DM self-care activities of adherence to diet, exercise, blood glucose monitoring, foot care and medications were queried to determine levels of self-care, and a recent glycohemoglobin was obtained to determine glycemic control.

Main results were that cognitive function in domains of attention, executive function, mental processing speed, or verbal episodic memory, after controlling for modifiable and non-modifiable covariates, did not independently explain glycemic control or the frequency of DM self-care activity performance by rural adults with DM. The covariates cardiovascular risk and depression independently explained cognitive function, and depression independently explained self-care performance.

CHAPTER I

Introduction

The prevalence of diabetes mellitus (DM) has increased dramatically in the United States (US) over the past two decades. According to the Centers for Disease Control (CDC, 2014), the number of newly diagnosed cases of DM in adults between the ages of 18-79 more than tripled from 493,000 in 1980 to over 1.4 million in 2014. The CDC (2014) reported that 21 million people in the US have been diagnosed with type 1 or type 2 DM, with type 2 accounting for 90-95% of the cases. Another 8.1 million are thought to have DM but are undiagnosed, bringing the total to 29.1 million, or 9.3% of the US population. The prevalence of DM increases as age increases (20-44 years =4.1%, 45-64 years = 16.2%, and over 65 years =25.9%) (CDC, 2014). Risk of death among adults with DM is almost twice that of adults without DM. Related comorbidities and health complications include structural brain changes and cognitive dysfunction, cardiovascular disease, blindness, kidney failure, nervous system damage, and lower limb amputations. These sequelae are estimated to increase the overall direct costs to the healthcare system by $176 billion annually (CDC, 2014).

Maintaining glycemic control by maintaining one's glycohemoglobin or HbA1c level at 7% or below reduces microvascular and neuropathic complications (American Diabetes Association (ADA), 2013). The ADA (2013) estimates that 57% of adults with DM achieve

adequate glycemic control through the combined effects of diet, exercise, and medication, all of which require some degree of self-care practice. The complexity of maintaining adequate glycemic control, however, requires the ability to perform ongoing self-care routines that require multiple cognitive processes. Hence, decreased cognitive function may influence one's ability to perform self-care and affect glycemic control (Qiu et al., 2006).

The Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes (ACCORD-MIND) study (n=2,977), an Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial (N=10,251) sub-study, examined differences between rate of cognitive decline and structural brain changes in ACCORD participants (Cukierman-Yaffe et al. 2009a). Measurements of cognitive domains included mental processing speed, learning capacity, attention, working and verbal memory, executive function based inhibition, and global cognition. Results revealed an inverse age-adjusted relationship between cognitive test scores and degree of chronic hyperglycemia, as measured by HbA1c levels. Findings supported the hypothesis of a progressive relationship between decreased cognitive function and chronic hyperglycemia, and in turn decreasing cognitive function and poorer glycemic control.   The findings were concerning, as achieving glycemic control requires decision based self-care that centers on information collection and processing, which are cognitive processes that appear to be at risk for impairment in persons with DM (Cukierman-Yaffe et al., 2009). The profile of affected cognitive domains in DM is well documented, and includes attention, executive function, mental processing speed, and verbal episodic memory (Reijmer et al., 2010). This profile of cognitive deficits is associated with impaired self-care performance (Nguyen et al., 2010; Primozic, Tavcar, Avbelj, Dernovsek, & Oblak., 2012; Qiu et al., 2006), and may affect glycemic control (Munshi et al., 2012, Thabit et al., 2012). In addition to DM, other factors contributing to

cognitive dysfunction may include comorbidities and sociodemographic variables (Manschot et a., 2007; Nguyen et al, 2010; Saczynski et al., 2008). Adults ($\geq$ 18 years of age) in rural communities are also at greater risk for poorer glycemic control than are adults in non-rural communities because they often have less access to DM resources, travel greater distances for health care, and have lower availability of specialty services (Hale, Bennett, & Probst, 2010).

There is a gap in our understanding about: 1) what factors influence cognitive function, self-care performance, and glycemic control in rural adults with DM, 2) the relationship between cognitive function and glycemic control in rural adults with DM, and 3) the relationship between cognitive function and DM self-care performance in rural adults with DM. The overall purpose of this study was to examine the relationship between cognitive function (i.e. attention, executive function, mental processing speed, verbal episodic memory), self-care performance (diet, blood glucose testing, foot care, exercise, medications), and glycemic control among rural adults with DM over the age of 45.

Specific Aims and Research Hypotheses

Aim 1: Examine the relationships between cognitive function, glycemic control, and contributing factors (age, years with DM, education category, cardiovascular (CV) risk, level of depression) in rural adults with DM who are ages 45 and older.

Hypothesis 1.1: Increased age, years with DM, CV risk, depression, and decreased years of education will correlate with declining function in cognitive domains of attention, executive function, mental processing speed, and verbal episodic memory.

Hypothesis 1.2: Increased age, years with DM, CV risk, depression, and decreased years of education will correlate with poorer glycemic control.

Aim 2: Examine whether cognitive function predicts glycemic control in rural adults with DM.

Hypothesis 2.1: Glycemic control, after controlling for contributing factors, would independently predict performance in cognitive function measures.

Hypothesis 2.2: Cognitive function, after controlling for contributing factors, would independently predict glycemic control.

Aim 3: Examine the relationship between cognitive function, self-care, and contributing factors (age, years with DM, education category, everyday problem-solving, and level of depression) in rural adults with DM.

Hypothesis 3: Increased age, years with DM, depression, and decreased years of education, everyday problem-solving, glycemic control, and cognitive function would correlate with poorer levels of DM self–care.

Aim 4: Examine whether cognitive function predicts self-care in rural adults with DM.

Hypothesis 4: Cognitive function, after controlling for contributing factors, would independently predict self-care performance.

Background

Pathophysiology Associated with Cognitive Dysfunction in DM

Although the exact mechanisms are unknown, four major physiological factors commonly contribute to cognitive dysfunction in DM: metabolic (hyper/hypoglycemia, impaired glucose metabolism); endocrine (hyperinsulinemia, insulin resistance, hypothalamic-pituitary-adrenal axis dysregulation); vascular (micro and macrovascular disease, endothelial dysfunction, inflammation, blood-brain barrier permeability changes, dyslipidemia); and, central nervous system disorders (neuronal homeostasis changes, genetics, amyloidal deposits, depression) (McCrimmon, Ryan & Frier, 2012).

Proper brain function requires continuous glucose and oxygen supply. Associations between impaired glucose metabolism (Lamport, Lawson, Mansfield & Dye, 2009; McCrimmon et al., 2012; Zhong et al, 2012), chronic hyperglycemia (Convit, 2005; Lamport et al., 2009), and impaired cognition have been reported. Mechanisms involving blood-brain barrier glucose transport have shown that cognitive effort increases glucose uptake leading to localized brain glucose level depletion (Convit, 2005; Lamport et al., 2009). Blood-brain barrier glucose transport is mediated by endothelial cell expressed transporter GLUT1. Increased contact between blood, endothelial cells, and GLUT1 require greater transport demands. Impaired endothelial vasodilation and insulin resistance (defined as reduced cellular response to intrinsic insulin) are associated, hence a dysfunctional compensatory mechanism for cognitive effort induced blood glucose reductions may result (Convit, 2005; Lamport et al., 2009).

Insulin resistance occurs in pre-DM and DM and appears to have several unclear effects on neuronal activity (Convit, 2005; Williamson, McNeilly, & Sutherland, 2012) and cognition (Baker et al. 2011; Yanagawa et al., 2011). Insulin resistance may potentiate detrimental brain effects of cortisol elevations. Increased cortisol exposure has been associated with reductions in hippocampal volume (Convit, 2005), which places the hippocampus, a brain structure essential for memory function, at risk for damage from hypoxia and hyperglycemia (Convit, Wolf, Tarshish, & de Leon, 2003; Convit, 2005; Wrighten, Piroli, Grillo & Reagan, 2009). Animal models support a physiological role of insulin as a cognitive modulator in the hippocampus with a critical role in hippocampal memory processing (McNay & Recknagel, 2011). Brain MRI has shown hippocampal atrophy in persons with DM (Convit et al., 2003; Convit, 2005; den Heijer et al., 2003; Gold et al., 2007). Reduced functional connectivity between hippocampus, temporal lobe and frontal cortex may be widespread in DM and associated with impaired executive

functions (Zhou et al., 2010). Associations have been found between brain atrophy and poorer cognitive scores in DM patients, but findings are inconsistent (Brundel et al., 2012; Christman, Vannorsdall, Pearlson, Hill-Briggs, & Schretlen, 2010; by de Bresser et al., 2010; vanElderen et al., 2010).

Cognitive Dysfunction in DM

The prevalence of cognitive dysfunction in DM was not evident in the literature, as little is known regarding stages of appearance and progression over time. In a systematic review of the relationship between glycemic control and cognitive function in individuals with DM Cukierman, Gerstein, & Williamson (2005) found that studies differed in their use of cognitive tests but overall results indicated DM participants had greater rates of cognitive decline and risk of future dementia than persons without DM. Early stages of DM are often undiagnosed; hence, early cognitive decline often goes unnoticed as well (Fischer, deFrias, Yeung, & Dixon, 2009; Nooyens, Baan, Spijkerman, & Vershuren, 2010; Okereke et al., 2008; Ruis et al., 2009; Saczynski et al., 2008; Yeung, Fischer, & Dixon, 2009). Impaired glucose metabolism and insulin sensitivity found in a pre-DM stage are linked to cognitive dysfunction. Metabolic syndrome (also a pre-DM stage) and DM have similar cognitive deficit profiles (Reijmer et al., 2010). The impact of associated risk factors for cognitive dysfunction, such as insulin resistance, chronic hyperglycemia, hypertension and hyperlipidemia is unclear (Cukierman-Yaffe et al., 2009a; Cukierman-Yaffe et al., 2009b; Umegaki et al, 2012a; Umegaki et al., 2012b; van den Berg et.al, 2008).

Cognitive domains most often affected in DM include attention, executive function, mental processing speed, and verbal episodic memory. Less affected domains include perception, visuoconstruction and language (Reijmer et al., 2010). Short term memory appears to

be affected more than long term memory (Reijmer et al., 2010). Different processes for cognitive decline in DM may occur. There is evidence for: 1) mild slowly progressing decline beginning in pre-DM stages, and 2) severe faster decline with high prevalence of vascular and Alzheimer's dementia (Reijmer et al., 2010).

Self-care in DM

For persons with DM, maintaining health necessitates performance of daily self–care activities essential for achieving and maintaining good glycemic control, which, in turn, reduces complication rates. The cognitive deficit profile in DM, especially executive function, has been linked to impairment in performance of self-care, activities of daily living (ADLs) and instrumental activities of daily living (IADLs) (Nguyen et al., 2010; Primozic et al., 2012; Qiu et al., 2006; Thabit et al., 2009; Thabit et al., 2012). Findings by Primozic et al. (2012) showed DM patients with poorer cognitive abilities, specifically related to planning and problem solving, were more likely to have difficulty understanding and recalling self-care instruction. Results by Nguyen et al., (2010) were unable to confirm links between executive function, DM knowledge and adoption of self-care practices, but did support an association between poorer executive function and poorer glycemic control. Findings suggested that complex relationships linking cognition, knowledge and self-care remain largely unknown. Future studies are needed to clarify these relationships.

Glycemic Control

Glycemic control, defined as the optimal level of average blood glucose levels associated with reduction of complications of DM (ADA, 2014). It is best measured by glycosylated hemoglobin, or HbA1c, which is a measure of the attachment, or glycation, of glucose to hemoglobin A, a predominant form of hemoglobin found in red blood cells. The HbA1c is

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reported as a percent of glycated hemoglobin in the blood, where the higher the level of glucose in the blood is, the higher the percent of HgA1will be. HbA1c reflects the average blood glucose over 3-4 months (the average life span of a red blood cell) and therefore has a strong predictive value for DM complications (ADA, 2014). Maintaining HbA1c at 7% or below has been shown to reduce microvascular and neuropathic complications, however individual recommendations may vary. More stringent goals (HbA1c $\leq$6.5%) may be appropriate with persons with a short DM duration and no significant cardiovascular disease. Less stringent goals (HbA1c $\leq$8%) may be more appropriate for those with a history of severe hypoglycemia, advanced microvascular or macrovascular complications, or extensive comorbid conditions (ADA, 2014).

Contributing Factors to Cognitive Function in DM

Age and DM.

The presence of DM in midlife (age 57-60 years) has been consistently associated with increased risk of accelerated cognitive decline in later years (Nooyens et al., 2010; Rawlings et al., 2014; Tuligenga et al., 2014), but study results have varied in the affected cognitive domains and the magnitude of the cognitive decline (Reijmer et al., 2010). In a systematic review by Reijmer and colleagues (2010), cognitive deficits were found to be more evident in persons with DM over the age of 65 years old when compared with control groups (Reijmer et al., 2010). Longitudinal studies showed cognitive decline in persons with DM over an average of five years that exceeded normal aging effects between 1.5 and 2 times. While these results demonstrated an increased risk of cognitive decline among older adults with DM, it must also be noted that cognitive testing differed between studies. Other longitudinal studies showed no accelerated cognitive decline (Reijmer et al., 2010). Reijmer and colleagues concluded that the decreases shown in cognition were subtle, slowly progressive, and resembled the pattern of normal aging,

suggesting the effects of age and DM on cognition share a common etiology, and DM is a risk factor for cognitive decline.

Number of years with DM.

Cognitive dysfunction in persons with DM has been associated with the length of time one has DM. Some studies have shown that increased duration is associated with a mild decline, and other studies have shown a faster rate of decline (Reijmer et al., 2010). Cognitive dysfunction in DM may have a specific time of onset with no further decline, and different cognitive domains may be affected at different times (McCrimmon et al., 2012). The duration of time with DM and associated cognitive decline may also reflect chronic exposure to other risk factors and comorbidities such as lifestyle, demographic, hypertension, obesity, and depression (Reijmer et al., 2010).

Cardiovascular risk factors in DM.

The brain can be considered a target end-organ in DM and pre-DM, but the causative factors for cognitive deficits are difficult to define due to the comorbidities associated with DM. Cardiovascular, or heart and blood vessel disease, includes numerous problems on a macrovascular (myocardial infarction, stroke, carotid, coronary or peripheral arterial disease) and microvascular (neuropathy, retinopathy, nephropathy) level, many of which are related to atherosclerosis. Macrovascular disease appears to have a strong association with DM and is estimated to cause around 80% of mortality in DM (McCrimmon et al., 2012). Macrovascular disease correlates with brain atrophy and cognitive deficits in DM, but association with cerebral perfusion is unclear (Manschot et al., 2006; Manschot et al., 2007; McCrimmon et al., 2012; Tiehus et al., 2008b). Microvascular disease has a primary role in cerebrovascular pathology, but mechanisms are not clearly defined (Manschot et al., 2006; Manschot et al., 2007; McCrimmon

et al., 2012; Nelson et al., 2009). Cerebrovascular or cardiovascular risk factors associated with DM may mediate or moderate cognition at various times for various durations (Cukierman, Gerstein, & Williamson, 2005). An aim of the proposed study is to examine the influence of cardiovascular disease on cognitive dysfunction in DM.

Depression in DM.

Although the relationship is unclear, depression is more prevalent in persons with DM than those without the disease. Some speculate that it may be a consequence of coping with a chronic disease or the result of damaging metabolic consequences affecting cerebral neurotransmitter levels or vascular integrity (Reijmer et al., 2010). Sullivan et al. (2013) found that depression in ACCORD-MIND participants was associated with greater cognitive decline in domains of mental processing speed (p=.003), verbal memory (p=.001), and executive function (p=.02). Also, depression may be a predictor for poor self-care (Primozic et al., 2012; Qiu et al., 2006). Depression can impair one's ability to adhere to self-care regimens, potentially worsening the course of a chronic illness and causing a downward spiral. Because depression and disability are associated, recognition and treatment of depression in chronically ill persons is thus an important part of clinical management (Lamers et al., 2008).

Health disparities and rurality.

A rural community is defined as an area with a population of fewer than 50,000 people, and has a core population density of fewer than 1000 persons per square mile (Hart, Larson, & Lishner, 2005). According to United States Census 2000 population statistics, nearly 21% of the population lives in rural areas (Bureau of the Census, 2010). Adults ($\geq$ 18 years of age) in rural communities are at greater risk for poorer glycemic control than adults in non-rural communities (Hale, Bennett, & Probst, 2010). This may be because rural populations often have less access to

DM resources when compared to non-rural populations and thus travel greater distances for health care (Hale, Bennett, & Probst, 2010; Quandt et al., 2005; Utz, 2008). A data analysis from the 2006 Behavioral Risk Factor Surveillance System (n=29,501) explored differences in DM care and DM outcomes associated with rural residence (Hale et al., 2010). Rural residents with DM were disadvantaged compared with non-rural residents with DM in education level (p<.001), income level (p<.001), and health insurance coverage (p<.009). Rural residents were also less likely to report having had DM screening exams (foot exam p=.006, eye exam p=.006), and more likely to report occurrence of retinopathy (p=.007) and foot ulcers (p=.036) (Hale et al., 2010). Because rural residents have a higher incidence of DM, longer distances to care, and lower availability of specialty services than do non-rural residents, they are an important public health target group.

Brown et al. (2009) and Kilbourne and colleagues (2006) proposed socioeconomic status as a major factor in health outcomes in health disparities research in vulnerable populations, as race/ethnicity alone is not fully explanatory. Community characteristics such as education and income levels are considered as risk factors of poorer health outcome (Brown et al., 2009; Kilbourne et al, 2006). The framework presented by Kilbourne et al, (2006) includes individual, household, and community factors as part of socioeconomic status, as the progression of a chronic disease such as DM is likely influenced by these factors over time. Gender, age, and racial/ethnic factors are considered as covariates in the framework. Socioeconomic status may influence health outcomes through mediating/moderating factors such as health behaviors, healthcare access and processes (Kilbourne et al., 2006).

Theoretical Framework

As previously noted, DM is a complex disorder with four major physiological factors that commonly contribute to cognitive dysfunction in DM (McCrimmon, Ryan, & Frier, 2012). The profile of affected cognitive domains in DM is also well documented, and includes attention, executive function, mental processing speed, and verbal episodic memory (Reijmer et al., 2010). This profile of cognitive deficits is associated with impaired self-care performance (Nguyen et al., 2010; Primozic, Tavcar, Avbelj, Dernovsek, & Oblak., 2012; Qiu et al., 2006), and may affect glycemic control (Munshi et al., 2012, Thabit et al., 2012). In addition to the structural brain changes associated with DM, other contributing factors for decreased cognitive function include sociodemographic variables, comorbidities, and duration of having DM (Saczynski et al., 2008). Based on the literature, a conceptual framework (Figure 1) was developed to describe the relationships among these factors. The framework incorporates biological, environmental and behavioral influences on cognitive function, self-care, and glycemic control in persons with DM.

Embedded in the framework is a model for DM self-care based on the self-care model by Song (2010). A situation-specific theory for self-care in heart failure patients (Riegel and Dickson, 2008) was adapted by Song (2010) for DM self-care. Situation-specific theories focus on specific phenomena seen in clinical practice, and are limited to a specific population or field of practice. They are theories that incorporate the complexity of nursing and which provide important frameworks for use in both nursing practice and research (Im & Meleis, 1999). The DM self-care model by Song (2010), self-care consists of two components: Self-care maintenance and Self-care management. Self-care maintenance includes behaviors one may utilize to maintain physiologic stability- symptom monitoring and treatment adherence. Song's (2010) model adaptation reflects relevant DM monitoring and adherence (diet, medications,

blood glucose testing, exercise, and foot examination). Self-care management incorporates active

decision making in response to awareness of sign and symptom changes, and includes five

stages: 1) recognition, 2) evaluation, 3) decision to take action, 4) treatment implementation, and

5) treatment evaluation. Self-care maintenance activities are routine and differ from decision

making and problem solving required in Self-care management. In this dissertation research,

cognitive function was added to the framework as a situation-specific influence on DM self-care.
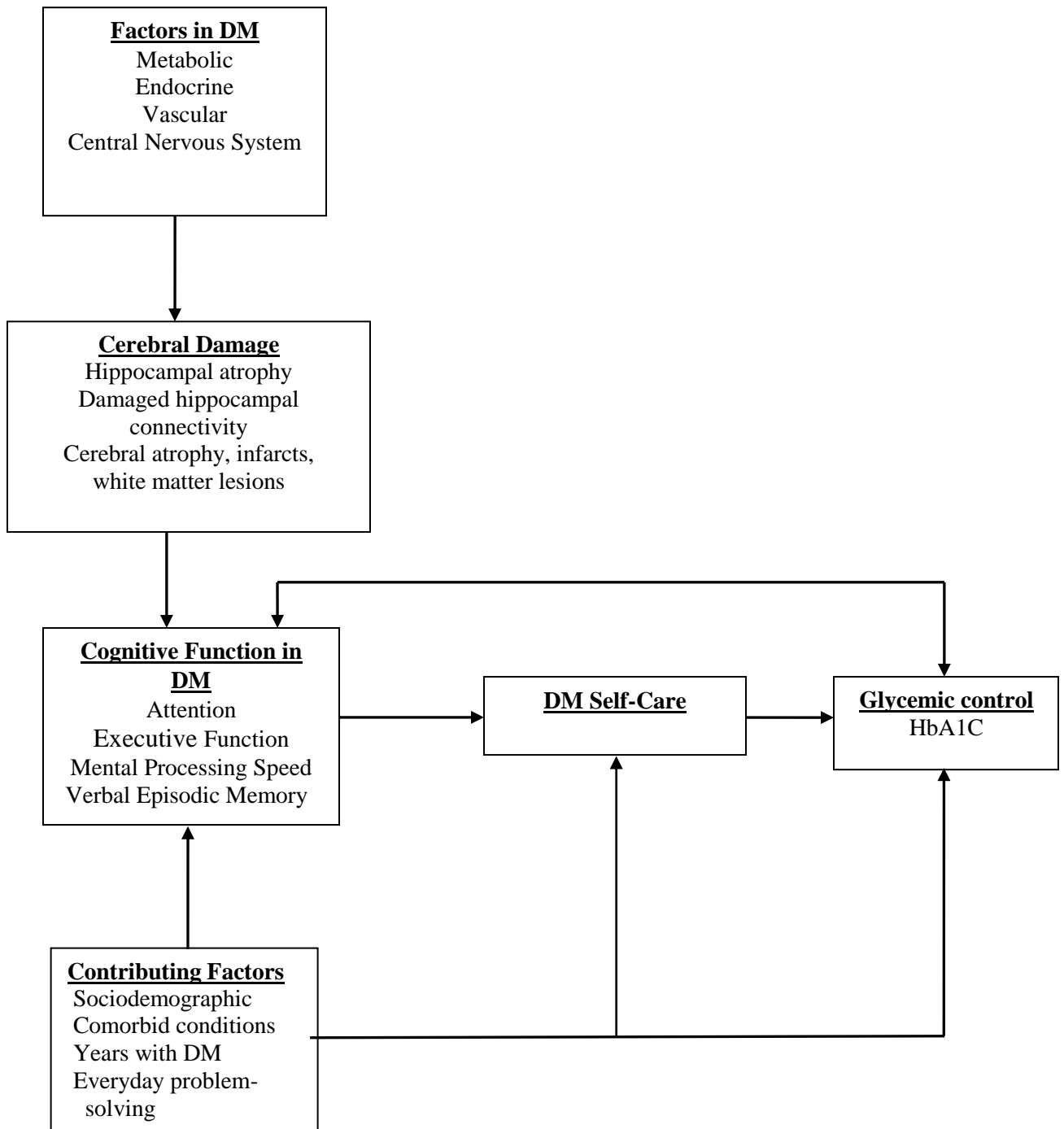
Figure 1.1. Conceptual Framework

Self-Care Maintenance   Self-Care Management

Self-Care
Knowledge

Monitor

Blood   Foot Exam
Glucose

Adherence

Diet   Exercise

Medications

Sign/Symptom
Recognition

Evaluation

Treatment
Implementation

Evaluation

Awareness

Decision Making
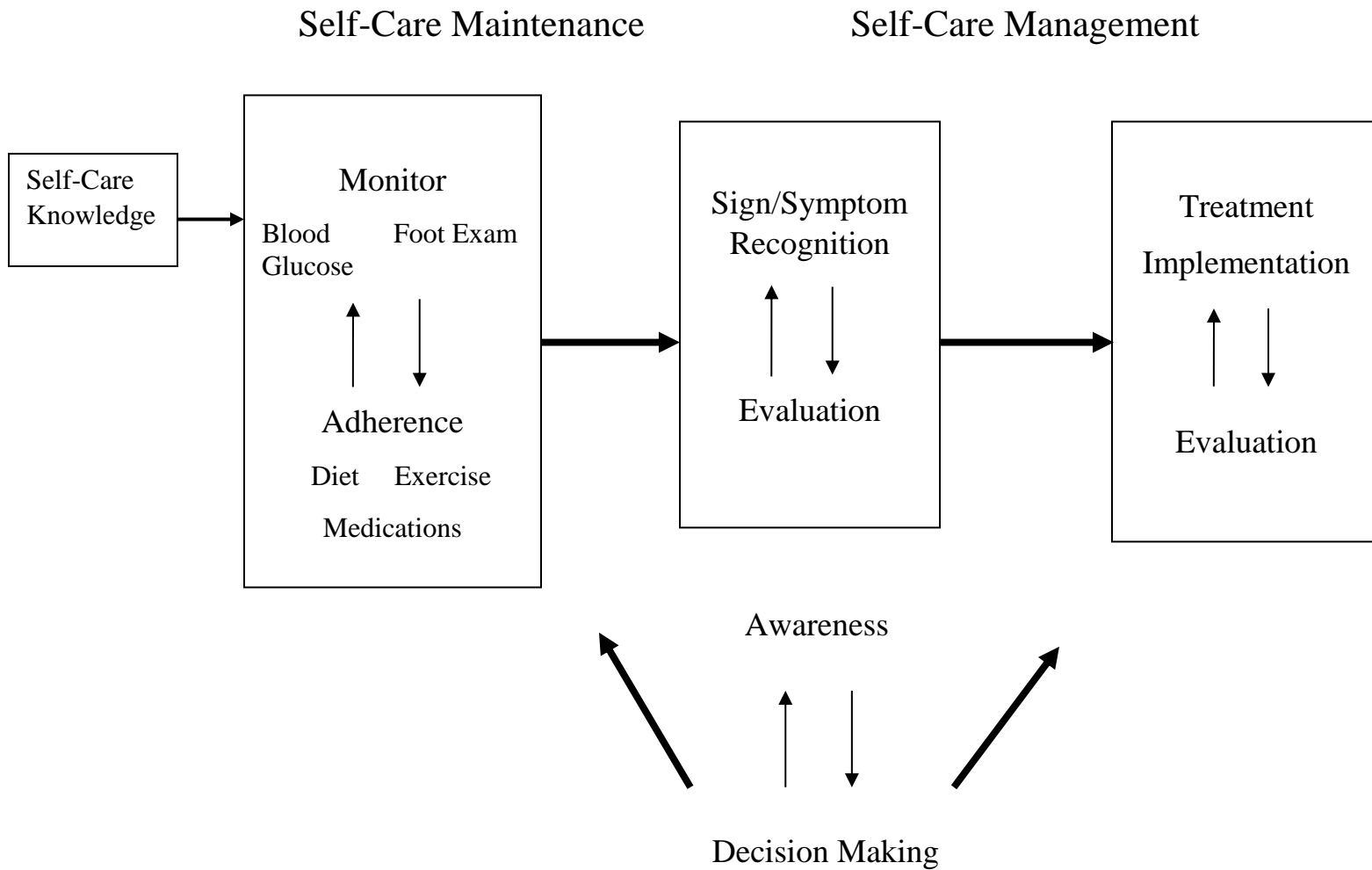
Figure 1.2 DM Self-Care Framework for Guiding Analysis

Adapted from: Song (2010). *Journal of Cardiovascular Nursing; 25*(2): 93-98.
Riegel & Dickson (2008). *Journal of Cardiovascular Nursing; 23*(3): 190-196.

Preliminary Study

A secondary analysis was conducted using data from the Cognitive Deficits in Chronic Heart Failure Study (PI: Pressler; NR008147). In the analysis, 414 participants (mean age 61.5 years; 51% women) were included. Cognitive deficits were measured and compared among four groups-persons with both heart failure (HF) and DM (n=94), persons with HF and not DM (n=157), persons with DM and not HF (n=30), and persons without HF or DM (n=133). Compared with persons with no HF and no DM, persons with HF and DM had significantly worse scores in cognitive processes of verbal memory (p<.001), visuospatial ability (p=.03), attention (p=.01, p=.03), executive function (p=.001), and mental processing speed (p<.001). Post hoc results with Tukey's Honestly Significant Differences also showed that patients with HF and DM had worse scores compared with patients without HF or DM in executive function, verbal memory, mental processing speed, working memory, and visuospatial ability recall. After controlling for age and years of education, group differences remained for tests in domains of verbal memory, mental processing speed and executive function. These important findings illustrate that the presence of comorbid DM in HF patients has a great impact on cognition and that little is still known about the combined effects of these two chronic diseases. These findings prompted further study into the cognitive processes of persons with DM and the impact on functional status and glycemic control.

Structure of the Dissertation

This dissertation follows a three-manuscript format consisting of five chapters: an introduction, three manuscript-style papers, and conclusion. In the first chapter, background knowledge, aims and hypotheses, theoretical framework, and preliminary study are presented. Chapter 2, which is the first manuscript, is a scoping review of the state of the science pertaining

to what is known about the relationship between cognitive function in DM and DM self-care ane where knowledge gaps exist. The second manuscript (Chapter 3) investigated the relationships between cognitive function, contributing factors, and glycemic control. Chapter 4, the third manuscript, investigated the relationships between cognitive function, self-care, contributing factors, and glycemic control. The final chapter provides a summary of the results, overall conclusions, clinical implications of the findings, strengths and weaknesses of the research, and directions for future study.

Summary

Glycemic control may be highly dependent on cognitive and self-care abilities. There is a lack of knowledge about the relationship between cognitive function, self-care, and glycemic control in rural adults with DM. While decreased ability to perform cognitively complex daily self-care tasks has been shown to be an early indicator of cognitive decline, however, the relationship of specific cognitive domains to self-care performance is unclear. The role of other contributing factors to cognitive and self-care performance is also uncertain. For persons with DM, activities involved with self-care routines are unique, yet have some similarities in cognitive requirements such as processing information, decision making and problem solving. There is a knowledge gap concerning the differences in level of cognitive function and performance of DM self-care routines. It is important to identify what factors put persons with DM at risk for cognitive decline, poor self-care performance and glycemic control, so appropriate screening and intervention can be implemented to reduce DM associated complications.

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CHAPTER II

Cognitive Function and Self-Care in Adults with Type 2 Diabetes-

State of the Science

Introduction

The prevalence of diabetes mellitus (DM) has increased dramatically in the United States (US) over the past two decades. According to the Centers for Disease Control (CDC, 2014) 21 million people in the US have been diagnosed with type 1 or type 2 DM, with type 2 accounting for 90-95% of the cases. Another 8.1 million are thought to have DM but are undiagnosed (CDC, 2014), bringing the total to 29.1 million, or 9.3% of the US population. The prevalence of DM increases as age increases (20-44 years =4.1%, 45-64 years = 16.2%, and over 65 years =25.9%) (CDC, 2014). Risk of death among adults with DM is almost twice that of adults without DM. Related comorbidities and health complications include structural brain changes and cognitive dysfunction, cardiovascular disease, blindness, kidney failure, nervous system damage, and lower limb amputations. These sequelae are estimated to increase the overall costs to the healthcare system; direct costs alone are estimated to add $176 billion annually (CDC, 2014). Glycemic control significantly reduces the occurrence of complications, and is fundamental to managing DM (American Diabetes Association, 2013). The American Diabetes Association (ADA) estimates that 57% of adults with DM achieve adequate glycemic control (ADA, 2013)

through the combined effects of diet, exercise, and medication, all of which require some degree of self-care practices.

The ACCORD-Memory in Diabetes (ACCORD-MIND) study (n=2,977), a sub-study of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial (N=10,251), examined differences between the rate of cognitive decline and structural brain changes in ACCORD participants (Cukierman-Yaffe et al. 2009). The results revealed an age-adjusted association between higher HbA1c levels and poorer cognitive test scores in the domains of global cognition (p<.0001), executive function (p=.0094), mental processing speed (p<.0001), and verbal memory (p=.0142), and supported the hypothesis of a progressive and positive relationship between chronic hyperglycemia and cognitive dysfunction. Also, the results with estimating the independent relationship between HbA1c and cognitive measures when adjusting for risk factors of duration with DM, history of cardiovascular disease and stroke, race, and language, revealed small but significant differences in R^2 values when HbA1c was included and excluded in the models. The researchers concluded that while the relationship between HbA1c and cognitive dysfunction may be explained by risk factors other than chronic hyperglycemia, HbA1c levels are modifiable with therapeutic decisions, and glycemic control is important for preserving cognitive function. The findings were concerning, as achieving glycemic control requires decision based self-care that centers on information collection and processing, which are cognitive processes that appear to be at risk for impairment in persons with DM (Cukierman-Yaffe et al., 2009).

DM is associated with structural brain changes and dysfunction in the cognitive processes essential for learning and performing ongoing self-care activities to maintain glycemic control and prevent complications. Several studies link these variables, but results have been equivocal

(Biessels, Strachan, Visseren, Kappelle, and Whitmer, 2014; Cukierman-Yaffe et al., 2009). In order to understand the link between brain changes in DM and glycemic control, it is necessary to examine the relationships between cognitive dysfunction in DM, self-care abilities, and glycemic control, and to identify contributing risk factors that may be modifiable.

Methods

The aim of this scoping literature review was to identify and summarize the existing state of knowledge about cognitive dysfunction in DM and DM self-care. The analysis was guided by the following questions: What factors are related to cognitive dysfunction in persons with DM? What is known about the association between cognitive dysfunction and performance of self-care activities among persons with DM?

Search Methods

A literature search was conducted from January 2005 through December 2014 to reflect contemporary research on the topic. Databases included were: MEDLINE, PubMed, CINAHL, and PsycINFO. Key search terms (MeSH) were: type 2 diabetes mellitus, cognition, cognition disorder, self-care, and self-management. Electronic searches were supplemented by hand searches from reference lists from publications that met the search criteria.

Inclusion and Exclusion Criteria

The searches were limited to English language, journal articles, meta-analyses, observational studies, randomized control trials, reviews, and systematic reviews. Data-based studies that included adult persons with type 2 DM, and pertained to cognitive dysfunction and /or self-care in type 2 DM were included. Commentaries, letters to the editor, summaries, and non-data- based publications were excluded.

Search Outcomes

The search yielded 373 publications, 11 of which were duplicates. Of the 362 unique publications, 288 were not directly related to cognitive dysfunction in DM or DM self-care, and did not meet eligibility criteria (see Figure 2.1).
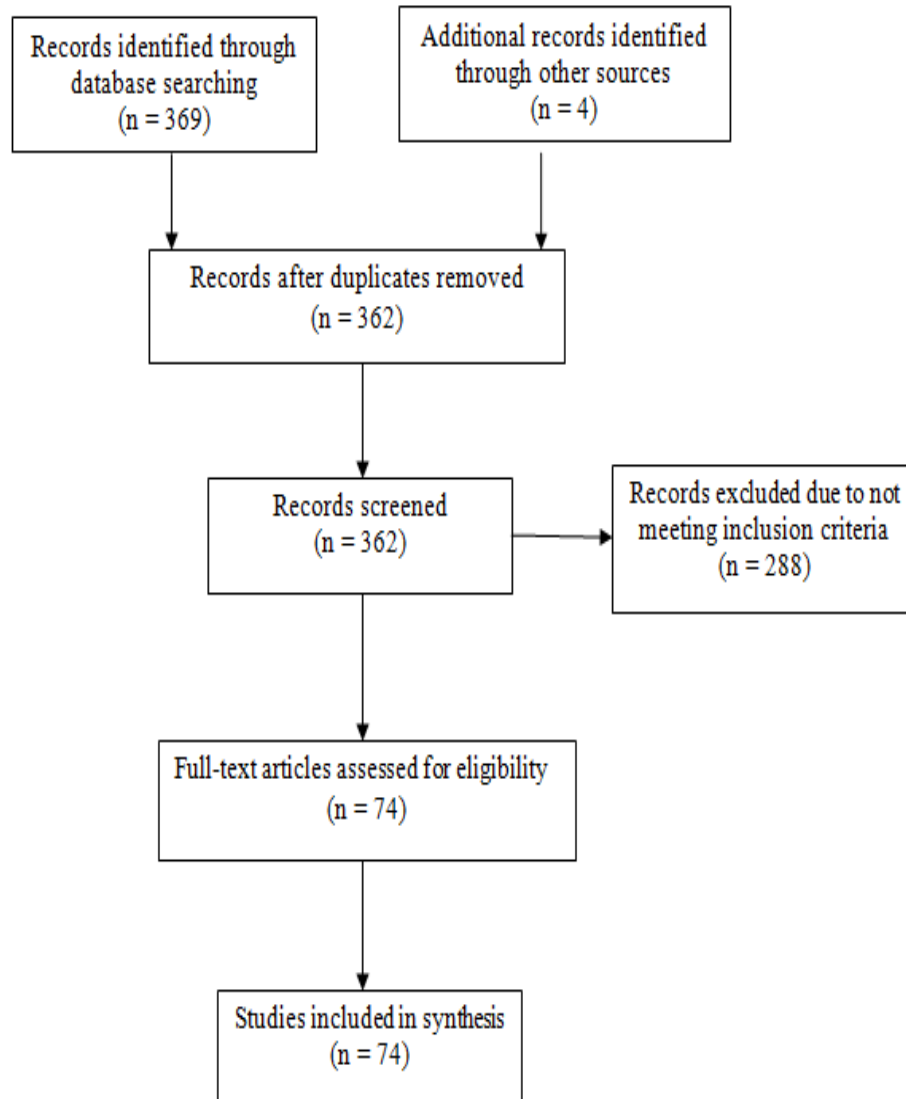
Figure 2.1. Flow Chart for Search Outcomes

The 74 publications were critiqued and categorized into four groups: 1) pathophysiology related to cognitive dysfunction in DM (n=39); 2) reviews of empirical studies related to cognitive dysfunction in DM (n=6); 3) data-based studies related to cognitive dysfunction in DM (n=18); and, 4) publications related to self-care in DM (n=11).

Pathophysiology Related to Cognitive Dysfunction in DM

The 39 publications in this category covered four major physiological factors that commonly contribute to cognitive dysfunction in DM: metabolic (hyper/hypoglycemia, impaired glucose metabolism); endocrine (hyperinsulinemia, insulin resistance, hypothalamic-pituitary-adrenal axis dysregulation); vascular (micro- and macrovascular disease, endothelial dysfunction, inflammation, blood-brain barrier permeability changes, dyslipidemia); and, central nervous system disorders (neuronal homeostasis changes, genetics, amyloidal deposits, depression) (McCrimmon, Ryan, & Frier, 2012).

Four publications specifically addressed the metabolic, endocrine, and vascular factors related to brain metabolism and cognitive dysfunction, finding that cognitive dysfunction was associated with impaired glucose metabolism (Lamport, Lawson, Mansfield & Dye, 2009; McCrimmon et al., 2012; Zhong et al, 2012), chronic hyperglycemia (Lamport et al., 2009), insulin resistance (Convit, 2005; Williamson, McNeilly, & Sutherland, 2012), and histories of severe hypoglycemia (Feinkohl et al., 2014). Affected cognitive domains included global cognition (Feinkohl et al., 2014; Zhong et al, 2012), executive function, mental processing speed, and nonverbal memory (Feinkohl et al., 2014). Studies of mechanisms involving blood-brain barrier glucose transport demonstrate that cognitive effort increases glucose uptake, thereby leading to localized brain glucose level depletion (Lamport et al., 2009). As blood-brain barrier

glucose transport is mediated by endothelial cell expressed transporter GLUT1, increased contact between blood, endothelial cells, and GLUT1 requires greater transport demands. Impaired endothelial cellular function and insulin resistance (defined as reduced cellular response to intrinsic insulin) are associated, hence a dysfunctional compensatory mechanism for cognitive effort induced blood glucose reductions may result (Lamport et al., 2009).

Seven other publications in this category addressed the relationship between insulin resistance and its anatomical and functional effects on the brain. Insulin resistance, which occurs in both pre-DM and DM, has been associated with hippocampal volume reductions (Convit, 2005), and appears to have several unclear effects on neuronal activity (Convit, 2005; Williamson et al., 2012), and cognition (Baker et al. 2011; Yanagawa et al., 2011). The hippocampus, essential for memory function, is susceptible to damage from hypoxia and hyperglycemia (Convit, 2005; Wrighten, Piroli, Grillo & Reagan, 2009), and potentially from hypothalamic pituitary adrenocortical axis dysregulation (Bruehl et al., 2009). Insulin resistance may potentiate the detrimental brain effects of cortisol elevations, which has been associated with hippocampal volume reductions and memory performance (Convit, 2005). Animal models have demonstrated the physiological role of insulin as a cognitive modulator in the hippocampus that is critical in hippocampal memory processing (McNay & Recknagel, 2011).

Twenty-two publications focused on vascular disease, anatomical brain changes, and cognitive dysfunction. In individuals with DM, macrovascular and microvascular disease, chronic hyperglycemia, hypertension, and hyperinsulinemia have been associated with cortical and subcortical brain atrophy and cognitive dysfunction (Manschot et al. 2006; Manschot et al., 2007; Tiehus et al., 2008; Tiehuis et al.,2009). Decreases in brain volume in DM vary from no difference to a rate of up to three times greater than decreases due to the normal aging process

(de Bresser et al., 2010; Espeland et al., 2013; van Elderen et al., 2010). Although hippocampal atrophy is evident among persons with DM (Convit, 2005; den Heijer et al., 2009; Gold et al., 2007), it is not clear whether the hippocampus is more severely affected than other brain areas (Biessels & Reijmer, 2014). In a study over a two-year period Samaras et al. (2014) demonstrated that baseline DM was associated with greater increases in cerebrospinal fluid volumes (p=.02), and with declines in hippocampal, parahippocampal, precuneus and total brain volumes compared to no DM at baseline. The relationships between brain volumes and cognitive performance in persons with DM varied between studies (Biessels & Reijmer, 2014; Brundel et al., 2012; Christman, Vannorsdall, Pearlson, Hill-Briggs, & Schretlen, 2010; Moran et al., 2013; Roberts et al., 2014; Verdelho et al., 2010; Zhang et al., 2014), however, two studies reported poorer performance in the cognitive domains of attention, executive function, memory, and mental processing speed in individuals with DM (Manschot et al., 2006; Manschot et al., 2007).

Small vessel disease changes in the brain (i.e., silent brain infarcts and white matter lesions) may be predictive of cognitive decline in DM (Imamine et al., 2011). Manschot et al. (2006) found more cerebral infarcts and deep white matter lesions in persons with DM than in controls, as well as dysfunction in the cognitive domains of attention, executive function, and mental processing speed (Manschot et al., 2006). Frontal and prefrontal system executive dysfunction may be associated with hyperglycemia-related neuronal degeneration or small vessel disease- induced regional cerebral blood flow changes (Thabit et al., 2009). Chronic hyperglycemia has been linked with formation of advanced glycation end-products, which are believed to be linked to microvascular disease in DM, impaired neuronal function, glucose hypometabolism, and Alzheimer's disease related pathology (Alosco & Gunstad, 2014;

Guerrero-Berroa, Schmeidler, & Beeri, 2014). Although cerebrovascular pathology appears to be severe in DM, histopathologic studies examining the neuropathology of small vessel disease in DM are lacking (Nelson et al., 2009).

Lastly, six publications presented the results of MRI studies pertaining to structural and functional brain network connectivity. Compared with controls, persons with DM showed microstructural abnormalities in white matter tracts connecting frontal, parietal and temporal brain regions, which are associated with cognitive functions including attention, executive function, mental processing speed, and verbal memory. Reductions in mental processing speed and memory were significant ($p<.05$) (Reijmer et al., 2013). Medial prefrontal and temporal parietal brain regions that are most active at rest and deactivated during cognitive tasks are called the default mode network (DMN). The DMN has high metabolic activity, making it susceptible to the effects of hypo and hyperglycemia found in DM (Hoogenboom et al., 2014; Marder et al., 2014). Recent studies have documented reduced functional connectivity between the hippocampus and several regions associated with the DMN (Hoogenboom et al., 2014; Musen et al., 2012; Zhou et al., 2010). Insulin resistance has been associated with decreased resting-state functional connectivity of the posterior cingulate cortex, a highly metabolically active area of the brain with high connectivity to other brain areas (Chen et al., 2014), and in other areas in the DMN where decreased functional connectivity occurs prior to the appearance of identifiable structural deficits (Musen et al., 2012). Marder et al. (2014) found reduced activation and deactivation in the DMN during cognitive task performance in persons with DM compared with controls. Zhou et al. (2010) demonstrated dysfunction in episodic memory and executive function in persons with DM compared with a control group, and speculated that the observed

reduced neuronal connectivity disturbances may be widespread in persons with DM and may impact learning and memory.

Reviews of Empirical Studies Related to Cognitive Dysfunction in DM

The six comprehensive reviews of empirical studies related to cognitive decline in DM focused on the risk of cognitive dysfunction and dementia, the effects of aging, and risk factors associated with cognitive decline. In their review of 25 studies, Cukierman and colleagues (2005) reported well documented evidence of a greater rate and risk of cognitive decline and dementia in persons with DM. Although various cognitive tests were used in the studies, overall results indicated that having DM was associated with a 1.5-fold greater risk for cognitive decline (Cukierman et al., 2005); as such, the authors concluded that cognitive dysfunction should be considered a complication of DM. A meta-analysis including 19 longitudinal studies by Cheng and colleagues (2012) documented relative risks for persons with DM compared with persons without DM: 1.2 for mild cognitive impairment, nearly 2.5 for vascular dementia, 1.5 for Alzheimer's disease, and 1.5 for any dementia. These findings suggest that DM is a risk factor for mild cognitive impairment as well as dementia. In addition, Biessels et al. (2014) found that having DM was associated with a 1.5-3 times greater conversion rate to dementia in persons with mild cognitive impairment, an intermediate stage between normal cognition and dementia.

Findings from cross-sectional case-control and population-based studies reviewed by Reijmer et al. (2010) showed worse performance for persons with DM compared to age-, sex-, and education- matched controls in the cognitive domains of attention, executive function, mental processing speed, and verbal memory. Effect sizes were small to medium (range 0.2-0.6), and were consistent across age groups (range 50-80 years) (Reijmer et al., 2010). Decreased cognitive performance in persons with DM was more evident in the over-65 age group (Biessels

et al., 2014; Reijmer et al., 2010). Longitudinal studies showed that cognitive decline exceeded normal aging effects by almost twice over an average of five years, and demonstrated slowly declining cognition across all age groups (Reijmer et al., 2010). However, observed differences were small and differed from the distinct decline typical for Alzheimer's disease (Reijmer et al, 2010). The accelerated decline typically seen with dementia is believed to be a result of processes different from that of normal aging, and the additive effect of DM may translate into a dementia onset 2.5 years earlier than that experienced by those without DM (Biessels et al., 2014). Often occurring years before DM diagnosis, impaired glucose tolerance (Lamport, Lawton, Mansfield, & Dye, 2009), hyperinsulinemia, and reduced insulin sensitivity (Reijmer et al., 2010) have been linked to cognitive decline similar to those with a diagnosis of DM. Metabolic syndrome (defined as the presence of three or more of these criteria: obesity, dyslipidemia, hypertension, elevated fasting blood glucose level, insulin resistance) has a cognitive deficit profile similar to that of DM (Reijmer et al., 2010).

The risk factors associated with DM (microvascular complications, hypertension, obesity, hyperlipidemia) are interrelated and may affect cognition at various times for various durations (Biessels et al., 2014; Cukierman, et al., 2005; Reijmer et al., 2010; van den Berg, Kloppenborg, Kessels, Kappelle & Biessels, 2009). A systematic review by van den Berg et al. (2009) compared the profile and magnitude of cognitive deficits associated with each of four vascular risk factors: DM, hypertension, dyslipidemia, and obesity. Cognitive test results from the included studies were converted to effect sizes using Cohen's d computations, and categorized into the pre-determined cognitive domains of attention, cognitive flexibility, general intelligence, language, perception/visuoconstruction, memory, and mental processing speed. Results indicated that all four vascular risk factors were associated with cognitive decline, with DM and

hypertension (HTN) showing the most associations. Median effect sizes (ranges: DM = 0 -1.9, HTN = 0.2 - 2.2) in the most commonly affected domains were memory (DM = 0.3, HTN = 0.4), attention (DM = 0.5, HTN = 0.4), and mental processing speed (DM =0.4, HTN = 0.2). This review suggests that early subtle changes in cognition maybe similar with DM, dyslipidemia, HTN, and obesity, and may provide opportunities for early intervention to improve control of the identified risk factors and reduce cognitive decline.

Depression in persons with DM has also been shown to increase the risk of cognitive dysfunction and dementia (Reijmer et al., 2010). The relationship between depression in DM and cognitive decline is unclear, but may result from coping with a chronic disease or from metabolically-induced damage that affects cerebral neurotransmitter levels or vascular integrity (Reijmer et al., 2010).

Data-Based Studies Related to Cognitive Dysfunction in DM

Eighteen studies focused on the relationship between cognitive dysfunction and DM, two studies on pre-DM, three on early DM, seven on duration of DM, and six on risk factors (see Table 1 for summaries).

Cognitive dysfunction in pre- and early DM.

Findings in studies pertaining to pre-DM (impaired fasting glucose or metabolic syndrome) showed that diagnosed and undiagnosed DM groups had slower mental processing speed than normoglycemic groups (Saczynski et al., 2008; van den Berg et.al, 2008). Undiagnosed DM groups had poorer verbal memory performance than either diagnosed DM or normoglycemic groups (Saczynski et al., 2008). In domains of attention and executive function, persons with metabolic syndrome had poorer performance than did controls (van den Berg et.al, 2008). Comparisons between early DM (duration 3.6-5 years) and control groups showed poorer

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performance by persons with DM in memory functions, mental processing speed (Nooyens, Baan, Spijkerman & Verschuren, 2010; Ruis et al., 2009), attention and executive functions, language comprehension, immediate memory and learning rate, and incidental memory (Ruis et al., 2009). Lower performance in executive functions was found in young adults with DM compared with controls, with the mean difference between groups largest at ages 35-44 years (p<.001) (van Eersel et al., 2013).

Cognitive dysfunction and duration of DM.

In studies examining the association between increased duration of DM and cognitive decline, similar results were found for several cognitive domains, and, in some domains, having DM was the cognitive equivalent of aging three years (Okereke et al., 2008). The presence of DM in midlife (age 57-60 years) has been consistently associated with an increased risk of accelerated cognitive decline in later years (Nooyens et al., 2010; Rawlings et al., 2014; Tuligenga et al., 2014). In studies comparing persons with DM to controls, decreases in global cognition over time tended to be worse with poor glycemic control (Ravona-Springer et al., 2014; Rawlings et al., 2014; Tuligenga et al., 2014), showing a19-24% faster decline (Rawlings et al., 2014; Tuligenga et al., 2014), while persons with low and stable glycohemoglobin levels had the best cognitive performance over time (Ravona-Springer et al., 2014). Associations between DM and decline in verbal memory became stronger with increased DM duration (Okereke et al., 2008; Spauwen Kohler, Verhey, Stehouwer, & van Boxtel, 2013). Over a period of 6 to 20 years, persons with DM showed decreased mental processing speed and executive function when compared with controls (Fischer, de Frias, Yeung, & Dixon, 2009; Rawlings et al., 2014; Saczynski et al., 2008; Spauwen et al., 2013; Yaffe et al., 2012).

In incident DM (DM diagnosed after baseline), significant decline in mental processing speed over 6 years was the only deficit noted compared with controls; this deficit increased with DM duration (Spauwen et al., 2013). Findings by Fischer et al. (2009), Rawlings et al. (2014), and Yeung, Fischer, and Dixon (2009) suggested that mental processing speed and speed-intensive executive function tasks may be early markers for decline. The cognitive domains of episodic and semantic memory and verbal fluency were measured less often and results varied (Fischer et al., 2009). No evidence of interaction between DM and gender on cognitive decline was found in studies by Nooyens et al., (2009), Okereke et al. (2008), Ruis et al., (2009), Tuligenga et al., (2014), van den Berg et al., (2008), or van Ersel et al., (2013).

Risk factors for cognitive dysfunction in DM.

Co-occurring comorbidities may be risk factors for cognitive dysfunction in DM, and cardiovascular disease may mediate the relationship between cognitive decline and DM (Cukierman-Yaffe et al., 2009). In a study of elderly persons with DM (mean age [SD] = 70.6 [$\pm$ 42.5] years), Umegaki et al. (2012) found that the comorbidities of diabetic nephropathy, high systolic blood pressure, and high triglyceride levels at baseline were predictors of global cognitive decline over 6 years. Changes in clinical indices during the 6 year follow-up period associated with cognitive decline were higher HbA1c, lower high-density lipoprotein and higher diastolic blood pressure.

Higher prevalence and persistence of depression has been found in persons with DM compared to control groups (Degmecic et al., 2014; Koekkoek et al., 2012; Trento et al., 2013). Prevalence of depression has been reported to be from 8-31% (mean 18%) with DM and from 5-24% (mean 10%) without DM (Koekkoek et al., 2012). Compared with controls, those with DM had more pathological anxiety (p=.002) and depression (p = .035), with the prevalence of

moderate, severe and very severe depression at 36.1% (Degmecic et al., 2014). The relationship

between DM and depression may be bidirectional and influenced by biologic and behavioral

factors (Degmecic et al., 2014; Sullivan et al., 2013; Trento et al., 2013). Studies examining

cognitive function and depression in DM have had differing results, likely due to differences in

sample size and assessment methods (Trento et al., 2013).

In a meta-analysis of three studies using identical depression scales and

neuropsychological tests for memory, Koekkoek et al. (2012) examined the role of depressive

symptoms (mild depression) on cognitive function and cognitive decline in persons with DM

versus controls. In overall cognition, performance was worse in those with DM compared with

the control group (p < .001). No difference was found in performance in all cognitive domains in

persons with DM both with and without mild depression, and no association was noted between

DM, mild depression, and accelerated cognitive decline (Koekkoek et al., 2012). Findings by

Trento et al. (2013) over four years from baseline showed stable mean scores for depression,

anxiety, and cognitive function in persons with DM who switched from non-insulin to insulin

treatment. Improvement in cognition was seen in two treatment groups (non-insulin and insulin)

four years after baseline (both p < .001). Depression and anxiety increased (both p <.001) in

those on insulin in the same time period, while depression decreased (p=04) and anxiety level

were unchanged in the non-insulin group. Women had higher levels of depression than men

(p<.001), and increased duration of DM was associated with increased anxiety scores (p = .01)

(Trento et al., 2013). A prospective study of participants in the ACCORD-MIND study,

conducted over 40 months, demonstrated the association of depression with greater cognitive

decline (but not necessarily cognitive impairment) in executive function (p = .02), mental

processing speed (p = .003), and verbal memory (p = .001) (Sullivan et al., 2013). In this study,

depression and cognitive decline were not associated with cardiovascular disease, baseline

cognition, age, or type of DM or hypertension treatment. These findings implicate depression as

a risk factor for the rapid development of cognitive decline in persons with DM (Sullivan et al.,

2013).

Table 2.1

Summary of Data-Based Studies Related to Cognitive Dysfunction in DM

Author/Year	Purpose	Conditions	Sample/Data source	Sample Characteristics	Design	Results
Cognitive Dysfunction in pre-DM						
Saczynski et al. (2008)	Examine differences in cognition by glycemic status. Measured domains: memory, mental processing speed (MPS) & executive function (EF)	Normal glycemic Impaired fasting glucose (IFG) Undiagnosed DM Diagnosed DM	1917 non-demented participants in the population-based AGE, Gene/Environment Susceptibility-Reykjavid Study (Iceland); 2002-2006	Normal (n=955, mean age=76 years, 64.4% female) IFG (n=744, mean age= 75.3 years, 54.4% female) Undiagnosed DM (n=55, mean age=75.9 year, 45.5% female) Diagnosed DM (n=163; mean age= 75.6 years; 44.2% female)	Cross-sectional	Compared with normal glycemic group: slower MPS in undiagnosed & diagnosed DM (both p<.01); poorer memory performance in undiagnosed DM (p<.05). DM duration > 15 years--slower MPS (p<.001) & poorer EF (p<.05). Role of DM duration, vascular and neurodegenerative comorbidities not well defined
van den Berg et al. (2008)	Compare cognitive function between DM patients, metabolic syndrome patients & controls. Measured domains: abstract reasoning, memory, MPS, EF, visuo-construction, & language**.**	DM MS (metabolic syndrome) Control	N=647 Cohort Hoorn study on glucose metabolism; Netherlands (2005-2007)	DM (n=64, mean age=74.1 years 50% female); MS (n=83, mean age=73 years, 53% female); Control (n=100, mean age=73.6 years, 50% female)	Cross-sectional	Compared with controls DM & MS patients had poorer scores in MPS, attention & EF (p<.05). DM & MS patient score differences were not significant. DM risk factors did not differ between DM & MS patients suggesting they may play a role in

						cognitive decline, potentially in pre-DM

Cognitive Dysfunction in Early DM

Nooyens et al. (2010)	Examine association of DM status and cognitive decline. Measured domains: memory, MPS, & cognitive flexibility (higher order information processing)	Prevalent DM (DM at baseline) Incident DM (DM diagnosed after baseline) No DM	N=2613 Subset of the Doetinchem Cohort Study (N=7769) to examine the impact of life style and biologic risk factors on health; Netherlands	Prevalent DM (n=61, mean age= 60.6 years, 49.2% female); Incident DM (n=78, mean age=57.4 years, 46.2% female); No DM (n=2460, mean age=55 years, 51% female)	Longitudinal	Baseline scores for with DM poorer compared to without DM. Prevalent DM compared with no DM had greater decline in: memory (p<.05), & cognitive flexibility (p<.01). Incident DM compared with no DM had greater decline in: memory, MPS, & cognitive flexibility (all p<.05) only for > 60 years age. Results supported that chronic hyperglycemia may affect different domains at different stages of DM

Ruis et al., (2009)	Examine type and severity of cognitive deficits in early DM (recent diagnosis). Measured domains: abstract reasoning, attention, & EF, language, memory (working, incidental, immediate / learning rate, forgetting rate), MPS, & visuoconstruction	DM No DM	N=3057, ADDITION cohort study, a national randomized treatment trial of DM participants comparing intensified and usual DM care (Netherlands, 2002-2004)	DM (n=183, mean age=61.2 years, 38.8% female); No DM (n=69, mean age=62.7 years, 52.2% female)	Cross-sectional	Compared with no DM group, with DM group had poorer performance in: memory (composite p<.05, immediate & incidental both p<.01), attention & EF, MPS, & language (all p <.05). Adjusted for IQ: DM group had poorer performance in: memory (composite & immediate both p<.05, incidental p<.01). Supports cognitive dysfunction already present in early DM.
Van Eersel et al. (2013)	Examine association of DM & cognitive function in persons aged 35-82 years. Measured domains: EF & memory (anterograde amnesia)	DM No DM	4158 participants from the Prevention of Renal & Vascular End-stage Disease (PREVEND) cohort (Netherlands)	DM (n=264, mean age=64 years, 37% female); No DM (n=3871, mean age= 54 years, 49% female)	Cross-sectional	With DM had poorer scores compared with no DM in EF & memory (both p<.001) Difference between groups in EF scores was largest at age 35-44 years (p<.001) & decreased with increasing age Differences between groups in memory scores were similar in all age groups. Findings support presence of cognitive dysfunction in young adults with DM.

Duration of DM and Cognitive Dysfunction						
Fischer et al. (2009)	Examine temporal stability and decline patterns of cognitive domains of DM patients and healthy control persons. Measured domains: declarative memory (episodic & semantic), verbal fluency, MPS (semantic speed, reaction time), EF (inhibition, task shifting)	DM No DM	Victoria Longitudinal Study, an ongoing multicohort study, sample three, wave 1 & 2 (initial N=570); initiated in late1980's (Canada)	Wave 1: DM (n=28, mean age=68.5 years, 64.3% female); No DM (n=272, mean age=66.7 years, 69.1% female); Wave 2: DM (n=28, mean age=72.8 years, 64.3% female); no DM (n=272, mean age=71.1 years, 69.1% female)	Longitudinal (3 years)	Repeated measures MANCOVAs group effects: DM poorer performance in EF (task shifting) & MPS (semantic speed) (p<.01); EF inhibition (p<.001, p<.05), MPS reaction time (p<.05). Findings supported deficits in MPS & speed intensive EF tasks may be early markers for cognitive decline in DM
Okereke et al. (2008)	Examine DM duration and cognitive decline in men and women. Measured domains: global cognition, verbal memory, EF (abstract concepts)	DM No DM	Participants in two large cohort studies: The Physicians' Health Study II (PHS) and the Women's Health Study (WHS)	PHS: DM (n=553; mean age=71.9 years; 100% male); no DM (n=5354; mean age=71.5 years; 100% male) WHS: DM (n=405; mean age=65.9 years; 100% female); no DM (n=5921; mean age=66.3 years; 100% female)	Cross-sectional	Compared with no DM, males & females with DM had lower baseline cognition scores. Association between DM & cognitive decline stronger with increased DM duration (trends p <.001). No interaction between DM & sex & 2-year cognitive decline

| Ravona-Springer et al. (2014) | Examine the relationships of long-term trajectories of glycemic control with cognitive performance in cognitively normal elderly persons with DM. Measured domains: attention/working memory, episodic memory, EF, semantic categorization | HbA1c trajectories (6) Based on level at entry (higher/lower), trend over 8.7 years mean duration (stable/decreasing/ increasing). Mean HbA1c measures per participant = 17.9. One-time cognitive assessment. | 835 participants from the Israel Diabetes and Cognitive Decline study randomly selected from the Diabetes Registry of the Maccabi Health Services, Israel (established 1998) | Lower/Stable (n= 227, mean age=72.99 years, mean entry HbA1c=5.96)

Higher/Stable (n= 365 mean age=72.91 years, mean entry HbA1c=6.84)

Lower/Increasing (n= 123, mean age=72.52 years, mean entry HbA1c=7.26)

Higher/Increasing (n= 46, mean age=70.78 years, mean entry HbA1c=7.76)

Lower/ Decreasing (n= 59, mean age=73.63years, mean entry HbA1c=9.19)

Higher/Decreasing (n= 15, mean age=69.73 years, mean entry HbA1c=10.73) | Cross-sectional | Higher/Decreasing group had lower scores in overall cognition (p range= .02-.002) & EF (p range= .03-.005) than all groups except the Higher/Increasing group

Higher/Decreasing group had lower scores in semantic (p range =.01-.005) than all groups except the Lower/Decreasing group

Lower/Stable group performed best in all cognitive domains |

Rawlings et al. (2014)	Examine association between DM in midlife and 20-year cognitive decline. Characterize long-term decline across levels of glucose control. Measured domains: EF, language, mental processing speed (MPS), verbal memory. Global z-score used to summarize all test performance.	No DM (HbA1c <5.7), Pre-DM (HbA1c 5.7 – 6.4), DM (HbA1c < 7.0 & ≥ 7.0)	13,351 participants in the Atherosclerosis Risk in Communities (ARIC) study, a prospective cohort study	No DM (n=11,572, mean age = 56.8 years, 55.3% female) With DM (n=1779, mean age =58.2 years, 57.2 % female)	Longitudinal	Average differences in 20-year decline comparing with DM & no DM (all p <.05): global, EF & MPS (19%), language (71%). Global decline over 20 years compared with no DM was greater with DM (all levels of control p=.037) & preDM (p= .005). DM with HbA1c ≥ 7.0 associated with greater decline than DM HbA1c <7.0(p=.071) Longer DM duration associated with greater decline for global & all domains (p for all trends ≤ .003)
Spauwen et al. (2013)	Investigate the effects of baseline & incident DM on decline in cognition over 12 years. Measured cognitive domains (at 6 & 12 year follow-ups): EF, global function, MPS, verbal memory	No DM, DM (at baseline), incident DM (found at follow up)	1290 participants at baseline from the Maastrich Aging Study (MAAS) (Netherlands).	NoDM (n-1,222; mean age= 59.4 years; 50% female) Baseline DM n=68; mean age = 68.8 years; 50% female) Incident DM-6years (n=54; mean age= 62.9 years; 33.3% female) Incident DM-12 years (n=57; mean age= 57.4 years; 47.4% female)	Longitudinal	Baseline DM decline over 12 years compared with noDM: MPS & EF (p<.01); verbal memory (p<.05) Incident DM compared with no DM: subtle early decline in MPS 12-year duration of DM had c on MPS (p<.05)

| Tuligenga et al. (2014) | Examine whether DM and pre-DM are associated with faster cognitive decline from late midlife (age 55 years) to early old age (age 65 years). Examine association of DM duration & glycemic control & cognitive decline. Measured cognitive domains: reasoning, semantic fluency, verbal fluency & verbal memory. Global score was derived. | Four groups: Normoglycemic, Pre-DM, New DM, Known DM | 5653 participants from the Whitehall II cohort study (London); Cognitive tests done 3 times over 10 years (1997-99, 2002-4, 2007-9); HbA1c done twice during follow up (2002-4, 2007-9) | Normoglycemic (n=4703, baseline mean age = 55.1 years, 27% female, mean HbA1c=5.4%) Pre-DM (n=648, baseline mean age = 57.5 years, 27% female, mean HbA1c=5.71%) New DM (n=115, baseline mean age = 59 years, 30% female mean HbA1c=6.27%) Known DM (n=187 baseline mean age = 57.4 years, 30% Female, mean HbA1c=6.84%) | Longitudinal | Known DM compared with Normoglycemic had faster decline in memory (45%; p=.046), reasoning (29%; p=.026, & global cognitive score (24%; p=.014). Pre-DM & New DM rates of decline similar to Normoglycemic. Poorer glycemic control in Known DM associated with faster decline in memory (p=.034). |

| Yaffe et al. (2012) | Determine if prevalent & incident DM increase risk of cognitive decline;

Determine if high HbA1c is related to worse cognitive performance

Measured cognitive domains: global cognition (MMSE); attention, EF, MPS (DSST) | DM, no DM at baseline

Incident DM identified over 10 years with HbA1c done at years 4, 6, &10 | 3069 participants in the Health, Aging, & Body Composition Study (Tennessee, Pennsylvania), began 1997 | DM at baseline (n = 717, mean age =74.2 years, 45.5% female)

NoDM at baseline (n = 2193, mean age = 74.1 years, 53.8% female)

Incident DM (n = 159, mean age = 73.7 years, 49.1% female) | Longitudinal | DM at baseline compared with noDM: lower MMSE & DSST scores (both p=.001). Incident DM at baseline compared with noDM MMSE & DSST similar, but lower than DM

DM at baseline compared with noDM decline over 9 years: lower MMSE (p=.008) & DSST (p = .001). Incident DM compared with noDM decline not significant, but lower than DM at baseline.

DM at baseline: at 3.5 years higher HbA1c associated with poorer scores in MMSE (p=.003) & DSST (p =.04) |
| Yeung et al., (2009) | Examine group differences in cognitive performance by DM status and age (young-old & old-old).

Measured cognitive domains: declarative memory (episodic & semantic), EF (inhibition, task shifting), MPS (semantic speed, reaction time), & verbal fluency | DM, no DM | Participants in the Victoria Longitudinal Study, sample three, wave 1(initial N=570); Canada (2002-2003) | DM: young-old (n=24, mean age=63.6 years, 66.7% female); old-old (n=17, mean age=75.6 years,41.2% female)

No DM: young-old (n=273, mean age=62.45 years, 72.5% female); old-old (n=151, mean age=77.6 years, 63.6% female) | Cross-sectional | DM group had poorer scores than non DM in EF (inhibition p=.003; task switching p=.013), MPS (semantic speed tests p=.015 & p =.008). Old-old group had poorer scores than young-old in all measures except semantic memory & verbal fluency (p range <.001-.047). There were no interaction effects with age group & DM status indicating DM related deficits maybe constant across age. |

Risk Factors and Cognitive Dysfunction in DM						
Cukierman-Yaffe et al. (2009)	To examine the relationship between the degree of hyperglycemia in DM & cognitive status. Measures included: HbA1c, FBG, global cognition (MMSE), visual motor speed, learning capacity, attention & working memory (DSST), verbal memory, EF-inhibition	DM	Participants in the ACCORD-MIND sub study, conducted to examine rate of cognitive decline between DM patients treated with standard or intensive blood glucose lowering	Baseline characteristics (n=2,977, mean age=62.5 years, mean DM duration=10.4 years, 47% female)	Cross-sectional data	Association between 1% higher HbA1c & poorer scores in global cognition, DSST (both p<.0001), verbal memory (p=.014), EF (p=.009). No associations found for FBG. Findings supported a relationship between poorer HbA1c & progressive cognitive decline.
Degmecic et al., 2014	Determine rate of depression & anxiety & cognitive function in DM patients compared with controls. Measured cognitive domains: global cognition (MMSE)	DM, no DM	N = 108, (mean age = 61 years) epidemiological study, Croatia	M (n=66, 42% female); no DM (n=33% female)	Cross-sectional	DM group have more depression & anxiety than no DM group (p=.035, p = .002) Prevalence of depression (moderate to very severe) in DM group = 36%. More cognitive dysfunction in DM group than no DM (p =.001)
Koekkoek, et al., (2013)	Investigate the influence of depressive symptoms (mild depression) on the	DM, noDM	Data from three studies (ADDITION, Hoorn, UDES)	ADDITION: DM (n=183, mean age = 63 years, 39% female), no	Meta-analysis	DM had worse performance than noDM in composite (p<.001), & no difference in any separate domain.

	relationship between DM & cognitive function with meta-analysis of three studies Measured cognitive domains: attention, executive function, memory, mental processing speed		using cross-sectional (all 3 studies) (N=570) & longitudinal (ADDITION & UDES) (N=228) analysis	DM (n=39, mean age = 62 years, 72% female) UDES: DM (n =99, mean age =66years, 49% female), no DM (n=33, mean age= 64 years, 58% female) Hoorn: DM (n=84, mean age = 75 years, 49% female), noDM (n=132, mean age = 74 years, 58% female)		Differences between DM with or without depression worse with depression but not significant in any cognitive domain. DM no greater cognitive decline over 3 years than noDM (p = .21) Difference between cognition in DM & no DM not mediated by mild depression
Sullivan et al., 2013	Determine whether comorbid depression in DM accelerates cognitive decline months Measures included: depression (PHQ-9) --at baseline, EF (Stroop Test), MPS (DSST), verbal memory (RAVLT)-- at baseline, 20 & 40 months	DM	Participants from the ACCORD-MIND sub-study	N= 2977 (mean age = 62.5 years, 46.6 % female) PHQ-9 score <10 None to mild depression (n=2446, mean age = 62.7 years, 44.7% female) PHQ-9 score ≥ 10 Moderate to severe depression (n=531, mean age =61.3 years, 55.6% female)	Longitudinal	Participants with PHQ-9 scores ≥ 10 compared with <10 showed greater decline over 40 months in: EF (p = .02), MPS (p=.003), & verbal memory (p=.001) Effect of depression on risk of cognitive decline did not differ with baseline age or cognition, prior cardiovascular disease, or type of DM treatment.
Trento et al., 2014	Investigate associations between clinical & sociodemographic variables in persons with DM, and depression, anxiety & global cognitive dysfunction (MMSE), over a 4-year time span.	DM insulin (IT) & non-insulin (NIT) treated at baseline (t0) & at 4 years (t4)	Participants from a diabetes clinic (Turin, Italy) (N=498)	IT t0 & t4 (n=214) NIT t0 & t4 (n=171) NIT t0 & IT t4 (n=41)	Longitudinal	IT t0 & t4: increased anxiety & depression (both p<.001), improved MMSE (p<.001) NIT t0 & t4: decreased depression (p=.04) improved MMSE (p<.001), anxiety unchanged NIT t0 & IT t4: no change in anxiety, depression or MMSE

						Females had higher levels of depression than males (p<.001) Anxiety increased with DM duration (p=.011)
Umegaki et al. (2012)	To examine the association of comorbidities in DM and cognitive decline over a six-year time span. Measures included MMSE, Geriatric Depression Scale, HbA1c, fasting blood glucose and other clinical variables.	DM	Japanese Elderly Interventional Trial	All participants (n = 61, mean baseline age= 70.6 years, 57.5% female) With MMSE 5 point decline (n=23, mean baseline age=72.8 years, 56.5% female) Without MMSE 5-point decline (n=238, mean baseline age=70.4 years, 57.6% female)	Longitudinal	Baseline clinical variables differed in those with 5 point MMSE decline: higher systolic BP, & triglycerides, lower HDL, more Nephro/retino/neuropathy/ (p ranges <. 001- <.05); Adjusted logistic regression: higher systolic BP (p=.047) & triglycerides (p=.029) associated with decline

The Relationship between Self-care and DM

Of the eleven publications that focused on the relationship between self-care and DM, six focused on cognitive dysfunction and DM self-care performance, three on cognitive dysfunction and self-care knowledge, and one on decision-making in DM self-care. (see Table 2 for summaries). Managing DM requires active participation in self-care, including both management strategies and daily performance of multiple tasks to maintain optimum health and quality of life, and to avoid complications (Song, 2010). Effective self-care positively correlates with better glycemic control, health outcomes, and perceived health (Song, 2010).

Cognitive Dysfunction and DM Self-care

Studies that examined the relationship between cognitive dysfunction and DM self-care revealed a cyclic association between DM self-care, increased comorbidities and cognitive dysfunction, and decreased functional abilities (Feil, Zhu, & Sultzer, 2012), and increased health care utilization (Tran, Baxter, Hamman, & Grigsby, 2014). Performance of self-care maintenance (diet, blood glucose monitoring, and medication use) and self-care management (sign/symptom recognition, treatment implementation and evaluation) activities likely influence hospitalizations in different ways (Song, Ratcliff, Tkacs, & Riegel, 2012). Among those with DM who were hospitalized, the majority reported taking all doses of DM medications (88.3%) and checking blood glucose readings (58.7%) daily; more were able to recognize hyperglycemic symptoms than hypoglycemic symptoms (58.3% and 16.8%, respectively). Diet adherence (fruits and vegetables) was associated with decreased likelihood of hospitalization (p<.001). The incidence rate of hospitalization decreased with having a target glycohemoglobin (IRR =.86. p=.001), and with eating two or more snacks or dessert foods per day (IRR = .914, p=.043), but increased when hyperglycemia was confirmed by checking blood glucose (IRR= 1.105, p =

.037). Fewer hospitalization days were associated with having a target glycohemoglobin (IRR =.728, p<.001), and confirming hypoglycemia by checking blood glucose (IRR = .832, p =.033). In contrast, hospitalization days increased with recommended blood glucose testing frequency (IRR=1.170. p =.016) (Song et al., 2012).

With increased DM comorbidities and cognitive impairment, the ability to manage and adhere to self-care domains of exercise, blood glucose monitoring, diet, and foot inspection decreased (all p< .05) (Feil et al., 2012). The ability to exercise and follow diet recommendations were the most affected, but medication management was unaffected. Compared with participants with the least cognitive impairment, those with moderate or severe impairment were less likely to exercise (moderate and severe both p=.05) or follow the recommended diet (moderate and severe both p=.01) (Feil et al., 2012).

Decreased executive function in persons with DM has been linked to poorer performance in activities of daily living (ADL) and instrumental activities of daily living (IADL)(Qiu et al., 2006; Tran et al., 2014). Decreased medication management ability was predictive for increased nursing home admission, clinic, and emergency visits (Tran et al, 2014). Executive dysfunction may affect self-care abilities through impairments in insight, abstraction, judgment, planning, and problem solving (Primozic, Tavcar, Avbelj, Dernovsek, & Oblak, 2012; Thabit et al., 2009). Although intact executive function is essential for adherence, establishing new behaviors, suppressing old behaviors, and self-regulation (Tran et al, 2014), one study of older adults (mean age [SD] = 73 [± 6.5] years) with mild impairment in executive function and verbal memory found no change in HbA1c over a two year time span (Palta et al., 2014). Some cognitive measures are more sensitive than others in detecting executive dysfunction in persons with DM,

consequently impaired executive function may be present yet undetected in persons with normal

global cognition, (Thabit et al., 2009).

Cognitive dysfunction and DM self-care knowledge.

Important antecedents to self-care are knowledge about DM and self-monitoring skill

acquisition (Song & Lipman, 2008). Relationships between the multiple mechanisms linking

cognition, knowledge and self–care are complex and not clearly delineated (Nguyen et al. 2010).

Hewitt, Smeeth, Chaturvedi, Bulpitt, and Fletcher (2011) reported that older persons (mean age

80.9 years) who took insulin and had global cognitive impairment had poorer knowledge about

managing hypoglycemia (p=.013, p = .008) and medications during an acute illness (p=.017)

than did those without impairment. Another study, which examined the relationship of self-care

to the conceptualization and understanding of self-care in DM patients (mean age [SD] = 53.9 [$\pm$

17.3] years), found that participants with poor glycemic control lacked understanding of basic

self-care (mechanisms of medications, concepts of glucose monitoring, symptom detection, role

of exercise, dietary instructions, and behavior-lifestyle adjustment), and had difficulty detecting

and solving problems (Lippa and Klein, 2008). Individuals with moderate glycemic control

demonstrated a vague understanding of medications, monitored their blood glucose regularly,

and inconsistently applied results to events. For example, while many of the participants could

detect symptoms of hyper- or hypoglycemia, they often lacked the ability to correct for these

states. Dietary rules tended to be broadly followed, but were overwhelming due to their number

and complexity. Also, the role of exercise was poorly understood and exercise beyond ADLs

was uncommon. Individuals with good glycemic control either had a fixed routine or utilized in-

depth medication knowledge to modify routines. They tended to monitor blood glucose several

times daily, and understood the relationship between exercise and glucose levels (although

exercise frequency was no greater than in the other two groups). Individuals in this group also used monitoring to develop diets and judge behavior success, and could effectively identify and manage episodes of hypo- and hyperglycemia (Lippa & Klein, 2008).

Decision-making in DM self-care.

The patient's role in chronic disease has evolved to include not only treatment adherence but active decision making (Song, 2010). Lippa, Klein, and Shalin (2008) examined relationships between levels of decision making and DM control, and the use of declarative (factual) and applied (procedural) knowledge in DM self-care. Levels of decision-making range from novice to expert, and differ in the cognitive processes of problem detection and cue utilization, functional relationship comprehension and organization, and problem solving strategies. Novice level decision-making utilizes more superficial organizational patterns when applying knowledge to functional relationships, and exhibits less efficient problem-solving strategies than expert level decision making. Greater use of problem detection cues was associated with better treatment adherence and lower blood glucose levels, and the more expert participants combined multiples cues to increase problem detection. Participants who identified more functional relationships and had better problem-solving abilities also exhibited better adherence, but not necessarily better glycemic control. The probability of having accurate declarative knowledge was greater than the probability of being able to apply that knowledge in critical situations of hyper and hypoglycemia. The study revealed that having DM knowledge alone does not necessarily coincide with the application of that knowledge to self-care actions (Lippa et al., 2008).

Table 2.2

Summaries of Data-Based Publications Related to the Relationship Between Self-Care and DM

Author,year	Purpose	Conditions	Sample/Data Source	Sample Characteristics	Design	Results
Feil et al. (2012)	To examine relationships between cognitive impairment and DM self-care ability. Measures: DM self-management adherence; Telephone Interview for Cognitive Status; Total Illness Burden (TIB) (with DM comorbidities categorized into 4 quartiles)	DM	Participants from the 2003 Health and Retirement Study Diabetes Survey	N=1,398 (mean age = 70 years; 52.8% female)	Cross-sectional	For each level of cognitive impairment (3 levels best to worst): ability to manage each self-care domain decreased as DM comorbidities worsened (all $p<.05$). The majority reported being able to manage medications at all levels. Those with the most cognitive impairment compared with those with the least impairment were less likely to: exercise (moderate OR =.725, most OR=.712, both $p<.05$); & follow diet (moderate OR = .906, most OR = .618, both $p <.01$). Results for checking blood glucose &

						feet were not significant.
Hewitt et al. (2011)	To examine DM knowledge & management of older persons Assess the impact of cognitive impairment (CI) on DM knowledge & management Measured cognitive domain: global cognition (MMSE)	DM	Participants from the MRC General Practice Research Framework (N= 15,095), United Kingdom	n=1,015 (mean age = 80.9 years, 53.3% female) MMSE ≤ 23 with CI (n=235, 22.5%) Insulin treated total (n=144,14%), with CI (n =37,4%)	Descriptive	Did home blood glucose testing: (n=247, 23.6%) daily (n=97,39.3%) weekly (n=138, 55.9%) with CI (n=50, 20.2%) Insulin treated comparing with & and without CI: with CI group gave more incorrect responses to DM management questions (p values = .013, .008, .017)
Lippa & Klein (2008)	To describe relationship of DM self-care behaviors (glucose regulation proficiency) & cognition (understanding of DM self-care)	DM	Participants recruited via psychology students or advertisement	N = 18 (mean age =53.9 years; 33% females) Glycemic control (HbA1c): poor (>7%, n=8), moderate (6.0-7.0 %, n=5), good (<6%, n=5)	Descriptive	Poor control: poor understanding of self-care, functional dynamics of DM, medications, relationship of glucose monitoring & role of exercise; poor problem detection & resolution; moderate adherence to medications; no exercise. Moderate control: vague under-standing of medications & role of exercise;

						moderate understanding of diet; able to detect problems, unable to correct hyper-glycemia.
						Good control: either had fixed routine, or in depth under-standing & adjusted routine; minimal exercise but understood link
Lippa et al. (2008)	To assess the relationship between decision making (problem detection, functional relationships, problem solving, types of knowledge—declarative & applied) and DM self-care (adherence-SSCA & glycemic control-glucose levels within past week)	DM	Participants recruited via psychology students or advertisement	N=18 (mean age =53.9 years; 33% females)	Descriptive	Problem detection: better use of cues associated with better adherence & glycemic control (both p<.05); Functional relationships: increased articulation associated with better adherence (p<.05), but not glycemic control; Problem solving: increased strategies associated with better adherence (p<.05), but not glycemic control Probability of having accurate

						declarative knowledge greater then probability of applying knowledge for high & low glucose (both p<.05)
Nguyen et al. (2010)	To examine role of EF in acquiring knowledge& adopting DM self-behaviors Cognitive measures: language ability, attention, & working memory aspects of EF, and a derived composite measure	DM	DM patients recruited from three rural counties in North Carolina	N = 90; (mean age =72.2 years;59% females)	Cross-sectional	Linear regressions adjusting for covariates: EF associated with glycemic control (p=.01); Final model including above, DM knowledge, DM meds & self-care: DM knowledge (.01) & DM meds (oral p<.05, insulin p=.01) EF & self-care not significant
Palta et al. (2014)	To examine the relationship between mild cognitive dysfunction and changes in DM control (HbA1c), systolic blood pressure and lipids (LDL).	DM	Participants in the Informatics for Diabetes Education and Telemedicine (IDEATel) Project; New York State, 2000-2008. N=1,665	Participants in 5-year ancillary study in second phase (2004-2008) n = 613 (mean age =73.0 years; 69.5% females)	Longitudinal	Having mild executive or verbal memory dysfunction (scores < 16th percentile) was not significantly associated with poorer HbA1c, systolic blood pressure or LDL measures.

	Measured cognitive domains: executive function, verbal memory.					
Primozic et al. (2012)	To identify independent association of cognitive functions & psychological factors with DM self-care To evaluate predictors of DM self-care Measures: immediate & delayed memory, attention, language & visuospatial (RBANS); EF—planning & problem solving, working memory (Tower of London); MPS & cognitive flexibility (Stroop Test); depression (HDI; distress (PAID)	DM	DM patients at a DM outpatient clinic—University Medical Center, Ljubljana, Slovenia	N=98 (mean age= 63.74 years; 51% females)	Descriptive	Significant association between self-care & cognitive functions: Tower of London planning & problem solving, (p=.002); RBANS total (p=.005), immediate memory (p=.04), visuospatial (p=.02), attention & depression (both p=.01) Multivariate model for prediction (R^2=.37, p<.001); Strongest predictors: better EF & absence of depression (both p=.017)
Qiu et al. (2006)	To examine patterns of cognitive deficits in relation to ADLs and DM status Measures: global cognition (MMSE); EF & visuospatial (Block design); MPS (Trails A); EF(Trails B)	DM No DM	Nutrition and Memory in Elders Study; Boston, MA N = 291	DM (n=115, mean age= 74.5 years, 74% female) no DM (n=176, mean age = 77.4 years, 78% female)	Cross-sectional	DM group compared with no DM, poorer scores for: MMSE (p=.02); ADLs (p=.04); EF/visuospatial (p =.003); EF (p=.03); Attention/WM/EF (p=.02);

	attention, working memory, EF (Digit Span); verbal memory (Word List Learning); EF language (COWA); depression scale, ADLs					verbal memory (p=.01&.04); & more depression (p=.03)
Song et al. (2012)	To evaluate the influence of DM self-care on health outcomes of health care resource utilization (number of hospitalization and number of days)	DM	Participants in the Healthy and Retirement Study (HRS) (2002-2004 N=1785); HRS-DM study (N=1509)	Subsample n=726 (mean age= 66.78 years, 48.5% female)	Cohort, secondary analysis	Hospitalizations: (n=459, 36.8%, mean frequency: 0.65 ± 1.18, mean stay: 3.83 ± 10.7days); 88.3% took all doses of DM meds daily; 58.7% checked daily blood glucose; Hyperglycemia was recognized more frequently (58.3%) than hypoglycemia (16.8%)
Thabit et al. (2009)	To assess for association between executive function (EF) test scores (EXIT25, FAB), DM self-care (SDSCA, IADLs) and metabolic parameters. MMSE for global cognition.	DM	DM patients recruited from a DM clinic in Dublin, Ireland	N=50 (mean age= 67.0 years; 32% females)	Descriptive	T-tests: EXIT25 mean score indicated 14% had impaired EF, FAB mean score indicated 48% had impaired EF in same sample; Correlations: FAB & SDSCA not significant, but those with below normal FAB scores had lower SDSCA scores; MMSE & SDSCA (p<.05);

						No association between glycemic control, DM duration, &EF, cognitive impairment, IADLs or SDSCA
Tran et al. (2014)	To examine whether older persons with DM had: 1) more cognitive dysfunction than older persons without DM, 2) executive dysfunction associated with impaired self-care, and 3) executive dysfunction associated with increased use of health services Measured cognitive domains included: constructional praxis, EF, global cognition, procedural learning, working memory	DM No DM	San Luis Valley Health and Aging Study; Colorado N=1,358	No DM & with DM n=1,063 (mean age= 72.8 years; 58.1% females) With DM subsample n=252 (mean age= 71.8 years; 58.7% females)	Cross-sectional	With DM group compared with no DM group scored worse in EF, global cognition, working memory (all p<.05), constructional praxis (p<.001), & procedural learning (p<.01) In the with DM group: impaired EF was associated with decreased IADL ability, medication & meal management (p values < .013- < .001) ; decreased global cognition was associated with decreased total IADL ability (p<.01) In the with DM group impaired EF was associated with increased nursing home admission (p = .008) & increased

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						clinic and emergency visits (p = .004)

Discussion

In this systematic state of the science review of 74 publications, the most important findings were: 1) recent research documenting the interplay of pathophysiological brain changes with cognitive dysfunction in DM, and the contribution of specific risk factors, 2) clarification of the presence of cognitive dysfunction in pre- and early DM, and 3) evidence relating cognitive dysfunction to DM self-care. Further research is urgently needed to link these recent advances in knowledge together to explore relationships to glycemic control.

Publications included in this review and categorized as pathophysiology, reviews of empirical studies, and data-based studies related to cognitive dysfunction in DM addressed guiding question one: What factors influence cognitive dysfunction in persons with DM? Although studies differed in the use of cognitive tests, overall results of two systematic reviews (25 and 19 studies) indicated that persons with DM had a 1.5 times greater risk than persons without DM for cognitive decline (Cukierman et al., 2005), Alzheimer's and any type of dementia, and 2.5 times greater risk for vascular dementia (Cheng et al., 2012). Longer duration of DM and poorer glycemic control were associated with a greater decline in several cognitive domains (Nooyens et al., 2010; Okereke et al., 2008; Ravona-Springer et al., 2014; Rawlings et al., 2014; Tuligenga et al., 2014). The cognitive domains most often affected in DM include attention, executive function, mental processing speed, and verbal memory (Reijmer et al., 2010).

Because early stages of DM are often undiagnosed, early cognitive decline often goes unnoticed as well (Fischer et.al, 2009; Nooyens et al., 2010; Okereke et al., 2008; Ruis et al., 2009; Saczynski et al., 2008; Yeung et al., 2009). Risk factors associated with DM-microvascular complications, hypertension, obesity, and hyperlipidemia-are interrelated and may

affect cognition at various times for various durations (Biessels et al., 2013; Cukierman, et al., 2005; Reijmer et al., 2010; van den Berg et al., 2009). Along with these interrelated risk factors, age-related changes are influential in cognitive decline (Biessels et al., 2010; Reijmer et al., 2010). A high prevalence of depression has been found in persons with DM (Degmecic et al., 2014; Koekkoek et al., 2012; Sullivan et al., 2013; Trento et al., 2013), and may be another risk factor for cognitive decline (Sullivan et al., 2013). Evidence suggests that cognitive decline may follow two different processes in DM: 1) mild slowly progressing decline beginning in pre-DM stages, and 2) severe faster decline with high prevalence of vascular and Alzheimer's dementia (Reijmer et al., 2010). Critical points of cognitive decline in specific cognitive domains in persons with DM have yet to be defined

Causative mechanisms of structural brain changes in DM are also yet to be clarified. Primary etiologies of structural brain changes are associated with commonly occurring metabolic, endocrine, vascular, and central nervous system factors (McCrimmon et al., 2012). Mechanisms of impaired neurogenesis, blood brain barrier and vascular dysfunction, inflammatory processes, insulin resistance, and hyperglycemia have all been documented to play a role in the development of DM-related cognitive dysfunction (Biessels et al., 2014; Umegaki, 2012). Several publications addressed the effects of insulin resistance on the anatomy and function of the brain. Insulin resistance, which occurs in both pre-DM and DM, appears to have several unclear effects on brain metabolism (Lamport et al., 2009; McKay & Recknagel, 2011), neuronal activity (Convit, 2005; Williamson et al., 2012), and vascular function (Lamport et al., 2009; McKay & Recknagel, 2011). Insulin resistance has been shown to be associated with both decreased brain structure volumes (Convit et al., 2005; Manschot et al., 2006; Manschot et al.,

2007) and impaired DMN functional connectivity (Chen et al., 2014; Marder et al., 2014; Musen et al., 2012).

Decreases in brain volumes in DM compared with that in the normal aging process have been found to vary from no difference to a rate of up to three times greater (de Bresser et al., 2010; Espeland et al., 2013; vanElderen et al., 2010). Hippocampal atrophy has repeatedly been shown in persons with DM (Convit, 2005; den Heijer et al., 2009; Gold et al., 2007); atrophy in other brain regions essential for memory and other higher cognitive functions has also been found (Samaras et al., 2014). Brain atrophy and poorer cognitive scores in DM patients are associated, but findings are inconsistent (Brundel et al., 2012; Christman et al., 2010; de Bresser et al., 2010; van Elderen et al., 2010).

Decreases in cognitive function associated with white matter tracts connecting frontal, parietal and temporal brain regions included attention, executive function, mental processing speed, and verbal memory (Reijmer et al., 2013). Recent studies have documented reduced functional connectivity between the hippocampus and the DMN (medial prefrontal and temporal parietal brain regions) (Chen et a., 2014; Hoogenboom et al., 2014; Musen et al., 2012; Zhou et al., 2010). Zhou et al. (2010) demonstrated dysfunction in episodic memory and executive function in persons with DM and postulated that reduced neuronal connectivity disturbances may be widespread in persons with DM, affecting learning and memory (Zhou, 2010).

Further research is needed to specifically target mechanisms of increased cognitive decline and prevalence of dementia in DM. Emerging technologies in imaging and biomarkers may assist in needed research to discover methods of preventing DM-related cognitive decline, potentially at pre-symptomatic and early stages of the disease. Contributing modifiable risk factors need to be clarified, and interventions developed to reduce them at crucial points in time.

Limitations identified in this review include inconsistent cognitive testing, secondary analyses of data not collected solely in DM participants, and the lack of prospective studies.

In addressing the second guiding question regarding the association between cognitive dysfunction and DM self-care activities, publications were categorized as follows: 1) cognitive dysfunction and DM self-care performance, 2) cognitive dysfunction and DM self-care knowledge, and 3) decision making in DM self-care.

Having DM requires active participation in self-care to maintain physiologic stability, and requires behaviors including treatment adherence, sign and symptom monitoring, recognition, evaluation, and treatment implementation (Song, 2010). The daily routine an individual adopts differs from the decision making and problem solving required for coping with condition changes. Knowledge gaps exist concerning differences in self-care maintenance and self-care management activities (Song, 2010).

A complex relationship exists among all elements of DM self-care performance, increased comorbidities, increased cognitive dysfunction, decreased functional abilities and increased health care utilization (Feil et al., 2012; Tran et al., 2014). Increased presence of DM comorbidities and cognitive dysfunction has been shown to be associated with decreased adherence to self-maintenance (Feil et al., 2012). Self-care maintenance and self-care management activities can influence health outcomes in different ways (Song et al., 2012). For example, achieving a target glycohemoglobin was associated with decreased rate and length of hospitalization, whereas adhering to recommended blood glucose testing frequency was associated with an increased length of hospitalization (Song, 2012).

Intact cognitive ability is necessary for the complex tasks necessary for daily DM self-care, and may be difficult to ascertain because impaired executive function may co-exist with

normal global cognition performance (Thabit et al., 2009). Executive dysfunction is linked to

impairment in insight, abstraction, judgment, (Thabit et al., 2009), planning and problem solving

(Primozic et al., 2012), and subsequently self-care, ADL and IADL performance (Nguyen et al.,

2010; Primozic et al., 2012; Qiu et al., 2006; Thabit et al., 2009). Executive function is essential

for adherence, establishing new behaviors, suppressing old behaviors, and self-regulation (Tran

et al, 2014). Factors such as age, comorbidities, education, medications and sociodemographic

variables may also contribute to cognitive dysfunction (Manschot et al., 2007; Nguyen et al.,

2010; Saczynski et al., 2008).

Important antecedents to self-care are knowledge about DM and self-monitoring skill

acquisition (Song & Lipman, 2008). The links between cognition, DM knowledge and DM self–

care performance are complex and not clearly delineated (Nguyen et al. 2010).

Lippa and Klein (2008) demonstrated a relationship between poor glycemic control, poor

understanding of basic self-care, and difficulty with problem solving. Better glycemic control

was associated with regular blood glucose testing and use of the test results to modify self-care

routines (Lippa & Klein, 2008). Lippa et al. (2009) highlighted the difference between the two

cognitive processes of having knowledge (declarative) and using knowledge (applied). The

probability of having accurate declarative knowledge was greater than the probability of

applying that knowledge in critical situations of hyper- and hypoglycemia. This suggests that

having DM knowledge does not necessarily determine self-care actions (Lippa et al., 2009).

Decision-making expertise requires problem detection, cue utilization, functional relationship

comprehension and organization, and problem solving strategies (Lippa et al., 2009). Increased

use of cues was associated with increased treatment adherence and lower blood glucose levels.

Better functional relationship comprehension and problem solving strategies were associated

with better treatment adherence, but not with lower blood glucose levels. Further research is needed to examine how cognitive processes are associated with self-care expertise, skill learning, and skill performance (Lippa et al., 2008).

Although declining cognitive function interferes with social and environmental interaction and affects quality of life and independence (Vance et al., 2011), it is often overlooked in chronic disease management until a neurologically based condition warrants attention. Cognitive dysfunction is also not typically considered when planning interventions for self-care and maintaining independence (Biessels et al., 2007; Rucker et al., 2012; Vance et al., 2011). Awareness of cognitive dysfunction is relevant not only for debilitated persons, but also for working adults whose job performance may suffer (Waclawski, 2012). Addressing cognitive dysfunction has many implications for nursing and other health care disciplines, since strategies for preventing or reducing complications can be tailored relative to cognitive abilities (Munshi, 2008; Rucker et al., 2012; Vance et al., 2011). The findings of this review supported the dynamic nature of DM self-care and the need for targeted teaching strategies that assess and recognize the cognitive skills necessary for learning, problem solving, decision making (Lippa & Klein, 2008; Song et al., 2012), and goal setting (Song et al., 2010). A limitation of this review was the lack of systematic reviews and meta-analyses pertaining to DM-related cognitive dysfunction and DM self-care performance.

In summary, the daily routine an individual adopts differs from the decision-making and problem-solving required in response to condition changes. Knowledge gaps exist concerning the differences in self-care maintenance and self-care management activities and the cognitive processes underlying the different self-care behaviors. Sign and symptom recognition in DM self-care is not well understood, and increased comprehension of these phenomena will be

important for providing guidance to persons with DM. Cognitive dysfunction and other factors may interfere with understanding, recalling, and applying instructions, and may contribute to poor daily routine performance and impaired sign and symptom recognition. Further studies exploring the links between cognition, DM self-care, and health outcomes are greatly needed.

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CHAPTER III

Glycemic Control and Cognitive Function in Rural Adults with Type 2 Diabetes

Introduction

The prevalence of type 2 diabetes mellitus (DM) is growing at epidemic proportions, especially among adults ages 45 and older (CDC, 2014). Persons with DM are at high risk for serious complications associated with chronic hyperglycemia, including structural brain changes and decreased cognitive function. Glycemic control, defined as maintaining a glycohemoglobin (HbA1c) at 7% or below, reduces microvascular and neuropathic complications associated with DM (ADA, 2016). The complexity of maintaining adequate glycemic control demands performance of ongoing self-care routines that require multiple cognitive processes (Nguyen et al, 2010; Saczynski et al., 2008). Other factors contributing to decreased cognitive function include sociodemographic variables, age, gender, comorbidities, education, medications, and duration of having DM (Saczynski et al., 2008). Rural adults (≥ 18 years of age) often have less access to DM resources and specialty care, and are at greater risk for poorer glycemic control than are adults in non-rural communities (Hale, Bennett, & Probst, 2010). While one's ability to maintain glycemic control may be highly dependent on cognitive abilities, there is limited understanding about the relationship between cognitive function and glycemic control (Nguyen et al, 2010). The overall purpose of this study was to examine the relationship between glycemic control and cognitive function in older rural adults with DM.

Background

Cognitive dysfunction in DM

      Research findings regarding the appearance and progression of cognitive decline in DM is equivocal (Moheet, Mangia, & Seaquist, 2015). Although it is well documented that persons with DM are at 1.5 times greater risk for cognitive decline (Cukierman et al., 2005), and all types of dementias (Cheng et al., 2012), early stages of DM and early cognitive decline are often undiagnosed (Fischer, deFrias, Yeung, & Dixon, 2009; Nooyens, Baan, Spijkerman, & Vershuren, 2010; Okereke et al., 2008; Ruis et al., 2009; Saczynski et al., 2008; Yeung, Fischer, & Dixon, 2009). There is evidence for both a mild slowly progressing decline beginning in pre-DM stages, and a severe faster decline with high prevalence of vascular and Alzheimer's dementia, with critical points of cognitive decline in specific cognitive domains have yet to be defined (Reijmer et al., 2010).

      The Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes (ACCORD-MIND) trial, a sub-study of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, examined differences between the rate of cognitive decline and structural brain changes in ACCORD participants (Cukierman-Yaffe et al. 2009). The results revealed an age-adjusted association between higher HbA1c levels and poorer cognitive test scores in the domains of global cognition, executive function, mental processing speed, and verbal memory, and supported the hypothesis of a progressive and positive relationship between chronic hyperglycemia and cognitive dysfunction. Also, the relationship between HbA1c and cognition became non-significant after controlling for age, sex, education, race, language, duration of DM, CV disease, and depression, in models with attention, executive function and global cognition, but remain significant in all models with verbal memory. Cukierman-Yaffe and colleagues

(2009) concluded that HbA1c levels may not be a major determinant in cognitive test performance; rather, sociodemographic and clinical factors are more influential.

Results by Manschot and colleagues (2006, 2007) indicated that cognitive domains of perception, visuoconstruction and language were less affected in persons with DM compared to age-, sex-, education- matched controls, and short-term memory appeared to be affected more than long-term memory (Reijmer et al., 2010). Cognitive processes of attention, executive function, mental processing speed and verbal episodic memory are essential for processing and learning new information, encoding and storing it in memory, and retrieving previously learned information, which is critical for performing good self-care (Cukierman-Yaffe et al. 2009). The hippocampus is highly vulnerable to the effects of hyperglycemia, with damage shown early in the course of DM. Hippocampal based cognitive functions such as verbal episodic memory may be initially affected, and as damage from DM progresses other associated cognitive processes show decline as well (Bruehl et al., 2009). Recent studies have documented reduced functional connectivity between the hippocampus and several associated regions (Hoogenboom et al., 2014; Musen et al., 2012; Zhou et al., 2010) where decreased functional connectivity occurs prior to the appearance of identifiable structural deficits (Musen et al., 2012).

Age, level of education, gender, and cognitive dysfunction in DM

Although DM in midlife (age 57-60 years) has been consistently associated with increased risk of accelerated cognitive decline in later years (Nooyens et al., 2010; Rawlings et al., 2014; Tuligenga et al., 2014), study results vary in the affected cognitive domains and the magnitude of the cognitive decline (Reijmer et al., 2010). In their systematic review of studies examining cognitive changes in persons with DM, Reijmer and colleagues (2010), noted that cognitive deficits were more evident in older adults (over age 65) with DM than healthy controls

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of the same age. Findings from cross-sectional case-control and population-based studies reviewed by Reijmer et al. (2010) showed worse performance for persons with DM compared to age-, sex-, and education-matched controls in the cognitive domains of attention, executive function, mental processing speed, and verbal memory. Effect sizes were small to medium (range 0.2-0.6), and consistent across age groups (range 50-80 years). In contrast, some longitudinal studies in the review showed cognitive decline in persons with DM over a five-year time span that exceeded normal aging effects by almost twice, where others showed no accelerated cognitive decline (Reijmer et al., 2010). The authors concluded that there is a dissociation between mild progressive cognitive decline and severe cognitive decline with regard to age groups, suggesting different processes (Reijmer et al., 2010).

Yeung, Fischer and Dixon (2009) examined performance differences in similar cognitive domains comparing groups with DM and without DM, and between age groups (young-old age 53-70 years; old-old age 71-90 years). Age group comparisons revealed poorer performance by the old-old group compared with young-old in all measures except for semantic memory and verbal fluency. Importantly, there was no interaction between age group and DM status, indicating that DM-related cognitive deficits may be constant across age. VanEersel et al. (2013) examined the association of DM and cognitive function in persons with and without DM age 35-82 years old. The participants with DM compared with those without DM had lower performance in executive function, with the mean difference between groups largest at ages 35-44 years. In persons without DM, the percentage with low memory performance gradually increased from 45% in age group 35-44 years to 81% in age group > 75 years, while in persons with DM the percentage of those with low memory performance was higher and similar in all age groups.

In systematic reviews by Moheet et al. (2015) and Reijmer et al. (2010), the level of education was noted to be included as confounders in the analyses of several studies and did not account for variances in the results. Level of education was included in this analysis because some of the cognitive function measures are affected by education (Lezak, Howieson, & Loring, 2004). There was no evidence of interaction between DM and gender on cognitive decline in studies by Nooyens et al., (2009), Okereke et al. (2008), Ruis et al., (2009), Tuligenga et al., (2014), van den Berg et al., (2008), and van Ersel et al., (2013).

Cognitive dysfunction and duration of DM.

The degree of cognitive dysfunction in persons with DM has been associated with the length of time one has DM. Some studies demonstrate that increased DM duration is associated with a mild decline, while others have shown a faster rate of decline (Reijmer et al., 2010). It also has been argued that cognitive dysfunction in DM may have a specific time of onset without further decline and that different cognitive domains may be affected at different times (McCrimmon et al., 2012). The duration of time with DM and associated cognitive decline may also reflect chronic exposure to other risk factors, comorbidities, and co-existing conditions (e.g. such as lifestyle, hypertension, obesity, and depression) (Reijmer et al., 2010).

Okereke et al. (2008) examined the duration of DM and cognitive decline in male and female participants from two longitudinal studies, and found that associations between DM and cognitive decline increased along with the length of time one lived with the disease (Okereke et al., 2008). In both gender groups with DM, baseline scores were poorer than those of men and women without DM in global cognition and verbal memory, and declined significantly over 4 years; each additional year of age was associated with a decline of 0.03 units on the global score, which equated having DM as the cognitive equivalent of aging three years. There was no

evidence of interaction between DM and gender and cognitive decline. Spauwen, Kohler,

Verhey, Stehouwer, and van Boxtel (2013) also found stronger decline in verbal memory in

persons with DM compared with controls over a time span of 12 years. With three-year

longitudinal data, Fischer, de Frias, Yeung, and Dixon (2009) examined temporal stability and

cognitive decline patterns in persons with and without DM. Compared with the group without

DM, the group with DM demonstrated poorer performance in episodic and semantic memory,

executive function, mental processing speed, and verbal fluency at baseline and three-year time

points. Group effects for significant deficits were found for speed-based cognitive tasks in

executive function (inhibition and task shifting) and mental processing speed (semantic speed

and reaction time), which may indicate that these tasks are potential early markers for decline. In

incident DM (DM diagnosed after baseline), a significant decline in mental processing speed

over 6 years was the only deficit noted compared with controls; this deficit increased with DM

duration (Spauwen et al., 2013). Findings by Rawlings et al. (2014), and Yeung, Fischer, and

Dixon (2009) also suggested that mental processing speed and speed-intensive executive

function tasks might be early markers for cognitive decline in individuals with DM.

 Comorbidities in DM that may affect cognitive function

The brain is a target end organ in DM and pre-DM, but the causative factors for cognitive

deficits are difficult to define due to the varied comorbidities associated with DM (McCrimmon

et al., 2012). Although the cause and effect mechanisms remain unclear, for example, the

cerebrovascular and cardiovascular (CV) risk factors associated with DM, affect cognition at

various times for various durations (Cukierman, Gerstein, & Williamson, 2005; Umegaki et al.,

2012a; Umegaki et al., 2012b). CV disease is associated with numerous problems on a

macrovascular (myocardial infarction, stroke, carotid, coronary or peripheral arterial disease) and

microvascular (neuropathy, retinopathy, nephropathy) level, many of which are related to atherosclerosis. Extent of macrovascular disease appears to have a strong association with DM and causes approximately 80% of mortality in persons with DM (McCrimmon et al., 2012). Macrovascular disease also correlates with brain atrophy and cognitive deficits in DM, but association with cerebral perfusion is unclear (Manschot et al., 2006; Manschot et al., 2007; McCrimmon et al., 2012; Tiehus et al., 2008). Microvascular disease has a primary role in cerebrovascular pathology and cognitive decline, but mechanisms are also not clearly defined (Manschot et al., 2006; Manschot et al., 2007; McCrimmon et al., 2012; Nelson et al., 2009). There is, however, evidence that reduced brain functional connectivity is associated with microvascular complications in DM as well as cognitive decline (Moheet et al., 2015).

The presence of depression has been associated with cognitive dysfunction in persons with DM (Sullivan et al., 2013), and there is a higher prevalence of depression in persons with DM (8-31%, mean 18%) than in persons without DM (5-24%, mean 10%) (Koekkoek et al., 2012). Depression may be a consequence of stress from coping with a chronic disease, or of damage from metabolic derangements that affect cerebral neurotransmitter levels or vascular integrity (Reijmer et al., 2010). Depression and DM may have common etiologies and share a similar pathway between dysregulation and over activation of the hypothalamus-pituitary-adrenal axis (HPA-axis) and sympathetic nervous system (SNS) (Champaneri, Wand, Malhotra, Casagranda, & Golden, 2010; Badescu et al., 2016). Both depression and chronic stress activate the HPA-axis and SNS which in turn causes prolonged increased levels of cortisol, adrenalin and noradrenaline, and promotes insulin resistance, obesity, and metabolic syndrome. Hypercortisolemia disrupts hippocampal neurogenesis (Badescu et al., 2016). Also, depression and chronic stress also induce increased production of inflammatory cytokines (Interleukin-6),

through SNS activation, which also promotes insulin resistance, and leads to development of DM, (Champaneri et al., 2010; Badescu et al., 2016).

In a meta-analysis of three studies using identical depression scales and neuropsychological tests for memory, Koekkoek et al. (2012) examined the role of mild depressive symptoms on cognitive function and cognitive decline in persons with DM versus controls. In overall cognition (composite z-score of domains attention, executive function, memory, and mental processing speed) performance was worse in those with DM compared with the control group. There were no performance differences in any cognitive domains in persons with DM, both with and without mild depression, and no association between DM, mild depression, and accelerated cognitive decline (Koekkoek et al., 2012).

Findings by Trento et al. (2013) over four years from baseline showed stable mean scores for depression, anxiety, and cognitive function in persons with DM who switched from non-insulin to insulin treatment. Cognition improved in the two treatment groups (non-insulin and insulin) four years after baseline. Depression and anxiety increased in those on insulin in the same period, while depression decreased and anxiety levels were unchanged in the non-insulin group. Women had higher levels of depression than men did, and increased duration of DM was associated with increased anxiety scores (Trento et al., 2013).

A prospective study of participants in the ACCORD-MIND study, conducted over 40 months, demonstrated the association of depression with greater cognitive decline (but not necessarily cognitive impairment) in executive function, mental processing speed, and verbal memory (Sullivan et al., 2013). Depression and cognitive decline were not associated with CV disease, baseline cognition, age, or type of DM or hypertension treatment. These findings

implicate depression as a risk factor for the rapid development of cognitive decline in persons with DM (Sullivan et al., 2013).

Glycemic control in DM

Glycemic control is the optimal level of average blood glucose levels associated with reduction of complications of DM (ADA, 2016). Glycosylated hemoglobin, or HbA1c, is a form of hemoglobin that measures the 3-month average plasma glucose concentration, and which has a strong predictive value for DM complications (ADA, 2016). The average, presented as a percentage, indicates how much glucose is adhering to red blood cells over their average life span (3-4 months). For people without DM, a normal range of 4-6% equates to blood glucose level of between 70-126 mg/dl. A HbA1c of 7%, or a blood glucose level of 154 mg/dl, indicates consistently elevated blood glucose levels, and maintaining HbA1c levels at 7% or below is thought to reduce microvascular and neuropathic complications. More stringent goals (HbA1c $\leq 6.5\%$) may be appropriate with persons with a short DM duration and no significant cardiovascular disease. Less stringent goals (HbA1c $\leq 8\%$) may be more appropriate for those with a history of severe hypoglycemia, advanced microvascular or macrovascular complications, or extensive comorbid conditions (ADA, 2016).

Ravona-Springer and colleagues (2014) examined the relationships between long-term trajectories (mean duration =8.7 (2.64) years) of glycemic control and cognitive performance in cognitively normal adults with DM (mean age at study entry= 72.75 (4.63) years). Six trajectories were based on trends of HbA1c levels, that is whether the level was high or low at entry, and was stable, increasing or decreasing over time. The group with the lowest HbA1c levels at entry (mean = 5.96%) and were stable over time had the best performance in cognitive domains of attention, episodic memory, executive function, and semantic categorization. The

group with the highest HbA1c levels at entry (mean =10.7%) and decreased over time had the worst overall cognitive performance, followed by the group with moderately high HbA1c levels (mean = 7.76%) that increased over time. There were no significant trajectory group differences in domains of attention or verbal memory after adjusting for sociodemographic and cardiovascular factors, duration of DM or DM medication therapy. Although the cognitive scores were within normal range, the researchers suggested that considering a pattern or trajectory of glycemic control rather than a single HbA1c level might be predictive of cognitive performance in persons with DM (Ravona-Springer et al., 2014).

Aims and Hypotheses

The specific aims of this study were to examine the relationships between covariates (age, years with DM, education category, cardiovascular risk, level of depression, and cognitive function), cognitive function, and glycemic control in rural adults with type 2 DM. The hypotheses were: 1) increased age, years with DM, levels of CV risk, depression, and decreased years of education would correlate with declining function in cognitive domains of attention, executive function, mental processing speed, and verbal episodic memory, 2) increased age, years with DM, levels of CV risk, depression, and decreased years of education would correlate with higher Hba1c levels, 3) HbA1c level, after controlling for the covariates, would independently predict cognitive function, and 4) cognitive function, after controlling for the covariates, would independently predict HbA1c level. Figure 3.1 displays the hypotheses.
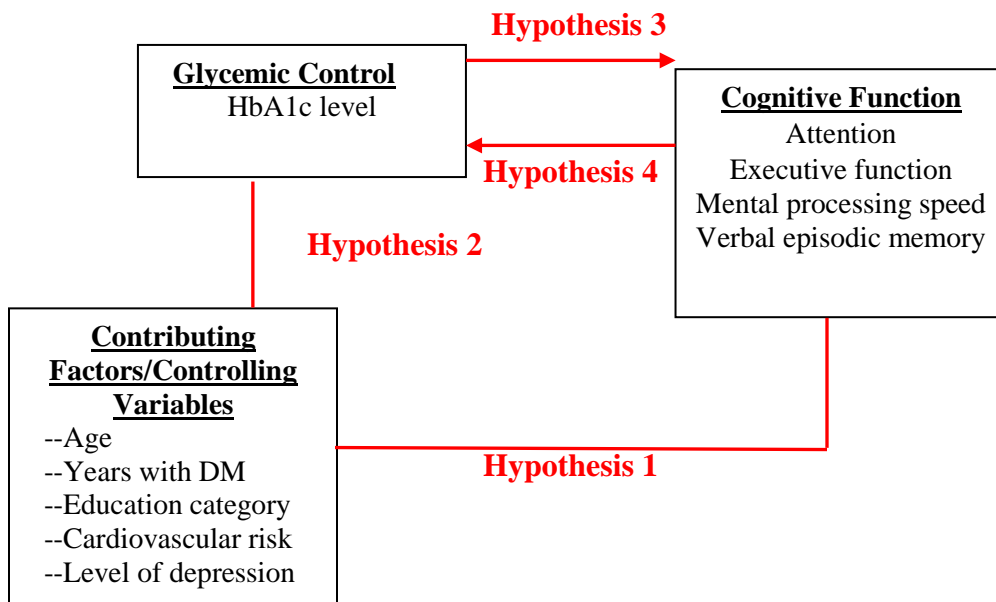
Figure 3.1. Hypothesis Model

<center>**Methods**</center>

Participants and settings

Using a descriptive design and with approval from the University of Michigan Institutional Review Board (Study HUM00085816), 56 rural-dwelling men and women were recruited from primary care providers and diabetes education centers in two rural counties in northern Wisconsin and three in the Upper Peninsula of Michigan. The prevalence of DM across the counties in each state is 8.9-10.6% and 10-12.2% respectively, which exceeds the overall national prevalence rate of 9.3% (CDC, 2014). Available healthcare in each county includes public hospitals, community and rural health clinics, primary and specialty care (e.g. internal medicine, cardiology, neurology, nephrology, diabetes education). After an initial telephone screening, interviews were scheduled and informed consent obtained. The interviews were conducted between 12/22/2014 and 10/15/2015 at a clinic-based conference room or during home visits.

Inclusion and exclusion criteria

As seen in Table 3.1, inclusion criteria were that participants had an established medical diagnosis of DM, were age 45 and over, had a HbA1c level within the past two months, and a total cholesterol and HDL within the past twelve months, completed at least the ninth grade, were able to read the English language, were available by telephone or mail for scheduling, and consented to participate in the study.

To limit confounding factors that could affect the relationship between study variables or affect cognitive function, exclusion criteria were: likelihood of dementia (Montreal Cognitive Assessment (MoCA) score <22) (Nasreddine et al., 2005), history of stroke with noted residual, or degenerative neurological conditions (e.g. Huntington's, Parkinson's, Lewy Body disease,

<center>95</center>

amyotrophic lateral sclerosis), current or recently treated (within the past 5 years) major

psychiatric disorders (e.g. schizophrenia, bipolar disorder, major depression), inadequate visual

acuity to read printed study materials, history of or current major alcohol or substance abuse,

hepatic encephalopathy, terminal illness, or dialysis dependence.

<div align="center">

Measures and Instruments

</div>

Sociodemographic and clinical data

Data was collected during a 60- 90 minute face to face interview and from review of

recent medical records. Sociodemographic data included age, gender, education category, work

and marital status, race and ethnicity, and distance to health care. Clinical data included years

with DM, presence of neuropathy (a complication of DM), and all medications. For participants

45- 79 years of age, CV risk was estimated using the American College of Cardiology/American

Heart Association (ACC/AHA) Task Force Cardiovascular Risk Calculator (Goff et al., 2013).

The ACC/AHA Cardiovascular Risk Calculation is an estimate of 10-year risk for persons 40-79

years of age (calculated as a percent) for atherosclerotic cardiovascular disease (ASCVD),

defined as coronary death or nonfatal myocardial infarction, or fatal or nonfatal stroke.

Additional information needed for the risk calculator was systolic blood pressure, smoking

status, and total and HDL cholesterol levels. Other clinical data included height, weight, and

body mass index. Age, years with DM, education category, CV risk, and level of depression

were covariates.

Dementia Screen for Exclusion Criteria

The Montreal Cognitive Assessment (MoCA) was administered to screen potential study

participants for the likelihood of dementia, and thus exclusion from the study. The MoCA has 30

items that briefly measure multiple cognitive domains affected in dementia including short-term

memory, visuospatial abilities, executive functions, verbal memory, attention and working

memory, language, and orientation. The test takes approximately 10 minutes to administer and

participants earn points for successful completion of various tasks. A perfect score is 30 with a

score of 26 or greater considered normal. Scores between 22 and 26 indicate mild cognitive

impairment, and scores below 22 indicates a likelihood of dementia, and provided the cutoff

score for participant enrollment in the study (Freitas et al., 2013; Nasreddine et al., 2005).

Glycemic Control

Glycemic control is the optimal level of average blood glucose levels associated with

reduction of complications of DM (ADA, 2016). This was measured with glycosylated

hemoglobin, or HbA1c, as previously discussed. As per the inclusion criteria, all participants had

a documented HbA1c level from a certified laboratory done within two to three months prior to

the interview.

Cognitive Function

The dependent variables representing aspects of cognitive function were the following:

attention, executive function, mental processing speed, and verbal episodic memory. A brief

description of the variables and measures follow, and are further described in Table 3.2.

Attention. Attention is the cognitive process of selectively concentrating on incoming

stimuli and shifting focus to other stimuli, while suppressing competing distractions. Attention

utilizes specialized brain networks that have limited information processing capacity (Posner &

Rothbart, 2007; Strauss, Sherman, & Spreen, 2006). Attentional processes are associated with

multiple sensory brain areas (Bear, Connors & Paradiso, 2007).

Digit Span. Digit Span measures attention capacity by exposing individuals to

increasingly larger amounts of information and then asking them to respond by immediately

recalling or further processing that information. It is comprised of two tests, Digits Forward and Digits Backward, which involve different cognitive activities of sustaining focus and short-term storage capacity (Choi et al., 2014; Strauss, Sherman, & Spreen, 2006). Participants repeat number sequences that the examiner reads aloud, with increasingly longer sequences being tested in each trial. In the forwards series, the sequences are repeated forwards, and in the backwards series, the sequences are repeated backwards. Raw scores for Digits Forward indicate length of digit span (possible score range is 0 to 8) and Digits Backward (possible score range is 0-7) were analyzed as a total sum (possible score 0 to 15). Choi and colleagues (2014) found that older age, lower education level and female gender were associated with poorer performance on both Digit Span forward and backward, although results in prior studies differed with gender.

*Trailmaking Test Part A***.** Trailmaking Test Part A (Trails A) measures attentional processes of scanning and visuomotor tracking of a sequence and speed of performance (Reitan, 1992). The test requires the participant to draw lines to connect randomly placed numbered circles into a consecutive numerical order. It is a timed test with scores based on the time required to complete the task, including time to correct any errors. The average completion time is 29 seconds for cognitively intact individuals, with greater than 78 seconds indicating cognitive impairment. To account for participants that could not complete the test, the scores were converted to a ratio of number correct per second, where a higher ratio indicated better performance. Problems with visual scanning and tracking on Trails A can indicate difficulties with conceptual tracking. Higher age and depression levels, and lower education levels and female gender are associated with poorer performance (Lezak et al., 2004; Reitan, 1992).

Executive function. Executive function comprises cognitive processes dependent upon the frontal and pre-frontal cortices that involve goal formation, organization, and sequencing,

switching between tasks, conflict resolution, and encoding information for short-term storage (Baddeley, 1998; Smith & Jonides, 1999). It is a supervisory system with two subsystems: one that processes visual and spatial input and the other that processes hearing and speech (Baddeley, 1998; Diamond, 2013).

Controlled Oral Word Association Test (COWA). COWA is a test of verbal fluency associated with frontal and pre-frontal cortex function. It requires the participant to generate as many words as possible (excluding proper nouns and numbers) beginning with a letter given by the tester. Raw scores reflect the total number of acceptable words generated with three different letters (C, F, L) during three separate 60-second trials. Scores are adjusted for age and education and converted to a percentile. Lower scores indicate greater impairment (Lezak et al., 2004). Older age is associated with poorer performance, higher education level is associated with better performance, and gender has no association (Lezak et al., 2004; Strauss et al., 2006).

Trailmaking Test Part B. Trailmaking Test Part B (Trails B) is similar to Trails A, but measures processes of scanning and visuomotor tracking of a sequence, speed of performance as well as divided attention and cognitive flexibility (Reitan, 1992). The test requires the participant to draw lines to connect randomly placed numbered and lettered circles into an alternating sequence (i.e. 1, A, 2, B, 3 C, etc.). Like Trails A, the test is scored based on the time required to complete the task and make corrections. The average completion time is 75 seconds for cognitively intact individuals, with greater than 273 seconds indicating cognitive impairment. To account for participants that could not complete the test, the scores were converted to a ratio of number correct per second, where a higher ratio indicated better performance. Elderly persons that perform poorly on Trails B tend to have problems with complex activities of daily living

(Lezak et al., 2004). Higher age and depression levels, and lower education levels and female gender are associated with poorer performance (Lezak et al., 2004).

Mental processing speed. Mental processing speed is the rate of processing information and includes variables of time to response (decision speed) and speed of response (perceptual speed) (Salthouse, 2000).

Digit Symbol-Coding. Digit Symbol-Coding is a timed paper-and-pencil test that asks participants to match numbers with paired symbols and then copy the symbols into rows containing blank squares under its corresponding number. The score is determined by counting the number of correctly drawn symbols in the allotted 120 seconds. The maximum score is 133 points (Lezak et al., 2004). Age and depression have been shown to negatively affect test performance, while level of intellect, memory or learning capability does not. It is particularly sensitive to dementia with demonstration of rapidly declining performance rates associated with dementia progression (Lezak et al., 2004).

Letter and Pattern Comparison. Letter Comparison task is a timed test where participants are asked to rapidly determine whether two side-by-side strings of letters are the same or different, then write 'S' (for same) or 'D' (for different) on a line between the pairs. Pattern Comparison task is similar, except the pages contain pairs of line segment patterns that require rapid classification as "same" or "different". Two separately timed (20 seconds each) trials of 21 pairs of letters and 30 pairs of patterns are administered, with the score derived by number of correct choices in the allotted time. The data reported are the average of the two attempts for each task (Salthouse & Babcock, 1991). Older age decreases performance (Salthouse, 2000). Both the letter and pattern comparison tasks are established measures of information

processing speed used extensively in a number of previous studies (Fisk & Warr, 1996; Salthouse and Babcock, 1991; Salthouse 1994).

Verbal episodic memory. Verbal episodic memory is the ability to learn, encode, store and retrieve information about everyday personal experiences. Dysfunction in episodic memory causes disruption in the ability to learn and recall new information (Budson, 2009; Cansino, 2008). Core brain areas associated with episodic memory are the medial temporal lobe and hippocampus, which may be damaged in DM (denHeijer et al., 2003; Manschot et al., 2007).

Hopkins Verbal Learning Test-Revised (HVLT-R). The HVLT-R Total and Percent of Retention scores measures verbal memory functions of word list learning and recall. In this test, the participant is asked to learn and remember a list of 12 words that are verbally presented in three learning trials and a delayed recall (after 20-25 minutes) trial. Immediately after each of the three learning trials, the participants are asked to repeat the words they remembered. Scores are calculated for a total list learning score (the sum of the 3 trials), and percentage of words remembered after the 20-25-minute delay. The score range for the total list learning score is 0 to 36, and for the percent of retention delayed recall 0 - 100 percent (Benedict et al., 1998; Strauss et al., 2006). The HVLT-R discriminates between patients with mild cognitive impairment and cognitively healthy persons. Older age and lower education levels decrease performance (Strauss et al., 2006; Woods et al., 2005).

Depression

As noted earlier, the presence of depression has been associated with cognitive dysfunction in persons with DM. Level of depression was a covariate in this study.

PHQ-8. The Patient Health Questionaire-8 (PHQ-8) measured level of depression. The PHQ-8 is an eight-item self-administered questionnaire consisting of questions regarding the

occurrence of depression symptoms over the last 2 weeks. Response options are "Not at all,"

"Several days," "More than half the days," and "Nearly every day," with 0 – 4 points associated

for each option, respectively. The score is the sum of responses, with score ranges from 0-24.

The levels of depression symptom severity levels are: none (0-4), mild (5-9), moderate (10-14),

moderately severe (15-19), and severe (20-24). The PHQ-8 is valid for diagnosing depression

and determining the severity of depression in primary care settings (Lamers et al., 2008).

Table 3.1

Table of Inclusion and Exclusion Criteria

Factor	Measure/Instrument	Description	Remarks
Inclusion & exclusion criteria	Pre-screening questionnaire	DM diagnosis, age, education HbA1c, total & HDL cholesterol, comorbidities	
Dementia screen for exclusion criteria	Montreal Cognitive Assessment (MoCA)	A 30-item test; measures multiple cognitive domains including short term memory, visuospatial abilities, executive functions, verbal memory, attention and working memory, language, and orientation score range 0-30; exclusion score <22. Test-retest correlation coefficient =0.92; Internal consistency Cronbachs alpha =0.83 Sensitivity for dementia=100%	Score range 0-30; exclusion score <22, indicating likelihood of dementia; has high sensitivity for identifying mild cognitive impairment & dementia; those scoring below 22 were not eligible to be enrolled as a participant

Table 3.2.

Table of Measures and Instruments

Factor	Measure/Instrument	Description	Remarks
Glycemic control	Glycosylated hemoglobin (HbA1c)	A blood test that reflects average blood glucose over three months. Obtained from medical record.	HbA1c at7% or below has been shown to reduce microvascular & neuropathic complications Processed by a CLIA certified laboratory.
Attention	Digit Span	Measures attention capacity by exposure to increasingly larger amounts of information & immediate response to processed information. Participants repeat pairs of progressively longer number sequences that the examiner reads aloud, both forwards and backwards; score is total correct. Test –retest reliability coefficients range = .66 -.89.	Raw scores of Digits Forward (range 0 -16), Digits Backward (range 0-14) analyzed as a total sum; Effects of age, education, and gender have varied between studies;
	Trails A:	Timed test to connect randomly placed numbered circles into consecutive order; measures visual scanning, tracking and attention capacity. Reliability coefficients range from .60 - >.90. Scores correlated with caudate atrophy (r=.72)	Score is time to complete tasks & correction or errors. Average time=29 seconds. Score was converted to ratio of number correct per second;

| Executive Function | Controlled Oral Word Association (COWA | Tests verbal fluency (associated with frontal & pre-frontal cortex function). It tests rapid word generation in three timed word-naming trials using letters C, F, & then L; score is number of words correctly generated in 60 seconds.

Test-retest reliability coefficients in elderly persons after one year, (FAS letter set): range=.70-.71 (for F & S): total score, with A, <.70. Correlations comparing performance of COWA & Weschler Intelligence Scales Digit Span = (.45); Vocabulary = (.41); memory= (.17-.22); figure fluency = (.24). | Raw score: total number of words generated with three letters during three separate 60 second trials. Adjusted score: sum of acceptable words from the trials adjusted for age, sex & education, converted to a percentile. Lower scores indicate greater impairment. |
| | Trails B | Timed test to connect randomly placed numbered & lettered circles into alternating sequence (1, A, 2, B, 3, C, etc.); measures visual scanning, tracking, divided attention & cognitive flexibility.

Reliability coefficients range from .60 - >.90. | Score is time to complete tasks & correction of errors. Average time=75 seconds. Score was converted to ratio of number correct per second; age, education, gender, & depression affect performance |

		Scores correlated with caudate atrophy (r=.80).	
Mental Processing Speed	Digit Symbol-Coding	Timed test requiring copying symbols paired with numbers from a key into blank squares underneath a corresponding number; time allotted is 120 seconds, score is number correctly copied.	Maximum score =133 points. Sensitive to dementia, with performance rapidly declining with dementia progression
		Test-retest reliability correlation coefficients range=.82-.88. In mild traumatic brain injury reliability =.74. Sensitive to dementia, with performance rapidly declining with dementia progression	
	Letter & Pattern Comparison	Two timed (20 seconds each) trials for each task: comparison of side-by-side strings of letters or line segment patterns, and written response of S (same) or D (different); score is number of correct choices.	Score is average of two trials for each task. Age has a large effect on performance
		Reliability coefficients: Letter = .35-.80; Pattern = .29-.73.	
Verbal Episodic Memory	HVLT-R	Word list learning task to learn and recall 12 spoken words in 3 learning trials; also delayed recall after 20-25 minutes;	Scores calculated for sum of 3 trails, delayed recall, percent retention. HVLT-R able to discriminate between mild

		score is based on number of words recalled.	cognitive impairment & normal cognition. Age & education affect performance
		Test-retest stability coefficient (r=.74). Discriminated btw mild cog impairment & cog healthy in two separate studies (sensitivities=.79 & .96; specificities =.95 & .80)	
Level of Depression	Patient Health Questionnaire-8 (PHQ-8)	An 8-item self-administered questionnaire that queried presence depression symptoms over 2 weeks; score was the sum of responses, with score range from 0-24. Cronbach's alpha range=.84-.89. Sensitivity=81-99%; specificity=92-99%; Positive predictive values=57-94%	Score range from 0-24; levels symptom severity levels were: none (1-4), mild (5-9), moderate (10-14), moderately severe (15-19), and severe (20-24); all items parallel symptoms of depression as described in the DSM-IV; valid for diagnosing & determining depression severity in primary care settings

Statistical Analysis

Data was analyzed using IBM SPSS statistics (version 22). Descriptive statistics (means, medians, standard deviations, ranges and frequencies) were generated to summarize the sociodemographic, clinical, and neuropsychological test data. To test hypotheses one and two Pearson's r and Spearman's rank-order correlations were used to examine the relationship between age, years with DM, education category, cardiovascular risk, level of depression, and each cognitive function measure and HbA1c level. Spearman's rank-order correlation, a nonparametric statistic with no requirement of normality, was used to account for outliers (Polit, 2010).

To test hypothesis three, hierarchical multiple regression was conducted to estimate the independent relationship between HbA1c and each of the cognitive function measures after controlling for non-modifiable (age, years with DM, education category) and modifiable covariates (cardiovascular risk, level of depression). The dependent variable, cognitive measures (attention, executive function, mental processing speed, verbal episodic memory), were entered in individual equations after first controlling for 1) age, years with DM, education category (model 1); 2) model 1 variables plus cardiovascular risk (model 2); 3) model 2 variables plus level of depression; and 4) model 3 variables plus HbA1c. To test hypothesis four, hierarchical multiple regression was conducted to estimate the independent relationship between each cognitive function measure and HbA1c after controlling for non-modifiable (age, years with DM, education category) and modifiable covariates (cardiovascular risk, level of depression). The dependent variable, HbA1c was entered in individual equations with each cognitive function measure after first controlling for 1) age, years with DM, education category (model 1); 2) model 1 variables plus cardiovascular risk (model 2); 3) model 2 variables plus level of depression; and

4) model 3 variables plus each cognitive measure individually; and 5) model 3 variables plus all cognitive measures concurrently.

<div align="center">**Results**</div>

Sample Characteristics

A convenience sample of 56 rural adults with DM was enrolled into this study. The sample size was determined by a medium-large effect size (determined from previous research), 80% power, and alpha .05. Table 3.3 displays the sample characteristics and a summary of the clinical data. Among this sample, 53.6% were female, 96.4% were White, and 67.9% had between 12-15 years of education. Twenty-seven percent were employed; and 57.1% were retired. Almost fifty-two percent consumed no alcohol and 86% were non-smokers. Mean distance to access primary care was 11 miles, 51 miles to specialty care, and 10 miles to access emergency care. The majority had health insurance coverage (98.2%) and had no problems obtaining their medications (89.3%). For the 10.7% who reported difficulty obtaining their medications, reasons included high co-pays and insurance non-coverage for non-generic medications.

Participants mean number of years with DM was 12.7 ((SD 9.9), median = 12.0), and their mean HbA1c was 7.7% ((SD 1.6), median = 7.2). Just over one-third of the study population (34%) had participated in some DM education, while 39% and 27% had completed a program or never participated respectively. The majority of participants reported neuropathy (61%). The mean score of 5.5 ((SD 4.8), median =4.5) on the depression screening instrument, PHQ-8, indicated the presence of mild depression. The mean percent of 10-year risk for atherosclerotic cardiovascular disease (defined as coronary death or nonfatal myocardial infarction, or fatal or nonfatal stroke) was 18.9% ((SD 13.8), median = 16.0), which was

calculated for persons 40-79 years of age. Mean systolic and diastolic blood pressure was 135.9

((SD 20.0), median = 135.5) and 76.3 ((SD 9.8), median = 78.5), respectively. The mean scores

for all cognitive function measures were below the established norms, as displayed in Table 3.4..

The MoCA test, which was used to screen participants for the presence of dementia, indicated

that 48% of the study sample had mild cognitive impairment. Figure 3.2. displays MoCA mean

scores by age category. Table 3.5. displays MoCA mean scores by level of depression.

Table 3.3
Sample Characteristics and Clinical Data (N=56)

Characteristic/Clinical Data	Result	Range
Age, years, mean (SD), median,	62.9 ± 9.2, 64.0	45-89
Gender, n (%)		
Male	26 (46.4)	
Female	30 (53.6)	
Race, n (%)		
African American	0	
Native American	2 (3.6)	
White	54 (96.4)	
Ethnicity, Non-Hispanic, n (%)	55 (98.2)	
Marital status, n (%)		
Married	20 (35.7)	
Not married	36 (64.3)	
Education category, n (%)		
Did not complete high school	2 (3.6)	
Completed high school	20 (35.7)	
Associate degree	17 (30.4)	
Bachelors or higher	17 (30.4)	
Employment status, n (%)		
Employed	15 (26.8)	
Unemployed	6 (16.1)	
Retired	32 (57.1)	
Health insurance, yes, n (%)	55 (98.2)	
Problems obtaining medications, n (%)		
Yes	6 (10.7)	
No	50 (89.3)	
Miles to primary care (n=56), mean (SD), median	10.8 ± 15.2, 5.0	1-85
Miles to specialty care (n=36), mean (SD), median	50.8 ± 73.1, 16.0	0-343
Miles to emergency care (n=56), mean (SD), median	10.1 ± 11.1, 5.0	1-40
Alcohol consumption frequency, n (%)		
2-3 times per week	2 (3.6)	

2-4 times per month	4 (7.1)	
Monthly or less	21 (37.5)	
Never	29 (51.8)	
Smoker, n (%)		
No	48 (85.7)	
Yes	8 (14.3)	
Prior smoker	16 (28.6)	
HbA1c%, mean (SD), median	7.7 ± 1.6, 7.2	5.3-12.4
Years with DM, mean (SD), median	12.6 ± 9.9, 12.0	1-44
DM education status, n (%)		
Yes	22 (39.3)	
Yes, completed	19 (33.9)	
No	15 (26.8)	
Neuropathy, n (%)		
No	22 (39.3)	
Yes	34 (60.7)	
Montreal Cognitive Assessment, mean score (SD)	25.6 ± 2.3, 26.0	22-30
Normal cognition (MoCA score ≥ 26-30), n (%)	29 (52)	
Mild cognitive impairment (MoCA score 22-25), n (%)	27 (48)	
Patient Health Questionaire-8, mean score (SD), median	5.5 ± 4.8, 4.5	0-17
Body Mass Index, mean (SD), median	37.4 ± 9.3, 35.9	22-65.1
Ten-year CV disease risk % (for those 40-79 years of age, n=52), mean (SD), median	19.1 ± 13.8, 16.0	1.2-60.7
Systolic Blood Pressure mmHg, mean (SD), median	135.9 ± 20.0, 135.5	83-181
Diastolic Blood Pressure mmHg, mean (SD), median	76.3 ± 9.8, 78.5	55-98
Total Cholesterol, mg/dl mean (SD), median	182.3 ± 43.2, 183.5	96-296
High Density Lipoprotein, mg/dl mean (SD), median	42.3 ± 11.7, 40.0	25-84
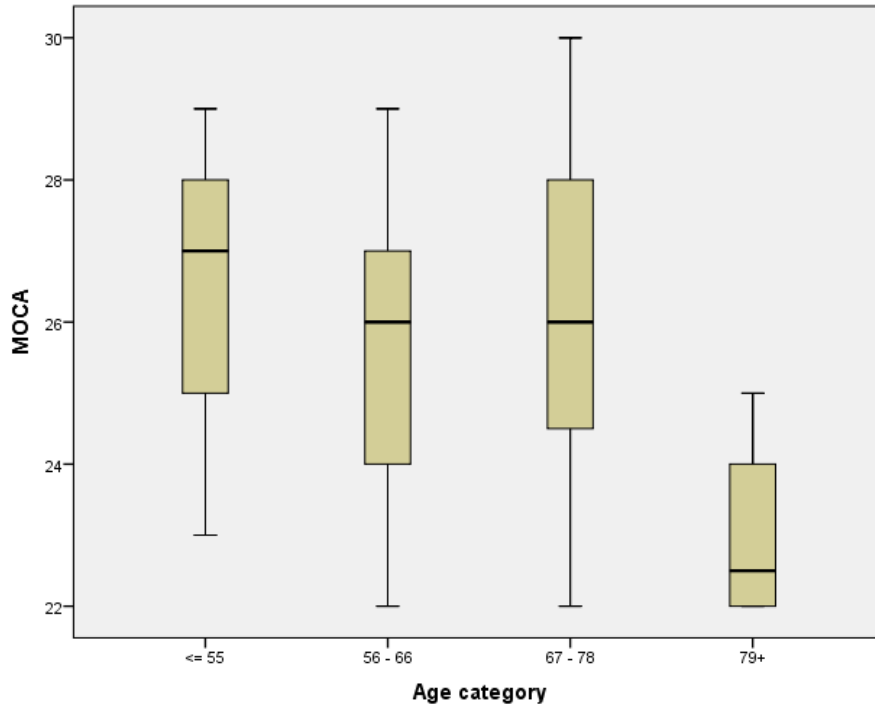
Figure 3.2. MoCA Mean Score (SD) by Age Category
  Note. $\leq$ 55years n=11, (26.5 (2.0)); 56-66 years n=29, (25.4(2.2));
  67-78 years n=12, (26.1 (2.5)); >79 n=4, (23.0 (1.4)).
  MoCA = Montreal Cognitive Assessment

Table 3.4.
Summary of Scores for Cognitive Function Measures (N=56)

Cognitive Measures	Mean Scores $\pm$ SD, median	Actual Score Ranges	Norms $\pm$ SD
Attention			
Digit Span Total	8.77 $\pm$ 2.5, 8.5	4-14	10.5 $\pm$ 1.0
Trailmaking Test A (seconds to complete)	36.9 $\pm$ 13.4, 35	15-86	31.3 $\pm$ 6.7
Trailmaking Test A (# correct per second)	.73 $\pm$ .25, .69	.28-1.6	
Executive Function			
COWA Raw Score	32.3 $\pm$ 13.8, 33.0	11-64	40.1 $\pm$ 10.5
Trailmaking Test B (seconds to complete)	97.0 $\pm$ 64.4, 71.0	35-274	64.6 $\pm$ 18.6
Trailmaking Test B (# correct per second)	.30 $\pm$ .15, .31	.01-.66	
Mental Processing Speed			
Digit Symbol Coding	53.5 $\pm$ 11.7, 54.0	26-81	54.3 $\pm$ 8.9
Letter Comparison	5.8 $\pm$ 1.6, 6.0	2.5-9.5	n/a
Pattern Comparison	11.0 $\pm$ 2.6, 11.5	6-16	n/a
Verbal Episodic Memory			
HVLT-R Recall Total	19.6 $\pm$ 6.5, 21.0	2-36	20.6 $\pm$ 5.2
HVLT –R % Retention	72.3 $\pm$ 28.3, 80.0	0-100	89.0 $\pm$ 25.8

Note. COWA=Controlled Oral Word Association Test; HVLT-R=Hopkins Verbal Learning Test-Revised

Table 3.5.
MoCA scores by Level of Depression

Depression Category		MoCA Mean scores $\pm$ SD
No depression (PHQ 0-4), n=30, 53.6%		25.7 $\pm$ 2.3
Mild (PHQ 5-9), n=11, 19.6%		26.4 $\pm$ 2.1
Moderate (PHQ 10 - 14), n= 11, 19.6%		25.5 $\pm$ 2.3
Moderate/Severe (PHQ 15-19), n=4, 7.1%		23.0 $\pm$ 1.4

Note. MoCA = Montreal Cognitive Assessment; PHQ-8 = Patient Health Questionaire-8.

Hypotheses 1 & 2: Relationship between Covariates, Cognitive Function, and Glycemic Control in Rural Adults with DM

Hypotheses one and two were tested using Spearman's rank-order correlation to examine the relationship between covariates of age, years with DM, education category, CV risk, level of depression, cognitive function and HbA1c levels. Results of Pearson's r correlations are shown for comparison. Preliminary analyses ensured no violation of the assumptions of normality, linearity, and homoscedasticity. The expected direction for the relationships between age, years with DM, CV risk score, level of depression, and cognitive function was negative, and for the relationships between age, years with DM, CV risk score, level of depression, and HbA1c levels were positive. The expected direction for the relationship between education category and cognitive function was positive, and for the relationship between education category and HbA1c levels was negative.

As seen in Table 3.6., for hypothesis one, there were moderate to large correlations between age and measures of attention (r= -.33, p<.05; r= -.36, p<.01), executive function (r= -.42, r= -.47, both p<.01), mental processing speed (r= -.50, p<.05; r= -.49, r= -.43, both p<.01), and verbal episodic memory (r= -.42, p<.01). Years with DM was small to moderately correlated with attention (r= -.33, p<.05), executive function (r= -.37, p<.01; r= -.28, p<.05), mental processing speed (r= -.35, p<.01; r= -.30, r= -.27, both p<.05), and verbal episodic memory (r= -.31, p<.05). Education category had small to moderate correlations with executive function (r= .29, p<.05), mental processing speed (r=.29, p<.05), and verbal episodic memory (r=.29, both p< .05). There were moderate to large correlations between CV risk and attention (r=. -.54, p<.01), executive function (r= -.34, p<.05; r = -.42, p<.01), mental processing speed (r= -.47, r= -.58, r= -.40, all p<.01), and verbal episodic memory (r= -.45, p<.01). Level of depression showed

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moderate correlation mental processing speed (r= -.43, p<.01). Results suggested that, in this

sample, increased age, years with DM and CV risk were associated with decreased attention,

executive function, mental processing speed, and verbal episodic memory. Increased education

was associated with increased performance in executive function, mental processing speed, and

verbal episodic memory. Increased level of depression was associated with decreased mental

processing speed. Results for hypothesis two showed that HbA1c had a moderate positive

correlation with depression (r=.34, p <.05).

Table 3.6.

Results for Hypotheses 1 & 2 Correlations between Contributing Factors, Cognitive Function Measures, & Glycemic Control (N=56)

Variables	Age	Years with DM	Education category	CV risk	Level Of Depression	HbA1c
Attention						
Digit span total	-.33*	-.33*	.15	-.09	.05	-.15
	(-.31*)	(-.32*)	(.18)	(-.08)	(.03)	(-.16)
Trailmaking Test A	-.36**	-.05	.18	-.54**	-.23	.02
(#correct/sec)	(-.41**)	(-.09)	(.22)	(-.41**)	(-.24)	(.01)
Executive Function						
COWA raw score	-.42**	-. 37**	.21	-.34*	-.03	.05
	(-.41**)	(-38**)	(.20)	(-.30*)	(-.12)	(.05)
Trailmaking Test B	-.47**	-.28*	.29*	-.42**	-.26	-.20
(#correct/sec)	(-.53**)	(-.32*)	(.29*)	(-.30*)	(-.23)	(-.24)
Mental Processing Speed						
Digit symbol	-.50**	-.35**	.21	-.47**	-.43**	-.13
	(-.56**)	(-.39**)	(.23)	(-.43**)	(-.39**)	(-.11)
Letter Comparison	-.49**	-.30*	.18	-.58**	-.12	.12
	(-.53**)	(-.35**)	(.19)	(-.46**)	(-.18)	(.09)
Pattern Comparison	-.43**	-.27*	.29*	-.40**	-.05	.13
	(-.47**)	(-.32*)	(.30*)	(-.39**)	(-.02)	(.12)
Verbal Episodic Memory						
HVLT recall total	-.42**	-.31*	.29*	-.45**	-.19	.04
	(-.53**)	(-.40**)	(.21)	(-.37**)	(-.20)	(.07)
HVLT% retained	-.23	.03	.29*	-.20	-.07	.17
	(-.41)	(-.14)	(.26)	(-.02)	(-.18)	(.21)
HbA1c	-.01	.17	.15	.06	.34*	
	(-.01)	(.24)	(.13)	(.11)	(.25)	

Note. Result of Pearson's r are in parentheses. COWA=Controlled Oral Word Association Test; HVLT-R=Hopkins Verbal Learning Test-Revised. *p<.05 **p<.01

Hypotheses 3: Relationship between Glycemic Control and Cognitive Function after Controlling for Covariates in Rural Adults with DM

The results for hypothesis three (glycemic control, after controlling for covariates age, years with DM, education category, CV risk, and level of depression, would independently predict cognitive function) hierarchical multiple regression model 4 are displayed in Table 3.7. None of the models with cognitive test Digit Span reached significance. With testing hypothesis two, model 4 (all covariates plus HbA1c) explained between twenty-one and forty-three percent of the variance in cognitive measure performance with overall significance levels between <.001 to .03. After controlling for the non-modifiable and modifiable covariates age, years with DM, education category, CV risk score, and level of depression, HbA1c did not independently explain cognitive test performance in any of the cognitive domains. Level of depression independently explained performance in mental processing speed (Digit Symbol) (B= -.36, p=.002), and verbal episodic memory (HVLT% retained) (B= -.26, p =.04). CV risk also independently explained performance in verbal episodic memory (HVLT% retained) (B = .31, p=.04). Non-modifiable variables age, years with DM, and education category, entered in model 1, accounted for fifteen to thirty-two percent of variance in cognitive measure performance with significance levels between <.001 to .01. The addition of CV risk in model 2 was significant only in verbal episodic memory (HVLT% retained) with an R^2 change of .07 (p=.04). The addition of level of depression in model 3 was significant only in mental processing speed (Digit Symbol) with an R^2 change of .12 (p=.002).

Table 3.7. *Results for Hypothesis 3 Hierarchical Multiple Regression Explaining Cognitive Function Measures Attention, Executive Function, Mental Processing Speed, & Verbal Episodic Memory (N=56)*

Predictors	Attention				Executive Function				Mental Processing Speed						Verbal Episodic Memory			
	Digit Span		TTA		COWA		TTB		Digit Symbol		Letter Compare		Pattern Compare		HVLT Recall		HVLT % Retained	
	Beta[a]	R^2 Δ	Beta[a]	R^2 Δ	Beta[a]	R^2 Δ	Beta[a]	R^2 Δ	Beta[a]	R^2 Δ	Beta[a]	R^2 Δ	Beta[a]	R^2 Δ	Beta[a]	R^2 Δ	Beta[a]	R^2 Δ
Model 1		.16*		.20*		.24**		.33**		.36**		.30**		.29**		.33**		.21**
Age (years)	-.28		-.32		-.21		-.53**		-.42**		-.30		-.21		-.34*		-.57***	
Years with DM	-.23		.16		-.27		-.01		-.10		-.16		-.22		-.22		.03	
Education Category	.17		.13		.14		.22		.14		.08		.22		.11		.16	
Model 2		.02		.05		.01		.00		.02		.04				.01		.07*
CV risk score	.16		-.24		-.11		.07		-.11		-.24		-.21		-.11		.31*	
Model 3		.01		.06		.003		.04		.12**		.02				.02		.05
Level of depression	.11		-.26		-.08		-.17		-.36**		-.18		-.01		-.18		-.26*	
Model 4		.03		.00		.01		.05		.00		.03				.02		.04
HbA1c	-.18		.04		.13		-.23		-.01		.19		.17		.16		.20	
R^2	.21		.31		.26		.42		.50		.40		.33		.38		.35	
Adjusted R^2	.10		.21		.17		.35		.43		.31		.25		.30		.27	
Overall significance	.09		.009**		.03*		<.001***		<.001***		.001***		.004**		.001***		.002***	

Note. COWA=Controlled Oral Word Association Test; HVLT-R=Hopkins Verbal Learning Test-Revised

*p<.05, **p<.01, ***p≤.001

Hypothesis 4: Relationship between Cognitive Function and Glycemic Control after Controlling for Covariates in Rural Adults with DM

For hypothesis 4, with HbA1c as the dependent variable, and after controlling for the non-modifiable and modifiable covariates age, years with DM, education category, CV risk, and level of depression, and entering each cognitive measure individually in the final model, none of the models reached significance. With HbA1c as the dependent variable, after controlling for the non-modifiable and modifiable covariates and entering each cognitive measure concurrently the model nearly reached significance (p=.06), with executive function (Trailmaking Test B,

B= -.57, p = .009) and independently explaining HbA1c levels. Results are displayed in Table 3.8.

Table 3.8.
Results for Hypothesis 4 Hierarchical Multiple Regression Model 5 Explaining HbA1c

Predictors	HbA1c
Age (years)	-.29
Years with DM	.19
Education Category	.16
CV risk score	.39
Level of depression	.17
Digit Span	-.28
Trailmaking Test A	.33
COWA	.13
Trailmaking Test B	-.57**
Digit Symbol	-.25
Letter Comparison	.32
Pattern Comparison	.04
HVLT Total Recall	.33
HVLT % Retained	-.06
R^2	.42
Adjusted R^2	.19
Overall significance	.06

Note. COWA=Controlled Oral Word Association Test; HVLT-R=Hopkins Verbal Learning Test-Revised.
**p<.01.

Discussion

As can be seen by the study data, the first hypothesis, that increased age, years with DM, levels of CV risk, and depression, and decreased years of education would correlate with declining function in cognitive domains of attention, executive function, mental processing speed, and verbal episodic memory was supported. Age, years with DM, and CV risks were negatively correlated with one or more measures in each cognitive domain, with the magnitude for age and CV risk being medium to large, and years with DM being small to medium Level of depression had a medium and negative correlation with mental processing speed. Education category had a small positive correlation with executive function, mental processing speed, and verbal episodic memory. Interestingly, for hypotheses two, Hba1c had a moderate and positive correlation with depression, but no significant correlations with any cognitive measures. As indicated by MoCA test, which screened for dementia with assessment of global cognitive function, 48% of the participants had mild cognitive impairment.

Hypothesis three was not supported, that glycemic control, after controlling for the covariates, would independently predict cognitive function, as HbA1c did not independently account for cognitive test performance in any of the cognitive domains. The results of multiple regressions for model 4, which included non-modifiable and modifiable covariates and Hba1c levels did explain between twenty-one and forty-three percent of the variance in performance in all cognitive domains.

Hypothesis four, that cognitive function, after controlling for the covariates, would independently predict HbA1c, was also not supported. The model with all covariates and cognitive measures entered simultaneously nearly reached significance ($p=.06$), and better executive function independently explained lower HbA1c, which was anticipated.

It was expected that glycemic control, or a HbA1c at or below 7%, would contribute significantly to participant performance on cognitive measures. The cognitive function performance of these participants was below the norms in all of the cognitive domains. These findings could reflect prior changes in brain integrity and cognitive performance earlier in the course of DM that are not affected by current glycemic status, such as hippocampal function and functional connectivity to other areas of the brain (Bruehl et al., 2009; Hoogenboom et al., 2014; Musen et al., 2012; Zhou et al., 2010).

In addition to the model predictors in this study, sample characteristics of education category, rural status, DM education, presence of comorbidities, or other undetermined factors may have been influential. In the ACCORD-MIND trial (Cukierman-Yaffe, 2009) the relationship between HbA1c and cognition varied after controlling for age, sex, education, race, language, duration of DM, CV disease, and depression. The researchers concluded that HbA1c levels may not be a major determinant in cognitive test performance compared to other more influential sociodemographic and clinical factors. However, since HbA1c is a modifiable factor, whereas other factors such as age, duration of DM, history of CV disease, and education level are not, it is important to achieve glycemic control to maximize cognitive function. Still, even though good glycemic control is associated with better cognitive function, optimal glycemic control differs from individual to individual, and Ravona-Springer and colleagues (2014) suggest that considering a pattern or trajectory of glycemic control rather than a single HbA1c level might be more predictive of cognitive performance in persons with DM.

In this study, entering non-modifiable covariates age, years with DM, and education category in model one accounted for 15 to 32% of variance in cognitive measure performance with significance levels between <.001 to .01. Lower age appeared to be most influential in

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predicting better executive function, verbal memory performance, and mental processing speed. An important consideration is that age influences performance on the cognitive tests used in this study, and commonly in other similar studies.

For this sample of rural adults with DM, the number of years with DM did not uniquely contribute to their performance on any of the cognitive measures. In model 4 results, the magnitude of the standardized coefficients for years with DM (mean 12.6 (9.9) years) ranged from -.27 to .16 (Beta). Results on the written speed-based test were as anticipated in executive function (Trailmaking Test B B=-.01) and mental processing speed (Digit Symbol B= -.10; Letter Comparison B= -.16; Pattern Comparison B = -.22). Results on verbal-based tests in executive function (COWA B= -.27) and verbal episodic memory (HVLT Total Recall B = -.22) were also as expected. Results of this study were consistent with previous studies comparing cognitive performance over time in persons with DM and without DM (Fischer et al., 2009; Okereke et al., 2008; Spauwen et al., 2013). With three-year longitudinal data (Fischer et al., 2009), poorer performance in the DM group compared with the control group at baseline and at three years was maintained in executive function, mental processing speed, verbal episodic and semantic memory, and verbal fluency. They (Fischer et al., 2009) also found group effects for deficits in speed based cognitive tasks in executive function (inhibition and task shifting) and mental processing speed (semantic speed and reaction time). Of note, is that the speed-based tasks were measured through computerized testing, and the mean number of years with DM was not specified (Fischer et al., 2009). The association between with DM groups (DM duration 0-4 years, 5-14 years, ≥ 15 years) and stronger decline in verbal episodic memory with increased DM duration was found over four years by Okereke and colleagues (2008). In persons with DM, Spauwen et al (2013) found stronger decline over a time span of 12 years in executive function,

mental processing speed, and verbal episodic memory compared with controls. Although participants' mean years with DM were not specified, results of the analysis of the effect of DM duration on cognitive decline were significant only for mental processing speed.

Although the history of CV disease is a non-modifiable factor, the risk of future CV events is modifiable with treatment. The 10-year cardiovascular risk calculation used in this study included age, gender, race, smoking status, systolic and diastolic blood pressure, total and high density lipid cholesterol level, treatment for hypertension (yes/no), and presence of DM (yes/no). Hypertension has a cumulative effect over time on cognitive decline in DM (Reijmer et al., 2010). The association between cholesterol levels and cognitive dysfunction in DM is unclear (Reijmer et al., 2010). In this study, the 10-year CV risk score uniquely contributed to the performance of episodic verbal memory (HVLT% retained). Factors that may have limited the contribution of the CV risk calculation included that the study participants had fairly well controlled blood pressure (mean systolic= 125.9 (20.0) mmHg; mean diastolic = 76.3 (9.8) mmHg) and cholesterol levels (total cholesterol = 182.3 (43.2) mg/dl; HDL = 42.3 (11.7) mg/dl). Also, the majority of the participants did not smoke tobacco cigarettes (86%), although 28.6% of all participants had a history of tobacco cigarette smoking.

The sample mean score for depression measure PHQ-8 was 5.5 ± 4.8, indicating the presence of mild depression. The level of depression uniquely contributed to the performance of mental processing speed (Digit Symbol) and verbal episodic memory (HVLT% retained). And, level of depression and HbA1c had a moderate positive correlation (r=.34, p=.05). These findings were similar to those of Sullivan et al., (2013), but differed from findings by Koekkoek et al. (2012).

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Strengths and Limitations

Strengths of this study include the examination of non-modifiable and modifiable sociodemographic and clinical variables that may influence cognitive function in rural adults with DM. A wide age range of adults (ages 45 to 89) were included, and each cognitive domain was tested with at least two measures to increase the reliability of the findings. Limitations included that study participants comprised a convenience sample from primary care and DM education centers, which may have biased the findings. The participants had access to and were receiving regular healthcare and likely, regular lab tests and treatment adjustments. Many were still employed and had health insurance and received DM education. The findings may have differed with a sample that was unemployed and had limited or no access to healthcare. Small sample size is also a limitation, and may have affected the nearly significant findings for hypothesis four. A larger sample size may have increased the opportunity for the trend of cognitive function significantly predicting glycemic control. In addition, because the study was cross-sectional, no longitudinal trends in the variables could be determined, nor any causality implied. Lower, but normal cognitive function may be associated with other factors, such as poor performance of self-care, which may lead to poor glycemic control. Other comorbidities not accounted for, such as heart failure, may contribute to poorer cognitive function. Also, the results are not generalizable to the entire population of rural adults with DM. The blood glucose level at the time of the administration of the cognitive tests was not determined. Extremes in blood glucose levels can affect cognitive performance. Also, the length and intensity of the interview could have caused fatigue or anxiety, contributing to performance issues.

Conclusion

This study provides evidence that decreased cognitive function in domains of attention, executive function, mental processing speed, or verbal episodic memory in rural adults with DM does not independently explain glycemic control after controlling for the modifiable and non-modifiable covariates. The progression of cognitive decline may have two different patterns, a slow progressive decline beginning in pre-DM stages, and a severe faster decline associated with dementia. The performance of this study's participants was below the norms in all four measured cognitive domains; however, it is unknown whether the results reflect a slow or rapid cognitive decline. The study sample included participants from ages 45 years and older, and nearly 28% were employed. It is concerning that performance in all cognitive domains were below the norms, and there was mild cognitive impairment present in some participants between the ages of 45 to 66 years old. Understanding the impairment in cognitive function in persons with DM is important, not only because the ongoing self-care activities for maintaining glycemic control requires multiple cognitive processes, but also because job performance may be affected.

In examining modifiable and non-modifiable factors that influence cognition, age and years with DM, both non-modifiable factors, were highly associated with cognitive function, and age was predictive of cognitive function. Modifiable factors of CV risk and the level of depression were predictive of cognitive function. Some elements of CV risk, such as blood pressure control, lipid levels, and smoking status are modifiable with intervention. Depression appears to be an important consideration. Depression may precede the onset of DM, or be consequential to the brain changes that occur in DM. Depression can impair one's ability to adhere to self-care regimens, potentially worsening the course and outcomes of DM. Routine screening for depression, along with mild cognitive impairment, will assist with identifying signs

of early cognitive decline and enable implementing changes in treatment regimens to maximize glycemic control. Medication and psychotherapy can decrease levels of depression, but it is yet to be determined which medications are most effective in persons with DM.

More research is required to identify how these findings impact one's everyday ability to perform self-care, instrumental activities of daily living, and perhaps job performance. Findings from this study imply that health care professionals caring for persons with DM need to monitor levels of cognitive function and depression along with glycemic control and CV risk factors. Decline in the cognitive domains needed for self-care planning and performance, such as attention, executive function, mental processing speed, and verbal episodic memory, varies with age and years with DM. At the present time, methods for monitoring cognitive decline in persons with DM is not standardized. Further research in this area is urgently needed, as it may be possible to improve some aspects of cognition with cognitive interventions.

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CHAPTER IV

Cognitive Function and Self-Care in Rural Adults with Type 2 Diabetes

Introduction

Persons with type 2 diabetes mellitus (DM) are at high risk for multiple serious

complications, including structural brain changes and decreased cognitive function that may

impair their abilities to perform the self-care activities associated with DM management (Nguyen

et al., 2010; Primozic, Tavcar, Avbelj, Dernovsek, & Oblak., 2012; Qiu et al., 2006) and the

decision making and problem-solving abilities needed to maintain glycemic control (Cukierman-

Yaffe et al., 2009, Munshi et al., 2012, Thabit, Tun, McDermott & Sreenen, 2012). Effective

self-care positively correlates with better glycemic control, health outcomes, and perceived

health (Song, 2010). Impaired cognitive functions, including attention, executive function,

mental processing speed, and verbal episodic memory, which are most often affected in persons

with DM, are often overlooked in clinical practice but may be crucial to one's ability to

maximize their health and prevent further DM complications (Reijmer et al. 2010).

Understanding the linkages between DM self-care and cognitive function is thus critical to

supporting patients and families living with DM in community settings. Toward that aim, this

study examined the cognitive processes associated with DM self-care tasks, and how DM

associated cognitive changes and other factors influence self-care. Using the self-care model

developed by Song (2010), this study tested whether cognitive function (attention, executive

function, mental processing speed, and verbal episodic memory), after controlling for the contributing factors of age, years with DM, level of depression, years of education, and everyday problem solving, independently predicted level of self-care activity performance in the study population.

Background

Song (2010) identified the main concepts of DM self-care as self-care maintenance and self-care management. Self-care maintenance refers to behaviors needed to sustain physiologic stability in DM, which include symptom monitoring and treatment adherence. Self-care management incorporates active decision making and problem-solving in response to sign and symptom changes that occur in DM (Song, 2010). Other factors that contribute to the performance of self-care activities include individual sociodemographic characteristics (e.g. age, level of education), one's the functional ability to perform activities of daily living (ADLs) and instrumental activities of daily living (IADLs), and the presence of comorbidities (e.g. depression) (Feil, Zhu, & Sultzer, 2012). Adapted from Riegel and Dickson's (2008) situation-specific theory for self-care in heart failure patients, Song's (2010) model is specific for DM self-care but, like the Self-Care of Heart Failure Model, emphasizes one's ability to perform self-care maintenance and self-care management activities. Self-care maintenance includes behaviors, such as symptom monitoring and treatment adherence to maintain physiologic stability. Self-care management represents how an individual responds to disease-related sign and symptom changes, and one's ability to recognize, evaluate, decide to take action, implement treatment or action, and evaluate the treatment or action related to the perceived changes. Song's (2010) model adaptation reflects relevant DM monitoring activities and behaviors (diet, medications, blood glucose testing, exercise, and foot examination). Self-care maintenance activities are

routine and differ from higher level decision making and problem solving behaviors required in self-care management. Routine DM self-care behaviors have been well studied while the latter have not (Song, 2010).

Cognitive processes required for the performance of DM self-care

As previously noted, attention, executive function, mental processing speed, and verbal episodic memory are cognitive domains most often affected in persons with DM (Reijmer et al., 2010). Attention involves cognitive processes that utilize specialized brain networks that allocate limited information processing capacity towards sensitivity to and selection of incoming stimuli, and sustaining focus on other stimuli (Posner & Rothbart, 2007). Executive functions include inhibition and interference control (behavioral and cognitive inhibition, selective attention); working memory (holding and manipulating information in mind); and cognitive flexibility (mental flexibility or mental set shifting) (Diamond, 2013). These processes are dependent upon the frontal and pre-frontal cortices and allow goal formation, organization, sequencing, switching between tasks, conflict resolution and encoding information for short-term storage (Baddeley, 1998; Smith & Jonides, 1999). Mental processing speed is the rate of cognitive processes for information processing, and when (decision speed) and how quickly (perceptual speed) one responds to situations (Salthouse, 2000). Multiple neuropsychological tests are used to evaluate executive function, and differ in the cognitive abilities that are examined (Salthouse, 2005).

In an analysis of sixteen different tests that measured executive functions of perceptual speed, functions of vocabulary, reasoning, spatial visualization, and verbal episodic memory, it was demonstrated that perceptual speed and reasoning had the most significant associations with the executive function measures. The results suggest that measures of executive function relate

more to speed based and reasoning tasks (Salthouse, 2005). Studies examining the effects of aging on mental processing speed have shown varying results but demonstrate that age alone may not independently influence reduced mental processing speed (Salthouse, 2000; Schretlen et al., 2000). Verbal episodic memory involves the ability to learn, store, and retrieve information, and encompasses knowledge acquired through life experiences (Dickerson & Eichenbaum, 2010; Squire & Kandel, 2009). It is highly dependent on the medial temporal lobe memory system, which also regulates critical functions in the processes of sensory perception (visual, auditory, olfactory, taste), learning, and memory consolidation (Dickerson & Eichenbaum, 2010; Squire & Kandel, 2009; Yang & Li, 2012). A useful analogy for conceptualizing the interplay between different cognitive processes is to consider the frontal cortex as a " file clerk" for the memory system, the medial temporal lobes as the "recent memory files," and other cortical regions (i.e. amygdala, basal ganglia, cerebellum, lateral temporal lobes, thalamus) as the "remote memory files" (Budson, 2009). If one of the regions are impaired, the " files" may be difficult to retrieve or, if available, distorted in some way (Budson, 2009).

The hippocampus is highly vulnerable to the effects of hyperglycemia in individuals with DM, with damage shown early in the course of the disease (Bruehl et al., 2009). Hippocampal based cognitive functions, such as verbal episodic memory may be initially affected and show further decline as the level of DM progresses to later stages (Bruehl et al., 2009). Recent studies have documented reduced functional connectivity between the hippocampus and several associated regions and the appearance of decreased functional connectivity prior to the appearance of identifiable structural deficits ((Hoogenboom et al., 2014; Musen et al., 2012; Zhou et al., 2010). Decreased neuronal connectivity disturbances are thought to be widespread in persons with DM such that they negatively impact learning and memory. Compared with healthy

controls, persons with DM have increased white matter lesion in tracts connecting frontal, parietal and temporal brain regions, areas associated with attention, executive function, mental processing speed, and verbal episodic memory, that significantly reduce mental processing speed and memory (Reijmer et al., 2013). Other comorbid conditions, such as heart failure, demonstrate similar declines in cognitive function that may compound the pattern of decline seen in DM (Dickson, Tkacs, & Riegel, 2007).

DM self-care knowledge.

Important antecedents to symptom monitoring include having adequate knowledge about DM and mastery of self-monitoring skills (Song and Lipman, 2008). The ability to acquire new knowledge and form memories to retain that knowledge over time is referred to as declarative memory, which includes verbal episodic memory (Dickerson & Eichenbaum, 2010; Squire & Kandel, 2009). Memory formation requires interaction with cognitive functions of attention, language and perception, and functional neuronal connectivity is essential for learning, memory storage and recall. Multiple factors influence long term memory formation including focus, perception, organizational ability, and existing knowledge (Squire & Kandel, 2009; Yang & Li, 2012).

Hewitt and colleagues (2011) reported that insulin-dependent older persons (mean age 80.9 years) with global cognitive impairment had poorer knowledge about managing hypoglycemia (p=.013, p = .008) and medications during an acute illness (p=.017) than did individuals without impairment. Another study, which examined the relationship of self-care to the conceptualization and understanding of self-care in DM patients (mean age [SD] = 53.9 [$\pm$ 17.3] years), found that participants with poor glycemic control lacked understanding of basic self-care (mechanisms of medications, concepts of glucose monitoring, symptom detection, role

of exercise, dietary instructions, and behavior-lifestyle adjustment), and had difficulty detecting and solving problems (Lippa and Klein, 2008). Individuals with moderate glycemic control demonstrated a vague understanding of medications, monitored their blood glucose regularly, and inconsistently applied results to events. For example, while many individuals could detect symptoms of hyper- or hypoglycemia, they often lacked the ability to correct for these states. Dietary rules tended to be broadly followed by these individuals and they demonstrated poor understanding of the role of exercise in managing their disease, often only exercising to minimally perform activities of daily living. Individuals with good glycemic control either had a fixed routine or utilized in-depth medication knowledge to modify routines. They tended to monitor blood glucose several times daily, and understood the relationship between exercise and glucose levels (although exercise frequency was no greater than in the other two groups). Individuals in this group also regularly monitored their diets and could effectively identify and manage episodes of hypo- and hyperglycemia (Lippa & Klein, 2008).

Treatment adherence in DM self-care.

Treatment adherence in DM self-care involves multiple activities and behaviors for controlling glucose levels and managing signs and symptoms. Included among these is medication adherence, or taking medications at the times and dosages prescribed, which requires that one has intact processes of executive function and working memory needed to develop and implement plans for and recall of adherence (Insel, Morrow, Brewer, & Figueredo, 2006). When a task is repetitive, such as routinely taking daily medication, remembering if the medication was taken becomes difficult in those with impairment in those cognitive domains. Medication adherence involves working memory functions of keeping the intention in mind until conditions are appropriate for action, such as correct time, getting the medication, and procuring water to

swallow pills or injection supplies for insulin administration (Insel, et al., 2006). Executive function is also essential for establishing new behaviors, suppressing old behaviors, and self-regulation (Tran et al., 2014).

Insel et al. (2006) examined the relationship between cognitive function and medication adherence among adults over the age of 67 years with multiple medical conditions. They found that executive function and working memory were significantly related to adherence (p<.05) while global cognition and memory composite scores were not. These findings support the importance of intact prefrontal cortex functions in self-care performance, which distinctly differ from global cognition and memory performance (Insel et al., 2006). In persons with DM, impaired executive function may co-exist with normal global cognitive performance and may not be detected with global cognition and memory measures (Thabit et al., 2012).

Sign and Symptom Recognition in DM.

Mechanisms behind how sign and symptom changes trigger decision making and problem-solving are not well understood. In order to recognize and interpret symptom changes, knowledge and understanding of the implications of the symptoms, and the ability to sense changes in body homeostasis are necessary (Dickson, Tkacs, & Riegel, 2007). An individual's inability to recognize altered homeostasis may also reflect impaired interoception or autonomic or peripheral neurological deficits (Dickson et al., 2007). For example, peripheral neuropathy is common in persons with DM, causing decreased pain sensation in the extremities that often results in skin breakdown and invasive infections (ADA, 2016). Autonomic neuropathy in DM can cause decreased cardiac responsiveness to exercise, postural hypotension, impaired thermoregulation and pupillary reactivity, and autonomic failure in response to hypoglycemia. Slowed gastric motility, or gastroparesis, can lead to unpredictable carbohydrate metabolism and

erratic blood glucose control (ADA, 2016). Intact mental processing and cognitive processes of

attention, executive function; memory and perception are key factors connecting these changes

to the need for self-care action (Dickson et al., 2007). Symptom detection differs among persons

with DM, as past experiences and DM knowledge vary between individuals and can be

influenced by their health beliefs and cultural perceptions of disease (Kirk et al. 2011; Song &

Lipman, 2008). Indeed, some individuals with DM may interpret their lack of symptoms to

mean that they no longer need to self-monitor their glucose levels at all (Song & Lipman, 2008).

Kirk et al. (2011) examined how older adults with DM ($\geq$ 60 years of age) identified

symptoms related to high and low blood glucose levels. Grouping symptoms into four major

areas: nerve perception, lightheadedness, energy levels and vision changes, they found that

participants described nerve perception as "tingling," "numbness," or "nervousness," and

reported these symptoms with more frequency than the symptoms in the other three categories.

Lightheadedness was most often described by participants as "dizziness," and several described it

as a feeling that "made it hard to think." Descriptions of low energy level included feeling tired

and weak, which were sometimes attributed to old age. Many participants were unable to

distinguish whether the symptoms of lightheadedness/dizziness, low energy levels, and vision

changes occurred with high or low blood glucose levels, exemplifying the multiple variations in

symptom perception experienced by persons with DM (Kirk et. al, 2011).

Decision making and self-care in DM.

Mechanisms behind how sign and symptom changes trigger decision making and

problem solving are also not well understood. What is known is that the neural basis of decision

making is centered in the prefrontal cortex, with connectivity to other brain areas for integration

of informational sources for multi-attribute, or higher level decisions (Krawczyk, 2002; Volz,

Schubotz, & vonCramen, 2006). Damage to the prefrontal cortex affects problem structuring and solution generation, creating difficulty in one's ability to consider the consequences of immediate actions or activities on the future, and rendering one incapable of connecting behavioral choices and corrective actions (Krawczyk, 2002; Munshi et al., 2012, Thabit et al., 2012). Impaired executive function interferes with one's processes of reasoning, association, insight, planning and decision making (Munshi et al., 2012, Thabit et al., 2012). These highly integrated processes are essential for complex tasks required for DM self-care such as dietary adjustments requiring carbohydrate counting, managing insulin based on sliding scales and meal timing, and activity adjustment based on blood glucose levels (Munshi et al., 2012, Thabit et al., 2012).

Lippa and colleagues (2008) examined the relationships between levels of decision making and DM control, and the use of declarative (factual) and applied (procedural) knowledge in DM self-care. Eighteen participants (mean age =53.9, range = 19-76 years, 33% female) were interviewed and asked to make decisions related to routine but critical DM self-care incidents. Three levels of decision making expertise (novice, intermediate, expert) were determined by the number of relevant answers given in categories of problem detection and cue utilization, functional relationship comprehension (ability to explain the decision), and problem solving (what action to take in response to the incident). Level of self-care adherence was measured using the Summary of Self-care Activity Scale, a 17 item self-report scale that queries frequency of performing activities of diet, exercise, blood glucose testing, foot care, and medications. Glycemic control was determined by rank ordering of either the highest reported blood glucose value in the past week, or by glycohemoglobin results. The relation between each decision-making process, self-care activity level and glycemic control was assessed. Novice level

decision-making utilized more superficial organizational patterns when applying knowledge to functional relationships, and exhibited less efficient problem-solving strategies than expert level decision making. Greater use of problem detection cues was associated with better treatment adherence and lower blood glucose levels; more expert participants combined multiples cues to increase problem detection. Participants who identified more functional relationships and had better problem-solving abilities also exhibited better adherence, but not necessarily better glycemic control. The probability of whether a participant had accurate knowledge to give an effective solution for the incident (declarative knowledge) predicted the probability of applying an effective solution (applied knowledge). The probability of having accurate declarative knowledge was greater than the probability of applying that knowledge in critical situations of hyper and hypoglycemia. The study showed that DM knowledge alone does not lead to greater decision-making ability related to DM self-care actions (Lippa et al., 2008).

Contributing Factors to DM Self-Care Performance

Age, duration with DM, level of education, glycemic control, rurality and DM self-care.

While increased age is associated with a decline in one's ability to perform DM self-care (Munshi et al., 2006; Tomlin & Sinclair, 2016), the length of time of DM diagnosis (Tomlin & Sinclair, 2016) and level of education (Insel et al., 2006; Lin et al., 2014; Tomlin & Sinclair, 2016) has not. Results of studies examining the relationship between self-care performance and glycemic control are varied (Lin et al., 2014; Lippa et al., 2008; Nguyen et al., 2010; Primozic et al., 2012). Women are more likely than men to encounter barriers to self-care, including income, education, and physical and cognitive limitations (McCollum, Hansen, Lu, & Sullivan, 2005).

Unden et al. (2008) found no difference in glycemic control between women and men, however, compared with men, women reported lower quality of life and less satisfaction with DM care.

Individuals living in rural communities, defined as areas with a population below 50,000 and a core population density of fewer than 1000 persons per square mile (Hart, Larson, & Lishner, 2005), may experience limited access to DM resources and greater challenges to proximal health care (Hale, Bennett, & Probst, 2010; Quandt et al., 2005; Utz, 2008). Rural residents across the United States comprise nearly 21% of the population (Bureau of the Census, 2010), with adults over the age of eighteen years old demonstrating greater risk for poorer glycemic control than adults in non-rural communities (Hale, Bennett, & Probst, 2010). Data from the 2006 Behavioral Risk Factor Surveillance System (n=29,501) explored differences in DM care and DM outcomes associated with rural residence and found that rural residents with DM had lower levels of education, income and health insurance coverage when compared to non-rural peers (Hale et al., 2010). Rural residents were also less likely to report having had screening foot or eye examinations, and more likely to report occurrence of retinopathy and foot ulcers (Hale et al., 2010).

Brown et al. (2009) and Kilbourne and colleagues (Kilbourne, Switzer, Hyman, Crowley-Matoka, & Fine, 2006) proposed socioeconomic status as a major health outcomes determinant among vulnerable populations. More specifically, Brown et al. (2009) included individual, household, and community factors as part of one's overall socioeconomic status and proposed that the progression of a chronic disease, such as DM, is likely influenced by these factors over time, especially as they may influence health outcomes through healthcare access and health behaviors (Brown et al., 2009). Gender, age, and racial/ethnic factors are considered as covariates in the framework that contribute to rather than cause health disparities.

Indeed, according to Brown and colleagues (2009), access to healthcare encompasses the availability of a consistent source of adequate care and financial and insurance resources. Health behaviors refer to performance of self-care and reduction behaviors such as exercise and smoking abstinence and smoking cessation. Better access to care decreases the negative effects of income inequality and frequency of poor self-reported health status. Lower frequency of blood glucose monitoring and exercise, and higher rates of smoking are associated with lower socioeconomic status and education levels. Compared with uninsured adults with DM, insured persons have greater odds of having foot and dilated eye examinations, and preventative care. Communication barriers such as poor interaction with health care staff, language barriers, and inability to understand instructions are linked with lower socioeconomic status. Also, the risk of social isolation and limited social support is greater in poorer populations, and is linked to poorer adherence to self-care (Brown et al., 2009).

Everyday problem-solving ability in IADLs and self-care in DM.

The inability or diminished ability to perform complex daily tasks, such as those required for instrumental activities of daily living (IADLs), has been shown to be an early indicator of cognitive decline, and has stronger correlations with cognition than do activities of daily living (ADLs) (Royall et al., 2007). ADLs refer to essential abilities for autonomous function at home, such as dressing, bathing and toileting. IADLs are cognitively complex daily tasks required for autonomy within society and include managing finances, medications, transportation, meal preparation and telephone use and which are commonly measured by performance-based and self-report tools (Lawton & Brody, 1969; Royall et al., 2007; Willis et al., 1998). Still, the relevance of specific cognitive domains to performance of IADLs is unclear. Royall et al. (2007) reviewed 68 studies across the neuropsychiatric, geriatric, rehabilitation and other literature

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testing associations between cognitive and functional outcome measures, including IADLs. Overall results reported weak to moderate associations (r≤.40) between cognitive measures and functional outcomes, with executive function and global cognitive measures explaining more variance than attention, memory, verbal or visuospatial measures (p<.001). Cahn-Weiner et al. (2007) examined cognitive and neuroimaging (MRI) predictors of change in IADL performance over 5 years in a community-based sample of persons with normal cognitive function (n=52, mean age (SD) = 72.5 ± 7.4 years), mild cognitive impairment (n= 35, mean age (SD) = 72.8 ± 8.4 years), and moderate dementia (n= 37, mean age (SD) = 73.1 ± 8.4 years) and moderate dementia (n=124, mean age 72.5 ±7.4 years). At baseline, lower episodic memory and executive function were associated with poorer IADL performance (p<.001), with executive function associated with decreased IADL performance over time (p<.01). Baseline MRI measures of cortical gray matter and hippocampal volume were associated with baseline IADL performance (both p<.001). Hippocampal volume was significantly associated with decreased IADL performance over time (p<.01), cortical gray matter nearly reached significant association (p=.05), and white matter lesions and lacunar infarcts had no association. The researchers speculated that executive function plays more of a role in daily IADL performance than episodic memory, and compensates for dysfunction in other cognitive domains until other cortical-dependent processes begin to fail and compromise everyday functional performance. Many persons have "mixed dementia," or dementia with multiple causative factors including vascular disease and other factors. In Alzheimer's dementia, episodic memory is affected early and progressively declines along with the disease. Hence, if executive function is poor at baseline, it is likely that one's dementia is already at an advanced state.

In two studies by Munshi and colleagues (2006, 2012) examining the association between cognitive dysfunction and glycemic control in persons with DM, decreased performance as an objective measurement of executive function was associated with poorer IADL performance and glycemic control. Depression was associated with decreased IADL performance, but not glycemic control (Munshi et al., 2006). Interestingly, a self-reported measure of executive function was not associated with glycemic control or IADL performance (Munshi et al., 2012), but was associated with depression. Although DM self-care performance was not measured by Munshi and colleagues, their results emphasized the importance of objective assessment of executive function and depression when someone with DM exhibits problems with performing complex self-care tasks such as managing insulin sliding scales, carbohydrate counting, and diet management.

Depression and self-care in DM.

Depression can impair one's ability to adhere to self-care regimens, potentially worsening the course and outcomes of DM (Lamers et al., 2008; Lin et al., 2004; Munshi et al., 2006; Primozic). The presence of depression has been associated with cognitive dysfunction in persons with DM (Sullivan et al., 2013). Compared with control groups, higher prevalence and persistence of depression has been shown in persons with DM (Degmecic et al., 2014; Trento et al., 2013) with estimates of depression prevalence between 8-31% (mean 18%) in persons with DM, and 5-24% (mean 10%) in persons without DM (Koekkoek et al., 2012). Depression in DM may result from coping with a chronic disease or from damaging metabolic consequences affecting cerebral neurotransmitter levels or vascular integrity (Reijmer et al., 2010). Others theories are that the relationship between DM and depression may be bidirectional and

influenced by biologic and behavioral factors (Degmecic et al., 2014; Sullivan et al., 2013; Trento et al., 2013).

Dysregulation and over activation of the hypothalamus-pituitary-adrenal axis (HPA-axis) and sympathetic nervous system (SNS) has been shown to be a common pathway for both depression and DM, and may increase the risk for both (Badescu et al., 2016; Champaneri, Wand, Malhotra, Casagranda, & Golden, 2010; Tataru et al., 2016). Depression and chronic stress activate the HPA-axis and SNS, causing increases in production of cortisol, adrenalin and noradrenaline, and chronic hypercortisolemia and prolonged SNS activation. This, in turn, promotes insulin resistance, obesity, and metabolic syndrome, a constellation of risk factors that includes elevations in blood pressure, blood sugar, and triglycerides; low levels of HDL cholesterol; and increased abdominal fat that increase the risk for cardiac and DM disease. Depression and chronic stress also induce immune dysfunction through SNS activation, causing increased production of inflammatory cytokines (Interleukin-6), which also promotes insulin resistance and leads to the development of DM, (Badescu et al., 2016; Champaneri et al., 2010). Hypercortisolemia disrupts hippocampal neurogenesis, and inflammatory cytokines interfere with normal functioning of the pancreatic B-cells, where insulin is stored and released (Badescu et al., 2016).

Aims and Hypotheses

It appears that every aspect of self-care can potentially be affected by DM-associated brain changes, making it difficult to determine which cognitive processes are problematic. How these processes relate to patient characteristics is also unclear. For example, there is no clear understanding concerning the relationship between cognitive function and self-care in rural adults with DM, who constitute a high-risk population for DM-related morbidity and mortality.

Guided by an adapted self-care model developed by Song (2010) and Riegel and Dickson (2008) and depicted in Figure 4.1, this study aims to address this gap, specifically examining the cognitive processes associated with DM self-care tasks and how DM-associated cognitive changes and other factors influenced self-care in this population. Towards these aims, this study explored rural-related sociodemographic factors (education level, employment, healthcare access, healthcare insurance) that potentially influence self-care performance. Next, it examined the relationship between performance in cognitive function measures (attention, executive function, mental processing speed and verbal episodic memory), levels of self-care activity (diet, blood glucose testing, exercise, foot care, and medication), and contributing factors (age, years with DM, education category, everyday problem-solving, HbA1c, level of depression). Finally, it tested whether cognitive function measures, after controlling for the contributing factors of age, years with DM, level of depression, years of education, and everyday problem solving, predicted DM self-care activity levels. As shown in Figure 4.2, the study hypotheses were that 1) increased age, years with DM, and level of depression, and decreased years of education, everyday problem-solving, glycemic control, and cognitive function would correlate with poorer levels of DM self–care adherence in a sample of rural adults with DM, and that: 2) cognitive function, after controlling for the afore noted contributing factors, would independently predict level of self-care activity performance in the population of study.

Self-Care Maintenance

Self-Care Management

Self-Care Knowledge

Monitor

Blood Glucose   Foot Exam

Adherence

Diet   Exercise

Medications

Sign/Symptom Recognition

Evaluation

Treatment Implementation

Evaluation

Awareness

Decision Making
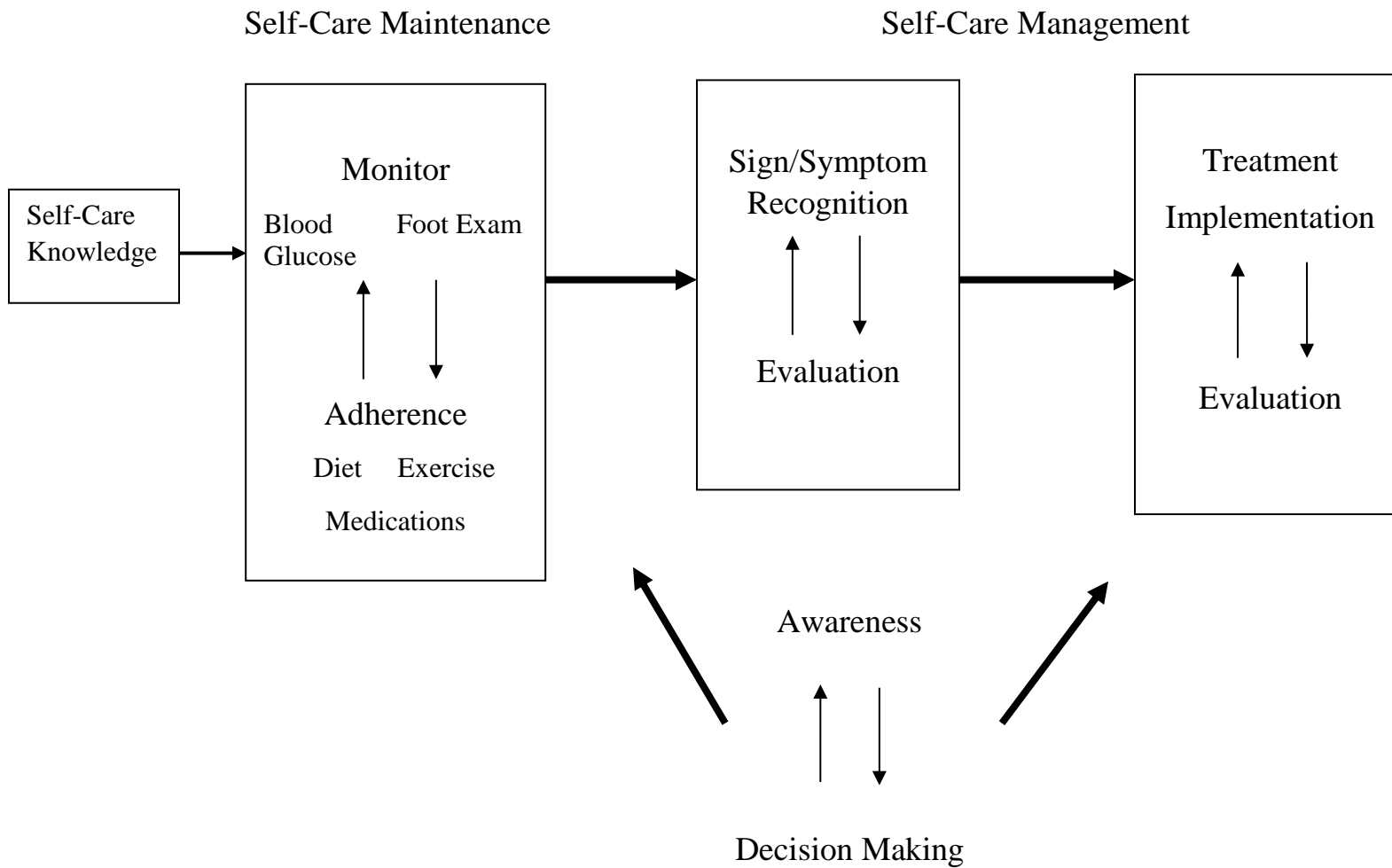
Figure 4.1. DM Self-Care Framework for Guiding Analysis

Adapted from: Song (2010). *Journal of Cardiovascular Nursing; 25*(2): 93-98.
Riegel & Dickson (2008). *Journal of Cardiovascular Nursing; 23*(3): 190-196.
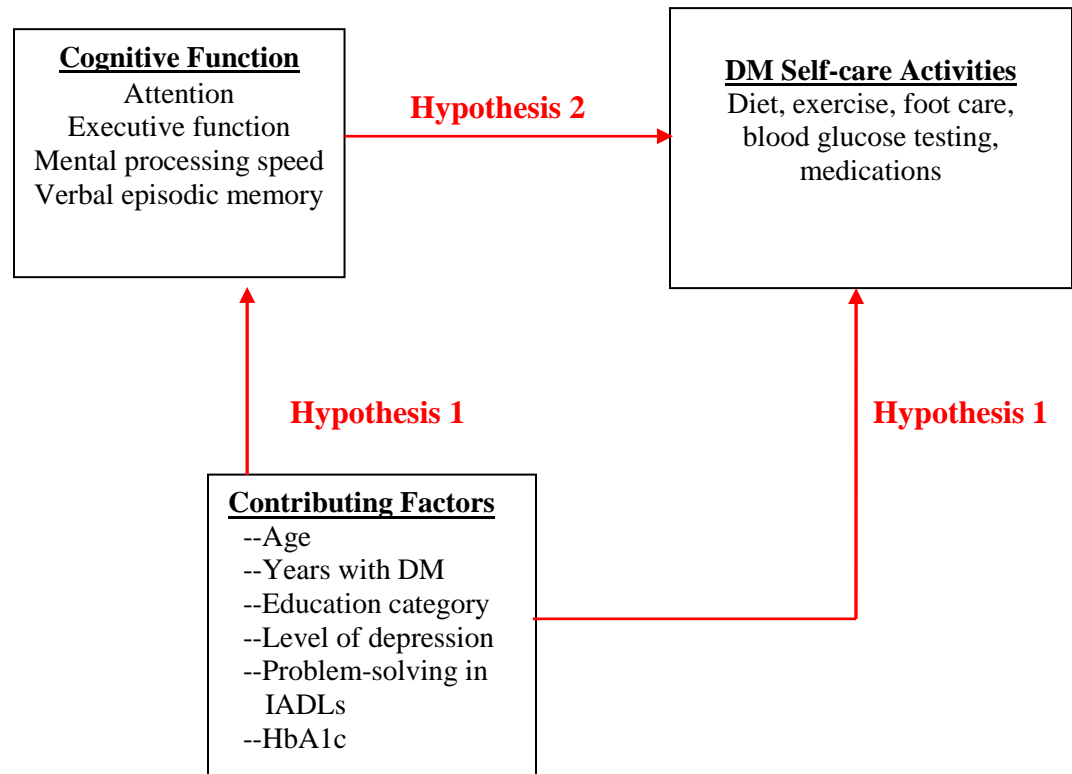
Figure 4.2. Hypothesis Model

Methods

Participants and settings

Using a descriptive and prospective design, and with approval from the University of Michigan Institutional Review Board (Study HUM00085816), 56 rural-dwelling men and women with DM were recruited from primary care providers and diabetes education centers in three rural counties located in the Upper Peninsula of Michigan and two rural counties in northeastern Wisconsin. The prevalence of DM in the Michigan and Wisconsin counties is 10-12% and 8.9-10.6%, respectively, which exceeds the 9.3% national prevalence rate of DM among adults (CDC, 2014). Available healthcare in each county includes public hospitals, community and rural health clinics, primary and specialty care (e.g. internal medicine, cardiology, neurology, nephrology, diabetes education).

Inclusion and exclusion criteria

Participants were included if they had an established medical diagnosis of type 2 DM, were over the age of 45 (due to increased DM prevalence after age 45 years), had a documented HbA1c level within two months of their interview for the study, had a documented total cholesterol and HDL within the past twelve months, completed at least the ninth grade, were able to read the English language, were available by telephone or mail for scheduling, and consented to participate in the study.

To limit confounding factors that could affect the relationship between study variables or affect cognitive function and the ability to perform the neuropsychological tests, participants were excluded if they had a diagnosis of dementia (MoCA score <22), history of stroke, or degenerative neurological conditions (e.g. Huntington's, Parkinson's, or Lewy Body disease, amyotrophic lateral sclerosis), current or recently treated (within the past 5 years) major psychiatric disorders (e.g. schizophrenia, bipolar disorder, major depression), inadequate visual

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acuity to read printed study materials, history of or current major alcohol or substance abuse as measured by the CAGE test (NIAAA, 2003), hepatic encephalopathy, terminal illness, dialysis dependence, or prisoner status.

<div align="center">**Measures and Instruments**</div>

Sociodemographic and clinical data.

Sociodemographic data characterized the sample and included age, gender, level of education, work and marital status, race and ethnicity, and distance to health care. Clinical data included years with DM, and presence of neuropathy (a complication of DM), height, weight, body mass index blood pressure, smoking status, HbA1c, and total and HDL cholesterol levels. The length of the interview was 60-90 minutes, which included all of the data collection listed below.

Dementia screen for exclusion criteria.

The Montreal Cognitive Assessment (MoCA) was used to screen potential study participants for the presence of dementia, and thus, exclusion from the study. The MoCA has 30 items that briefly measure multiple cognitive domains that are affected in dementia including short-term memory, visuospatial abilities, executive functions, verbal memory, attention and working memory, language, and orientation. The test takes approximately 10 minutes to administer and points are allocated for successful completion of various tasks. A perfect score is 30 with a score of 26 or greater considered normal. Scores between 22 and 26 indicate mild cognitive impairment, and scores below 22 indicate the likelihood of dementia, and provided the cutoff score for participant enrollment (Nasreddine et al., 2005).

Self-care.

The revised version of the Summary of Diabetes Self-Care Activities Measure (SDSCA) was used to measure levels of self-care activities across six components of the DM regimen (Toobert, Hampson & Glasgow, 2000). The SDSCA is a brief self-report instrument that asks participants to identify the frequency with which they perform activities related to diet, exercise, blood glucose testing, foot care, and medications. Questions for general diet include the number of days per week that they follow a healthful eating plan and the number of days per week that they follow their prescribed eating plan. Specific questions ask about the frequency per week of eating five or more servings of fruits and vegetables, eating high fat foods, and spacing carbohydrates evenly throughout the day as recommended by one's healthcare provider. Exercise questions ask participants about the number of days per week in which they participate in at least 30 minutes of physical activity, and specifically whether they participate in a specific exercise session other than their usual activities around home or work. Similarly, the SDSCA asks how many days per week one tests his/her blood glucose and the frequency with which it corresponds to the frequency recommended by one's healthcare provider. Foot care questions ascertain the number of days participants checked their feet, inspected the inside of their shoes, washed and/or soaked their feet, and dried the spaces between their toes after washing. Medications questions included the number of days DM medications were taken, or if on insulin, the number of days recommended insulin injections were taken. Scores were calculated for each regimen area, creating a subscale for each area, and means and standard deviations were calculated for each subscale. The SDSCA has been widely used in adults with DM. Instrument reliability of the original 11-question SDSCA was demonstrated across seven different studies (n-1,988) (Toobert, Hampson, & Glasgow, 2000). The inter-item correlation mean was r=.47 for

internal consistency of the scales, and test-retest Pearson's correlations mean r=.40. Evidence of criterion validity was shown with validity coefficients significant with p ranges for Pearson's correlations r=.001 to .05, using SDSCA dietary and exercise subscales and criterion variables from 5 of the 7 reviewed studies. Sensitivity to change results varied widely with a responsiveness index score (range -0.09-.43). The revised version of the SDSCA has 14 additional questions that included items pertaining to self-care recommendations and medications, although there is no currently available reliability or validity data (Communication with SDSCA developer, Dr. Deborah J. Toobert, PhD, 10/21/2013).

Glycemic control.

Glycemic control, defined as the optimal level of average blood glucose levels associated with the reduction of DM complications, was measured with glycosylated hemoglobin, or HbA1c levels (ADA, 2016). HbA1c is a form of hemoglobin that is measured primarily to identify the 3-month average plasma glucose concentration, and which has a strong predictive value for DM complications (ADA, 2016). The average, presented as a percentage, indicates how much glucose is adhering to red blood cells over their average life span (3-4 months). For people without DM, a normal range of 4-6% equates to blood glucose level of between 70-126 mg/dl. A HbA1c of 7%, or a blood glucose level of 154 mg/dl, indicates consistently elevated blood glucose levels, and maintaining HbA1c levels at 7% or below is thought to reduce microvascular and neuropathic complications (ADA, 2016).

As per the inclusion criteria, all participants had documentation of an HbA1c level from a Clinical Laboratory Improvement Amendments certified laboratory done within two months prior to the interview.

Cognitive function measures.

The variables representing aspects of cognitive function included attention, executive function, mental processing speed, and verbal episodic memory. A brief description of the variables and measures follow. A more comprehensive discussion of the measures is included in Table 3.2. on page 102.

Digit Span. The Digit Span Test was used to measure participants' attention capacity by exposing them to increasingly larger amounts of information and then asking them to immediately recall or process that information. Digit Span is comprised of two tests, Digits Forward and Digits Backward, which involve different cognitive activities of sustaining focus and short-term storage capacity (Choi et al., 2014; Strauss et al., 2006). Participants repeat number sequences that the examiner reads aloud, with increasingly longer sequences being tested in each trial. In the forwards series, the sequences are repeated forwards, and in the backwards series, the sequences are repeated backwards. Raw scores for Digits Forward indicate length of digit span (possible score range is 0 to 8) and Digits Backward (possible score range is 0-7) were analyzed as a total sum (possible score 0 to 15). The effects of age, education, and gender have varied between studies (Choi et al., 2014). Reliability and validity have been supported (Strauss et al., 2006).

Trailmaking Test Part A. Trailmaking Test Part A (Trails A) was used to measure participants' attentional processes of scanning and visuomotor tracking of a sequence and their overall speed of performance (Lezak et al., 2004; Reitan, 1992). The test requires that the participant draw lines to connect randomly placed numbered circles into a consecutive numerical order. The test is timed and scored based on the time it takes for the individual to complete the task, including additional time to correct errors. The average completion time is 29 seconds, for

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cognitively intact individuals, with greater than 78 seconds indicating cognitive decline. To account for participants that could not complete the test, the scores were converted to a ratio of number correct per second, where a higher ratio indicated better performance (Reitan, 1992). Problems with visual scanning and tracking on Trails A can indicate difficulties with conceptual sequencing of numbers and decreased mental flexibility. Increased age and depression, as well as lower education level, are associated with decreased performance (Lezak et al., 2004).

Executive function.

Several instruments were used to measure executive function given that, as previously discussed, it comprises a wide array of processes and includes visuospatial and auditory and speech functions (Baddeley, 1998; Diamond, 2013; Smith & Jonides, 1999).

Controlled Oral Word Association Test (COWA). The COWA was used to test participants' verbal fluency as a measure of frontal and pre-frontal cortex function. The test requires that the participant generate as many words as possible (excluding proper nouns and numbers) beginning with a letter given by the tester. Raw scores reflect the total number of acceptable words generated with three different letters (in this case: C, F, and L) during three separate 60 second trials. Scores adjusted for age and education are then converted to a percentile. Lower scores indicate greater impairment (Lezak et al., 2004). Reliability and validity have been supported (Lezak et al., 2004).

Trailmaking Test Part B. The Trailmaking Test Part B (Trails B) measures processes of scanning and visuomotor tracking of a sequence, speed of performance, divided attention, and mental flexibility and mental set shifting (Lezak et al., 2004). The test requires participants to draw lines to connect randomly placed numbered and lettered circles into an alternating sequence (i.e. 1, A, 2, B, 3 C, etc.) Like its Part A counterpart, Part B is scored based on the time it takes

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participants to complete the task, including time to correct errors. The average completion time is 75 seconds for cognitively intact individuals, with greater than 270 seconds (4.5 minutes) indicative of cognitive decline. Scores are converted to a ratio of number correct per second, where a higher ratio indicated better performance, in order to accommodate participants that are unable to complete the test after 270 seconds. Older adults who perform poorly on Trails B tend to have problems with complex activities of daily living (Lezak et al., 2004).

Mental processing speed.

Participants' decision speed and perceptual speed were measured using two instruments.

Digit Symbol-Coding. Digit Symbol-Coding is a timed paper-and-pencil test that asks participants to match numbers with paired symbols and then copy the symbols into rows containing blank squares under its corresponding number. The score is determined by counting the number of correctly drawn symbols in the allotted 120 seconds. The maximum score is 133 points (Lezak et al., 2004). Age and depression have been shown to negatively affect test performance, while level of intellect, memory or learning capability does not. It is particularly sensitive to dementia with demonstration of rapidly declining performance rates associated with dementia progression (Lezak et al., 2004).

Letter and Pattern Comparison. The Letter Comparison task consists of a timed test where participants are asked to quickly determine whether two side-by-side strings of letters are the same or different, then write 'S' (for same) or 'D' (for different) on a line between the pairs. The Pattern Comparison task is similar, except that the pages contain pairs of line segment patterns that require rapid classification as "same" or "different". Two separately timed (20 seconds each) trials of 21 pairs of letters and 30 pairs of patterns were administered, with the score derived by the number of correct choices in the allotted time. The data reported are the

average of the two attempts for each task (Salthouse & Babcock, 1991). Advancing age significantly reduces overall performance (Salthouse, 2000). Both the letter and pattern comparison tasks are established measures of information processing speed that have been used extensively in a number of previous studies (Fisk & Warr, 1996; Salthouse, 2005).

Verbal episodic memory.

Verbal episodic memory is the ability to learn, encode, store and retrieve information about everyday personal experiences. Dysfunction in episodic memory causes disruption in the ability to learn and recall new information (Budson, 2009; Cansino, 2008). Core brain areas associated with episodic memory are the medial temporal lobe and hippocampus, which have been shown to be damaged in DM (denHeijer et al., 2003; Manschot et al., 2007).

Hopkins Verbal Learning Test-Revised (HVLT-R). The HVLT-R Total and Percent of Retention scores measured verbal memory functions of word list learning and recall. In this test, participants are asked to learn and remember a list of 12 words that are verbally presented in three learning trials and a delayed recall (after 20-25 minutes) trial. Immediately after each of the three learning trials, participants in this study were asked to repeat the words they remembered. Scores were calculated for a total list learning score (the sum of the 3 trials), along with the percentage of words remembered after the 20-25-minute delay. The score range for the total list learning score was 0 to 36, and for the percent of retention delayed recall 0 - 100 percent (Benedict et al., 1998; Strauss et al., 2006). The HVLT-R discriminates between patients with mild cognitive impairment and cognitively healthy persons (Strauss et al., 2006; Woods et al., 2005. Older age and lower education decrease performance (Strauss et al., 2006; Woods et al., 2005).

Depression.

Participants' level of depression was measured with the Patient Health Questionaire-8 (PHQ-8), an eight-item self-administered questionnaire asking about depression symptoms over the last 2 weeks. Response options are "Not at all," "Several days," "More than half the days," and "Nearly every day," with 0 – 4 points associated for each option, respectively. The score is the sum of responses, with an overall range from 0-24. The levels of depression symptom severity levels are: none (1-4), mild (5-9), moderate (10-14), moderately severe (15-19), and severe (20-24). The PHQ-8 is valid for screening for depression and determining the severity of depression in primary care settings (Lamers et al., 2008)

Everyday problem-solving in instrumental activities of daily living (IADLs).

Problem-solving ability in IADL performance was assessed using the Everyday Problems Test for Cognitively Challenged Elderly (EPCCE) (Allaire and Willis, 2006). The EPCCE is an objective performance-based measure of tasks that require cognitive processes of executive function to solve problems associated with IADLs. Willis et al. (1998) support the use of the EPCCE as an adjunct to self-report measures of functional status and cognitive measures. It was developed for use with non-demented older adults at risk for cognitive decline. It is a 32-item performance-based measure that uses printed material describing 16 everyday scenarios, such as use of the telephone, medication label interpretation, meal preparation, household chores, financial issues, and driving. The test requires solving a problem related to each example, and choosing an answer. The score range for correct answers is 0-32, with higher scores indicating better performance. Two-month test-retest reliability was r=.93 with Spearman-Bowman correction. Internal consistency demonstrated with Cronbach's alpha was r=.90) (Allaire and Willis, 2006). Cronbach's alpha for total test .90 with split-half reliability of .87. Six-month test-

retest stability was r=.81. Validity was examined by comparing the parent Everyday Problems Test, from which the EPCCE was derived, to two other functional measures with significant correlations of r = .67 and r = .87 (Willis et al., 1998).

Statistical Analysis

Data analysis was performed using IBM SPSS statistics (version 22). Descriptive statistics (means, standard deviations, ranges and frequencies), were generated to summarize the sociodemographic, clinical, neuropsychological test, self-care measure and everyday problem solving data. To test hypothesis one, Spearman's rank-order correlation, a nonparametric statistic with no requirement of normality, was used to examine the relationship between age, years with DM, education category, level of depression, HbA1c level, everyday problem solving, each cognitive function measure (attention, executive function, mental processing speed, verbal episodic memory), and levels of self-care. Preliminary analyses were performed to ensure no violation of the assumptions of normality, linearity, and homoscedasticity.

To test hypothesis two, hierarchical multiple regression was used to estimate the independent relationship between each cognitive measure, and each self-care activity after controlling for age, years with DM, education category, level of depression, and everyday problem solving. The dependent variable, each self-care activity measure (general diet, specific diet, actual blood glucose testing, recommended blood glucose testing, foot care, exercise, medication adherence) was entered in individual equations after first controlling for 1) age, years with DM, education category (model 1); 2) model 1 variables plus level of depression; 3) model 2 variables plus every day problem solving; 4) model 3 variables plus each cognitive measure individually; and 5) model 4 variables plus all cognitive measures simultaneously.

Results

Sample Characteristics

A convenience sample of 56 rural adults with DM from 5 counties across two Midwestern states was enrolled into this study. Table 4.1. displays the sample characteristics and a summary of the clinical data. Among this sample, 53.6% were female, 96.4% were White, 96.4% completed high school, and 30.4% had a bachelor's degree or higher. Nearly 27% were employed, 3.6 % were unemployed, and 57.1% were retired. Almost 52% consumed no alcohol and 86% were non-smokers. The majority had health insurance (98.2%) and had no problems obtaining their medications (89.3%). For the 10.7% that had problems obtaining medications, reasons included high co-pays and insurance non-coverage for medications that were not generic.

Compared with national data (United States Census Bureau, 2015), which estimates that the U.S. population is 77.1% White, 13.3% African American, 5.6% Asian, 1.2% Native American, and 17.6% of Hispanic ethnicity, the study sample had a higher percentage of White residents. The sample also slightly exceeded estimates from the 2009-2014 Health Indicators Warehouse (HIW) (Health Indicators Warehouse, 2016) that 78% of the U.S. population completed high school with a diploma by age 18 years, that 30% of adults ages 25 years and older had completed a bachelor's degree, that 6.2% of the population was unemployed, that 10.4% of the U.S. population was unable to obtain medical or dental care or prescriptions, and that nearly 16% of the U.S. population under the age of 65 years had no health insurance (HIW, 2016). Also of interest was that the study samples' reported rates of smoking was 7% lower than the reported national average of 21.9% of all individuals over the age of sixteen HHIW, 2016).

Participants' mean number of years with DM was 12.6, and their mean HbA1c was 7.7%. Thirty-nine percent had a HbA1c level below 7, and 16% had Hba1c levels greater than 9%. For

diabetes education participation, 34% had participated in some DM educational programming, 39% had completed it, and 27% had never participated in it. National data from the HIW (2016) reported that in persons over 18 years of age with DM, 48.2% had a HbA1c lower than 7% and 21% had a HbA1c greater than 9%. However, the report did not specify whether they had type 1 or type 2 DM. Also, the HIW (2016) reported that 57.6% of adult with DM ages 45-64 years received diabetes education. In adults with DM between ages 65-84 and 85 years and older, 51.6% and 38.4% respectively, received DM education. Compared with HIW data, the study sample had lower percentages of HbA1c below 7 and HbA1c greater than 9, and appeared to have more access to DM education.

Nearly 61% of the study participants reported having neuropathy. The mean score on the PHQ-8 was 5.5 (mild depression), with 53% having no depression, and 19% having either mild or moderate depression. Mean systolic and diastolic blood pressure was 135.9 and 76.3, respectively, which was within the ADA guidelines for BP management in persons with DM that did not have multiple cardiovascular risk factors (ADA, 2016). The mean scores for all cognitive function measures were below the established norms, and are displayed in Table 4.2.

Table 4.3. displays a summary of scores for the self-care and everyday problem solving measures. Self-care activities most frequently performed were taking medications (mean 6.7 days) and performing foot care (mean 5.2 days). Diet was adhered to on average 4.5 days out of seven for general diet (following a healthful eating plan) and 4 days out of seven for diets specific for the consumption of fruits and vegetables, avoiding high fat foods, and evenly spacing carbohydrates. Participants reported actual blood glucose testing 4.9 days per week on average and the frequency of blood glucose testing as recommended by their health care provider, and which could be more than once daily, an average of 4.2 days. Study participants reported lower

exercise performance compared to other self-care activities, with a mean of 2.9 days of exercise

per week.

Table 4.1.
Sample Characteristics and Clinical Data (N=56)

Characteristic/Clinical Data	Result	Range
Age, mean (SD), years	62.6 ± 9.3	45-89
Gender, n (%)		
Male	26 (46.4)	
Female	30 (53.6)	
Race, n (%)		
African American	0	
Native American	2 (3.6)	
White	54 (96.4)	
Ethnicity, Non-Hispanic, n (%)	55 (98.2)	
Marital status, n (%)		
Married	20 (35.7)	
Not married	36 (64.3)	
Education category, n (%)		
Did not complete high school	2 (3.6)	
Completed high school	20 (35.7)	
Associate degree	17 (30.4)	
Bachelors or higher	17 (30.4)	
Employment status, n (%)		
Employed	15 (26.8)	
Unemployed	6 (16.1)	
Retired	32 (57.1)	
Health insurance, yes, n (%)	55 (98.2)	
Problems obtaining medications, n (%)		
Yes	6 (10.7)	
No	50 (89.3)	
Alcohol consumption frequency, n (%)		
2-3 times per week	2 (3.6)	
2-4 times per month	4 (7.1)	
Monthly or less	21 (37.5)	
Never	29 (51.8)	
Smoker, n (%)		
No	48 (85.7)	
Yes	8 (14.3)	
Prior smoker	16 (28.6)	
HbA1c, mean (SD)	7.7 ± 1.6	5.3-12.4
HbA1c <7, n (%)	22 (39)	
HbA1C ≥ 7 & ≤ 9, n (%)	29 (45)	
HbA1c > 9, n (%)	9 (16)	
Years with DM, mean (SD)	12.6 ± 9.9	1-44

DM education status, n (%)		
Yes	22 (39.3)	
Yes, completed	19 (33.9)	
No	15 (26.8)	
Neuropathy, n (%)		
No	22 (39.3)	
Yes	34 (60.7)	
MoCA, mean score (SD)	25.6 ± 2.3	22-30
Normal cognition, n (%)	29 (52)	
(MoCA score $\geq$ 26-30)		
Mild cognitive impairment, n (%)	27 (48)	
(MoCA score 22-25)		
PHQ-8, mean score (SD)	5.5 ± 4.8	0-17
No depression, n (%)	30(53.6)	
(PHQ-8 score 0-4)		
Mild depression, n(%)	11(19.6)	
(PHQ-8 score 5-9)		
Moderate depression, n (%)	11(19.6)	
(PHQ-8 score 10-14)		
Moderate/Severe depression, n(%)	4(7.1)	
(PHQ-8 score 15-19)		
Body Mass Index, mean (SD)	37.4 ± 9.3	22-65.1
Systolic Blood Pressure, mean (SD), mmHg	135.9 ± 20.0	83-181
Diastolic Blood Pressure, mean (SD), mmHg	76.3 ± 9.8	55-98
Total Cholesterol, mean (SD), mg/dl	182.3 ± 43.2	96-296
High Density Lipoprotein, mean (SD), mg/dl	42.3 ± 11.7	25-84

Note. MoCA=Montreal Cognitive Assessment; PHQ-8=Patient Health Questionaire-8.

Table 4.2.
Summary of Scores for Cognitive Function & Problem Solving Measures (N=56)

Cognitive Measures	Mean Scores $\pm$ SD	Score Ranges	Norms $\pm$ SD
Attention			
Digit Span Total	8.77 $\pm$ 2.5	4-14	10.5 $\pm$ 1.0
Trails A	36.9 $\pm$ 13.4	15-86	31.3 $\pm$ 6.7
(seconds to complete) Trails A	.73 $\pm$ .25	.28-1.6	
(# correct per second)			
Executive Function			
COWA Raw Score	32.3 $\pm$ 13.8	11-64	40.1 $\pm$ 10.5
Trails B	97.0 $\pm$ 64.4	35-274	64.6 $\pm$ 18.6
(seconds to complete)			
Trails B	.30 $\pm$ .15	.01-.66	
(# correct per second)			
Mental Processing Speed			
Digit Symbol Coding	53.5 $\pm$ 11.7	26-81	54.3 $\pm$ 8.9
Letter Comparison	5.8 $\pm$ 1.6	2.5-9.5	n/a
Pattern Comparison	11.0 $\pm$ 2.6	6-16	n/a
Verbal Episodic Memory			
HVLT-R Recall Total	19.6 $\pm$ 6.5	2-36	20.6 $\pm$ 5.2
HVLT –R % Retention	72.3 $\pm$ 28.3	0-100	89.0 $\pm$ 25.8
EPCCE- number correct (SD)	26.1 $\pm$ 4.7	9-32	n/a

Note. COWA=Controlled Oral Word Association Test; EPCCE=Everyday Problems Test for Cognitively Challenged Elderly; HVLT-R=Hopkins Verbal Learning Test-Revised

Table 4.3.
Summary of Scores for Self-Care & Problem Solving Measures (N=56)

Measure	Mean Scores $\pm$ SD	Score Ranges
Summary of Diabetes Self-Care Activities Measure (number of days each activity was performed (SD))		
General Diet	4.5 $\pm$ 1.7	0-7
Specific Diet	4.0 $\pm$ 1.5	0.3-7
Exercise	2.9 $\pm$ 2.3	0-7
Actual Frequency of Blood Glucose Testing	4.9 $\pm$ 2.8	0-7
Recommended Frequency of Blood Glucose Testing	4.2 $\pm$ 2.9	0-7
Foot Care	5.2 $\pm$ 1.4	2-7
Medication Adherence	6.7 $\pm$ 1.1	0-7

Hypothesis 1: Increased age, years with DM, and level of depression, and decreased years of education, everyday problem-solving, glycemic control, and cognitive function would correlate with poorer levels of DM self–care adherence in a sample of rural adults with DM,

Hypothesis one was tested using Spearman's rank-order correlation to first examine the relationship between contributing factors of age, years with DM, education category, level of depression, everyday problem solving, HbA1c, and levels of self-care. Next the relationship between cognitive function, everyday problem solving, and levels of self-care were examined. Preliminary analyses ensured no violation of the assumptions of normality, linearity, and homoscedasticity occurred. The expected direction of the relationships between age, years with DM, level of depression, HbA1c, and levels of self-care were negative. The expected direction of the relationships between education category, everyday problem solving, cognitive function, and levels of self-care were positive.

As seen in Table 4.4., age, years with DM, and education category were moderately correlated only with everyday problem solving (r= -.44, r= -.36, r= .45, all p<.01 respectively). There were small to moderate correlations between depression and adherence to general diet (r = -.38, p <.01), specific diet (r= -.46, p<.01), and exercise (r= -.34, p<.05). HbA1c was moderately correlated with level of depression (r=.34, p<.05), general diet (r= -.43, p<.01), and actual blood glucose testing (r=.35; p<.01). As depicted in Table 5, there were moderate to large correlations between all cognitive domains and everyday problem solving as follows: attention (r= .36 p<.05; r= .61, p<.01), executive function (r= .41, p <.01, r= .49, p<.001), mental processing speed (r= .31, p<.05; r= .37, r= .40, both p<.01), and verbal episodic memory (r= .35, p<.01; r= .56, p<.001). Attention and mental processing speed had small correlations with exercise frequency (r

= .28, r = .27, both p<.05 respectively). Verbal episodic memory had a small correlation with foot care (r = .27, p<.05). Results suggest lower age, fewer years with DM, and higher education category are associated with better performance in everyday problem solving in IADL tasks. Also, higher function in all measured cognitive domains was associated with better performance in everyday problem solving in IADL tasks. Increased level of depression was associated with decreased adherence to general and specific diet, and exercise. Poorer glycemic control was associated decreased adherence to general diet, increased frequency of blood glucose testing, and higher level of depression. Increased frequency of blood glucose testing may reflect the recognition of poor diet and hyperglycemia, and attempts to try to achieve better glycemic control. Cognitive function was minimally associated with level of self-care activity.

Table 4.4.

Spearman's Rho Correlations between Contributing Factors, Problem Solving & Self-Care Measures (n=56)

	General Diet	Specific Diet	Actual Blood Glucose Testing	Recommended Blood Glucose Testing	Foot Care	Exercise	Medication Adherence	EPCCE	HbA1c
Age	.17	-.01	.05	.11	-.14	-.17	.06	-.44**	-.001
Education Category	-.18	.03	-.23	-.11	.06	-.03	-.12	.45**	.15
Level of Depression	-.38**	-.46**	.28*	.04	-.11	-.34*	-.19	-.13	.34*
Years with DM	-.004	-.01	.21	.13	.05	.04	-.12	-.36**	.17
HbA1c	-.43**	-.25	.35**	.14	.24	-.23	-.18	.06	
EPCCE	.06	-.14	-.16	-.09	.01	-.03	-.06		

Note. EPCCE=Everyday Problems Test for Cognitively Challenged Elderly.

*p<.05 **p<.01

Table 4.5.

Spearman's Rho Correlations between Cognitive Function, Problem Solving & Self-Care Measures (n=56)

	General Diet	Specific Diet	Actual Blood Glucose Testing	Recommended Blood Glucose Testing	Foot Care	Exercise	Medication Adherence	EPCCE
Attention								
Digit span Total	-.08	.002	-.25	-.12	-.09	.06	.01	.61***
Trailmaking A	-.07	.24	.15	.10	.17	.28*	-.21	.36**
Executive Function								
COWA raw score	-.13	-.06	-.15	-.18	.12	-.05	-.10	.41**
Trailmaking B	-.10	.18	-.16	-.14	.14	.17	-.11	.49***
Mental Processing Speed								
Digit Symbol	-.07	.24	-.08	.06	.09	.27*	-.08	.40**
Letter comparison	-.17	.10	-.07	-.06	.06	-.08	-.02	.37**
Pattern comparison	-.26	.07	-.13	-.07	.17	.12	-.17	.31*
Verbal Episodic Memory								
HVLT recall total	-.12	.02	-.04	-.002	.09	.20	-.18	.56***
HVLT % retained	-.22	.12	.02	-.02	.27*	.23	-.18	.35**

Note. COWA=Controlled Oral Word Association Test; EPCCE=Everyday Problems Test for Cognitively Challenged Elderly; HVLT-R=Hopkins Verbal Learning Test-Revised.

*p<.05 **p<.01 ***p<.001

Hypothesis 2: Cognitive function, after controlling for the contributing factors, would independently predict level of self-care activity performance

The results of multiple regression models 4 (all variables plus each cognitive measure individually) reaching significance are in Tables 4.6., 4.7., and 4.8. With testing hypothesis two, the models explained between 13-14% of the variance in specific diet adherence, 23% of the variance in actual frequency of blood glucose testing, and 22-24% of the variance in frequency of exercise. After controlling for age, years with DM, and education category, level of depression independently explained specific diet adherence when entered with all cognitive domains, and had the highest Beta values (-.41 to -.49, p<.01 and p<.001). Level of depression also independently explained performance in the actual frequency of blood glucose testing when entered with measures of mental processing speed (B = .36, p<.01). Level of depression also independently explained adherence to exercise when entered with measures of attention (B= -.37, p<.05), mental processing speed (B= -.38, p<.01), and verbal episodic memory (B= -.29, p<.05). None of the models with adherence to general diet, recommended frequency of blood glucose testing, foot care or medications reached significance. In model 5, where all variables and all cognitive function measures were entered simultaneously, the equations with frequency of exercise and actual blood glucose testing were significant (adjusted R^2=.25, p=.02, adjusted R^2= .23, p = .03, respectively). Everyday problem solving independently explained exercise frequency (B=-.49, p=.02), and level of depression independently explained frequency of actual blood glucose testing (B= .48, p = .003).

Table 4.6.

Results of Hierarchical Multiple Regression—Contributing Factors and Cognitive Measures Explaining Self-Care Measures—Dependent Variable Specific Diet (n=56)

	Attention				Executive Function				Mental Processing Speed						Verbal Episodic Memory			
Predictors	Digit Span		Trails A		COWA		Trails B		Digit Symbol		Letter Compare		Pattern Compare		HVLT Recall		HVLT % Retained	
	Beta[a]	$R^2\Delta$	Beta[a]	$R^2\Delta$	Beta[a]	$R^2\Delta$	Beta[a]	$R^2\Delta$	Beta[a]	$R^2\Delta$	Beta[a]	$R^2\Delta$	Beta[a]	$R^2\Delta$	Beta[a]	$R^2\Delta$	Beta[a]	$R^2\Delta$
Model 1		.001		.001		.001		.001		.001		.001		.001		.001		.001
Age (years)	-.10		-.02		-.13		-.03		.01		-.05		-.07		-.13		-.10	
Years with DM	.15		.10		.11		.14		.15		.15		.15		.13		.14	
Education Category	.01		-.01		.01		-.02		-.02		-.01		-.02		.00		.00	
Model 2		.22***		.22***		.22***		.22***		.22***		.22***		.22***		.22***		.22***
Level of depression	-.49***		-43***		-.49***		-.45**		-.41**		-.46**		-.48**		-.49***		-.48**	
Model 3		.00		.00		.00		.00		.00		.00		.00		.00		.00
EPCCE	-.06		-.05		-.01		-.06		-.03		-.04		-.02		.01		-.01	
Model 4		.01		.03		.01		.02		.02		.01		.01		.01		.00
Cognitive function	.09		.19		-.11		.17		.20		.12		.09		-.10		-.01	
R^2		.22		.24		.23		.24		.24		.23		.22		.22		.22
Adjusted R^2		.13		.15		.13		.14		.14		.14		.13		.13		.12
Overall significance		.04*		.03*		.04*		.03*		.03*		.04*		.04*		.001***		.05

Note. COWA=Controlled Oral Word Association Test; EPCCE= Everyday Problems Test for Cognitively Challenged Elderly; HVLT-R=Hopkins Verbal Learning Test-Revised.

*p<.05 **p<.01 ***p<.001

Table 4.7.

Results of Hierarchical Multiple Regression--Contributing Factors and Cognitive Measures Explaining Self-Care Measures—Dependent Variable Actual Blood Glucose Testing (n=56)

Mental Processing Speed

Predictors	Digit Symbol	
	Beta[a]	R^2 Δ
Model 1		.11
Age (years)	.03	
Years with DM	.15	
Education Category	-.32	
Model 2		.04
Level of depression	.36*	
Model 3		.00
EPCCE	.03	
Model 4		.07*
Cognitive function	.38	
R^2	.23	
Adjusted R^2	.13	
Overall significance	.04*	

Note. EPPCE= Everyday Problems Test for Cognitively Challenged Elderly

*p<.05

Table 4.8.

Results of Hierarchical Multiple Regression--Contributing Factors and Cognitive Measures Explaining Self-Care Measures—Dependent Variable Exercise (n=56)

| Predictors | Attention | | | | Mental Processing Speed | | | | Verbal Episodic Memory | | | |
| | Digit Span | | Trails A | | Digit Symbol | | Letter Comparison | | HVLT Total Recall | | HVLT % Retained | |
	Beta[a]	R^2 Δ	Beta[a]	R^2 Δ	Beta[a]	R^2 Δ	Beta[a]	R^2 Δ	Beta[a]	R^2 Δ	Beta[a]	R^2 Δ
Model 1		.06		.06		.06		.06		.06		.06
Age (years)	-.37*		-.26		-.24		-.48**		-.30		-.30	
Years with DM	.25	.	.16		.24		.20		.24		.16	
Education Category	.00		-.03		-.05		.00		-.02		-.01	
Model 2		.10*		.10*		.10*		.10 *		.10*		.10*
Level of depression	-.37*		-.27		-.24		-.38**		-.31*		-.29*	
Model 3		.03		.03		.03		.03		.03		.03
EPCCE	-.35		.28		-.25		-.20		-.30		-.36	
Model 4		.04		.05		.04		.04		.03		.05
Cognitive function	.23		.27		.28		-.25		.23		.28	
R^2	.22		.24		.23		.22		.22		.24	
Adjusted R^2	.13		.14		.13		.13		.12		.14	
Overall significance	.04*		.03*		.04*		.04*		.05		.03*	

Note. EPCCE=Everyday Problems Test for Cognitively Challenged Elderly; HVLT-R=Hopkins Verbal Learning Test-Revised.

*p<.05 **p<.01

Discussion

The framework by Song (2010) used to guide the analysis portrayed the complexity of DM self-care. In this study, cognitive function was applied to the framework as a situation-specific influence on DM self-care. This approach attempted to link theory, research and clinical practice in a way that would be useful to clinicians who provide care to persons with DM. Based on the measures used, this analysis was limited to the evaluation of DM self-care activities that reflected adherence (diet, exercise, foot care, medications) and monitoring (blood glucose testing). Measurement of symptom awareness and recognition, direct self-care management, and decision making was not included, as it was beyond the scope of this study. Knowledge of DM self-care was also not directly measured, but the capacity for gaining knowledge was reflected by examining cognitive processes essential for learning (attention, executive function, verbal episodic memory). Level of depression and everyday problem solving ability for IADL tasks were included as factors that may influence DM self-care.

Rural-related sociodemographic factors that can influence self-care performance were also explored. The characteristics of the sample were slightly higher in levels of education, employment, healthcare access, and healthcare insurance when compared to national trends, suggesting that this population had no disparities in education, employment, or healthcare access.

Adherence to medication and foot care were the most frequently performed self-care activity among the study participants. The frequency of recommended glucose testing being lower than the actual number of days blood glucose was tested could be due to the lack of blood glucose testing supplies available due to insurance non-coverage, forgetting to test multiple times per day, and the burden of multiple daily blood glucose testing being overwhelming.

The first hypothesis was not supported. Age, level of education, and number of years with DM were associated with everyday problem solving, but with none of the self-care activities. Lower level of depression was associated with higher diet and exercise adherence, and better glycemic control. As expected, all cognitive domains were positively associated with everyday problem solving ability, which illustrates the cognitive complexity of performing IADLs. Contrary to expectations, cognitive function was minimally associated with self-care activity performance, and the number of years with DM had no association with self-care activities. Better glycemic control was associated only with general diet adherence.

The second hypothesis was not supported, that cognitive function, after controlling for the contributing factors, would independently predict level of self-care activity performance. The results of hierarchical multiple regression models (model 4 with all variables plus each cognitive measure individually) with specific diet adherence as the dependent variable explained 13-15% of the variance in adherence to specific diet. Only the level of depression independently explained adherence to specific diet. Higher levels of depression independently accounted for decreased self-reported adherence to the specific diet parameters (eating fruit and vegetables, avoiding high fat foods, and evenly spacing carbohydrate intake throughout the day). With actual blood glucose testing as the dependent variable, results of regression model 4 (cognitive domain mental processing speed) explained 13% of the variance in the model. Unexpectedly, higher levels of depression independently accounted for increased frequency of blood glucose testing with faster mental processing speed and lower education. With exercise frequency as the dependent variable in regression model 4, results showed that 13-14% of the variance was explained with attention, mental processing and verbal episodic memory as cognitive measures.

Lower levels of depression independently explained higher frequency of exercise in models with all three cognitive domains.

Age independently explained only exercise frequency (B= -.37, p<.05, B = -.48, p<.01), which likely reflects decreased physical ability in older age. Another factor that may have impeded the ability to exercise was the high incidence of neuropathy or presence of foot ulcers in the study population. Number of years with DM did not independently explain any of the self-care activities, which was consistent with a systematic review of 12 studies regarding DM self-care by Tomlin & Sinclair (2016). Level of education independently accounted for variance only in actual blood glucose testing frequency in one model with mental processing speed (B= -.32, p<.05). Everyday problem solving also did not independently explain variance in any self-care activity, and mainly had negative beta values. These findings could be due to the nature of the self-care activities that were measured, which were monitoring and adherence tasks that do not require problem-solving or decision making. Also, the problem-solving tasks in the EPCCE were not specific to DM, but were general IADL tasks concerning finances, meal preparation, medications, household maintenance, telephone use, and transportation. The EPCCE score reflected total performance in all categories. Perhaps if the categories were analyzed separately the results would be different.

In this group of 56 rural adults with DM, level of depression was highly influential in adherence to specific diet recommendations. Higher levels of depression predicted decreased healthy diet choices (i.e. specific recommendations), and also decreased frequency of exercise. In this study, potential participants were screened and excluded if they had a major depressive disorder. Hence, the results pertaining to the affected self-care activities were moderated by the participants having only mild to moderate levels of depression.

In previous studies using the SDSCA to assess self-care activity levels (Lin et al., 2004; Primozic et al., 2012), results of comparison of persons with DM with major depression (n=536) and no depression (n=3927) by Lin and colleagues (2004) showed that major depression was associated with infrequent fruit and vegetable intake, more frequent fat intake, and infrequent exercise. Differences in adherence to blood glucose testing and foot care were not significant between those with and without major depression (Lin et al., 2004). Primozic and colleagues demonstrated that absence of major depression, better executive function, and lower body mass index, were predictive of better self-care (diet, exercise, foot care).

The dysregulation and over activity of the HPA-axis and SNS that co-exist in depression and DM may help explain these findings. Behavioral consequences of HPA-axis and SNS dysfunction include anxiety and food craving (Badescu et al., 2016). And, as a consequence of the inflammatory effects of depression on hippocampal function, neurotransmitter metabolism, neuroendocrine function and synaptic plasticity are affected (Badescu et al., 2016). Decreased neuronal connectivity between the hippocampus and several brain regions has been documented with persons with DM (Hoogenboom et al., 2014; Zhou et al., 2010), and has been shown to be associated with dysfunction in executive function (Zhou et al., 2010). Also, insulin resistance has been associated with decreased functional connectivity of the posterior cingulate cortex (which is associated with attentional functions) to other brain areas (Chen et al., 2014). Treatment adherence is dependent on prefrontal cortex based executive functions and working memory (Insel et al., 2006), and depression has been associated with decline in executive function and mental processing speed in persons with DM (Sullivan et al., 2013). Perhaps the disruption in the functional connectivity between key brain areas involved in treatment adherence is an important explanatory factor in problems with adherence.

Self-motivation is strongly association with good glycemic control (Bruce et al., 2015; Padala et al., 2007). Presence of apathy, defined as lack of motivation, manifests as decreased goal-directed behavior, and symptoms of apathy frequently overlap with depression. Apathy is considered to be a syndrome distinct from depression, can exist in the absence of depression, and may be a major factor in one's ability to adhere to DM self-care (Bruce et al., 2015; Padala et al., 2007). In a sample of predominately males with DM (N= 81, mean age (SD) = 58.6 ± 11.9 years), 50 tested positive for apathy without depression, and were less likely to follow an exercise plan and take their insulin as instructed (Padala et al, 2007). Apathy was found to have a higher incidence in adults (without dementia) with DM (n = 122, mean age (SD) = 73.5 ± 7.0), than adults without DM (n = 69, mean age (SD) = 74.6 ± 7.0) (Bruce et al., 2015). Using the 14-item Apathy Scale, the with DM group, 13.9% had apathy versus 1.4% in the without DM group. In the with DM group, apathy was significantly associated with mild cognitive impairment, depression and poorer glycemic control. After approximately 18 months, the group with DM had a clinically relevant decrease in glycemic control, and significant cognitive decline since baseline. The researchers concluded that apathy is an important syndrome in older persons with DM that likely is a barrier to effective self-care (Bruce et al., 2015; Padala et al, 2007).

Strengths and Limitations

An important aspect of this study was conducting face-to-face interviews to examine cognitive function, self-care activities, performance-based everyday problem solving, and glycemic control in rural adults with DM. Each cognitive domain was tested with at least two measures that assessed slightly different cognitive processes. Cognitive function was applied to a situation-specific theory based framework for self-care in persons with DM to guide analysis. Adults of age 45 years and older and were included, where the majority of recent related studies

focused on an older population (age 55 years and older). Also, other factors that may impact self-care performance, such as education category and depression were included. Of note is that the depression measure, the PHQ-8, referred to signs of depression within the last two weeks of the interview, and the HbA1c could have been done up to 2 months prior. And, an exclusion criterion for participation was a diagnosis of major depression. Limitations include selection bias in sample recruitment due to a limited rural area with a racial majority of white residents. Also, these participants were receiving health care in primary care and specialty DM clinics, and did not appear to have barriers to health care access, which may have skewed the results more positively. Everyday problem-solving IADLs was not specific to DM, but was of a general nature. Self-care activities were self-reported, and not performance-based. Acquisition of DM knowledge was not measured, but may have been influential in assessing self-care performance. In addition, because the study was cross-sectional, no longitudinal trends in the variables could be determined.

<div align="center">**Conclusion**</div>

This study provides evidence that the frequency of DM self-care activity performance by rural adults with DM is not independently explained by cognitive function in domains of attention, executive function, mental processing speed, or verbal episodic memory. A consideration is that the self-care measure was self-reported, not observed, and the reporting could be affected by memory or poor understanding of the instrument. Increased years with DM did not uniquely explain self-care activity, but appeared to have a positive influence on adherence to specific diet, blood glucose testing and exercise. Of concern is that 48% of the participants had mild cognitive impairment, including those under the age of 65 years. Although self-care performance was not predicted by cognitive function, cognition should be evaluated in

persons with DM of all ages, not just the elderly. Knowledge of DM self-care, which is likely associated with cognitive function, was not measured, and may influence self-care performance. It is unclear whether decreasing cognitive function leads to poor self-care, or whether poor self-care leads to decreasing cognitive function. In either case, in clinical practice both need to be addressed as a potential contributor to lack of adherence to treatment plans.

Increased global cognitive impairment was associated with higher depression levels, and level of depression was influential in diet and exercise adherence. The dynamics of the structural brain changes that occur in DM may contribute to the effect that depression has on self-care performance, which emphasizes the importance of screening for depression in persons with DM. As was emphasized by Bruce et al. (2015) and Padala et al. (2007), apathy may be present without depression in persons with DM, and may contribute to decreased self-care performance. Screening for apathy, and differentiating it from true depression, may provide insight into poor adherence to self-care. Further research is needed to examine whether treating depression and apathy has an effect on treatment adherence, and ultimately glycemic control.

Everyday problem solving in IADL tasks did not influence DM self-care performance, but as mentioned previously, the self-care activities that were evaluated may not be highly dependent on problem-solving. Each IADL category could be evaluated separately, which may provide different results. A performance based measure of problem solving related specifically to DM self-care would be beneficial. Further study is needed to examine the self-care management processes of sign and symptom recognition and treatment implementation, which do require decision making and problem solving. Klein and Lippa (2008) proposed that DM education should be based on decision-making research that assists persons with DM to develop cognitive skills that promote problem detection, decision making, and planning and re-planning. Ideally,

DM education should strive to conceptualize DM self-care as a dynamic and complex process that requires problem solving, and not merely adherence to set rules and procedures. The process of DM education should include simulations and scenarios that allow practice in progressively difficult situations, and consider each individual's cognitive abilities (Klein & Lippa, 2008). Finding ways of including support systems, such as family, friends, and significant other, may facilitate the patient's expertise in problem detection and management.

These findings provide a foundation for further studies that can impact clinical practice. As the prevalence of DM rises and affects younger people, there is an urgent need to further understand how DM impacts learning, memory, job performance and quality of life. Future research is needed to validate the importance of cognitive, depression and apathy screening as part of the overall DM management regimen for all age groups.

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CHAPTER V

Conclusion

This research adds to the growing knowledge base of the relationships between cognitive function, self-care and glycemic control in rural adults with DM, and offers insights for health care professionals seeking to improve care for persons with DM. This chapter provides a summary of the findings, strengths and limitations of the study, and implications for future research and nursing practice. The overall purpose of the study was to examine the relationship between cognitive function in domains of attention, executive function, mental processing speed and verbal episodic memory, self-care performance and glycemic control among rural adults with DM age 45 years and older. Based on the literature, a conceptual framework was developed to describe the relationships among these factors, and is presented in Figure 1.1.

The framework incorporates biological, environmental and behavioral influences on cognitive function, self-care, and glycemic control in DM, and identifies the reciprocal associations among cognitive function, self-care, glycemic control, and contributing factors. Structural brain changes in DM are associated with multiple pathophysiological factors that play a role in the profile of cognitive decline. Declining cognitive function can create barriers to performing self-care, which is an important part of achieving glycemic control and reducing complications. Poor glycemic control contributes to further cerebral damage and cognitive

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decline. Embedded in the framework is a model for DM self-care based on the self-care model

by Song (2010). Song's model for DM self-care is based on a situation-specific theory for self-

care in heart failure patients (Riegel and Dickson, 2008). Situation-specific theories focus on

specific phenomena seen in clinical practice, and are limited to a specific population (Im &

Meleis, 1999). The DM self-care model by Song (2010), self-care consists of two components:

Self-Care Maintenance and Self-Care Management. Self-care maintenance includes behaviors to

maintain physiologic stability: symptom monitoring and treatment adherence (diet, medications,

blood glucose testing, exercise, and foot examination), and self-care management incorporates

active decision making in response to awareness of sign and symptom changes. In this

dissertation research, cognitive function was applied to the framework as a situation-specific

influence on DM self-care.

First, a scoping review of the literature was conducted to summarize the existing state of

knowledge about cognitive function in DM and DM self-care. The main findings of a review of

74 publications were: 1) documentation of the interplay between pathophysiological brain

changes, cognitive function, and modifiable and non-modifiable risk factors for cognitive

decline, 2) clarification of the presence of cognitive decline in pre- and early DM, and 3)

evidence relating cognitive decline to DM self-care. Risk factors of hypertension and

hyperlipidemia are interrelated, may affect cognition at various times for various durations, and

are modifiable with treatment. Depression, which is also modifiable, has a high prevalence in

persons with DM, and is associated with cognitive decline. Other factors that contribute to

cognitive decline, and are not modifiable, include sociodemographic variables (i.e. age, gender,

education level) and the duration of having DM. Because early stages of DM are often

undiagnosed, early cognitive decline often goes unnoticed as well. Evidence suggested that

cognitive decline may follow two different processes in DM: 1) mild slowly progressing decline beginning in pre-DM stages, and 2) severe faster decline with high prevalence of vascular and Alzheimer's dementia.

Intact cognitive ability is necessary for the complex tasks necessary for daily DM self-care, and cognitive decline interferes with understanding, recalling, and applying instructions, and contributes to impaired sign and symptom recognition. Decline in cognitive domains of attention, executive function, mental processing speed and verbal episodic memory may be present with normal global cognition. Knowledge gaps exist concerning the cognitive processes underlying the different self-care behaviors, and the link between cognition, DM knowledge and DM self–care performance.

Chapter three, the second manuscript, investigated the relationships between cognitive function, contributing factors, and glycemic control. First, Pearson's r and Spearman's rank-order correlations were used to examine the relationship between age, years with DM, education category, CV risk, level of depression, and each cognitive function measure and HbA1c level. Older age, more years with DM, and higher CV risk were correlated with poorer performance in each cognitive domain, with a medium to large magnitude for age and CV risk, and small to medium magnitude for years with DM. Higher level of depression was moderately correlated with slower mental processing speed, and poorer glycemic control. Higher education category had a small correlation with better executive function, mental processing speed, and verbal episodic memory. HbA1c had no significant correlations with any cognitive measures. Next, hierarchical multiple regression was conducted to determine whether HbA1c, after controlling for non-modifiable (age, years with DM, education category) and modifiable covariates (cardiovascular risk, level of depression), would independently predict cognitive function. With

all covariates plus HbA1c and each separate cognitive measure, the models explained between 21 and 43 percent of the variance in cognitive performance with overall significance levels between <.001 to .03. HbA1c did not independently explain cognitive test performance in any of the cognitive domains. Level of depression independently explained performance in mental processing speed (Digit Symbol), and level of depression and CV risk independently explained performance in verbal episodic memory (HVLT% retained). It was concluded that HbA1c levels may not be a major determinant in cognitive test performance, rather other sociodemographic and clinical factors are more influential. However, HbA1c is a modifiable factor, whereas other factors such as age, duration of DM, history of CV disease, and education level are not. Last, hierarchical multiple regression was conducted to determine whether cognitive function, after controlling for the covariates, would independently predict HbA1c. Only the model with all covariates and cognitive measures entered simultaneously nearly reached significance (p=.06), and better executive function independently explained lower HbA1c, which was anticipated.

Chapter four, the third manuscript, investigated the relationships between cognitive function, self-care, contributing factors, and glycemic control. The DM self-care model by Song (2010) was used to guide the analysis and portrayed the complexity of DM self-care. Self-care activities most frequently performed were taking medications and doing foot care, followed by diet adherence and blood glucose testing. Exercise was the least performed self-care activity and exhibited low frequency levels consistent with other research and national samples. The education level, employment, healthcare access, and healthcare insurance profiles of the study sample also appeared to be similar to national data, suggesting that this population had no disparities in education, employment, or healthcare access. Spearman's rank-order correlation was used to examine the relationship between age, years with DM, education category, level of

depression, HbA1c level, everyday problem solving, each cognitive function measure (attention, executive function, mental processing speed, verbal episodic memory), and levels of self-care. Lower age, and number of years with DM, and higher level of education, was moderately correlated with everyday problem solving, but with none of the self-care activities. Lower level of depression was moderately correlated with higher diet and exercise adherence, and better glycemic control. Better performance in all cognitive domains was moderate to largely correlated with better everyday problem solving ability, and was minimally associated with self-care activity performance. Better glycemic control was associated only with general diet adherence. Next, hierarchical multiple regression was used to estimate the independent relationship between each cognitive measure, and each self-care activity after controlling for age, years with DM, education category, level of depression, and everyday problem solving. The results of the hierarchical multiple regression models that included all variables, plus each cognitive measure separately, explained 13-15% of the variance in adherence to specific diet. In all cognitive domains, higher levels of depression independently predicted decreased self-reported adherence to the specific diet parameters (eating fruit and vegetables, avoiding high fat foods, and evenly spacing carbohydrate intake throughout the day). Only the model with mental processing speed explained 13% of the variance in actual blood glucose testing. With exercise frequency as the dependent variable, 13-14% of the variance was explained with attention, mental processing and verbal episodic memory as cognitive measures, and level of depression independently explained lower frequency of exercise in models with all three cognitive domains.

Strengths of the Study

An important strength of this study was that face-to-face interviews were conducted that included a wide age range of participants, and examined cognitive function, self-care activities,

performance-based everyday problem solving, and glycemic control in rural adults with DM. Performance in multiple cognitive domains was tested using at least two measures per domain. Non-modifiable and modifiable sociodemographic and clinical variables that influence cognitive function and self-care performance in rural adults with DM were investigated. To guide analysis of self-care performance, cognitive function was applied to a situation-specific theory based framework for self-care in persons with DM.

Limitations of the Study

Study limitations include recruitment of a convenience sample from primary care and DM education centers, which may have biased the findings. The participants had access to regular healthcare and lab work, DM education, and treatment adjustments. Many were employed and had health insurance. These factors may have skewed the results more positively, and would likely differ from a sample that was unemployed and had limited or no access to healthcare. The blood glucose level at the time of the administration of the cognitive tests was not determined, and extremes in blood glucose levels may have affected cognitive performance. Lower, but normal cognitive function may be associated with other factors, such as poor performance of self-care, which may lead to poor glycemic control, and other comorbidities not accounted for such as heart failure. Also, the length and intensity of the interview could have caused fatigue or anxiety. Self-care activities were self-reported, and not performance-based. Small sample size is also a limitation, as some nearly significant results may have been significant in a larger study population. Because the study was cross-sectional, no longitudinal trends in the variables could be determined, nor any causality implied. In addition, the results are not generalizable to the entire population of adults with DM.

Implications for Future Research and Clinical Practice

This study provides evidence that cognitive function in domains of attention, executive function, mental processing speed, or verbal episodic memory in rural adults with DM, after controlling for modifiable and non-modifiable covariates, does not independently explain glycemic control or the frequency of DM self-care activity performance by rural adults with DM. These findings suggest that exposure to risk factors and comorbidities are more influential in explaining glycemic control and self-care performance. Higher CV risk and level of depression, both modifiable factors, were predictive of poorer cognitive function. Higher levels of depression were predictive of decreased adherence to blood glucose testing, diet, and exercise. Some elements of CV risk, such as blood pressure control, lipid levels, smoking status, and depression are modifiable with intervention.

Increased global cognitive impairment was associated with higher depression levels, and although depression can impair one's ability to adhere to self-care regimens, it is unclear whether decreasing cognitive function leads to poor self-care, or whether poor self-care leads to decreasing cognitive function. Apathy may be present without depression in persons with DM, and may contribute to decreased self-care performance. Further research is needed to examine whether treating depression and apathy has an effect on treatment adherence, and ultimately glycemic control. In either case, it is imperative for clinicians to routinely screen for depression and mild cognitive impairment, and both need to be addressed as a potential contributor to lack of adherence to treatment plans.

Of concern is that 48% of the participants had mild cognitive impairment, including those under the age of 65 years. Although self-care performance was not predicted by cognitive function, cognition should be evaluated in persons with DM of all ages, not just the elderly,

especially given that DM is a chronic disease and associations have been made between declining cognitive function and poorer glycemic control. More research is required to identify how these findings impact one's everyday ability to perform self-care, instrumental activities of daily living, and required job tasks. Decline in the cognitive domains of attention, executive function, mental processing speed, and verbal episodic memory, varies with age and years with DM. Presently, there is no standardized method to monitor for cognitive decline in persons with DM. Further research in this area is greatly needed, as it may be possible to improve some aspects of cognition with cognitive interventions such as training in memory, reasoning, problem solving, and mental processing speed.

Everyday problem solving in IADL tasks did not influence DM self-care performance, but as mentioned previously, the self-care activities that were evaluated may not be highly dependent on decision making and problem-solving. A performance based measure of problem solving related specifically to DM self-care would be beneficial. Further study is needed to examine the self-care processes of sign and symptom recognition and treatment implementation, which do require decision making and problem solving. That research would be beneficial in designing DM education programs that assists persons with DM to develop cognitive skills that promote problem detection, decision making, and problem-solving

These findings provide a foundation for further studies that can impact clinical practice. As the prevalence of DM rises and affects younger people, there is an urgent need to further understand how DM impacts learning, memory, self-care, job performance and quality of life.