Psychosocial and Cardiovascular Contributors to Longitudinal Cognitive Aging in Type 2 Diabetes

by

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DEDICATION

To my mother, Harbans Kaur.

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ABSTRACT

Type 2 diabetes (T2D) confers substantial risk for dementia and accelerated cognitive decline in older adulthood. Glycemic control, indexed by hemoglobin A1c (HbA1c), is a marker of T2D severity, with higher levels of HbA1c reflecting poorer glycemic control. Poor glycemic control is associated with adverse cognitive outcomes in older adults with T2D, and chronically uncontrolled T2D may pose greater risk for dementia in comparison to controlled T2D. Although mechanisms underlying the association between T2D/HbA1c and cognition in older adulthood are underdeveloped, prior studies have implicated psychosocial factors, such as depressive symptoms, as well as cardiovascular factors, such as elevated homocysteine levels, in pathways linking T2D to cognitive decline and dementia. In comparison to risk pathways, relatively less is known regarding the role of potentially protective psychosocial factors such as emotional support. Consistent with the stress-buffering hypothesis, higher levels of support may buffer against T2D-related risk for poor cognitive function in older adults.

The overarching goals across all three studies in this dissertation are two-fold: (1) to characterize the associations between markers of T2D severity (HbA1c and homocysteine) and cognitive outcomes, and (2) to test the role of emotional support as a potential buffer against T2D-related risk for cognitive morbidity. Specifically, Study 1 examined the role of depressive symptoms as a mediator of the association between HbA1c and cognition as well as the role of emotional support as a moderator of these associations in a sample of older adults with T2D. Study 2 examined the cross-sectional association between homocysteine and four domains of cognition

as well as the moderating role of emotional support in homocysteine-cognition associations in older adults with uncontrolled T2D. Study 3 was a longitudinal extension of Studies 1 and 2 using data from a U.S.-wide sample of older adults with T2D. Study 3 examined the mediating role of four-year changes in depressive symptoms in the association between HbA1c and six-year memory decline as well as the role of emotional support as a cross-sectional and longitudinal moderator of associations.

Findings from this dissertation suggest that for older adults with T2D, poor glycemic control may lead to increases in depressive symptoms and contribute to subsequent episodic memory decline. Furthermore, for older adults with uncontrolled T2D, higher levels of homocysteine may lead to lower performance in frontally mediated cognitive domains. Additionally, emotional support may represent an important psychosocial resource that can be targeted to reduce the impact of T2D-related risk for increases in depressive symptoms and poor memory. Emotional support may also reduce the adverse impact of depression on processing speed. Together, findings from this dissertation provide preliminary evidence for behavioral and biological mechanisms underlying T2D-related cognitive morbidity, and point to emotional support as a potentially protective factor against cognitive decline and dementia. Implications and future directions are discussed.

Chapter 1

Overview of the Three-Paper Project

Dementia is a leading cause of death and disability for older adults in the United States and is presaged by accelerated cognitive decline and cognitive impairment. This illness represents a major societal issue worldwide primarily due to the absence of any disease-modifying treatment (The Lancet, 2014). Interventions targeting disease mechanisms and risk factors are considered to be most effective in delaying the onset of dementia (Srikanth & Arvanitakis, 2018). Such interventions may be particularly impactful as delaying dementia symptom onset by one year may reduce its global prevalence by over 9 million cases over the next 30-40 years (Brookmeyer, Johnson, Ziegler-Graham, & Arrighi, 2007). Notably, approximately 35% of dementia cases could be prevented by targeting modifiable risk factors, including Type 2 diabetes (T2D; Livingston et al., 2017).

Type 2 Diabetes and Cognitive Aging

T2D is a chronic metabolic condition characterized by reduced production of insulin or inability to use the insulin produced. Over time, this state of insulin resistance results in problems with regulating blood sugar, which in turn leads to the onset of T2D (World Health Organization (WHO), 2006). T2D is an increasingly prevalent chronic health condition that is projected to continue rising (WHO, 2006). It increases risk for microvascular and macrovascular complications leading to lower limb amputation, renal failure, loss of vision, cardiovascular disease, and growing evidence shows that it confers substantial risk for dementia (WHO, 2006). Specifically, T2D is estimated to result in an approximately two-fold increased risk for incident dementia (Sutherland,

Lim, Srikanth, & Bruce, 2017). Furthermore, T2D is associated with accelerated cognitive decline and cognitive impairment in older adults (Biessels, Strachan, Visseren, Kappelle, & Whitmer, 2014), with mounting evidence suggesting that hyperglycemia plays a key role in T2D-related cognitive decrements. Of note, findings from most studies on the adverse cognitive effects of T2D have limited generalizability to racially and ethnically diverse older adults, as prior investigations utilize primarily non-Hispanic White samples or samples with a low proportion of racial and ethnic minority older adults. In order to address this gap in the literature, this dissertation included a study comprising a sample with a relatively high proportion of racially and ethnically diverse older adults (Study 1).

Central to T2D severity and disease management is glycemic control, indexed by hemoglobin A1c (HbA1c), with higher levels of HbA1c reflecting hyperglycemia or poor glycemic control. HbA1c is a specific glycated hemoglobin that is produced from the attachment of glucose to erythrocytes, specifically to the N-terminal valine of the hemoglobin β-chain (Sacks, 2006). Erythrocytes, or red blood cells, have a lifespan of approximately 120 days. Therefore, HbA1c represents integrated glucose concentration over the past two to three months (i.e., the predicted half-life of erythrocytes) and does not have the large fluctuations typical of daily blood glucose concentrations (Goldstein et al., 2004). The fact that HbA1c provides a reliable and valid index of relatively long-term blood glucose has led it to be considered the gold standard marker of T2D severity and glycemic control by clinicians and researchers alike. In the United States, HbA1c is typically reported as a percentage (unit: %) of total hemoglobin using measurement standards based on the National Glycohemoglobin Standardization Program (Little & Sacks, 2009). HbA1c is used to diagnose T2D and inform clinical care (i.e., monitor disease progression and adjust treatment in T2D). The American Diabetes Association (ADA; 2019) has established guidelines

for diagnosing T2D based on levels of HbA1c (normal: <5.7%, pre-diabetes: 5.7%- < 6.5%; diabetes: ≥ 6.5%). Although patients' glycemic targets are determined by clinicians, HbA1c ≥ 7.5% is generally considered poor glycemic control or uncontrolled T2D in older adults (ADA, 2019).

The role of HbA1c as a marker of T2D severity and its clinical relevance in terms of evaluating and monitoring T2D treatment and self-care activities has led to an increasing number of research studies examining HbA1c-related effects on cognitive aging. Specifically, previous studies show that elevations in HbA1c predict lower concurrent cognitive performance, greater declines in cognitive function (Marden et al., 2017; Pappas et al., 2017), and incident cognitive impairment (Rawlings et al., 2019) in older adults with T2D. The salience of glycemic control to understanding pathways leading to T2D-related poor health outcomes is underscored by a growing body of research suggesting that HbA1c levels may modulate T2D effects on physical and cognitive health outcomes in older adults (ADA, 2019; Xu, Von Strauss, Qiu, Winblad, & Fratiglioni, 2009). Specifically, a population-based longitudinal study showed that uncontrolled T2D confers a higher risk for dementia in comparison with controlled T2D (Xu et al., 2009). The effects of chronically high blood glucose on various physiological functions that lead to greater cardiovascular and cerebrovascular burden likely contribute to heightened dementia risk in this group, although research on uncontrolled T2D in older adults is scarce. In order to better understand the greater risk for dementia in older adults with uncontrolled T2D, this dissertation included a study that exclusively recruited older adults with uncontrolled T2D (Study 2).

Depression Mechanisms in HbA1c Links to Cognitive Aging Outcomes

HbA1c Associations with Depression/Depressive Symptoms

Multifactorial and complex behavioral and physiological mechanisms likely contribute to T2D-related cognitive decrements. This dissertation examined the mediating role of depressive symptoms in the association between HbA1c and cognition, as depressive symptoms may represent a potentially modifiable behavioral factor linking HbA1c to poor cognitive outcomes in older adults with T2D. Indeed, a large body of research from systematic reviews and meta-analyses provide robust evidence in support of T2D and/or high HbA1c as a risk factor for elevated depressive symptoms and/or clinical depression in older adults (Chireh, Li, & D'Arcy, 2019; Nouwen et al., 2010; Rotella & Mannucci, 2013). However, exact mechanisms underlying the effect of T2D/HbA1c on increases in depressive symptoms are likely multifaceted and are not completely understood.

From a behavioral standpoint, it is possible that managing T2D-related self-care activities may be perceived as burdensome, which in turn may negatively impact mood (Rotella & Manucci, 2013). With increasing levels of HbA1c, individuals with T2D typically face more a more demanding treatment regimen (ADA, 2019). For instance, patients may be required to monitor glucose levels more frequently throughout the day as well as take higher daily dosages of glucose-lowering treatment agents (which may involve more frequent and/or a larger number of oral medications and/or intramuscular insulin injections). Although the burden of managing T2D self-care may contribute to specific forms of distress (i.e., diabetes distress), there may be spillover effects that lower mood more generally. Additionally, prior research indicates that the gastrointestinal adverse effects (e.g., nausea and diarrhea) of first-line medication used to manage glycemic control in T2D (i.e., metformin; Bonnet & Scheen, 2017; Inzucchi et al., 2015) may have secondary effects that can negatively impact mood.

From a biological standpoint, potential mechanisms may involve dysregulation related to insulin as well as perturbed inflammatory responses. For instance, hyperglycemia-related symptoms such as fatigue may lead to depressed mood and/or decreased engagement in pleasurable activities, which in turn may lead to depressed mood (Kalra & Sahay, 2018; Rotella & Manucci, 2013). It has been postulated that T2D-specific fatigue may occur as a result of T2D-related reductions in insulin, which can shift the energy substrate from carbohydrate to fat, leading to decreases in energy metabolism, which in turn results in fatigue (Kalra & Sahay, 2018).

Furthermore, disruptions in centrally mediated insulin function may link T2D to depressive symptoms. Specifically, previous studies show that poor brain insulin signaling in individuals with T2D is associated with impaired insulin transport across the blood-brain barrier (Gray, Aylor, & Barrett, 2017). In animal models of T2D (*db/db* mice), perturbed brain insulin signaling has been associated with greater psychological distress (Sharma, Elased, Garrett, & Lucot, 2010). However, additional research is needed to clarify whether these preliminary findings shown in mice models can explain observed associations in older adults with T2D. Another potential biological mechanism may involve pro-inflammatory pathways. Individuals with T2D have higher levels pro-inflammatory markers, such as tumor necrosis factor-alpha (TNF-α; Mirza et al., 2012) relative to non-T2D individuals. In turn, higher levels of TNF-α are associated with more depressive symptoms (Postal et al., 2016).

Associations between Depression/Depressive Symptoms and Cognitive Aging

Separate from studies involving the effect of HbA1c on depression/depressive symptoms, a distinct body of literature indicates that clinical depression/depressive symptoms augments dementia risk and contributes to poor cognitive function and accelerated cognitive decline (Katon et al., 2012; Rock, Roiser, Riedel, & Blackwell, 2014; Sullivan et al., 2013; Ownby et al., 2010).

For instance, a longitudinal study in a sample of older adults with T2D showed that participants with clinically significant depressive symptom scores (9-item Patient Health Questionnaire, ≥10; Kroenke, Spitzer, & Williams, 2001) showed greater declines in attention, processing speed, executive function, and memory in comparison to non-depressed older adults with T2D (Sullivan et al., 2013). One potential mechanism linking depression/depressive symptoms to cognitive decline may involve hypothalamic-pituitary-adrenal (HPA) axis dysregulation. Specifically, depressive symptoms are associated with greater secretion of glucocorticoids, which in turn can damage brain areas such as the hypothalamus and dampen hippocampal neurogenesis (Elder, De Gasperi, & Gama Sosa, 2006; Lee et al., 2007; Sheline, Sanghavi, Mintun, & Gado, 1999; Videbech & Ravkilde, 2004), which are essential for cognitive function.

A significant limitation of existing literature that has suggested depression may mechanistically link T2D/HbA1c to cognitive aging outcomes is that associations among T2D/HbA1c, depressive symptoms, and cognitive functioning are examined separately. This methodological limitation necessarily limits interpretation regarding the nature of relationships between these variables. However, a recent study evidences a potential mediating role for depressive symptoms in T2D-related effects on poor cognitive outcomes in older adulthood (Schmitz et al., 2018). Specifically, cardiometabolic dysregulation was longitudinally associated with changes in cognition via increases in depressive symptoms. However, because the authors utilized a general composite of various cardiovascular disease risk factors, additional research is needed to determine whether these findings can be extended to T2D-specific samples. Indeed, Study 3 (Aim 1) of this dissertation examined whether the association between HbA1c and cognitive decline operated in part through depressive symptoms.

Homocysteine Mechanisms in T2D-Related Cognitive Aging Outcomes

Another potential explanation for T2D-related risk for dementia and accelerated cognitive decline may involve physiological pathways. In recent years, studies evidence a contribution of higher levels of plasma homocysteine to greater cardiovascular risk and disease in those with T2D (Hoogeven et al., 1998; Hoogeveen et al., 1999; Stehouwer, Gall, Hougaard, Jakobs, & Parving, 1999) as well as those without T2D (Eikenboom et al., 1999; Graham et al., 1997). Homocysteine is a sulfur-containing, non-protein, amino acid produced from the metabolic demethylation of methionine, which is an essential amino acid ingested from foods such as cheeses, meat, and poultry (Venes & Clarence, 2005). Homocysteine can be remethylated to methionine through the 5-methyltetrahydrofolate metabolic pathway. Methionine is a central component of methylation reactions in the brain, such as DNA, RNA, and phospholipids and is also part of the synthesis of neurotransmitters, such as dopamine, serotonin, and noradrenaline (Bottiglieri, 2005). Reduced remethylation of homocysteine to methionine results in higher concentrations of homocysteine, which in turn has direct toxic effects to vascular endothelial cells as well as neuronal cells (Lipton et al., 1997; Mattson & Shea, 2003). Homocysteine's toxic effects occur via oxidative-redox stress processes, including the auto-oxidation of homocysteine and formation of homocysteine mixed disulfides (Blom, 2000; Misra, 1974).

Homocysteine in the General Population

The role of homocysteine in promoting oxidant injury explains the observed associations between higher levels of homocysteine and increased risk of endothelial dysfunction, cardiovascular disease, stroke, and mortality (Eikenboom et al., 1999; Graham et al., 1997). Although there is no consensus on the thresholds for clinically significant levels of homocysteine, the population-based reference range is generally considered 5-15 micromol/L, with values from 11 micromol/L associated with gradual increases in risk for cardiovascular disease. Of note,

findings from a meta-analysis showed that reducing homocysteine levels by 25% (approximately 3 micromol/L) predicted lower risk for ischemic heart disease and stroke (11% and 19%, respectively; Homocysteine Studies Collaboration, 2002). Furthermore, studies in non-T2D older adult samples suggest that homocysteine confers risk for Alzheimer's disease and related dementias (Blasko et al., 2012; Luchsinger, Tang, Shea, & Mayeux, 2004; Ravaglia et al., 2005; Seshadri et al., 2002) as well as declines in global cognition (Ravaglia et al., 2003) and specific cognitive domains (Dufoil, Alpérovitch, Ductos, & Tzourio, 2003; Prins et al., 2002). Furthermore, plasma homocysteine levels above 14 micromol/L have been shown to double the risk of dementia due to Alzheimer's disease (Seshadri et al., 2002).

Homocysteine in Type 2 Diabetes

Studies in T2D older adult samples show a similar pattern of association between homocysteine levels and risk for cardiovascular disease, stroke, and mortality (Hoogeven et al., 1998; Hoogeveen et al., 1999; Stehouwer et al., 1999). Of note, the association between HbA1c and levels of plasma homocysteine are unclear, with separate studies suggesting positive (Bansal, Kapoor, Singh, & Yadav, 2016) and inverse (Mazza, Bossone, Mazza, & Distante, 2005) associations. However, preliminary evidence suggests that HbA1c-homocysteine associations may be modulated by glycemic control. Specifically, a previous investigation showed that higher levels of HbA1c was associated with higher levels of homocysteine only among those with uncontrolled T2D whereas no association was found in "well" controlled T2D (Drzewoski, Czupryniak, Chwatko, & Bald, 2000). Although additional research is needed to replicate this finding, it is possible that the higher dementia risk observed in older adults with uncontrolled T2D versus controlled T2D (Xu et al., 2009) may be explained in part through pathways involving homocysteine.

Notably, there is a dearth of research examining the association between homocysteine and cognitive aging outcomes in *older* adults with T2D. Preliminary research shows an association between higher levels of homocysteine and lower global cognition performance (de Luis, Fernandex, Arranz, Aller, & Izaola, 2002; Robbins et al., 2005) in older adults with T2D. However, these studies did not investigate patterns of association specifically in older adults with uncontrolled T2D who may be particularly at risk for homocysteine-related cognitive declines, given prior research that showed HbA1c-related increases in homocysteine occur in uncontrolled but not controlled T2D (Drzewoski et al., 2000). Furthermore, prior studies examining the association between homocysteine levels and cognition in T2D utilized global cognition screening measures which have well-documented ceiling effects and may not be sensitive to T2D-related cognitive changes in older adults. In order to address these gaps related to uncontrolled T2D and measures of cognition demonstrated, this dissertation examined the associations between homocysteine levels and four cognitive domains (i.e., processing speed, executive function, working memory, and episodic memory) using well-established neuropsychological measures in a sample of older adults with uncontrolled T2D (Study 2; Aim 1).

Modulating T2D-related Cognitive Decrements: The Buffering Role of Support

Emerging research implicates a potentially protective role for psychosocial factors, such as emotional support, in health outcomes for older adults with T2D, although findings have been inconsistent. Substantial heterogeneity across disciplines and empirical research exists in the operationalization of social support. In psychology, social support is theorized as a multidimensional construct comprising instrumental support (i.e., provision of material assistance such as transportation), informational support (i.e., provision of information), and emotional support (i.e., availability of advice or empathy when needed; Cohen & Wills, 1985).

Overall, prior studies show that the various dimensions of support confer beneficial effects on physical and mental health outcomes in T2D (for a review, see Strom & Egede, 2012; Ju et al., 2018). However, contrasting research has documented negative or non-significant effects of support on diabetes health management behaviors (Rosland et al., 2008) and physical health outcomes in T2D (Chlebowy et al., 2006; Nicklett & Liang, 2009), although studies with older adult samples are scarce (Nicklett & Liang, 2009). These inconsistent findings, however, are in line with the primary conceptual framework underlying the theorized health effects of support. Specifically, the buffering hypothesis posits that support is protective, or acts as a buffer, in stressful situations (Cohen & McKay, 1984; Cohen & Wills, 1985; Uchino, 2009). Within this framework, health-related stressors exert negative effects on health outcomes in those with low support, and these effects are attenuated or eliminated in those with greater support. This line of research has also shown that support may conversely exacerbate stressful experiences when it is perceived as excessive (e.g., when support is not wanted or reduces autonomy).

Empirical evidence in T2D samples indicate that the adverse impact of T2D severity (indexed by T2D complications and insulin use) on T2D-specific distress shown in those with low support is attenuated in those with higher levels of support (Baek, Tanenbaum, & Gonzalez, 2014). Of note, the authors operationalized support using items that assessed satisfaction with social support. Scarce research has explored the buffering effect of support on T2D-related cognitive decrements in older adulthood. In a cross-sectional study of older adults with T2D, Strizich and colleagues (2016) showed a stronger negative association between T2D severity and cognition in older adults with low (versus high) family support. Of note, the authors operationalized "family support" using a measure that assessed the frequency of contact with children, spouse/partner, and other relatives rather than traditional operationalizations of support (e.g., material assistance and/or

advice and empathy). Although more frequent contact with family members can lead to higher levels of support, contact frequency and support represent two distinct aspects of social engagement (e.g., Cohen & Wills, 1985) that operate via unique mechanisms and demonstrate independent associations with cognitive outcomes (Zahodne, Ajrouch, Sharifian, & Antonucci, 2019).

A separate cross-sectional investigation comprising a subsample of T2D participants in the Health and Retirement Study showed that higher levels of social support (operationalized as a composite of emotional and instrumental support) weakened the negative association between glycemic control and global cognition (Okura, Heisler, & Langa, 2009). With respect to the conceptualization of support as a buffer against T2D-related effects on cognition in older adults, examining the moderating role of instrumental support (i.e., material assistance) may introduce bias related to reverse causation. Specifically, higher levels of instrumental support (e.g., more help with meal preparation) may reflect a consequence of advancing T2D severity and/or lower cognitive function, as social networks typically provide greater assistance in the face of deteriorating health.

Within the framework of the stress-buffering model of support (Cohen & Wills, 1985), emotional support may pose the fewest concerns related to reverse causation in the context of T2D-related cognitive decrements. Specifically, the second aim across all three studies (and the third aim of Study 1) in this dissertation examined whether emotional support attenuates the adverse impact of HbA1c (Studies 1 and 3) or homocysteine (Study 2) on various domains of cognitive function in older adults with T2D. According to the stress-buffering hypothesis, the impact of support is far-reaching and likely operates through various mechanisms (Cohen & Willis, 1985). Grounded in theoretical and empirical work on stress-buffering in T2D and non-T2D samples, this

dissertation examined the role of emotional support as a buffer against the effects of: (1) T2D severity on depressive symptoms, (2) depressive symptoms on cognition, and (3) T2D severity on cognition.

Support Buffers the Impact of HbA1c on Depressive Symptoms

In the presence of a health stressor such as high levels of HbA1c, one potential mechanism underlying the buffering effect of support on health outcomes may involve its promotion of psychological well-being. For instance, a previous study in midlife adults showed that more severe T2D was associated with greater T2D-specific distress in those with low levels of support whereas no association was found in those with high levels of support (Baek et al., 2014). Short-term intervention studies document a similar effect of support contributing to better psychosocial function (i.e., less distress, fewer depressive symptoms, and better quality of life) in adults and older adults with T2D (Bond et al., 2010; McEwen et al., 2010). However, it remains unclear whether may attenuate the impact of glycemic control on psychological variables such as depressive symptoms. Given the prospective links between higher levels of HbA1c and depressive symptoms, this dissertation examined the role of emotional support in attenuating the association between HbA1c and depressive symptoms (Aim 3 of Study 1; Aim 2 of Study 3).

Support Buffers the Impact of Depressive Symptoms on Cognition

Support may also attenuate the impact of psychological distress, such as depressive symptoms, on cognitive function in older adults with T2D. As previously described, depressive symptoms may contribute to lower cognitive test performance via stress-related pathways. Briefly, depressive symptoms may increase HPA axis activation, which in turn contributes to greater glucocorticoid secretion, which can damage brain regions that mediate cognitive function (Elder et al., 2006; Lee et al., 2007; Sheline et al., 1999; Videbech & Ravkilde, 2004). Emotional support

is theorized to facilitate higher levels of self-efficacy in part by promoting existing coping skills and/or providing new strategies to cope with potential stressors (Cohen & Wills, 1985) such as depressive symptoms. Therefore, higher levels of emotional support may dampen physiological reactivity to stress (Cohen & Wills, 1985), thereby potentially reducing the negative effect of depressive symptoms on cognitive function.

Support Buffers the Impact of HbA1c on Cognitive Function

Separate from pathways involving psychological distress and/or depressive symptoms, the buffering effect of emotional support on cognitive outcomes may operate through cognitive stimulation. Specifically, activities involved in receiving emotional support, such as conversations with friends, family members, and healthcare providers may represent cognitively demanding tasks. For instance, in order to maintain a conversation, language functions are heavily utilized to understand and respond to verbal information (and, potentially, non-verbal cues). In addition, conversations with others may require one to process information quickly, mentally manipulate information to understand and apply it to one's concerns, recall information to discuss, and engage in problem-solving or similar strategy-based endeavors. Indeed, these mental processes employed during conversations likely represent sources of cognitive stimulation (for a review, see Hickok & Small, 2015).

Summary

Clarifying the mediators and moderators of hyperglycemia-related declines in cognition may point to potential targets for improving the well-documented cognitive morbidity in older adults with T2D. Study 1 examined the direct effect of HbA1c on cognitive function and the indirect effect via depressive symptoms as well as the moderating role of emotional support across all paths in a regionally-representative sample of racially and ethnically diverse older adults with

T2D. Study 2 examined the association between homocysteine and multiple domains of cognitive function as well as the moderating role of emotional support in a sample of older adults with chronically uncontrolled T2D. Study 3 employed U.S. wide data comprising a sample of older adults with T2D to test the mediating role of depressive symptoms in the longitudinal association between HbA1c and six-year memory changes. Study 3 also examined the role of emotional support as a moderator of concurrent and longitudinal associations. Together, the results from these three studies reveal how biological, psychological, and social factors potentially shape cognitive aging in T2D.

Chapter 2

Study 1: Cross-Sectional Associations among Glycemic Control, Depressive Symptoms, and Cognition and the Moderating Role of Emotional Support

Type 2 Diabetes and Cognitive Aging

Robust evidence shows that Type 2 Diabetes (T2D) confers substantial risk for dementia (e.g., Livingston et al., 2017) and accelerates cognitive decline (e.g., Marden et al., 2017) in older adults. Empirical studies suggest that T2D-related cognitive decrements are associated with greater T2D severity, for which glycemic control indexed by hemoglobin A1c (HbA1c) is the gold-standard marker (American Diabetes Association (ADA), 2019). Specifically, higher HbA1c has been associated with a higher rate of cognitive decline in middle-aged and older adults (Marden et al., 2007; Pappas et al., 2017; Zheng et al., 2018).

With regard to individual cognitive domains, T2D is most commonly associated with deficits in attention and processing speed performance (for a review of meta-analyses, see: Monette et al., 2014; Palta et al., 2014; Vincent & Hall, 2015). Most studies examining processing speed compare test performance between older adults with and without T2D, with fewer studies examining associations within T2D. Of note, although some previous studies evidence a negative association between HbA1c and processing speed performance in older adults with T2D, findings have been mixed (for a review, see Ganmore & Beeri, 2018). Despite the preponderance of studies describing the negative cognitive health effects of T2D, substantially less is known regarding potential mechanisms linking T2D to cognitive outcomes in older adulthood.

Depressive Symptoms as a Mechanism Underlying T2D-Related Cognitive Decrements

Mechanisms underlying the effects of T2D on cognition in older adulthood are multifactorial and remain unclear. Nonetheless, empirical evidence points to depressive symptoms as one potential pathway linking T2D to cognitive decrements in older adulthood. Specifically, meta-analyses of longitudinal studies indicate that T2D augments risk for depressive symptoms and clinical depression (Chireh, Li, & D'Arcy, 2019; Nouwen et al., 2010; Rotella & Mannucci, 2013) in older adults. Studies in samples of older adults with T2D prospectively link HbA1c to incident elevations in depressive symptoms (Maraldi et al., 2007; Hamer, Batty, & Kivimaki, 2011). In turn, depression in older adulthood may increase risk for Alzheimer's disease (Ownby et al., 2010) and poor cognitive function (Rock et al., 2014) both in the general population as well as older adults with T2D (Katon et al., 2012).

Of note, most previous studies examined associations between T2D/HbA1c, depressive symptoms, and cognitive functioning separately, which restricts interpretation regarding the inter-relationships between these variables. However, a recent study provides evidence supporting a potential mediating role of depressive symptoms in the association between T2D and cognitive function in older adulthood (Schmitz et al., 2018). Specifically, Schmitz and colleagues (2018) found an indirect effect of cardiometabolic dysregulation on cognitive change through depressive symptoms using longitudinal data from two independent community-based adult cohorts from the Netherlands and United Kingdom. However, given that the authors modeled cardiometabolic dysregulation as a latent factor (comprising glycemic control in addition to blood pressure, dyslipidemia, central obesity, and inflammation), additional research is needed to determine whether the mediating role of depressive symptoms can be extended to the specific association between HbA1c and cognitive function in T2D. Furthermore, because each component of

cardiometabolic dysfunction requires unique treatment, greater specificity regarding their effects on cognition may yield more precise targets for intervention.

Emotional Support and Cognition

Emotional support, or the perceived availability of advice or empathy when needed, has been positively associated with physical and mental health outcomes in T2D (for a review, see Strom & Egede, 2012; Ju et al., 2018). Based on the buffering model of social support (Cohen & McKay, 1984; Cohen & Willis, 1985), health-related stressors are posited to exert negative effects on psychological well-being and cognitive function in those with limited support, and these effects are attenuated or eliminated in those with greater support (Cohen & McKay, 1984; Cohen & Willis, 1985). In the context of T2D-related cognitive decrements, emotional support may represent a buffer against the negative effects of HbA1c on cognition both directly as well as indirectly by attenuating the HbA1c-depression association and/or the depression-cognition association.

With respect to the association between T2D and depressive symptoms, emotional support may attenuate associations by contributing to greater psychological well-being and/or facilitating coping skills (Cohen & Willis, 1985). For instance, a previous study in midlife adults showed an association between T2D severity and T2D-specific distress in those with low levels of support; in contrast, for those with high levels of support, T2D severity was not associated with T2D-specific distress (Baek et al., 2014). Additional research is needed to determine whether prior findings can be extended to emotional support as a buffer against the impact of T2D severity on more general forms of distress, such as depressive symptoms.

With respect to cognitive outcomes, emotional support may promote cognitive stimulation, which may attenuate the adverse effects of depressive symptoms and T2D severity on cognitive function. Indeed, activities involved in the process of obtaining emotional support, such as

conversations with loved ones, may represent cognitively demanding tasks, as one has to quickly process information in order to maintain communication (for a review, see Hickok & Small, 2015). A previous study in older adults with T2D showed that higher levels of support attenuates the negative association between glycemic control and global cognition (Okura et al., 2009). However, the authors operationalized support using items assessing both instrumental (i.e., material assistance) and emotional support, which poses concern for reverse causality. Specifically, higher levels of instrumental support may reflect an outcome of poor glycemic control and/or cognitive health, as social networks may mobilize in response to poor health.

Less is known regarding the role of support as a buffer against the negative effects of depressive symptoms on cognition in T2D. Emotional support may promote existing coping skills and/or contribute to the development of new coping skills, which may dampen physiological stress reactivity (Cohen & Willis, 1985) and potentially lower the impact of depressive symptoms on cognition. Taken together, the stress-buffering theoretical framework (Cohen & Willis, 1985) and empirical evidence from its application in T2D (e.g., Baek et al., 2014; Okura et al., 2009) suggest that emotional support may reduce the negative effect of HbA1c on cognition. Specifically, emotional support may operate in part by attenuating the impact of HbA1c on depressive symptoms and/or cognition, as well as the impact of depressive symptoms on cognition.

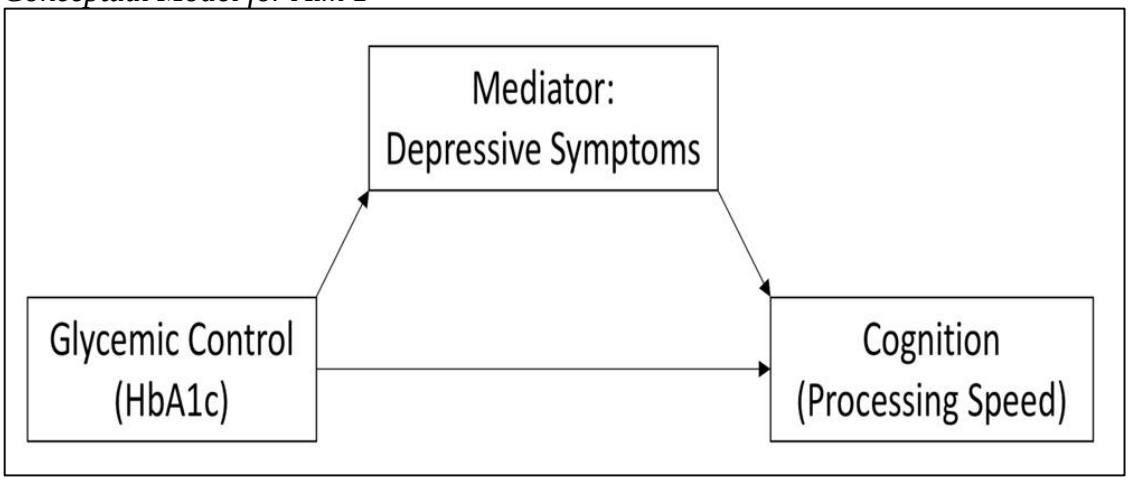
The Current Study

Using a sample of racially and ethnically diverse older adults with T2D, the overall goal of the current cross-sectional study is to examine the relationships among glycemic control, depressive symptoms, emotional support, and cognitive functioning via the following three aims. First, the study aims to test the role of depressive symptoms as a mediator of the association between HbA1c and cognition (Figure 2.1), hypothesizing that more depressive symptoms will at

least partially mediate the negative HbA1c-cognition association. Second, the study aims to test the role of emotional support as a moderator of the association between HbA1c and cognition (Figure 2.2), hypothesizing that the negative association between HbA1c and cognition would be stronger for older adults with less emotional support. Third, the study aims to test the role of emotional support as a moderator of the indirect effect of HbA1c on cognitive function through depressive symptoms as well as the direct effect of HbA1c on cognitive function, independent of the pathway involving depressive symptoms (Figure 2.3). The third hypothesis is that lower levels of emotional support would result in stronger negative associations between HbA1c and depressive symptoms, depressive symptoms and cognition, and HbA1c and cognition.

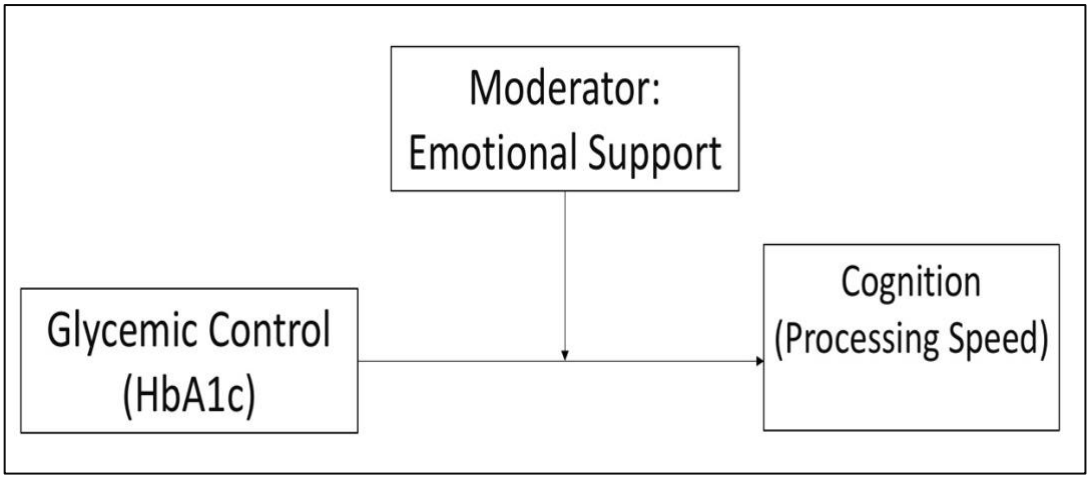
Figure 2.1

Conceptual Model for Aim 1



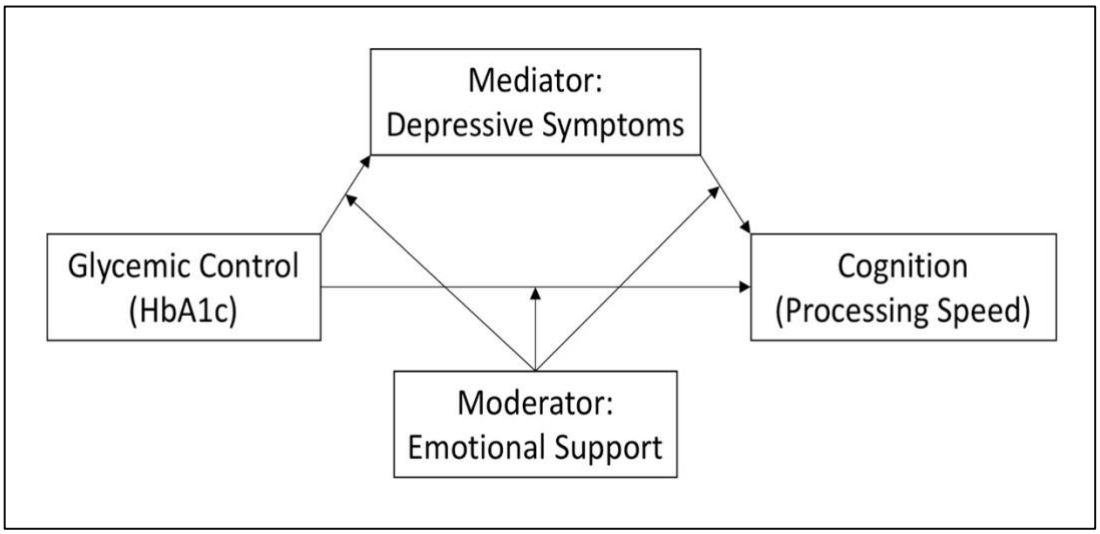
Note. For simplicity, covariates are not depicted.

Figure 2.2
Conceptual Model for Aim 2



Note. *For simplicity, covariates are not depicted.*

Figure 2.3
Conceptual Model for Aim 3



Note. For simplicity, covariates are not depicted.

Method

Participants and Procedure

Participants (N=213) comprised older adults from the Washington Heights Inwood Columbia Aging Project (WHICAP), which is a longitudinal study on aging and dementia in New York. Study procedures have been previously described (Manly et al., 2005; Tang et al., 2001). Briefly, participants were recruited using Medicare records or a commercial marketing company beginning in 1992, with two additional recruitment waves beginning in 1999 and 2009. Beginning in 2013, participants from the 2009 wave completed psychosocial measures as part of an ancillary study (Zahodne, Watson, Seehra, & Martinez, 2017). Thus, the current study includes data from participant visits between 2013 and 2017. All participants provided informed consent and the study was approved by the Columbia University Institutional Review Board.

In WHICAP, participants undergo cognitive, functional, and health assessments in their preferred language of Spanish or English administered by bilingual research staff. The study visits were conducted at the Columbia University Medical Center. The current study included participants who met the following criteria: (1) no baseline diagnosis of dementia and (2) self-reported diagnosis of T2D. Dementia was determined according to DSM-III criteria with a diagnosis consensus group comprising neuropsychologists, neurologists, and psychiatrists. T2D diagnosis was self-reported during the medical history portion of the health assessment.

Measures

Outcome

Cognitive functioning. Cognitive functioning was determined by performance on a processing speed task using the Color Trails Test (D'Elia, Satz, Uchiyama, & White, 1994). Processing speed has been shown to be negatively affected by diabetes and hyperglycemia (Ganmore & Beeri, 2018), and represents a domain of cognitive function sensitive to the cardiovascular contributions to dementia risk. The Color Trails Test comprises two timed subtests

that require participants to connect numbers in ascending order. The first subtest requires participants to connect numbers, which alternate in color but do not require participants to choose between colors, and the second subtest requires participants to choose between two colors to ensure a sequence of alternating colors. Scores (i.e., completion time) were reverse coded so that higher scores indicate better performance (i.e., faster processing speed). A composite score was computed by averaging z-scores from both trials using means and standard deviations of the larger WHICAP sample (Siedlecki et al., 2010).

Exposure

Glycemic Control. Glycemic control was indexed by HbA1c, which is a specific glycated hemoglobin that is produced from the attachment of glucose to erythrocytes and is a marker of glucose concentration over the past 2 to 3 months. In the United States, HbA1c is typically reported as a percentage of total hemoglobin (unit: %) using measurement standards based on the National Glycohemoglobin Standardization Program (Little & Sacks, 2009). HbA1c represents an index of an individual's glycemic control (ADA, 2019) and is used to diagnose T2D and inform clinical care (i.e., monitor disease progression and treatment adjustment in T2D). The ADA (2019) has established guidelines for diagnosing T2D based on levels of HbA1c (normal: <5.70%, pre-diabetes: 5.70% - 6.49%; diabetes: ≥ 6.50%).

In WHICAP, participants' HbA1c was assessed from blood collected via venipuncture by trained WHICAP research staff as part of the research study. As previously described (Reitz et al., 2017), HbA1c was assayed by boronate affinity chromatography with the Primus CLC 385 (Primus, Kansas City, MO). Participants who self-reported T2D diagnosis were included in primary analyses regardless of HbA1c levels. Follow-up sensitivity analyses were restricted to participants with T2D who had non-normal (i.e., elevated) HbA1c (≥ 5.7%).

Mediator

Depressive Symptoms. Depressive symptoms over the past week were assessed using a short version of the Center for Epidemiological Studies Depression Scale (Irwin et al., 1999; Appendix A) in which participants self-reported responses (*yes* or *no*) to 10 items. Responses were summed and higher scores correspond to more depressive symptoms. A score of 4 or higher has been suggested to represent clinically significant depressive symptoms.

Moderator

Emotional Support. Emotional support was self-reported using the NIH Toolbox Emotional Support Survey (Appendix B), which comprises 10 items. Participants completed this questionnaire in their preferred language of Spanish or English on a computer under the supervision of trained research staff at the Columbia University Medical Center. This questionnaire has good psychometric properties (Cronbach's alpha was 0.97 and convergent validity was 0.78) and has been validated for use with older adults (Salsman et al., 2013). Participants rated the frequency of items such as "I have someone to turn to for suggestions about how to deal with a problem" and "I have someone who will listen to me when I need to talk". Responses ranged from 1 (*Never*) to 5 (*Always*). An unadjusted, standardized (theta) score was computed for each participant, with higher score corresponding to more emotional support.

Covariates

Sociodemographics. Age (years), education (0-20 years), sex/gender, race, and ethnicity were self-reported and included as covariates. Age was participants' self-reported age in years. Education was self-reported years of education (0-20). Sex/gender was modeled with male/man as the reference category. Race and ethnicity were dummy coded into three, mutually exclusive

categories: non-Hispanic Black, non-Hispanic White, and Hispanic of any race, with Non-Hispanic White as the reference category.

Diabetes treatment. Diabetes treatment was participants' self-reported treatment (*yes* or *no*) for diabetes. Self-reported absence of treatment was modeled as the reference group.

Analytic Strategy

Primary Analyses

Analyses were conducted using IBM SPSS v. 25 (IBM Corp., Armonk, NY). Continuous variables with unstandardized values (i.e., age, education, depressive symptoms, and HbA1c) were centered at the sample mean (Hayes, 2018; Hayes & Rockwood, 2017). All models adjusted for covariates. Primary analyses comprised three analytical models. First, to test Aim 1, the role of depressive symptoms as a mediator of the HbA1c-cognition association (Figure 2.1) was examined. This model was estimated using the PROCESS modeling system (Model 4) for SPSS (Hayes, 2018; Hayes & Rockwood, 2017). Of note, emotional support was not included in this model.

Second, to test Aim 2, a computed interaction (HbA1c x emotional support) tested the role of emotional support as a moderator of the HbA1c-cognition association (Figure 2.2). Of note, depressive symptoms were not included in this model. This analysis was conducted using linear regression in SPSS. Third, to test Aim 3, moderated mediation analyses tested the role of emotional support as a moderator of the direct effect of HbA1c on cognition and the indirect effect involving depressive symptoms (Figure 2.3). Models were estimated using the PROCESS system for SPSS (Hayes, 2018; Hayes & Rockwood, 2017); specifically, the role of emotional support as a moderator was tested using Model 7 for the HbA1c-depressive symptoms association, Model 14

for the depressive symptoms-cognition association, and Model 5 for the HbA1c-cognition association.

Sensitivity Analyses

A series of sensitivity analyses were conducted to test the robustness of findings. First, analyses were restricted to T2D participants with non-normal (i.e., elevated) HbA1c (≥ 5.7%), as HbA1c levels below 5.7% reflects well-controlled T2D that may be in remission. Second, separate models additionally adjusted for other chronic health conditions, which was a continuous variable computed by summing participant's responses to the presence of: arthritis, heart disease, hypertension, chronic obstructive pulmonary disease, thyroid disease, liver disease, renal insufficiency, peptic ulcer disease, peripheral vascular disease, cancer, Parkinson's disease, Essential Tremor, and Multiple Sclerosis. While previous studies suggest that chronic health conditions may reflect factors in the causal pathway linking T2D to cognitive decline (Feinkohl, Price, Strachan, & Frier, 2015; Xia et al., 2020), a separate body of research suggests that physical health conditions may represent a risk factor for T2D and/or poor glycemic control and independently contribute to poor cognition (Gress, Nieto, Shahar, Wofford, & Brancati, 2000; Iadecola, 2014). Furthermore, data regarding when these health conditions were diagnosed in relation to T2D are unavailable. Third, cholesterol medication use was included as a covariate, given previous research suggesting that statin use may independently lead to worse glycemic control (Cui et al., 2018) and decreased cognitive performance in older adulthood (Feldman et al., 2010). Fourth, although primary analyses tested emotional support as a moderator of direct and indirect paths in separate models (Aim 3), subsequent sensitivity analyses tested the role of emotional support as a simultaneous moderator of paths in the mediation model. Additional details

regarding these models are presented in the Sensitivity Analyses subsection of the Results section below.

Results

Participant characteristics are provided in Table 2.1. Briefly, participants were, on average, 76 years old, had approximately 12 years of education, and mean HbA1c levels were clinically elevated (7.3%). The sample comprised approximately 41% Black, 42% Hispanic, and 63% women. Bivariate correlations between HbA1c, depressive symptoms, emotional support, and cognition are provided in Table 2.2.

Table 2.1
Participant Characteristics

Variable	Value	%	Sample Range
Age (years)	76.26 (5.98)		62-89
Education (years)	11.79 (4.62)		1-20
Female/Woman		63.00	
Black Race		41.20	
Hispanic Ethnicity		42.30	
Diabetes Treatment		89.30	
Depressive Symptoms	1.36 (1.64)		0-8
≥4 Depressive Symptoms		9.90	
HbA1c (%)	7.33 (1.34)		5.44-12.46 [Median=7.18]
Emotional Support (standardized score)	-0.26 (1.01)		-3.20-1.25
Processing Speed (composite score score)	0.41 (0.90)		-2.08-1.63

Note. HbA1c=Hemoglobin A1c

Table 2.2
Bivariate Correlations between HbA1c, Depressive Symptoms, Emotional Support, and Cognition

	HbA1c	Depressive Symptoms	Emotional Support
Depressive Symptoms	0.008		
Emotional Support	0.213**	-0.202**	
Cognition (Processing Speed)	0.044	-0.156*	-0.105

Note. HbA1c=Hemoglobin A1c
*$p < 0.05$. **$p < 0.01$.

Primary Analyses

Results from the mediation analysis (Aim 1) showed that depressive symptoms did not mediate the association between HbA1c and cognition (indirect effect of HbA1c on cognition through depressive symptoms: *b*= -0.003, bootstrapped SE=0.007, bootstrapped 95% CI [-0.020, 0.010]). Specifically, HbA1c was not significantly associated with depressive symptoms, and neither depressive symptoms nor HbA1c were significantly associated with cognition (Table 2.3). Patterns of association persisted after excluding covariates that were not statistically significant (i.e., sex/gender, race, ethnicity, and treatment for diabetes).

Table 2.3
Model Estimates for the Mediation Model (Aim 1)

Outcome: Depressive Symptoms						
	b	*SE*	*t*	*p*	LLCI	ULCI
Constant	-0.167	0.500	-0.334	0.739	-1.153	0.819
Age	-0.021	0.018	-1.133	0.258	-0.057	0.015
Education	-0.048	0.029	-1.660	0.099	-0.106	0.009
Female/Woman	0.224	0.217	1.030	0.304	-0.205	0.652
Black Race	-0.611	0.327	-1.867	0.063	-1.256	0.034
Hispanic Ethnicity	-0.711	0.375	-1.895	0.060	-1.451	0.029
Diabetes Treatment	0.536	0.390	1.374	0.171	-0.233	1.304
HbA1c	0.042	0.082	0.515	0.607	-0.120	0.205
Outcome: Cognition						
	b	*SE*	*t*	*p*	LLCI	ULCI
Constant	0.580	0.237	2.444	0.015	0.112	1.048
Age	-0.055	0.009	-6.306	0.000	-0.072	-0.038
Education	0.065	0.014	4.630	0.000	0.037	0.092
Female/Woman	0.007	0.103	0.063	0.950	-0.197	0.210
Black Race	0.134	0.157	0.855	0.394	-0.175	0.443
Hispanic Ethnicity	-0.156	0.180	-0.866	0.388	-0.510	0.199
Diabetes Treatment	-0.120	0.186	-0.644	0.520	-0.486	0.247
Depressive Symptoms	-0.061	0.033	-1.827	0.069	-0.126	0.005
HbA1c	0.020	0.039	0.503	0.616	-0.057	0.097

Note. HbA1c=hemoglobin A1c. LLCI=95% confidence interval lower limit. SE=standard error. ULCI=95% confidence interval upper limit.

Results of the moderation analysis (Aim 2) showed that the association between HbA1c and cognition did not vary by level of emotional support (*b*=0.037, SE=0.036, *p*=0.298; Table 2.4). Patterns of association persisted in follow-up analyses that: (1) included depressive symptoms as a covariate (HbA1c x emotional support: *b*=0.046, SE=0.035, *p*=0.195); (2) excluded all non-significant covariates (i.e., sex/gender, race, ethnicity, and treatment for diabetes; HbA1c x emotional support: *b*=0.039, SE=0.035, *p*=0.273); and (3) excluded depressive symptoms and non-significant covariates (HbA1c x emotional support: *b*=0.047, SE=0.035, *p*=0.179).

Table 2.4
Model Estimates for the Interaction between HbA1c And Emotional Support on Cognition (Aim 2)

Variable	*b*	*SE*	β	*t*	*p*
Constant	0.507	0.242	-	2.098	0.037
Age	-0.056	0.009	-0.380	-6.366	<0.001
Education	0.067	0.014	0.333	4.791	<0.001
Female/Woman	0.013	0.105	0.007	0.128	0.898
Black Race	0.204	0.157	0.115	1.301	0.195
Hispanic Ethnicity	-0.028	0.185	-0.015	-0.150	0.881
Diabetes Treatment	-0.170	0.186	-0.054	-0.915	0.362
HbA1c	0.022	0.039	0.034	0.551	0.582
Emotional Support	-0.086	0.053	-0.101	-1.605	0.110
HbA1c x Emotional Support	0.037	0.036	0.060	1.043	0.298

Note. HbA1c= hemoglobin A1c. SE=standard error.

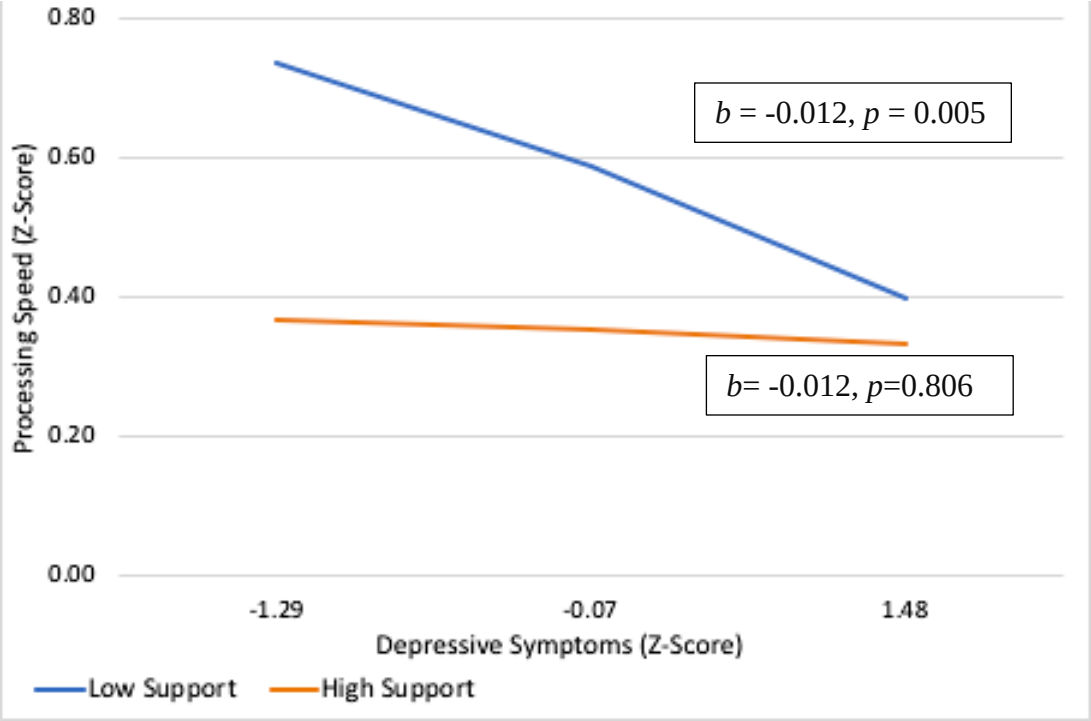
Results from the moderated mediation analysis (Aim 3) showed that, in general, emotional support did not significantly moderate patterns of association between HbA1c, depressive symptoms, and cognition. Specifically, levels of emotional support did not significantly alter associations between HbA1c and depressive symptoms (*b*=0.111, SE=0.073, *p*=0.131) or depressive symptoms and cognition (*b*=0.053, SE=0.031, *p*=0.089), although the latter interaction showed a trend towards statistical significance. Independent of depressive symptoms, levels of

emotional support did not alter the direct effect of HbA1c on cognition (*b*=0.046, SE=0.036, *p*=0.195).

Because the current study may not have been adequately powered to detect interactions, post-hoc analyses probed the non-significant (*p*=0.089) interaction between depressive symptoms and emotional support on cognition. As depicted in Figure 2.4, for older adults with low emotional support, depressive symptoms were negatively associated with cognition (*b*= -0.122, SE=0.043, *p*=0.005; Table 2.5). Furthermore, depressive symptoms were not significantly associated with cognition in older adults with high levels of emotional support (*b*= -0.012, SE=0.050, *p*=0.806). In order to identify the range of values of emotional support where depressive symptoms was negatively associated with cognition, the Johnson-Neyman technique for analyzing interactions (Bauer, Curran, & Thurstone, 2005; Johnson & Neyman, 1936) was implemented using the PROCESS modeling system (Hayes, 2018). Results showed a statistically significant negative association between depressive symptoms and cognition for levels of emotional support below -0.228 (range of statistically significant values: -3.200 to < -0.228; Table 2.6), which comprised 52.58% of the sample (Figure 2.5).

Figure 2.4

Model Predicted Trajectories Showing the Interaction between Depressive Symptoms and Emotional Support on Processing Speed



Note. Processing speed (z-score) was residualized for covariates.

Table 2.5

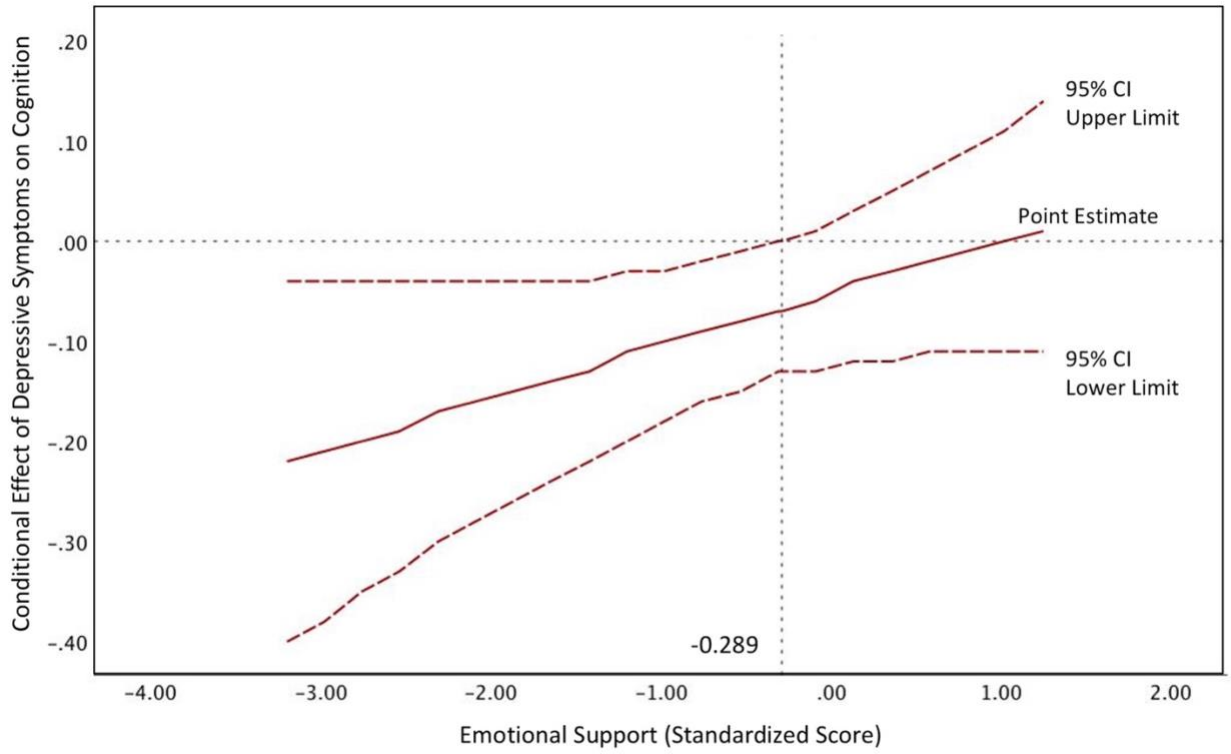
Model Estimates for the Moderated Mediation Model with Cognition as the Outcome (Aim 3)

Variable	*b*	SE	*t*	*p*	LLCI	ULCI
Constant	0.522	0.239	2.189	0.030	0.052	0.993
Age	-0.057	0.009	-6.519	0.000	-0.075	-0.040
Education	0.063	0.014	4.560	0.000	0.036	0.090
Female/Woman	0.040	0.104	0.383	0.702	-0.165	0.245
Black Race	0.136	0.155	0.877	0.381	-0.170	0.441
Hispanic Ethnicity	-0.062	0.182	-0.341	0.734	-0.421	0.297
Diabetes Treatment	-0.143	0.184	-0.776	0.439	-0.505	0.220
HbA1c	0.022	0.039	0.558	0.578	-0.055	0.099
Depressive Symptoms	-0.052	0.036	-1.425	0.156	-0.123	0.020
Emotional Support	-0.109	0.054	-2.022	0.045	-0.215	-0.003
Depressive Symptoms x Emotional Support	0.053	0.031	1.712	0.089	-0.008	0.113

Note. HbA1c=hemoglobin A1c. LLCI=95% confidence interval lower limit. SE=standard error. ULCI=95% confidence interval upper limit.

Figure 2.5

The Conditional Effect of Depressive Symptoms on Cognition (Processing Speed) as a Function of Emotional Support



Note. There is a statistically significant negative association between depressive symptoms and cognition at values of emotional support below -0.289. The magnitude of the negative association between depressive symptoms and cognition decreases as self-reported emotional support increases.

Table 2.6

Estimates of the Conditional Effect of Depressive Symptoms on Cognition at Values of Emotional Support

Emotional Support	*b*	SE	*t*	*p*	95% CI
-3.204	-0.220	0.091	-2.420	0.016	[-0.400, -0.041]
-2.981	-0.209	0.085	-2.463	0.015	[-0.376, -0.042]
-2.759	-0.197	0.079	-2.509	0.013	[-0.352, -0.042]
-2.536	-0.185	0.072	-2.559	0.011	[-0.328, -0.043]
-2.314	-0.174	0.066	-2.614	0.010	[-0.304, -0.043]
-2.091	-0.162	0.061	-2.671	0.008	[-0.281, -0.042]
-1.869	-0.150	0.055	-2.728	0.007	[-0.259, -0.042]
-1.646	-0.138	0.050	-2.780	0.006	[-0.237, -0.040]
-1.424	-0.127	0.045	-2.818	0.005	[-0.215, -0.038]
-1.201	-0.115	0.041	-2.823	0.005	[-0.195, -0.035]
-0.979	-0.103	0.037	-2.770	0.006	[-0.177, -0.030]
-0.756	-0.092	0.035	-2.627	0.009	[-0.160, -0.023]
-0.534	-0.080	0.034	-2.372	0.019	[-0.146, -0.014]
-0.311	-0.068	0.034	-2.014	0.045	[-0.135, -0.001]
-0.288	-0.067	0.034	-1.972	0.050	[-0.134, 0.000]
-0.089	-0.056	0.035	-1.596	0.112	[-0.126, 0.013]
0.134	-0.045	0.038	-1.175	0.242	[-0.120, 0.030]
0.356	-0.033	0.042	-0.791	0.430	[-0.115, 0.049]
0.579	-0.021	0.046	-0.462	0.645	[-0.112, 0.070]
0.801	-0.010	0.051	-0.188	0.851	[-0.110, 0.091]
1.024	0.002	0.056	0.038	0.970	[-0.109, 0.113]
1.246	0.014	0.062	0.223	0.824	[-0.108, 0.136]

Note. Values for the unstandardized estimates (i.e., b) represent the estimated effect of depressive symptoms on cognition for given values of emotional support using the Johnson-Neyman interaction analysis technique.

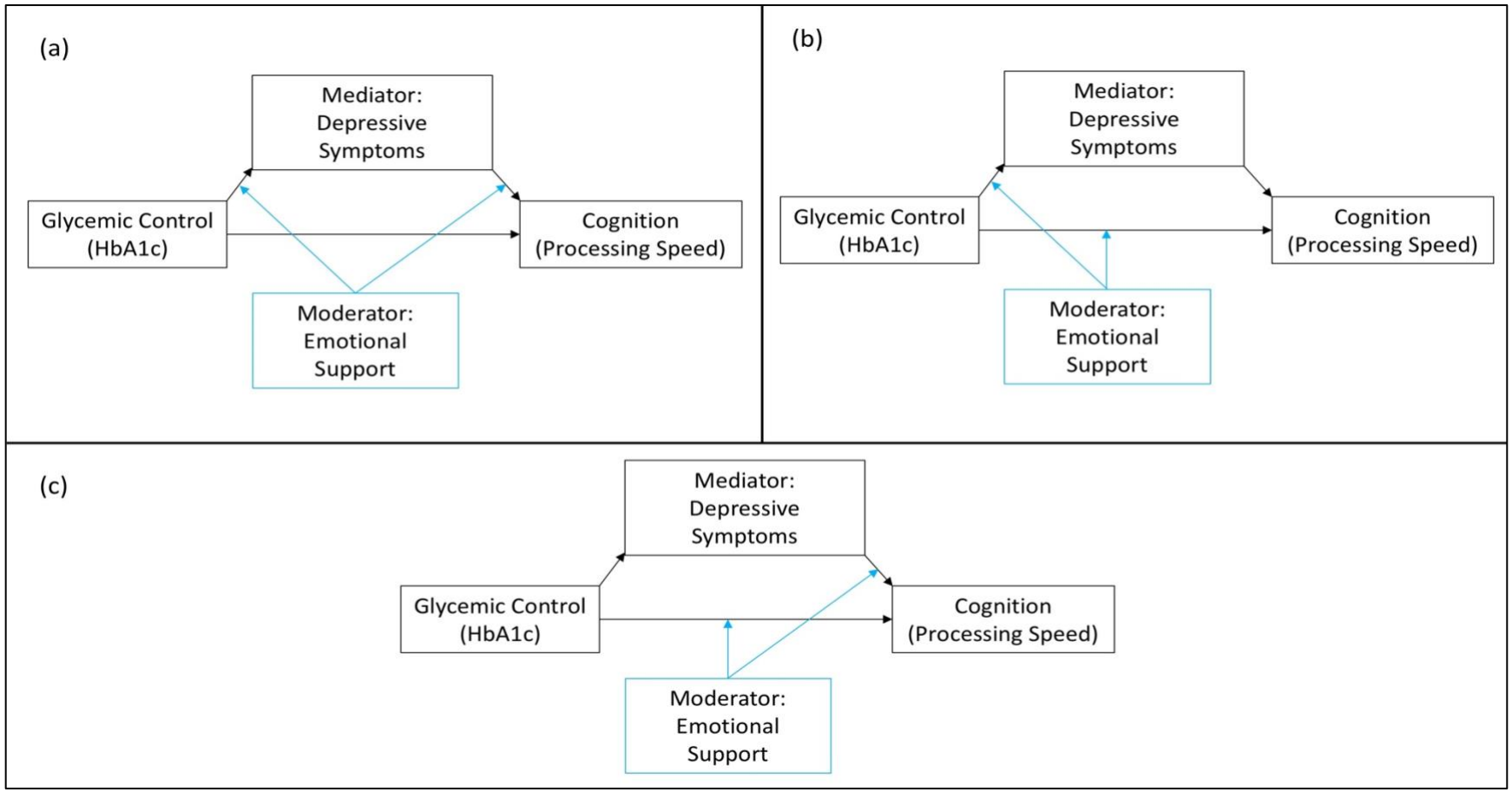
Sensitivity Analyses

A series of four sensitivity analyses was conducted to test the robustness of results. First, analyses were restricted to participants with T2D whose HbA1c levels were elevated (≥ 5.70%). Patterns of association persisted across all models in this restricted sample of 208 participants (note: primary models comprise 213 participants). Second, models adjusted for participants' self-reported chronic health conditions. Patterns of association persisted across all models in this

sample of 213 participants. Independent of HbA1c, emotional support, and all other covariates, significant covariate effects showed more chronic health conditions was associated with more depressive symptoms in the mediation and moderated mediation models. Third, models adjusted for participants' self-reported cholesterol medication use. Patterns of association persisted across all models in this sample of 208 participants. Independent of HbA1c, depressive symptoms, emotional support, and all other covariates, significant covariate effects showed a negative association between cholesterol medication use and cognition across models. Fourth, moderated mediation models tested whether emotional support simultaneously moderated (1) associations between HbA1c and depressive symptoms as well as depressive symptoms and cognition (Figure 2.6a); (2) associations between HbA1c and depressive symptoms as well as HbA1c and cognition (Figure 2.6b); (3) associations between depressive symptoms and cognition as well as HbA1c and cognition (Figure 2.6c). Patterns of association found in primary analyses persisted across all models. Of note, the PROCESS modeling system does not allow for simultaneously testing moderation of all direct and indirect paths in a mediation model.

Figure 2.6

Conceptual Models for the Three Moderated Mediation Sensitivity Analyses that Tested Moderation of Two Paths Simultaneously



Note. For simplicity, covariates are not depicted.

Discussion

The current study tested the mediating role of depressive symptoms (Aim 1) and the moderating role of emotional support (Aims 2 and 3) in the association between HbA1c and cognition in a racially and ethnically diverse sample of older adults with T2D from the Washington Heights Inwood Columbia Aging Project. Findings from the current study do not support the hypotheses for Aims 1 and 2, while there was partial support for the hypothesized moderating role of emotional support in Aim 3. Specifically, findings from this cross-sectional study show that emotional support may act as a buffer against the negative effects of depressive symptoms on cognition in older adults with T2D, independent of glycemic control. The current study suggests that emotional support may represent a target for reducing depression-related cognitive morbidity with beneficial effects to older adults with T2D.

Depressive Symptoms as a Mediator of the HbA1c-Cognition Association

In the current study, depressive symptoms did not mediate the association between HbA1c and cognition (Aim 1), contrasting previous work showing an indirect effect of cardiometabolic dysregulation on cognition via depressive symptoms (Schmitz et al., 2018). Of note, there was no statistically significant association between HbA1c and depressive symptoms whereas there was a statistical trend towards a negative association between depressive symptoms and cognition. Thus, the null mediation finding appears to be driven largely by a non-significant association between HbA1c and depressive symptoms, which differs from previous longitudinal work that prospectively linked HbA1c to depressive symptoms (Hamer et al., 2011). Of note, findings from previous studies do not provide a consistent pattern of association between HbA1c and depressive symptoms, with prior studies showing no association between HbA1c and elevated depressive symptoms (Icks et al., 2013) while others posit a bidirectional association (Golden et al., 2008;

Pan et al., 2010). Together, these inconsistencies highlight the need for additional longitudinal research to clarify patterns of associations among T2D, markers of T2D severity, and depressive symptoms, as findings may have important implications for informing clinical care of T2D in older adulthood.

Although the current study's mediation model showed a non-significant association between HbA1c and depressive symptoms, the model showed that depressive symptoms were negatively associated with cognition, although this effect did not reach statistical significance (b= -0.061, p= 0.069). A recent systematic review in older adults with T2D provides compelling evidence for the negative effect of depressive symptoms on cognition (Danna, Graham, Burns, Deschênes, & Schmitz, 2016), suggesting that a larger sample size would provide the power needed to detect a statistically significant effect. Yet, in older adults with T2D, very little is known regarding the contribution of depression symptoms to cognitive function in relation to T2D severity. Clarifying the role of depressive symptoms in pathways from T2D to cognition may inform future interventions aimed at preserving cognitive health in older adults with T2D, particular with advancing T2D progression. However, interpreting the findings from the current study's mediation model results should be done cautiously as variables were measured contemporaneously. Indeed, longitudinal research employing time lags between HbA1c, depressive symptoms, and cognitive function would provide the methodological rigor necessary to test mediation (Kraemer, Stice, Kazdin, Offord, & Kupfer, 2001; Maxwell & Cole, 2007). To that end, the first aim of Study 3 in this dissertation examines the role of depressive symptoms as a longitudinal mediator of the association between HbA1c and cognitive change in a population-based sample of older adults with T2D in the United States.

Support may not Moderate HbA1c-related Effects

In the current study, emotional support did not alter the effects of HbA1c on depressive symptoms or cognition. In contrast, findings from previous cross-sectional studies show that satisfaction with social support buffers the effect of insulin use (a marker of T2D severity) on T2D distress (Baek et al., 2014) in adults with T2D. Given prior studies suggesting HbA1c confers a stronger adverse effect on T2D distress versus depressive symptoms (e.g., Strandberg et al., 2014), future studies should examine whether support may attenuate the impact of HbA1c on T2D distress in relation to cognitive aging. The current study's findings are also inconsistent with previous work showing that social support (measured using items assessing emotional and instrumental support) attenuates the negative association between HbA1c and cognition in older adults with T2D (Okura et al., 2009). One potential explanation for the discordant results in the current study versus those in previous studies may be that different measures of support were used across studies. The current study focused on *emotional* support because it is less prone to reverse causation than other types of social support. Specifically, instrumental support refers to material support from others to carry out logistical tasks such as managing medical appointments and treatment (Cohen & Willis, 1985; House & Kahn, 1985). Thus, participants who report higher levels of instrumental or social support (which represents a composite of both emotional and instrumental support) may do so as a consequence of poor glycemic control and/or cognitive function. Ultimately, the cross-sectional design of the current study and previous studies precludes temporal inferences regarding the moderating role of support.

Support as a Buffer of the Impact of Depressive Symptoms on Cognition

The stronger negative association between depressive symptoms and cognition in older adults with low emotional support relative to those with high emotional support is consistent with the buffering model of support (Cohen & Willis, 1985). Specifically, the support buffering

framework theorizes that the negative effect of a stressor (e.g., depressive symptoms) on an outcome (e.g., cognitive function) will be attenuated or eliminated when one perceives receiving support from other people. Previous studies provide empirical support for the buffering model, including studies showing that support buffers concurrent associations between worse T2D severity (indexed by glycemic control or T2D complications/ treatment), greater T2D-specific distress (Baek et al., 2014), and poorer cognition (Okura et al., 2009). Extending on these prior investigations in T2D, the current study's findings (Aim 3) suggest that support attenuates the deleterious effects of depressive symptoms on cognition independent of glycemic control. Support may dampen the impact of depressive symptoms on cognition through various pathways, such as by increasing one's ability to cope with distress, reducing physiological (e.g., neuroendocrine) reactivity to depressive symptoms, and/or promoting healthy behaviors (Cohen & Willis, 1985). In turn, better coping skills, decreased physiological reactivity, and more frequent engagement in healthy behaviors have all been associated with better cognitive functioning (Godbout, & Johnson, 2009; Lee et al., 2009; Sartori, Vance, Slater, & Crowe, 2012; Zhu et al., 2019).

Furthermore, support may buffer against the effects of depressive symptoms on cognition as it is a means through which one may receive solutions to problems (Cohen & Willis, 1985). For instance, during conversations in which one receives support from others, friends or family members may provide potentially useful suggestions for pleasurable activities to engage in. Although these suggestions may not necessarily decrease the level of one's depressive symptoms, these solution-focused conversations may provide novel ideas to minimize the adverse cognitive consequences of depression. Indeed, obtaining solutions to one's problems from others may be especially beneficial for older adults with T2D as previous research suggests that this population

may have difficulties with engaging in effortful cognitive strategies (Wong, Scholey, & Howe, 2014), which are needed to solve problems.

Support may also represent a source of cognitive stimulation via the behaviors inherent to obtaining emotional support. For instance, in order to receive support, one typically engages in conversations, which involves verbal (and potentially visual (e.g., facial expressions and hand gestures)) communication. The ability to quickly process information is a crucial and heavily utilized component of this cognitively demanding activity (for a review, see Hickok & Small, 2015). Higher levels of perceived support likely reflect a higher frequency of engaging in thought-provoking conversations (e.g., Appendix B), entailing heightened activation of the neurocognitive processes exacted by this behavior. Consistent with the 'use it or lose it' hypothesis (Hultsch, Hertzog, Small, & Dixon, 1999), more frequent engagement in activities used to solicit and/or process emotional support may potentially lead to the preservation or improvement in cognitive functioning. Future longitudinal studies are needed to replicate findings and incorporate imaging techniques to identify the neural and cognitive correlates of conversations in which emotional support is transmitted. Nonetheless, the current study provides preliminary evidence suggesting that, in the context of psychological distress, emotional support may be targeted to maintain or improve information processing cognitive functions in older adults with T2D.

Limitations and Strengths

Primary limitations of the current study are its cross-sectional design and small sample size. Longitudinal investigations with larger sample sizes are needed to both clarify patterns of association over time and improve the methodological rigor needed for conducting mediation analyses (Kraemer et al., 2001; Maxwell & Cole, 2007). Furthermore, the relatively low prevalence of older adults with clinically significant depressive symptoms (9.9% of the current

sample had a Center for Epidemiological Studies Depression Scale score ≥ 4) contrasts with the estimated comorbidity of depression in T2D (20%; Anderson, Freedland, Clouse, & Lustman, 2001) in community samples. Future studies with more nationally representative samples may yield patterns of association similar to those documented in previous investigations. Additionally, the current study focused exclusively on depressive symptoms, which represents only one of many potential mediators linking HbA1c to cognition in T2D. Future studies should examine physiological processes such as inflammatory or oxidative stress mechanisms as emerging evidence suggests that these pathways may link diabetes to dementia (Wong, Wanrooy, & Bruce, 2018). Strengths of this study include its comprehensive set of sensitivity analyses used to assess the robustness of results. Another strength of this study is its racially and ethnically diverse sample comprising 41.2% Black and 42.3% Hispanic older adults. It is possible that differences in results found in this study versus previous studies may in part reflect the larger proportion of racial and ethnic minority older adults, though additional research is needed to empirically test this potential explanation.

Conclusion

In conclusion, this cross-sectional study of racially and ethnically diverse older adults with T2D provides preliminary evidence for the relevance of emotional support for reducing the cognitive effects of depressive symptoms independent of T2D severity. Although a longitudinal investigation is needed to replicate findings, these results are consistent with the buffering hypothesis of support (Cohen & Willis, 1985) and suggests that emotional support may represent a psychosocial resource that can be targeted to optimize cognitive health in older adults with T2D.

Chapter 3

Study 2: Homocysteine, Emotional Support, and Cognitive Outcomes in Uncontrolled T2D

Type 2 Diabetes and Cognitive Aging

Type 2 diabetes (T2D) is associated with accelerated cognitive decline (Biessels, Strachan, Visseren, Kappelle, & Whitmer, 2014) and an approximately two-fold increased risk for incident dementia (Sutherland, Lim, Srikanth, & Bruce, 2017). It has been postulated that glycemic control, for which hemoglobin A1c (HbA1c) is the gold standard measure, plays a key role in pathways leading to T2D-related poor cognitive health outcomes. For instance, chronically high levels of HbA1c or hyperglycemia, otherwise known as uncontrolled T2D (HbA1c > 8.0%), poses substantial cardiovascular disease risk (American Diabetes Association (ADA), 2019). Additionally, population-based longitudinal investigations show that uncontrolled T2D confers greater risk for dementia relative to controlled T2D (Xu et al., 2009). While some of the mechanisms underlying the greater cognitive morbidity observed in older adults with uncontrolled versus controlled T2D have been examined, they are multifactorial and not well understood.

Homocysteine in the General Older Adult Population

Growing evidence has implicated homocysteine in pathways linking T2D and chronically poor glycemic control to cognitive decline and dementia. As previously described (see Chapter 1), homocysteine is a sulfurated non-protein amino acid formed in the metabolism of methionine, which is an essential amino acid ingested from foods such as cheeses, meat, and poultry (Venes & Clarence, 2005). Although homocysteine is necessary as part of one carbon metabolism, it is toxic

to neurons and peripheral cells in blood vessels and can lead to apoptosis and DNA breakage (Lipton et al., 1997; Mattson & Shea, 2003). Furthermore, prior studies suggest that homocysteine's production of reactive oxygen species indicates that it is a mechanism and marker of oxidative stress (Loscalzo, 1996; McCuly, 1996).

With respect to its physical health effects, studies in samples of older adults unrestricted to those with T2D, homocysteine has been associated with increased risk of cardiovascular diseases, stroke, and mortality (Elkenboom et al., 1999; Ganguly & Alam, 2015; Graham et al., 1997). Of note, findings from a meta-analysis showed that reducing homocysteine levels by 25% (approximately 3 micromol/L) predicted lower risk for ischemic heart disease and stroke (11% and 19%, respectively; Homocysteine Studies Collaboration, 2002). The literature in non-T2D samples has since been expanded to show that homocysteine's adverse cardiovascular effects may also extend to cognition. A previous longitudinal study in an older adult sample prospectively linked increases in homocysteine levels with higher risk for all-cause dementia and dementia due to Alzheimer's disease (Seshadri et al., 2002), with subsequent studies replicating these associations (Blasko et al., 2008; Luchsinger et al., 2004; Ravaglia et al., 2005). Indeed, plasma homocysteine levels above 14 micromol/L has been associated with a two-fold increase in risk for dementia due to Alzheimer's disease (Seshadri et al., 2002). Findings from longitudinal studies also show a relationship between increases in homocysteine levels and declines in global cognition (Ravaglia et al., 2003) and domain-specific functions, such as executive function (Dufoil et al., 2003; Prins et al., 2002).

Homocysteine in Older Adults with Type 2 Diabetes

Previous studies in samples of older adults with T2D evidence homocysteine's adverse effects on risk of cardiovascular diseases, stroke, and mortality (Hoogeven et al., 1998; Hoogeveen

et al., 1999; Stehouwer et al., 1999). However, patterns of these associations between HbA1c and homocysteine in T2D have been inconsistent. For instance, previous studies have shown an inverse association between HbA1c and homocysteine (e.g., Mazza et al., 2005) whereas other studies suggest the opposite pattern of association (e.g., Bansal, Kapoor, Singh, & Yadav, 2016). One potential explanation for these discordant findings may be that the role of HbA1c in increasing levels of homocysteine is applicable only to individuals with poorly controlled T2D (Drzewoski et al., 2000). Together, these findings provide preliminary evidence that hyperglycemia-related increases in homocysteine, which in turn contribute to homocysteine-induced poor health outcomes, represent a unique risk to older adults with uncontrolled T2D but not to those with controlled T2D.

Substantially fewer studies have examined the association between homocysteine and cognitive aging outcomes in the context of T2D. Although the effects of homocysteine on dementia risk in T2D remain unknown, previous studies show associations between homocysteine and poorer cognitive performance in T2D (de Luis et al., 2002; Robbins et al., 2005). However, these studies utilized global cognition screening measures which have well-documented ceiling effects, and therefore may not be sensitive to age- and T2D-related cognitive changes. Given that declines in domains of processing speed, executive function, and memory in older adulthood presage a dementia diagnosis, understanding the association between homocysteine and these cognitive domains may reveal important insights to reduce cognitive morbidity in older adults with T2D.

Emotional Support and Cognitive Aging

Nonpharmacological approaches to reducing the impact of homocysteine on health outcomes may be particularly important for older adults with T2D, especially for those with uncontrolled T2D, given the significant burden of managing T2D self-care activities. Emerging

research implicates a potentially protective role for psychosocial factors, such as emotional support, in health outcomes for older adults with T2D. Emotional support, or the perception of receiving advice or empathy when needed, has been positively associated with physical and mental health outcomes in T2D (Ju et al., 2018; Strom & Egede, 201). As previously described, the buffering model of support (Cohen & McKay, 1984; Cohen & Willis, 1985) suggests that health-related stressors exert negative effects on health outcomes in those with limited support, and these effects are attenuated or eliminated in those with greater support (Cohen & McKay, 1984; Cohen & Willis, 1985). Empirical studies provide evidence for the stress-buffering effect of support on various outcomes (for a review, see Strom & Egede, 2012). One potential mechanism underlying the stress-buffering effect of emotional support on cognitive outcomes may include its potential to reduce psychological distress, and lower psychological distress is associated with better cognitive health outcomes (e.g., Almeida, Hankey, Yeap, Golledge, & Flicker, 2017; Byers & Yaffe, 2011). Another potential mechanism may involve cognitive stimulation, as activities used to obtain emotional support (e.g., thought-provoking conversations) actively recruit various cognitive processes.

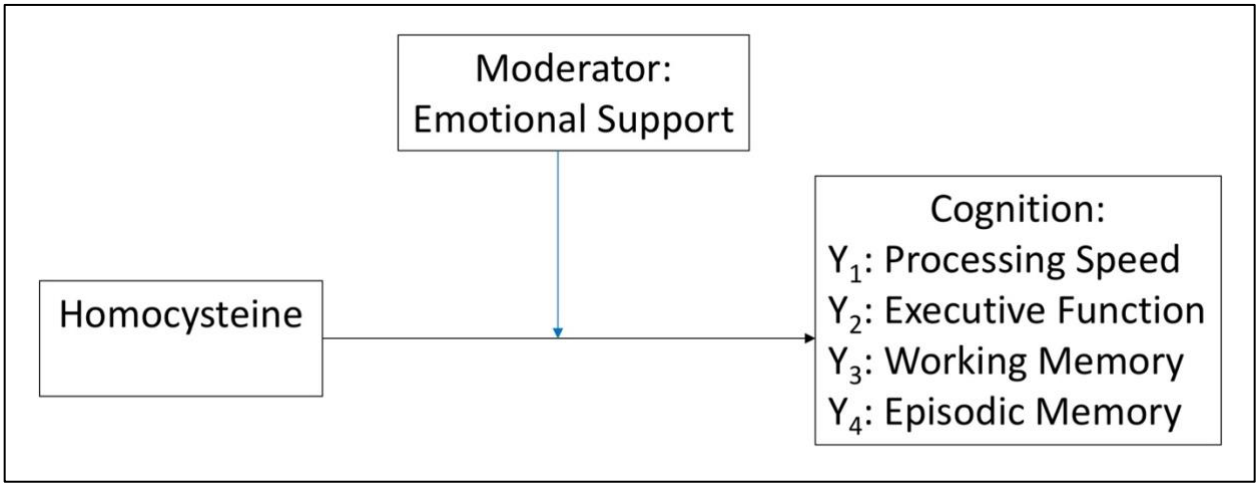
Prior studies in samples of older adults with T2D indicate that higher levels of support weaken the negative association between HbA1c and global cognition (Okura et al., 2009). Furthermore, a separate study of older adults showed a stronger negative association between T2D severity and cognition in older adults with low (versus high) family support (Strizich et al., 2016). Less is known regarding the buffering role of emotional support on cognitive outcomes in older adults with uncontrolled T2D. The inherent medical complexity of uncontrolled T2D suggests that older adults with chronically poor glycemic control may have a greater need for support relative to their controlled T2D counterparts. Support has been shown to promote coping skills and self-

efficacy related to diabetes management behaviors (Ikeda & Shimazawa, 2019; Shao et al., 2017), and such behaviors are especially important for effectively managing uncontrolled T2D. In addition to a greater need for support, the complexity and consequences of uncontrolled T2D may reduce access to support. Uncontrolled T2D is typically accompanied by T2D-related complications such as amputations, retinopathy, and neuropathy (ADA, 2019). The mobility and sensory (e.g., vision) difficulties associated with these complications may significantly reduce opportunities for socialization activities in which emotional support can be accessed. Older adults with uncontrolled T2D may also be more sensitive to potential protective factors such as support because they are at particularly high risk for cognitive impairment.

The Current Study

Using a sample of older adults with uncontrolled T2D, the overall goal of the cross-sectional study is to examine associations among homocysteine, emotional support, and cognitive functioning via the following two aims. First, the study aims to examine the associations of homocysteine with processing speed, executive function, working memory, and episodic memory, hypothesizing that homocysteine would be negatively associated with each of the cognitive domains (Figure 3.1). Second, the study aims to examine the role of emotional support as a moderator of the associations between homocysteine and cognitive function, hypothesizing that lower levels of emotional support would result in stronger negative associations between homocysteine and cognitive function (Figure 3.1).

Figure 3.1
Conceptual Model for Study 2



Note. Aim 1 examines independent associations between homocysteine and four cognitive domains (black arrow). Aim 2 examines emotional support as a moderator of homocysteine-cognition associations (blue arrow). For simplicity, covariates are not depicted.

Method

Participants and Procedure

Participants comprised older adults recruited from the Southeastern Michigan region, primarily from University of Michigan clinics and research registries. Participants were enrolled if they were between 65 and 75 years old, had a T2D diagnosis with their most recent HbA1c level at 8.0% or higher, and self-reported non-Hispanic Black or White racial background. Eligibility criteria are provided in Appendix C. All participants provided written informed consent, and the study was approved by the University of Michigan Medical School Institutional Review Board.

Twenty-nine participants underwent physical health and cognitive assessments as well as a clinical interview at the Michigan Clinical Research Unit within Michigan Medicine. Physical health assessments (i.e., blood draw) were conducted by nursing staff. The clinical interview and cognitive assessments were conducted by trained research staff.

Measures

Outcomes

Processing Speed and Executive Function. The Trail-Making Test (henceforth referred to as "Trails") comprises two subtests (A and B). Trails A was used to measure processing speed, and Trails B was used to measure executive function. The tests were administered using the National Alzheimer's Coordinating Center procedures. Briefly, Trails A requires participants to connect numbers (1 to 25) in ascending order as quickly and accurately as possible. Trails B requires participants to connect a sequence of ascending numbers and letters in alternating order (i.e., 1-A-2-B-…) as quickly and accurately as possible. Z-scores for both tests were computed using means and standard deviations from the study sample and multiplied by -1 so that higher scores reflect better performance.

Working memory. Working memory was assessed using the Backward Number Span test from the National Alzheimer's Coordinating Center Uniform Data Set cognitive battery. Briefly, participants hear a sequence of numbers and are required to immediately repeat the numbers in reverse order. Number sequences range from a span of two to eight digits, with two trials administered per each sequence length (e.g., two trials for the two-span sequence and two trials for the three-span sequence). Participants who correctly responded to at least one of the two trials for a given number sequence length are administered the next sequence of numbers. Scores represent the sum of all correct trials. Z-scores were computed using means and standard deviations from the study sample.

Episodic memory. Episodic memory was assessed using the Hopkins Verbal Learning Test (Brandt, 1991), which is a word list-learning task comprising three learning trials, one delayed free recall trial administered after a 20-minute delay, and one recognition trial administered immediately after delayed recall. The list includes 12 words, with 4 words from each of three

semantic categories. The test has been shown to have good construct and content validity (Shapiro, Benedict, Schretlen, & Brandt, 1999). Performance across the three learning trials was summed to compute an immediate recall score. Z-scores for the immediate recall, delayed recall, and recognition trials were computed using means and standard deviations from the current sample. An episodic memory composite was calculated by averaging z-scores from the immediate, delayed, and recognition trials.

Exposure

Homocysteine. Homocysteine is blood-based biological marker of risk for cardiovascular dysfunction. Venous blood samples were drawn under fasting conditions. Data from participants who self-reported not fasting prior to the study appointment (n=4) or did not have a blood sample to analyze (n=2) were excluded from the current study. Thus, the current study's analytical sample comprised 23 participants. Plasma total homocysteine was assayed using the chemiluminescent enzyme immunoassay method by the Department of Pathology at Michigan Medicine (population-determined reference range: 5-15 micromol/L). Based on Michigan Medicine's Department of Pathology clinical interpretation guidelines, there is a gradual increase in cardiovascular disease risk as homocysteine levels increase above 11 micromol/L. Consistent with previous studies (e.g., Seshadri et al., 2002), homocysteine was log transformed prior to statistical analyses.

Moderator

Emotional Support. Emotional support was operationalized using participants' responses to one question querying the perceived level of support from four potential relationship categories: spouse/partner, child(ren), other relatives, and friends, as applicable. Responses ranged from 1 (*Never*) to 4 (*Always*) and averaged across all applicable (up to four) relationship categories. Higher scores correspond to a higher level of support.

Covariates

Age was participants' self-reported age in years. Self-reported sex/gender was dichotomized, with male as the reference category. Education was participants' self-reported years of education (0-20). Self-reported race was dichotomized (non-Hispanic Black, non-Hispanic White), with non-Hispanic White as the reference category.

Analytic Strategy

Analyses were conducted using SPSS Version 26 (IBM Corp., Armonk, NY). To test Aim 1, separate linear regressions estimated the association between homocysteine and each of the cognitive outcome variables, adjusting for covariates. To test Aim 2, the PROCESS modeling system (Hayes, 2018; Hayes & Rockwood, 2017) was used to examine the role of emotional support as a moderator of associations between homocysteine and the cognitive outcomes. Variables were mean centered as statistically appropriate.

Results

Participant characteristics for the 23 older adults included in the analytical sample are provided in Table 3.1. Briefly, participants were, on average, 69 years old, had approximately 16 years of education, and average (non-transformed) homocysteine levels were clinically elevated (14.38 ±9.77 micromol/L). The sample comprised 50% women and 25% Black older adults. Bivariate correlations between homocysteine, emotional support, depressive symptoms, cognitive variables are provided in Table 3.2.

Table 3.1
Participant Characteristics

Variable	Value	Sample Range
Age (years)	68.50 (2.93)	65-74
Education (years)	15.79 (3.16)	9-20
% Female/Woman	50.00	
% Black	25.00	
Homocysteine (micromol/L)	14.38 (9.77)	7-57
Homocysteine (Log Transformed)	1.11 (0.18)	0.85-1.76
Emotional Support	2.85 (0.68)	2-4
Depressive Symptoms	3.96 (3.41)	0-14
Processing Speed (raw score; seconds)	32.78 (10.62)	19.00-61.08
Executive Function (raw score; seconds)	101.83 (58.68)	51-300
Working Memory (raw score)	6.57 (2.04)	3-11
Episodic Memory: Learning Trials (raw score)	23.33 (4.49)	17-31
Episodic Memory: Delayed Trial (raw score)	7.38 (2.41)	3-12
Episodic Memory: Recognition Trial (raw score)	10.39 (1.83)	5-12

Note. Values presented are percentages or means with standard deviations in parentheses.

Table 3.2
Bivariate Correlations between Homocysteine, Emotional Support, Depressive Symptoms, and Cognitive Outcomes

	Emotional Support	Depressive Symptoms	Processing Speed	Executive Function	Working Memory	Episodic Memory
Homocysteine	0.160	-0.109	0.036	-0.623**	-0.540**	-0.155
Emotional Support		-0.095	-0.184	-0.214	-0.252	-0.088
Depressive Symptoms			0.072	0.025	0.070	-0.126
Processing Speed				0.370	0.282	0.266
Executive Function					0.525*	0.591**
Working Memory						0.461*

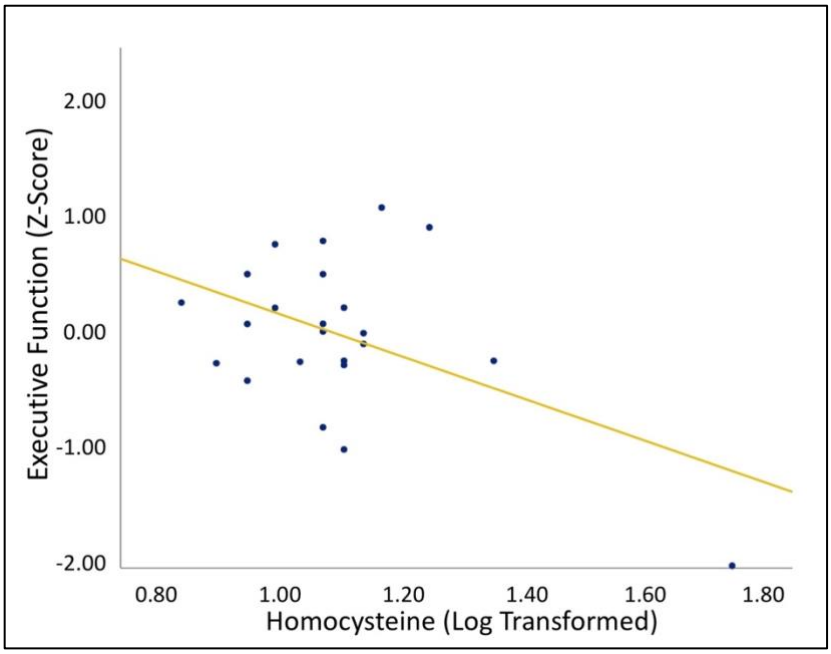
*p< 0.05. **p<0.01.

Results from Aim 1 showed that higher levels of homocysteine were associated with lower scores on measures of executive function (b= -3.035, SE=0.904, p=0.004; Figure 3.2) and working memory (b= -3.386, SE= 1.206, p= 0.012; Figure 3.3). There were no statistically significant associations of homocysteine with processing speed (b= -0.041, SE=1.358, p=0.976) or episodic

memory (*b*= -0.589, SE=0.990, *p*=0.559). Model estimates and summary statistics are provided in Table 3.3. Analyses repeated using raw (i.e., non- log transformed) values of homocysteine showed a similar pattern of associations albeit with large effect sizes. Analyses excluding a potential outlier score showed a similar pattern of associations. Results from Aim 2 showed that associations between homocysteine levels and cognitive outcomes did not vary by level of emotional support (Table 3.4).

Figure 3.2

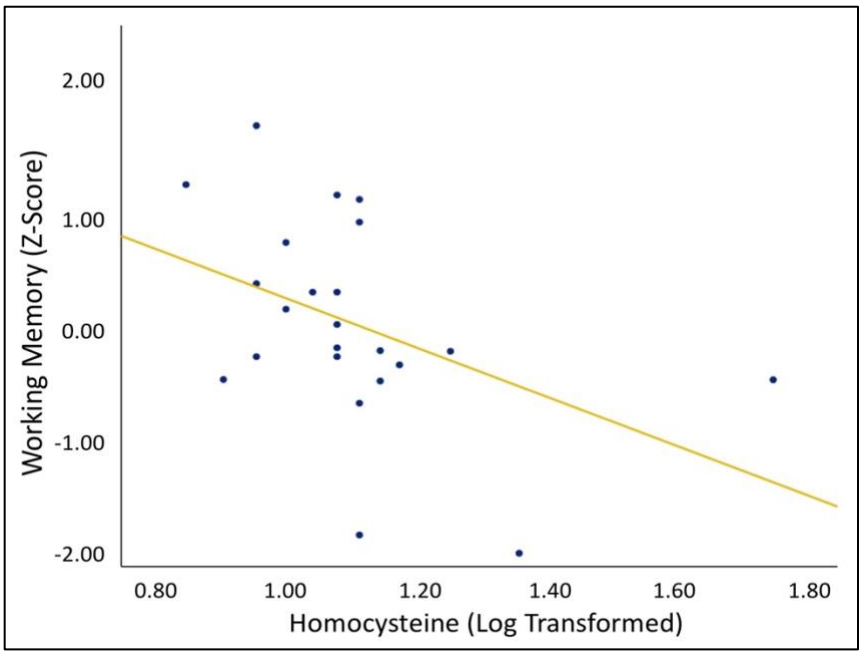
Scatterplot Showing the Negative Association between Homocysteine and Executive Functioning Performance



Note. Executive function (z-score) was residualized for covariates.

Figure 3.3

Scatterplot Showing the Negative Association between Homocysteine and Working Memory Performance



Note. Working memory (z-score) was residualized for covariates.

Table 3.3.
Model Estimates for Associations between Homocysteine and Cognitive Outcomes

Outcome: Executive Function (Trails B)							
	b	*SE b*	β	*t*	*p*	R^2_{adj}	*F*
Model Summary Statistics						0.278	2.767
Constant	3.792	3.215		1.179	0.254		
Age	-0.036	0.048	-0.126	-0.738	0.471		
Black Race	-0.593	0.375	-0.295	-1.581	0.132		
Female/ Woman	0.384	0.321	0.232	1.199	0.247		
Education	0.133	0.048	0.504	2.75	0.014		
Homocysteine	-3.035	0.904	-0.652	-3.355	0.004		
Outcome: Working Memory (Backwards Number Span)							
	b	*SE b*	β	*t*	*p*	R^2_{adj}	*F*
Model Summary Statistics						0.350	3.369
Constant	0.644	4.288		0.150	0.882		
Age	0.01	0.064	0.031	0.157	0.877		
Black Race	-0.282	0.500	-0.121	-0.564	0.58		
Female/ Woman	0.304	0.427	0.158	0.711	0.487		
Education	0.150	0.065	0.489	2.318	0.033		
Homocysteine	-3.386	1.206	-0.628	-2.808	0.012		
Outcome: Processing Speed (Trails A)							
	b	*SE b*	β	*t*	*p*	R^2_{adj}	*F*
Model Summary Statistics						-0.038	0.839
Constant	0.960	4.827		-0.199	0.845		
Age	-0.006	0.073	-0.021	-0.085	0.934		
Black Race	-0.699	0.563	-0.338	-1.242	0.231		
Female/ Woman	0.787	0.481	0.460	1.635	0.120		
Education	0.082	0.073	0.301	1.131	0.274		
Homocysteine	-0.041	1.358	-0.009	-0.03	0.976		
Outcome: Episodic Memory (Hopkins Verbal Learning Test-Revised)							
	b	*SE b*	β	*t*	*p*	R^2_{adj}	*F*
Model Summary Statistics						0.278	2.767
Constant	-1.699	3.438		-0.494	0.627		
Age	0.003	0.052	0.010	0.051	0.960		
Black Race	-0.507	0.389	-0.291	-1.303	0.209		
Female/ Woman	0.039	0.345	0.026	0.113	0.911		
Education	0.142	0.053	0.583	2.702	0.015		
Homocysteine	-0.589	0.990	-0.139	-0.596	0.559		

Note. SE=standard error. R^2_{adj} = adjusted R^2.

Table 3.4

Model Estimates for the Interaction between Homocysteine and Emotional Support on Cognitive Outcomes

Outcome	Effect	*b*	*SE*	*p*	LLCI	ULCI
Executive Function (Trails B)						
	Homocysteine	-2.744	1.068	0.021	-5.021	-0.467
	ES	0.507	1.319	0.706	-2.304	3.318
	Homocysteine x ES	-0.586	1.254	0.647	-3.259	2.088
Working Memory (Backwards Number Span)						
	Homocysteine	-2.367	1.312	0.090	-5.174	0.440
	ES	2.187	1.623	0.199	-1.279	5.652
	Homocysteine x ES	-2.283	1.546	0.160	-5.580	1.013
Processing Speed (Trails A)						
	Homocysteine	1.139	1.431	0.438	-1.911	4.189
	ES	2.346	1.767	0.204	-1.420	6.112
	Homocysteine x ES	-2.540	1.680	0.151	-6.121	1.042
Episodic Memory (Hopkins Verbal Learning Test-Revised)						
	Homocysteine	0.235	1.115	0.836	-2.130	2.600
	ES	2.091	1.386	0.151	-0.847	5.029
	Homocysteine x ES	-2.026	1.318	0.144	-4.820	0.768

Note. ES=emotional support. LLCI=95% confidence interval lower limit. SE=standard error. ULCI=95% confidence interval upper limit.

Discussion

This study of older adults with uncontrolled T2D shows that, in the context of chronic hyperglycemia, higher levels of homocysteine are associated with worse executive functioning and working memory performance but not with processing speed and episodic memory, which partially supports the first hypothesis. The second hypothesis was not supported, as levels of emotional support did not moderate homocysteine-cognition associations. Together, these findings suggest that elevations in homocysteine levels may have deleterious impacts on frontally-mediated cognitive functions, and additional research is needed to identify psychosocial factors that can be targeted to buffer against the potentially harmful cognitive effects of homocysteine.

Homocysteine Associations with Different Cognitive Domains

The negative associations of homocysteine with executive function and working memory are in line with previous studies that suggest homocysteine confers adverse effects on cognitive health outcomes in older adults. Specifically, previous studies link increases in homocysteine to heightened risk for dementia (Seshadri et al., 2002) and poor cognitive function (Dufoil et al., 2003; Prins et al., 2002; Ravaglia et al., 2003) in community-based samples of older adults, with very few studies examining associations in T2D. In a sample of older adults with T2D, de Luis and colleagues (2002) showed a negative association between homocysteine levels and cognitive performance measured using a global dementia screening instrument, with a separate study replicating this pattern of association (Robbins et al., 2005). Extending on previous investigations, the current study utilized well-established neuropsychological measures to assess four separate cognitive domains, as these tests have greater sensitivity to detect cognitive abilities in older adulthood compared with global cognitive screening tests. Furthermore, the current study's findings suggest that higher levels of homocysteine may contribute to poor executive function and working memory rather than to an overall impairment in cognitive abilities. Although these findings warrant replication, the cognitive effects of elevations in homocysteine may subsequently manifest as difficulties in everyday activities that require complex and/or multi-step tasks. For older adults with uncontrolled T2D, poor executive functioning and working memory might portend difficulties with managing the complex demands of T2D self-care activities.

The negative associations of homocysteine with executive function and working memory but not with processing speed or episodic memory is generally consistent with previous findings on cardiovascular effects on cognition in T2D. Specifically, prior studies suggest that higher levels of homocysteine are associated with greater cardiovascular risk and cardiovascular disease in T2D

(Lei et al., 2018; Nygard et al., 1995). Of note, findings from a meta-analysis of studies (not restricted to T2D samples) showed that a 25% reduction of homocysteine level (approximately 3 micromol/L) was associated with 11% lower ischemic heart disease risk and 19% lower stroke risk (Homocysteine Studies Collaboration, 2002). In turn, increases in cardiovascular risk and cardiovascular diseases are associated with stronger effects on frontally mediated executive functions rather than hippocampal-dependent memory function in older adults (Aljondi et al., 2020; Leritz et al., 2011).

The adverse health effects of homocysteine occur via oxidative-redox stress processes, including the auto-oxidation of homocysteine, formation of homocysteine mixed disulfides, protein homocysteinylation, and interaction of homocysteine thiolactones (Blom, 2000; Tyagi & Hayden, 2004; Jakubowski, Zhang, Bardaguez, & Aviv, 2000; Misra, 1974). Indeed, homocysteine's production of reactive oxygen species contributes to reduced insulin secretory responsiveness and cell apoptosis (Patterson, Flatt, Brennan, Newsholme, & McClenaghan, 2006; Scullion et al., 2012). Thus, homocysteine's toxic effects on both neuronal cells as well as the vascular endothelial cells supporting cerebrovascular function heighten risk for white matter lesions and likely explain its effect on poor cognitive outcomes (Currò et al., 2014; Ganguly & Alam, 2015).

According to the 'vascular hypothesis of cognitive aging' (Spiro & Brady, 2008), cardiovascular dysfunction largely impacts cognitive functions supported by frontal regions (Jellinger, 2013; Kling, Tojanowski, Wolk, Lee, & Arnold, 2013; van den Berg, Kloppenborg, Kessels, Kappelle, & Biessels, 2019). Furthermore, prior studies in non-T2D-specific samples show that homocysteine poses greater risk for vascular dementia versus dementia due to Alzeimer's disease (e.g., Seshadri et al., 2002). Indeed, the current study observed larger effects

of homocysteine on measures of executive function and working memory (β= -0.652 and β= -0.628, respectively) relative to those on processing speed and episodic memory (β= -0.009 and β= -0.139, respectively). This finding suggests that a larger sample size is needed to test the associations between homocysteine and processing speed as well as episodic memory. Of note, however, the current study's finding showing a small association between homocysteine and processing speed was unexpected and is inconsistent with previous findings showing cardiovascular dysfunction diminishes processing speed (for a meta-analysis, see Vasquez & Zakzanis, 2015). One potential explanation is that Trails A (used in the current study to measure processing speed) is less cognitively demanding compared with tests used by other studies. For instance, previous studies linking cardiovascular dysfunction to slower processing speed have utilized tests such as the Weschler Adult Intelligence Scale – Digit Symbol Coding Test and Letter-Number Matching (Vasquez & Zakzanis, 2015), which may require a higher degree of visual attention and working memory as well as more complex motor functions. Additional research on homocysteine's effects on various cognitive domains may reveal important insights into mechanisms underlying T2D-related cognitive decrements. In particular, the finding that homocysteine-cognition associations were largest for executive function and working memory point to vascular-related frontal lobe dysfunction as a potential pathway leading to the higher dementia risk documented in older adults with uncontrolled T2D versus well-controlled T2D (Xu et al., 2009).

Support may not Moderate Homocysteine Effects on Cognition in Uncontrolled T2D

Emotional support did not alter associations between homocysteine and cognitive function in the current study. In contrast, findings from previous cross-sectional studies show that other dimensions of support, including family support (Strizich et al., 2016) and social support (Okura

et al., 2009), attenuate the negative association between HbA1c and cognition in older adults with T2D. One potential explanation for the discordant results in the current study versus previous studies may be that the current study was not adequately powered to detect emotional support moderation effects. Another potential explanation may be that the variables utilized across studies differ. For instance, the current study examined the moderating role of emotional support (rather than social support or family support, as higher levels of the latter support dimensions may be a consequence of T2D disease progression and/or lower cognition, as described in Chapters 1 and 2). Furthermore, the current study examined the role of emotional support in attenuating the negative association between homocysteine and cognition rather than HbA1c and cognition. Although both homocysteine and HbA1c are blood-based biological markers that reflect cardiovascular risk, the potential contribution of emotional support to modulating their effect on cognition may vary. For instance, in the context of uncontrolled T2D, higher levels of emotional support may facilitate greater T2D self-care behaviors such as more frequent physical activity, which may attenuate the impact of HbA1c on cognition to a greater degree than that for homocysteine on cognition. However, given the dearth of research on the conditional effect of homocysteine on cognition as a function of support, additional research with larger sample sizes is needed to clarify the current study's null findings.

Another potential explanation for the null finding showing no emotional support moderation may be related to the psychological distress reduction mechanism theorized to underlie the buffering effects of support (Cohen & McKay, 1984; Cohen & Wills, 1985). In the current study, homocysteine was not significantly associated with depressive symptoms (r= -0.11). Although prior studies suggest homocysteine increases depressive symptoms in non-T2D samples (Almeida et al., 2008; Folstein et al., 2007), it is unclear whether this association can be extended

to older adults with T2D, as both homocysteine levels and depressive symptoms may differ as a function of T2D (Agulló-Ortuño et al., 2002; Anderson et al., 2001; Folsom et al., 1998; Katon, 2010). Furthermore, in the current study, depressive symptoms were not associated with cognitive function ($-0.13 \leq rs \leq 0.07$), which is inconsistent with previous findings showing depression-related risk for poor cognitive outcomes in T2D (Katon et al., 2012). Of note, the current study's small sample size suggests that additional research utilizing larger sample sizes is needed to replicate findings and identify psychosocial factors that may attenuate the potentially deleterious effects of homocysteine on cognitive aging outcomes.

Limitations and Strengths

As previously described, a primary limitation of the current study is its small sample size, which may have limited power to detect effects. Furthermore, the current study's cross-sectional design limits interpretation regarding directions of effects among variables. Of note, however, prior longitudinal studies in community samples of older adults show a prospective link between higher levels of homocysteine and worse subsequent cognitive health outcomes (Dufoil et al., 2003; Prins et al., 2002; Ravaglia et al., 2003; Seshadri et al., 2002). Another limitation is that the current study's clinical sample recruited primarily from the University of Michigan health system limits the generalizability of results to community-dwelling older adults as well as those in other geographic regions. Longitudinal studies with larger and more population-representative samples are needed to replicate and extend observed patterns of association in the current study. Strengths of this study include its use of well-established neuropsychological measures in order to assess four separate domains of cognitive function, which allowed for an examination into the nature of cognitive effects most strongly impacted by homocysteine. Furthermore, the current study's focus on a sample of older adults with uncontrolled T2D addresses an important gap in the literature

regarding potential explanations for the significantly higher dementia risk among older adults with well-controlled versus uncontrolled T2D (Xu et al., 2009).

Conclusion

In conclusion, this cross-sectional study of older adults with uncontrolled T2D provides preliminary evidence for the potentially adverse effects of homocysteine on executive function and working memory. Observed associations suggest that emotional support may not buffer against the impact of homocysteine on cognition in uncontrolled T2D. Nonetheless, for older adults with uncontrolled T2D, elevations in homocysteine may potentially erode frontal lobe function and contribute to nontrivial difficulties in everyday life related to managing the comprehensive treatment demands of T2D. Longitudinal studies are needed to replicate these findings and identify other potential psychosocial factors that may be targeted to reduce the significant T2D-related cognitive health morbidity in older adulthood.

Chapter 4

Study 3: Hyperglycemia Effects on Episodic Memory Decline are Longitudinally Mediated by Depressive Symptoms and Attenuated by Emotional Support

effect of emotional support on depressive symptoms may be its contribution to psychological well-being (Cohen & Willis, 1985). Separately, emotional support may facilitate greater coping skills, which in turn may dampen physiological stress reactivity (Cohen & Willis, 1985), thereby decreasing depression-related poor cognitive function. Furthermore, emotional support may lower the impact of HbA1c on cognition through reduced physiological stress activation. Additionally, emotional support may attenuate the impact of T2D severity on cognition via cognitive stimulation. Specifically, activities used to obtain emotional support (e.g., thought-provoking conversations) actively recruit various cognitive processes, including memory, and may therefore represent cognitively demanding tasks. Notably, to date, little is known regarding the potential long-term stress-buffering effects of emotional support, as most prior studies have been limited to cross-sectional and short-term intervention studies (e.g., Okura et al., 2009). Examining the role of emotional support as a moderator of longitudinal cognitive outcomes may yield evidence that can inform interventions aimed at reducing T2D-related cognitive morbidity in older adulthood.

The Current Study

Using a sample of older adults with T2D from the U.S.-wide Health and Retirement Study, the overall goal of the current study is to examine whether longitudinal associations between glycemic control and memory changes are linked by depressive symptoms and altered by

emotional support via the following two aims. First, this study aims to test the role of depressive symptoms as a longitudinal mediator of the prospective association between HbA1c and subsequent memory change (Figure 4.1), hypothesizing that increases in depressive symptoms will at least partially mediate the negative effect of HbA1on six-year changes in memory. Second, the study aims to examine the role of emotional support as a moderator of the associations described in Aim 1 (Figure 4.1). The hypotheses are that, relative to lower levels of emotional support, higher levels of emotional support would result in weaker cross-sectional and longitudinal associations between (1) higher HbA1c and more depressive symptoms, (2) more depressive symptoms and worse memory, and (3) higher HbA1c and worse memory independent of depressive symptoms.

Method

Participants and Procedure

The HRS is a population-based, nationally representative study of adults aged 51 years and older in the US who have been followed since 1992 and interviewed biennially (Sonnega & Weir, 2014). Details of the HRS longitudinal panel design, sampling methodology, and all assessment instruments are available on the HRS website (http://hrsonline.isr.umich.edu). In 2006, the HRS initiated an enhanced face-to-face interview, which comprised psychosocial and blood-based biological data collection from a random one-half of participants (referred to as 'Sample A'; Tables 4.1 and 4.2). In 2008, the other half of the study sample were selected to participate (referred to as 'Sample B'; Tables 4.1 and 4.2). Participants completed a follow-up enhanced face-to-face interview four years later (i.e., 2010 for Sample A and 2012 for Sample B).

Table 4.1
HRS Sampling Design for Variables of Interest

Variable	2006	2008	2010	2012	2014
HbA1c (Exposure)	Sample A	Sample B	-	-	-
Depressive Symptoms (Mediator)	Samples A+B	Samples A+B	Samples A+B	Samples A+B	-
Emotional Support (Moderator)	Sample A	Sample B	Sample A	Sample B	-
Episodic Memory (Outcome)	Samples A+B	Samples A+B	Samples A+B	Samples A+B	Samples A+B

Note. HbA1c=hemoglobin A1c.

Data from Samples A and B were combined to maximize sample size and included a single time point for the exposure variable (HbA1c, described below), two time points for the mediator variable (depressive symptoms, described below), two time points for the moderator variable (emotional support, described below), and three time points for the outcome variable (episodic memory, described below). Details regarding data combination are provided in Tables 4.1 and 4.2. Participants were included if they: (1) participated in the 2006 or 2008 blood-based biological substudy of the HRS, (2) self-reported diagnosis of T2D, and (3) had non-normal HbA1c (≥ 5.7%; details provided below under "Exposure") at the current study's baseline (i.e., Time 1). All participants provided written informed consent, and all study procedures were approved by the University of Michigan institutional review board.

Table 4.2
Data Combination for Study 3

Data Characteristic	Exposure: HbA1c	Mediator: Depressive Symptoms	Moderator: Emotional Support	Outcome: Episodic Memory
T1	2006 (A) & 2008 (B)	2006 (A) & 2008 (B)	2006 (A) & 2008 (B)	2006 (A) & 2008 (B)
T2		2010 (A) & 2012 (B)	2010 (A) & 2012 (B)	2010 (A) & 2012 (B)
T3				2012 (A) & 2014 (B)
Number of data points per participant	One	Two	Two	Three

Note. A=Sample A in the HRS. B=Sample B in the HRS. T1=Time 1 (2006/2008; baseline). T2=Time 2 (2010/2012; 4 years after baseline). T3=Time 3 (2012/2014; 6 years after baseline).

Measures

Outcome

Memory. Although processing speed is one of the primary cognitive domains implicated in studies of T2D (Ganmore & Beeri, 2018; see Study 1), the HRS has not routinely included a measure of processing speed. Therefore, episodic memory was selected as the cognitive performance measure because it is sensitive to age- and T2D-related cognitive decline and is a well-documented primary determinant of dementia risk (Backman, Small, & Fratiglioni, 2001). Furthermore, preliminary research suggests that chronically elevated glucose levels may lead to neurodegeneration and reduced memory performance (Marden et al., 2017; van Bussel et al., 2016). Episodic memory in the HRS is assessed biennially with a list-learning task, which is routinely used to assess episodic memory (Lezak, 1995; Rabin, Barr, & Burton, 2005). In the HRS, participants hear a list of 10 words (nouns) and recall the words immediately and after a 5-minute delay. Z-scores were calculated from raw scores on the immediate and delayed trials using means

and standard deviations from the current study's baseline in the combined sample (2006 and 2008; Time 1). Episodic memory composites were computed by averaging z-scores from the immediate and delayed trials.

The current study utilized three time points of episodic memory data obtained over six years (Tables 4.1 and 4.2). That is, participants' Time 1 memory score corresponded to their memory performance in either 2006 or 2008, depending on when their HbA1c and psychosocial questionnaire data were collected. Participants' Time 2 memory score was obtained four years later (i.e., in 2010 for data collected in 2006 and 2012 for data collected in 2008) and Time 3 was two years after Time 2 (2012/2014).

Exposure

Glycemic control. As previously described, HbA1c is a well-established index of glycemic control and is a stable, two- to three-month, marker of circulating glucose levels used to diagnose T2D and monitor disease progression (American Diabetes Association (ADA), 2019). The ADA (2019) has established guidelines for diagnosing T2D based on levels of HbA1c (normal: <5.70%, pre-diabetes: 5.70-6.49%; diabetes: ≥ 6.50%). In the HRS, HbA1c was measured in capillary blood via a dried blood spot. A detailed description of HbA1c collection and assay procedure have been previously described (Crimmins et al., 2013). Based on HRS recommendations, the current study utilized HbA1c values equivalent to values obtained from venous blood in the National Health and Nutrition Examination Survey. In line with previous research in the HRS that examined the association between HbA1c and longitudinal memory function (Marden et al., 2017), primary models utilized one time point of HbA1c (Tables 4.1 and 4.2), but follow-up analyses incorporated an additional time point of HbA1c (see Sensitivity Analyses). Participants were included in primary analyses if they self-reported a T2D diagnosis and had non-normal (i.e., elevated) HbA1c

(≥ 5.70%; ADA, 2019) at Time 1. Follow-up sensitivity analyses included participants who did not self-report a T2D diagnosis but had non-normal levels of HbA1c (i.e., HbA1c ≥ 5.70%) as well as participants who reported a T2D diagnosis but who no longer met the primary diagnostic criterion for pre-T2D or T2D (i.e., HbA1c < 5.70%).

Mediator

Depressive Symptoms. Depressive symptoms were assessed with eight items from the Center for Epidemiologic Studies Depression scale (Radloff, 1977). In the HRS, items were modified for a yes/no format and administered by HRS research staff. The current study included two time points of depressive symptoms (Time 1 in 2006/2008 and Time 2 in 2010/2012), which were assessed four years apart, and modeled as continuous variables. Higher scores correspond to more depressive symptoms. In the HRS, a score of three or higher suggests clinically significant depressive symptoms, with prior studies showing that this cutoff has a sensitivity of 71% and a specificity of 79% in comparison to "true cases" identified using the World Health Organization's Composite International Diagnostic Interview (Steffick et al., 2000; Turvey Wallace, & Herzog, 1999).

Moderator

Emotional support. Emotional support was operationalized using participants' responses to four items querying the level of support received from four potential relationship categories: spouse/partner, child(ren), other relatives, and friends, as applicable. The HRS selected these questions from a well-established assessment of emotional support in health research (Schuster, Kessler, & Aseltine, 1990) and equivalent items have been used in other, population based longitudinal studies in the US (e.g., Midlife in the United States) and Europe (e.g., English Longitudinal Study of Aging). In the HRS, Cronbach's alpha for these items across the four

relationship categories for all four waves (2006 to 2012) of data collected was adequate (range: 0.76-0.81).

Responses were coded from 1 (*Not at all*) to 4 (*A lot*). Items were scored according to HRS scoring guidelines and have been described elsewhere (Smith, Ryan, Fisher, Sonnega, & Weir, 2017). Briefly, responses across the four items were averaged for all applicable (up to four) relationship categories. For a given relationship category, data with two or more missing responses were coded as missing. The final score was computed by averaging scores across applicable relationship categories. The current study included two time points of emotional support assessed four years apart (Time 1 in 2006/2008 and Time 2 in 2010/2012). Higher scores correspond to a higher level of emotional support.

Covariates

All covariates correspond to data obtained at Time 1 (2006/2008). Age was participants' age in years. Sex/gender was dichotomized, with male as the reference category. Education was participants' self-reported years of education (0-17). Wealth was the sum of assets (e.g., stocks, bonds) minus debts (e.g., loans, mortgages). Race and ethnicity were dummy-coded into mutually exclusive categories (non-Hispanic Black, Hispanic of any race, and non-Hispanic "other" race), with non-Hispanic White as the reference group. Chronic disease burden was the sum of the following self-reported diagnoses: arthritis, hypertension, lung disease, cancer, and heart problems. Medication adherence to prescription medications was assessed with the question "Do you regularly take your prescription medication?" and self-reported responses (yes/no) were dummy-coded. Time 1 biomarker and psychosocial questionnaire completion year (2006 or 2008) was dummy-coded, with 2006 as the reference category.

Analytic Strategy

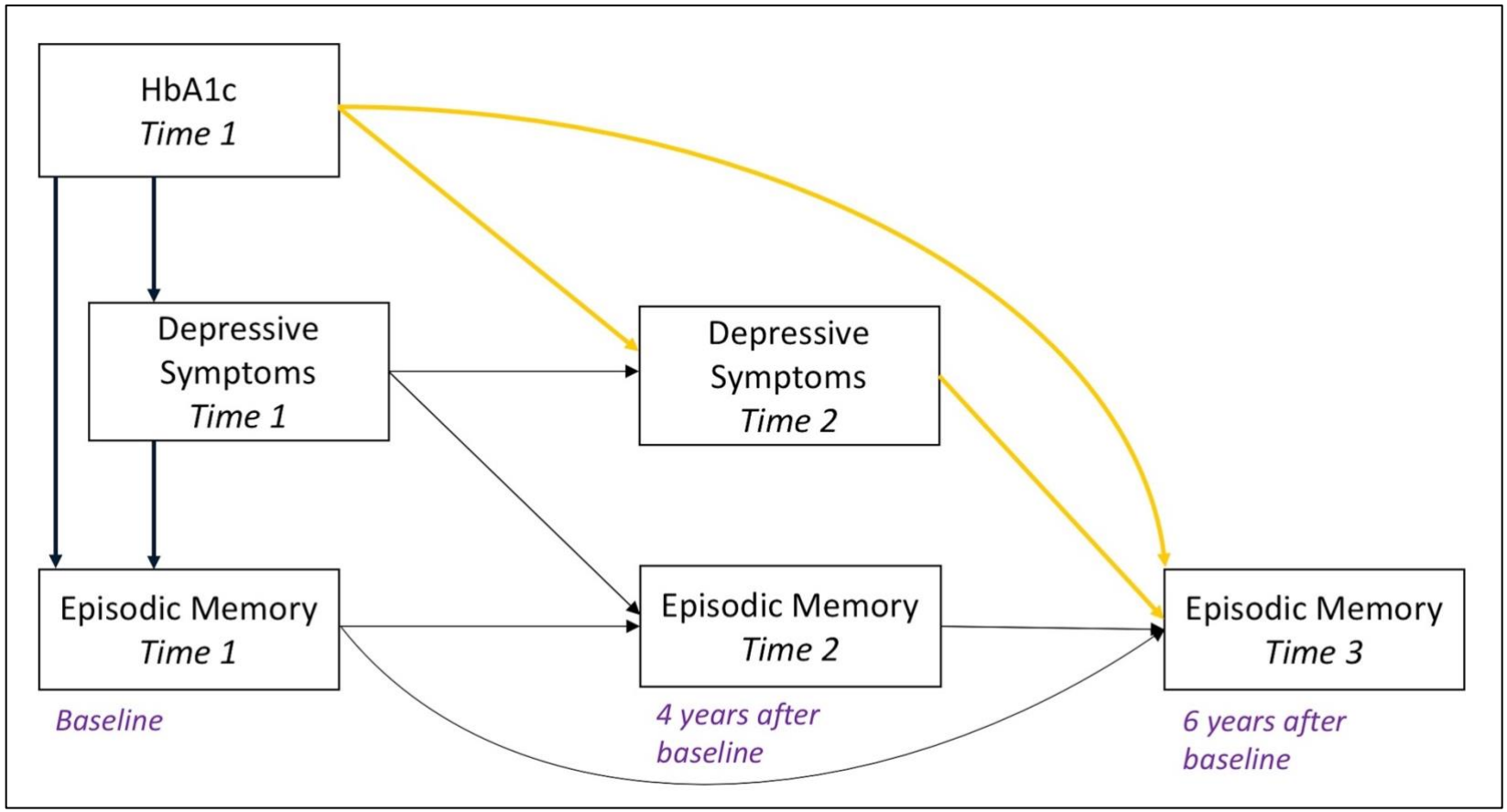
Primary Analyses

Descriptive statistics were computed using SPSS Version 26 (IBM Corp., Armonk, NY). Longitudinal mediation models (Maxwell & Cole, 2007) were used to examine the effects of HbA1c on concomitant and subsequent depressive symptoms and episodic memory (Aim 1) and the role of emotional support as a moderator of these effects (Aim 2) in Mplus Version 8 (Muthén and Muthén, 2007). Missing data were managed with full information maximum likelihood. Model fit was evaluated with the following commonly used indices: comparative fit index (CFI), root-mean-square error of approximation (RMSEA), and standardized root mean square residual (SRMR). CFI > 0.95, RMSEA < 0.06, and SRMR < 0.05 were used as criteria to determine adequate model fit (Hu & Bentler, 1999).

To test Aim 1 (Figure 4.1), memory at Time 3 was regressed onto depressive symptoms at Time 2, which was regressed onto HbA1c at Time 1. All autoregressive paths (e.g., memory at Time 3 onto memory at Time 2) were included. Within the same model, cross-sectional associations between HbA1c, depressive symptoms, and memory were examined by regressing memory at Time 1 onto depressive symptoms and HbA1c at Time 1, and by regressing depressive symptoms at Time 1 onto HbA1c at Time 1. All variables were regressed onto covariates.

Next, to test Aim 2 (Figure 4.1), continuous variables were each centered at the sample's mean value. The model used to test Aim 1 was repeated with the addition of a computed interaction term (HbA1c and emotional support). The interaction term was entered into the model separately to test the role of emotional support as a moderator of all paths linking HbA1c to the memory outcomes. Emotional support was regressed onto all covariates.

Figure 4.1
Conceptual Model for Study 3



Note. For simplicity, covariates are not depicted. For Aim 1, the model tested the direct and indirect paths from HbA1c at Time 1 to Episodic Memory at Time 3 as depicted. For Aim 2, subsequent models tested the role of emotional support as a moderator of all paths depicted. Bolded, blue-colored lines represent cross-sectional mediation paths. Bolded, maize-colored lines represent longitudinal mediation paths.

Sensitivity Analyses

A series of four sensitivity analyses was conducted in order to test the robustness of associations. First, the exposure and mediator were swapped, such that depressive symptoms (Time 1) was the exposure and HbA1c (Time 1 and Time 2) were mediators in order to assess the directionality of associations. Second, analyses were restricted to participants who self-reported T2D and whose HbA1c levels met the criterion for a T2D diagnosis (≥ 6.50%; ADA, 2019) at Time 1. Third, analyses included participants without self-reported T2D but who had non-normal HbA1c levels (≥ 5.70%) at Time 1. Fourth, analyses included participants with self-reported T2D at Time 1 but who did meet the clinical diagnostic criterion for pre-T2D or T2D (i.e., HbA1c < 5.7% and HbA1c < 6.5%, respectively; ADA, 2019). Fifth, given previous research suggesting level of cognitive functioning may predict future glycemic control, an alternative model tested whether memory at Time 1 predicted change in HbAc1 from Time 1 to Time 2 using latent difference score analysis (McArdle & Nesselroade, 1994). Instead of calculating raw difference scores between HbA1c at Time 1 and Time 2, the model defines a latent variable corresponding to the residual of the follow-up value independent of what is predicted by the baseline value. In this framework, features of HbA1c change that are of interest (e.g., mean change, inter-individual variability in change, relationship between the baseline value and change) are modeled as explicit parameters (McArdle, 2009).

Results

Participant characteristics of the 2,155 individuals in the current study are provided in Table 4.3. Briefly, participants were, on average, 69 years old, had approximately 12 years of education, and 2 chronic health conditions. The sample comprised 55.0% women and 19.3% Black

and 14.0% Hispanic participants. Bivariate correlations among exposure, mediator, moderator, and outcome variables are provided in Table 4.4.

Table 4.3
Participant Characteristics

	Mean (SD)	%	Sample Range
Age	69.39 (9.12)		51-97
Education	11.75 (3.42)		0-17
Female		55.00	
Race and Ethnicity			
Non-Hispanic Black		19.30	
Non-Hispanic 'Other Race'		2.90	
Hispanic (Any Race)		14.00	
Non-Hispanic White		63.80	
Wealth (in $100,000s)	3.27 (7.49)		-1.37-162.78
Medication Adherence		98.50	
Chronic Disease Burden	2.08 (1.12)		0-5
T1 enrollment in 2006		49.10	
HbA1c (%)	7.18 (1.43)		5.70-16.99 [Median=6.72]
HbA1c: 5.70 - 6.49%		39.80	
HbA1c 6.50 - 7.99%		42.30	
HbA1c ≥ 8.00%		17.90	
Depressive Symptoms T1	1.84 (2.18)		0-8
≥3 Depressive Symptoms T1[a]		28.4	
Emotional Support T1	1.70 (0.51)		1-4
Emotional Support T2	2.47 (0.97)		1-4
Immediate Recall T1 (Raw Score)	5.04 (1.57)		0-10
Delayed Recall T1 (Raw Score)	3.87 (1.95)		0-10

Note. [a]Three or more depressive symptoms suggests clinically elevated scores. HbA1c=hemoglobin A1c. T1=Time 1 (baseline). T2=Time 2 (4 years after baseline). T3=Time 3 (6 years after baseline).
[a]Three or more depressive symptoms suggests clinically elevated scores.

Table 4.4
Bivariate Correlations among Exposure, Mediator, Moderator, and Outcome Variables

	Depressive Symptoms T1	Depressive Symptoms T2	Emotional Support T1	Emotional Support T2	Episodic Memory T1	Episodic Memory T2	Episodic Memory T3
HbA1c	0.068**	0.096**	-0.122	0.014	-0.045*	-0.029	-0.011
Depressive Symptoms T1		0.563**	-0.232**	-0.102	-0.138**	-0.128**	-0.135**
Depressive Symptoms T2			-0.241**	-0.055	-0.165**	-0.172**	-0.179**
Emotional Support T1				-0.093	-0.007	-0.049	-0.063
Emotional Support T2					-0.087	-0.055	-0.071
Episodic Memory T1						0.592**	0.494**
Episodic Memory T2							0.571**

Note. HbA1c=hemoglobin A1c. T1=Time 1 (baseline). T2=Time 2 (4 years after baseline). T3=Time 3 (6 years after baseline).
*p<0.05. **p<0.01.

Associations between glycemic control and episodic memory via depressive symptoms

The first model quantifying the association between HbA1c and episodic memory over six years via four-year depressive symptoms (Aim 1) fit well: RMSEA=0.052, 90%CI [0.034, 0.071], CFI=0.993, SRMR=0.009. Standardized estimates of the total effects, direct effects, and specific indirect effects of interest are provided in Table 4.5. All cross-sectional and longitudinal paths described below are independent of covariates.

Cross Sectional. As depicted in Figure 4.2, the association between HbA1c and episodic memory at Time 1 operated in part through concurrent depressive symptoms. Specifically, higher HbA1c was associated with more depressive symptoms, which in turn, was associated with lower episodic memory performance. Independent of depressive symptoms, there was a significant, direct negative effect of HbA1c on memory.

Longitudinal. As depicted in Figure 4.2, depressive symptoms longitudinally mediated the association between HbA1c and episodic memory six years later at Time 3. Specifically, HbA1c at Time 1 was associated with more depressive symptoms at Time 2, controlling for depressive symptoms at Time 1. In turn, depressive symptoms at Time 2 predicted lower episodic memory at Time 3, controlling for episodic memory at Time 1 and Time 2. Overall, depressive symptoms accounted for 19.0% of the total effect of HbA1c on six-year memory decline.

Table 4.5

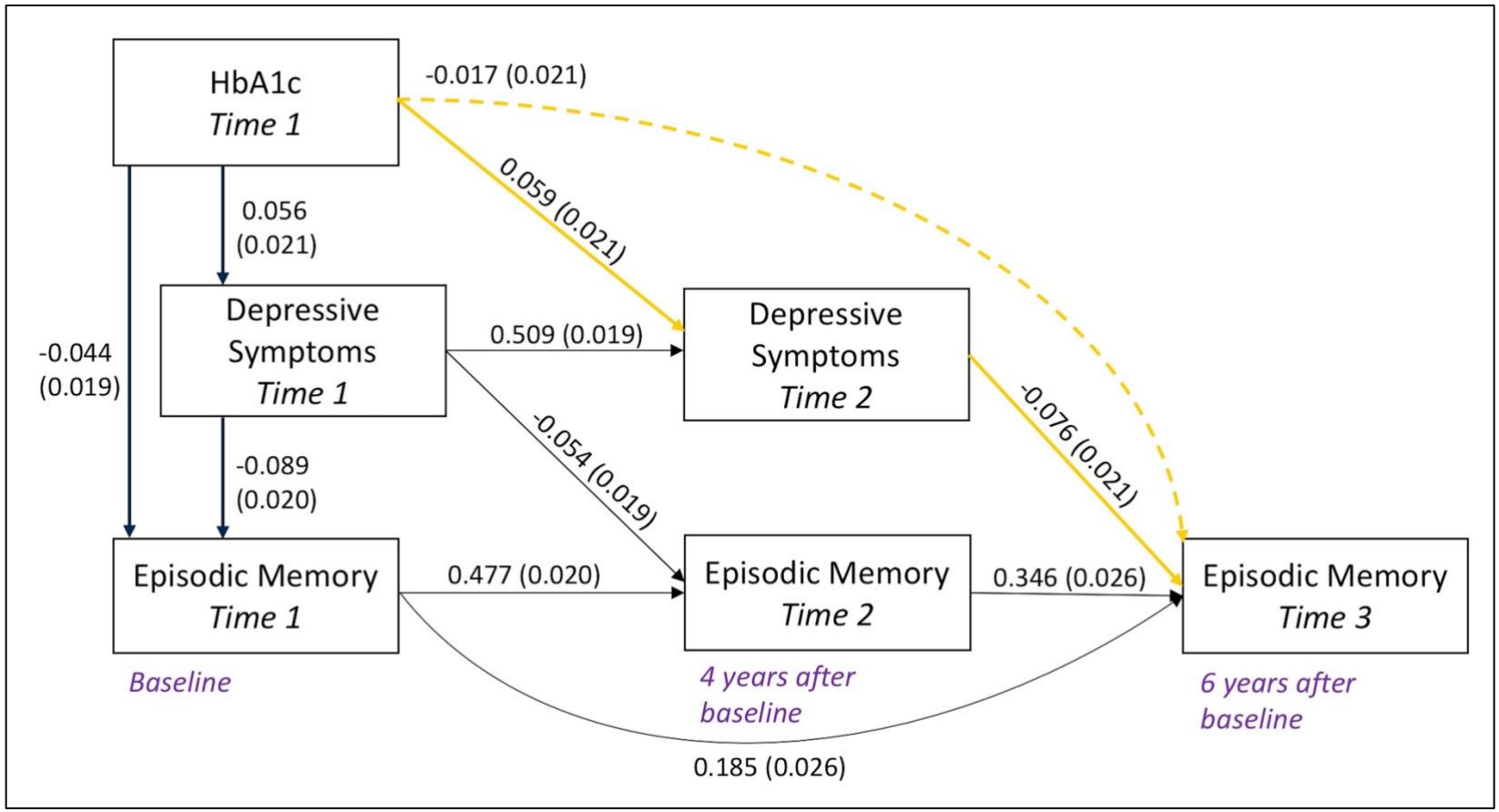
Standardized Estimates for the Longitudinal Mediation Model (Aim 1)

	Initial Memory Level (T1)	
	Estimate (*SE*)	*p*
Total Effect	-0.048 (0.019)	0.011
Direct Effect		
HbA1c	-0.044 (0.019)	0.022
Specific Indirect Effects		
Depressive Symptoms T1	-0.005 (0.002)	0.021
	Memory Change Six Years Later (T3)	
Total Effect	-0.042 (0.022)	0.058
Direct Effect		
HbA1c	-0.017 (0.021)	0.415
Specific Indirect Effects		
Depressive symptoms T2	**-0.004 (0.002)**	**0.029**

Note. SE=standard error. T1=Time 1 (baseline). T2=Time 2 (4 years after baseline). T3=Time 3 (6 years after baseline). Bolded items represent statistically significant longitudinal mediation.

Figure 4.2

Standardized Estimates for the Longitudinal Mediation Model (Aim 1)



Note. Bolded, blue-colored lines represent cross-sectional mediation paths. Bolded, maize-colored lines represent longitudinal mediation paths. For simplicity, covariates are not depicted. Solid lines indicate statistically significant paths ($ps < 0.05$). Dotted lines indicate non-significant paths ($ps \geq 0.05$).

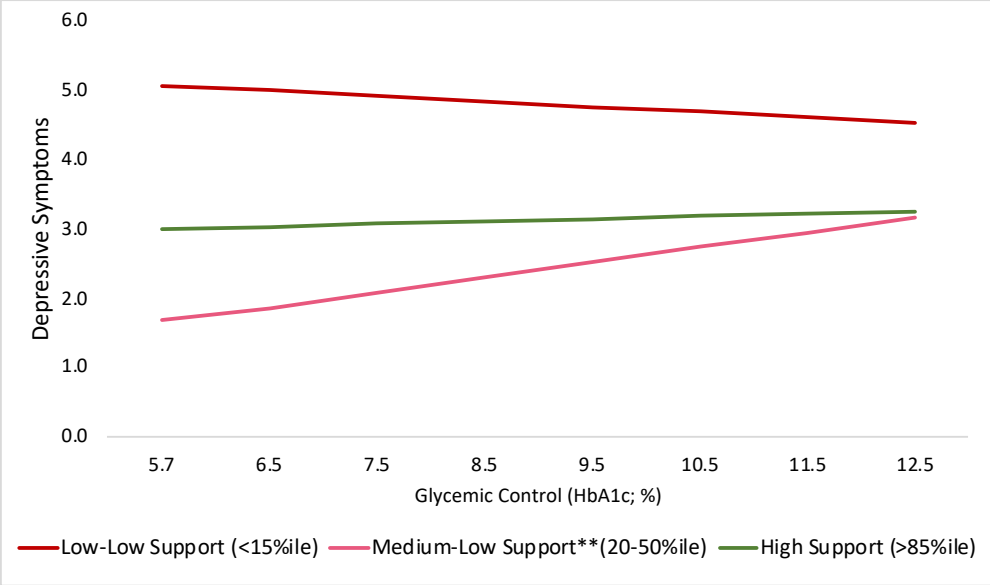
Emotional Support as a Moderator of Associations between Glycemic Control, Depressive Symptoms, and Episodic Memory

Subsequent models separately tested the role of emotional support as a moderator of all direct and indirect paths from HbA1c at Time 1 to memory at Time 3. These models fit well, and a summary of fit indices are provided in Table 4.6. As described in Table 4.6, emotional support at Time 1 moderated the cross-sectional associations between HbA1c and depressive symptoms at Time 1 (β = -0.051, *SE* = 0.021, *p* = 0.017) and HbA1c and episodic memory at Time 1 (β = -0.049, *SE* = 0.020, *p* = 0.014).

Specifically, in older adults with relatively lower emotional support, higher HbA1c levels were associated with more depressive symptoms (β = 0.078, *SE* = 0.023, *p* = 0.001; Figure 4.3). There was no association between HbA1c and depressive symptoms in older adults with high emotional support. Independent of depressive symptoms, in older adults with the lowest emotional support scores, higher HbA1c levels were associated with lower episodic memory performance (β = -0.069, *SE* = 0.030, *p* = 0.001; Figure 4.4). There was no statistically significant association between HbA1c and episodic memory performance in older adults with high levels of emotional support. In a subsequent model that tested the role of emotional support as a moderator of all paths at Time 1 (HbA1c-depressive symptoms, depressive symptoms-memory, HbA1c-memory) simultaneously within a single model, patterns of association persisted. Emotional support did not moderate other paths in the model (*p*s > 0.05; Table 4.6).

Figure 4.3

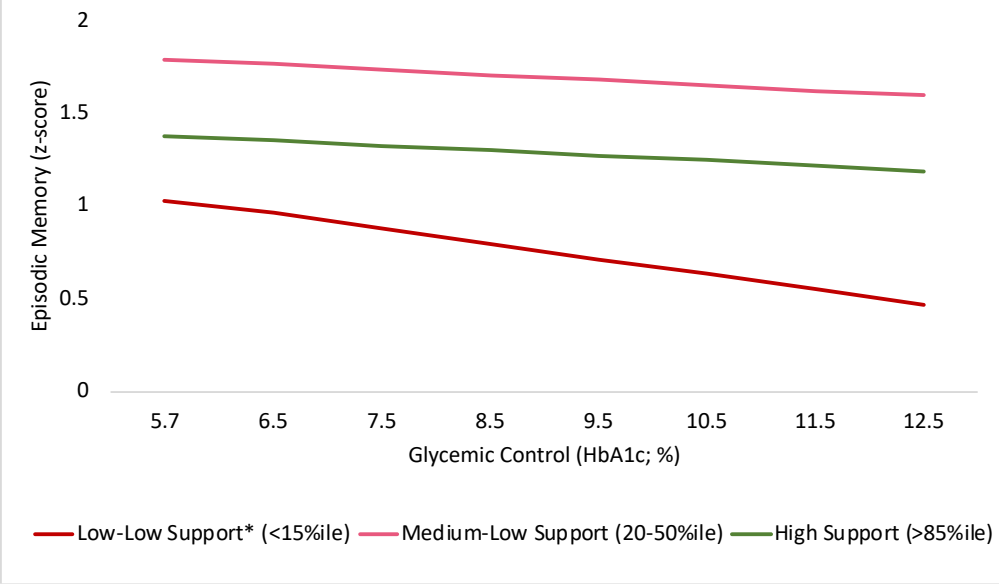
The Association between Higher HbA1c and More Depressive Symptoms is Attenuated at High Levels of Support



Note. Depressive symptoms represent the (non-centered) raw score residualized for covariates.
***p*<0.01.

Figure 4.4

The Association between Higher HbA1c and Lower Episodic Memory is Attenuated at High Levels of Support



Note. Episodic memory represents (non-centered) z-scores residualized for covariates and depressive symptoms.
**p*<0.05

Table 4.6

Model Fit Indices and Standardized Estimates of Emotional Support Moderation in the Longitudinal Mediation Model (Aim 2)

Interaction Term	Outcome Variable	Model Fit Indices			Interaction Term Statistics		
		RMSEA [90% CI]	CFI	SRMR	β	*SE*	*p*
Cross-sectional mediation paths: HbA1c T1 → Depressive Symptoms T1 → Memory T1							
HbA1c x ES T1	**Depressive Symptoms T1**	**0.030 [0.022, 0.039]**	**0.987**	**0.013**	**-0.051**	**0.021**	**0.017**
Depressive Symptoms T1 x ES T1	Memory T1	0.059 [0.051, 0.067]	0.957	0.022	-0.003	0.021	0.877
HbA1c x ES T1	**Memory T1**	**0.030 [0.022, 0.039]**	**0.988**	**0.013**	**-0.049**	**0.020**	**0.014**
Longitudinal mediation paths: HbA1c T1 → Depressive Symptoms T2 → Memory T3							
HbA1c x ES T1	Depressive Symptoms T2	0.050 [0.042, 0.057]	0.966	0.021	0.006	0.021	0.780
Depressive Symptoms T2 x ES T2	Memory T3	0.026 [0.018, 0.035]	0.993	0.013	-0.002	0.023	0.925
HbA1c x ES T1	Memory T3	0.054 [0.047, 0.062]	0.959	0.025	0.021	0.021	0.300
HbA1c x ES T2	Memory T3	0.022 [0.012, 0.031]	0.996	0.011	-0.020	0.023	0.386

Note. CFI=comparative fit index. CI=confidence interval. ES=emotional support. HbA1c=hemoglobin A1c. RMSEA=root mean square error of approximation. SE=standard error. SRMR= standardized root mean square residual. T1=Time 1 (baseline). T2=Time 2 (4 years after baseline). T3=Time 3 (6 years after baseline). Bolded items represent statistically significant moderation associations.

Sensitivity Analyses

Subsequent models tested a series of four sensitivity analyses. First, the exposure and mediator were swapped to allow for the possibility that HbA1c may mediate the association between depressive symptoms and memory. The model fit well. In cross-sectional associations, HbA1c at Time 1 did not mediate the concurrent association between depressive symptoms and memory at Time 1 (specific indirect effect of depressive symptoms at Time 1 on memory at Time 1 via HbA1c at Time 1: β=-0.003, SE=0.001, *p*=0.083). In longitudinal associations, depressive symptoms at Time 1 did not predict HbA1c at Time 2 (β= -0.020, SE=0.026, *p*=0.445). Furthermore, HbA1c at Time 2 did not mediate the longitudinal association between depressive symptoms at Time 1 and memory six years later at Time 3 (specific indirect effect: β=-0.001, SE=0.001, *p*=0.487).

Second, analyses were restricted to participants who self-reported a T2D diagnosis at Time 1 and whose HbA1c was 6.50% or higher (i.e., clinical criterion for T2D diagnosis; ADA, 2019). The model fit well and comprised 1,298 participants (sample size of primary analyses = 2,155). Patterns of association were similar to the primary model, with the exception of a numerically larger effect magnitude for longitudinal mediation (sensitivity analysis specific indirect effect: β= -0.009, SE=0.004, *p*=0.021; primary model specific indirect effect: β= -0.004, SE=0.002, *p*=0.029). Third, analyses included participants with and without a T2D diagnosis who had non-normal HbA1c (i.e., ≥ 5.70%, corresponding to levels at or above the pre-T2D threshold; ADA, 2019) at Time 1. The model fit well and comprised 5,682 participants (sample size of primary analyses = 2,155). Patterns of direct and indirect paths from HbA1c to episodic memory six years later were largely similar in comparison to those in the primary model, with the exception of a significant direct effect of HbA1c at Time 1 to memory at Time 3 (β= -0.032, SE=0.012, *p*=0.007).

Fourth, analyses included participants with self-reported T2D at Time 1 but who did meet the primary clinical diagnostic criterion for pre-T2D or T2D (i.e., HbA1c < 5.70% and HbA1c < 6.50%, respectively; ADA, 2019). The model fit well and comprised 2,560 participants, and patterns of association were comparable to findings from the primary model. However, in this sample that comprised 15.8% of participants with normal HbA1c, the direct negative effect of HbA1c on episodic memory at Time 1 was not statistically significant (β= -0.033, SE=0.017, *p*=0.061). Fifth, the association between episodic memory at Time 1 and change in HbA1c from Time 1 to Time 2 was tested, given previous research suggesting that baseline level of cognitive functioning may predict future glycemic control. The latent difference score model fit well and showed that episodic memory at Time 1 was not significantly associated with HbA1c change from Time 1 to Time 2 (β= -0.010, SE=0.025, *p*=0.696).

Discussion

Findings of this U.S.-wide longitudinal study suggest that depressive symptoms longitudinally mediate the association between HbA1c and episodic memory six years later in older adults with T2D. Furthermore, results show that higher levels of emotional support eliminate the negative cross-sectional effects of HbA1c on both depressive symptoms and memory performance. Altogether, the current study suggests that depressive symptoms may represent a primary mechanism linking glycemic control to T2D-related cognitive decrements. Furthermore, the current study provides preliminary evidence for the relevance of psychosocial factors as potential targets to reduce the significant psychiatric and cognitive morbidity prevalent in the rapidly growing population of older adults with T2D.

Depressive Symptoms as a Mechanism underlying HbA1c effects on Cognition (Aim 1)

The indirect effect of HbA1c on six-year memory decline through more depressive symptoms is in line with previous studies suggesting that depression represents a potential mechanism underlying the well-established finding that older adults with T2D have greater cognitive morbidity in comparison to those without T2D. Specifically, previous studies link HbA1c and/or T2D with an increased prevalence in depressive symptoms and clinical depression (Chireh et al., 2019; Hamer et al., 2011; Maraldi et al., 2007; Nouwen et al., 2010; Rotella & Mannucci, 2013). A separate body of literature evidences that depression/depressive symptoms heightens dementia risk and is associated with worse cognitive function and accelerated cognitive decline (Katon et al., 2012; Rock et al., 2014; Sullivan et al., 2013; Ownby et al., 2010). Of note, results from a previous longitudinal study comprising two independent cohorts of midlife and late-life adults suggest that depressive symptoms may represent a pathway linking cardiometabolic dysregulation to cognitive decline (Schmitz et al., 2018). However, the authors' operationalization of cardiometabolic dysregulation as a latent factor comprising six dichotomously defined indicators, which included the components of metabolic syndrome in addition to C-reactive protein >3 mg/L, precludes generalizing their findings to cognitive decrements specifically related to T2D. Extending on previous investigations, the current study provides the first evidence for the mediating role of depressive symptoms in the association between glycemic control and episodic memory decline in older adults with T2D.

Mechanisms Linking HbA1c to Depressive Symptoms

Multiple mechanisms likely underlie the link from HbA1c to depressive symptoms in older adults with T2D. Physiological mechanisms may involve inflammatory pathways, as T2D is associated with higher levels of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α; Mirza et al., 2012), which in turn is associated with more depressive symptoms (Postal et

al., 2016). Another physiological mechanism may involve impaired energy metabolism stemming from T2D-specific dysregulations in insulin signaling that contribute to hyperglycemia-related fatigue (Kalra & Sahay, 2018). In turn, hyperglycemia-related fatigue may lead to depressive symptoms such as low mood directly and/or indirectly through fatigue-associated activity disengagement (Kalra & Sahay, 2018; Rotella & Manucci, 2013). However, given that fatigue also represents a symptom of depression, additional research is needed to clarify the distinct contribution of T2D-related fatigue to depressive symptoms.

With respect to behavioral mechanisms, the manifold demands of managing diabetes may be perceived as burdensome and may negatively impact mood (Rotella & Manucci, 2013). For instance, as levels of HbA1c increase, individuals with T2D may be required to monitor glucose levels more frequently throughout the day as well as take higher daily dosages of glucose-lowering treatment agents (which may involve more frequent and/or a larger number of oral medications and/or intramuscular insulin injections). Similarly, low mood and behaviors contributing to low mood may also arise secondary to the gastrointestinal adverse effects (i.e., nausea and diarrhea) of first-line medication used to manage glycemic control in T2D (i.e., metformin; Bonnet & Scheen, 2017; Inzucchi et al., 2015).

Mechanisms Linking Depressive Symptoms to Memory

Mechanisms underlying the association between depressive symptoms and memory decline may involve similar physiological components to those for HbA1c's associations with depressive symptoms. Furthermore, more depressive symptoms are associated with worse systemic inflammation, which may explain depression-related risk for dementia; however, because these physiological disturbances are also associated with T2D, it is challenging to disentangle variance contributed by depression, T2D, and their comorbidity (Carney & Freedland, 2008;

Fernandez-Real & Pickup, 2008; Timonen et al., 2006). Additionally, depression-related effects on cognitive decline may occur via hypothalamic-pituitary-adrenal (HPA) axis dysregulation, which in turn increases glucocorticoid secretion and dampens negative feedback (Elder et al., 2006; Lee et al., 2007). Consequently, higher levels of cortisol may lead to atrophy and impede neurogenesis in memory-dependent brain areas (Sheline et al., 1999; Videbech & Ravkilde, 2004).

Mechanisms Linking HbA1c to Memory Independent of Depressive Symptoms

In the current study, HbA1c was not associated with longitudinal memory decline independent of depressive symptoms in older adults with self-reported T2D. However, a sensitivity analysis of adults with and without T2D (without controlling for T2D diagnosis) showed a direct effect of HbA1c on memory decline independent of depressive symptoms. One potential mechanism may involve hyperglycemia-related disruptions to brain network topology. Specifically, a prior neuroimaging study showed that higher HbA1c levels were associated with worse white matter network characteristics (specifically, both decreased global efficiency and increased lengths of connection paths), which the authors suggested may be related to hyperglycemia-related nerve deterioration in the brain (Kim, Yu, Shin, Shin, & Kim, 2016).

Previous studies in the HRS that suggest a direct inverse effect of baseline HbA1c on episodic memory (Marden et al., 2017; Pappas et al., 2017) included baseline depressive symptoms as a covariate and did not examine the potential mediating role of longitudinal changes in depressive symptoms. Thus, differences in findings between the current study and previous work in the HRS may be attributable to the differing statistical methodologies and/or inclusion criteria as well as how the memory variable was operationalized. For instance, Marden et al. (2017) operationalized episodic memory using performance on the word recall test (used in the current study) or, for those who were too impaired to participate in the memory assessments, the authors

used scores from a proxy-reported questionnaire on cognitive decline. Although this method may address attrition-related bias in missing memory data, the study's findings are limited in generalizability as Hispanic adults (comprising 14.0% of the current study's sample) were excluded from the authors' analytic sample due to algorithm-related restrictions in combining the objective and informant-reported data sources.

Given that multiple mechanisms likely underlie the association between T2D/hyperglycemia and cognitive aging, future studies should investigate the role of additional pathways in associations between HbA1c/T2D and cognitive aging outcomes. Previous studies implicate physiological functions including endocrine (e.g., insulin resistance and hyperinsulinemia), central nervous (e.g., amyloid deposits and neuronal homeostasis), and vascular (e.g., micro and macrovascular complications, endothelial dysfunction, and inflammation) systems (McCrimmon, Ryan, & Frier, 2012). Because depressive symptoms have also been implicated in pathways involving these physiological functions, experimental studies characterizing the causal role of depressive symptoms in physiological pathways may help clarify mechanisms underlying T2D-related cognitive decrements.

Broad Benefits of Support: Attenuated Impacts of HbA1c on both Depressive Symptoms and Memory (Aim 2)

The current study showed that the detrimental impacts of HbA1c on depressive symptoms as well as episodic memory performance found in older adults with relatively lower levels of emotional support were eliminated in those with relatively higher levels of emotional support. These cross-sectional findings are consistent with the buffering model of support (Cohen & McKay, 1984; Cohen & Willis, 1985) as well as results from empirical studies (Baek et al., 2014; Okura et al., 2009). Specifically, previous studies suggest a buffering role of social support against

the effect of T2D severity (indexed by insulin use) on distress (Baek et al., 2014) as well as on the negative HbA1c-cognition association (Okura et al., 2009). By simultaneously modeling effects of HbA1c on depressive symptoms and episodic memory within a mediation framework, the current study extends results from these previous studies and showed that emotional support buffers against both the direct and indirect effects of HbA1c on episodic memory performance through depressive symptoms. These findings point to the potential for emotional support to confer broad benefits to both psychological and cognitive health in older adults with T2D.

Emotional Support Buffers against HbA1c Effects on More Depressive Symptoms

Based on the buffering model of support (Cohen & Willis, 1985), the current study posits that hyperglycemia may represent a significant health-related stressor, potentially due to the demanding self-care regimen associated with managing T2D. As noted above, worsening glycemic control typically results in more exacting T2D self-care activities. The effects of hyperglycemia such as fatigue (Kalra & Sahay, 2018) and the adverse effects of T2D medications such as gastrointestinal distress (Bonnet & Scheen, 2017) may also represent a source of stress. Furthermore, additional treatment demands beyond those to control blood sugar may be needed to manage subsequent hyperglycemia-related health complications. These may include additional medication, more healthcare appointments, and new forms of apparel (e.g., special footwear to improve blood circulation adversely affected by diabetic neuropathy). Thus, emotional support may function as a buffer to reduce the stress associated with hyperglycemia and hyperglycemia-related disease burden. Specifically, in the face of HbA1c-related treatment demands and T2D disease burden, higher levels of support may lead to increases in one's coping skills for managing T2D self-care behaviors as well as decreases in levels of T2D-specific distress and stress-induced physiological reactivity (Bond et al., 2010; Ford, Tilley, & McDonald, 1998; McEwen et al., 2010;

Nicklett & Liang, 2010; Tang et al., 2008). In turn, better coping skills, lower T2D-specific distress, and reduced physiological stress reactivity have been associated with fewer depressive symptoms (Andrew & Dulin, 2007; Fisher, Gonzalez, & Polonsky, 2014; Fiske, Wetherell, & Gatz, 2010; Gaffey, Bergeman, Clark, & Wirth, 2016).

Of note, in the current study, higher levels of HbA1c were associated with more depressive symptoms in older adults with medium-low emotional support scores (20^{th} to 50^{th} percentile). Consistent with the buffering model of support (Cohen & Wills, 1985), there was no association between HbA1c levels and depressive symptoms at higher levels ($\geq 85^{th}$ percentile) of support. However, the finding showing no association between HbA1c and depressive symptoms at the lowest levels of emotional support ($\leq 15^{th}$ percentile) was unexpected. Post-hoc comparisons showed that HbA1c levels did not vary across these subgroups, yet participants within the "low-low" emotional support subgroup reported more depressive symptoms (2.93 ± 2.62) relative to participants in the "medium-low" (1.76 ± 2.04) and "high" (1.75 ± 2.14) subgroups. More depressive symptoms in the "low-low" subgroup may reflect habituation to a lack of support, such that greater T2D severity may not confer any additional depressive symptoms.

It is also possible that older adults with higher levels of depressive symptoms may be less likely to solicit emotional support or perceive it even when it is received. Furthermore, prior work has suggested that dynamic models that account for the transactional nature of interpersonal relationships in the context of stress-related outcomes may help clarify the non-linear effects of the stress-buffering model (Field & Schuldberg, 2011). Specifically, older adults with the lowest levels of emotional support may not have social relationships from which they can solicit empathy or advice and/or may not be satisfied with the support received. A prior cross-sectional study showed that, for those with low levels of support satisfaction, greater T2D severity

(operationalized as insulin use and diabetes-related health complications) was associated with more T2D-related distress whereas no association was found in participants with high levels of support satisfaction (Baek et al., 2014). Future studies should examine the role of satisfaction with relationships and/or satisfaction with support as they represent unique aspects of social relationships (Antonucci, Ajrouch, & Birditt, 2014) that may be targeted to reduce the mental health impact of T2D-related stress.

Emotional Support Buffers against HbA1c Effects on Lower Cognition

Cognitive stimulation may partly explain the attenuated association between HbA1c and episodic memory at higher levels of emotional support. Specifically, cognitive stimulation may be inherent to behaviors used to obtain emotional support, such as conversations. Memory processes may be actively recruited in order to recall specific situations or concerns for which one is seeking emotional support. Thus, higher levels of perceived support may provide more opportunities to engage in these conversations. Consistent with the 'use it or lose it' hypothesis (Hultsch et al., 1999), more frequent engagement in activities used to obtain emotional support may potentially lead to the preservation or improvement in cognitive functioning. Future studies utilizing an experimental design and imaging techniques may help clarify the neural and cognitive bases of conversations related to emotional support.

Reductions in physiological stress reactivity and markers of inflammation may represent another potential mechanism of underlying the buffering effect of emotional support on HbA1c-related poor episodic memory function. As previously described, worsening glycemic control may represent a source of stress due to resulting higher T2D-related treatment burden, which may heighten activations of the sympathetic nervous system and HPA axis. In turn, heightened physiological stress responses confer risk for cardiovascular disease and poor cognitive health

outcomes (Cohen, Janicki-Deverts, & Miller, 2007; Justice, 2018), potentially via systemic inflammation (Misiak et al., 2012; Rohleder, 2014; Zahodne, Kraal, Sharifian, Zaheed, & Sol, 2019) and neuroinflammation (Wong, Wanrooy, & Bruce, 2018). Of note, emotional support may not be able to modify inflammatory dysregulation resulting from T2D/hyperglycemia-related disease mechanisms (Wong et al., 2018. However, it is plausible that emotional support may buffer against the cognitive effects of physiological perturbations secondary to hyperglycemia-related psychosocial stress independent of depression-related pathways, which would be consistent with findings from the current study. However, additional research is needed to both replicate and clarify mechanisms underlying the current study's observed patterns of association. Nonetheless, the current study provides preliminary evidence for the utility of emotional support as one potential nonpharmacological target to reduce the cognitive morbidity associated with worsening T2D in older adulthood.

Support may not Moderate Associations between Depressive Symptoms and Cognition

The finding that emotional support did not moderate the association between depressive symptoms and cognition was unexpected and inconsistent with the buffering model of support. One potential explanation may be that depressive symptoms may not capture the extent of the health-related stress experienced by older adults with T2D. Indeed, T2D distress is a construct that reflects the psychosocial distress uniquely associated with managing T2D treatment demands (Polonsky et al., 2005). Furthermore, T2D distress has been shown to be distinct from more general forms of emotional distress such as those assessed by self-reported depressive symptom questionnaires (Esbitt, Tanenbaum, & Gonzalez, 2013; Polonsky et al., 2005). Furthermore, previous studies show a buffering role of support in attenuating the impact of T2D burden (operationalized as T2D microvascular complications and insulin use) on T2D distress (Baek et

al., 2014). Given that higher levels of support predict lower levels of subsequent T2D distress (Karlsen & Bru, 2014), future studies are needed to determine if the buffering role of support can be extended to reduce the impact of T2D distress effects on cognitive aging outcomes.

Another potential explanation may be that the general construct of emotional support that was measured in the current study may not be beneficial in reducing the impact of depressive symptoms on cognition in older adults with T2D. However, prior studies examining associations with diabetes-specific support measures have not included cognitive outcomes, and extant studies evidence associations that could be biased by reverse causation. For instance, a previous study showed that more illness-related support is associated with greater adherence to diabetes self-care behaviors (Nicklett & Liang, 2010), yet greater adherence may be a cause rather than a consequence of more illness-related support. Experimental studies are needed to examine whether the construct of diabetes-specific support may buffer the negative impact of depressive symptoms on cognitive outcomes in older adults with T2D.

Support may not Confer Longitudinal Buffering Effects

Levels of emotional support did not moderate longitudinal associations among HbA1c, depressive symptoms, and episodic memory. One potential explanation may be that the effects of emotional support dissipates over time, and the duration between assessments in the current study (four years between T1 and T2; two years between T2 and T3) may be too long to capture potential buffering effects. From a methodological standpoint, the current study's inclusion of autoregressive paths (i.e., T3 memory scores were controlled for T2 and T1 memory scores) resulted in substantially less variance in T3 memory scores relative to memory scores at T1 or T2, as would be expected. Thus, the reduced variance of T3 memory scores may have posed a greater challenge for detecting small interaction effects in longitudinal associations versus cross-sectional

ones. However, prior research in older adults with T2D points to a longitudinal health benefit conferred by social experiences. Specifically, a previous longitudinal study showed that older adults with T2D who reported higher levels of support had reduced T2D-related mortality risk relative to those with low levels of support (Zhang et al., 2007). However, the authors operationalized support using items assessing the frequency with which individuals went to community centers, religious institutions, and sporting events as well as the frequency of their social contact with other people. Although these items may be indicative of potential social activities through which individuals obtain social support, they are reflective of conceptually distinct aspects of social engagement and have been shown to have independent associations with health (e.g., Uchino, 2009), cognitive aging (e.g., Zahodne et al., 2019), and T2D-related complications (Brinkhues et al., 2018). Future studies should examine the unique roles of these different aspects of social relationships in attenuating the longitudinal effects of T2D/hyperglycemia on cognitive aging outcomes.

Limitations

A primary limitation of the current study is its use of self-report measures. First, depressive symptoms were measured using a self-report questionnaire (Center for Epidemiological Studies – Depression scale; Radloff, 1977) which assesses the number of depressive symptoms but is not specific for a clinical diagnosis of depression (Goldman et al., 1999). A meta-analysis of longitudinal studies on the association between T2D and depression showed an association between T2D and incident depression when depression was measured using diagnostic interviews, but this association failed to reach statistical significance when self-reported questionnaires were utilized (Rotella & Manucci, 2013). Indeed, the authors note that the diagnostic imprecision of

questionnaires is not a determining factor of the T2D-depression association although it produces error that leading to an underestimation of the association.

Second, the current study's use of self-reported T2D diagnosis may have underestimated the prevalence of T2D (Bowlin, Morril, Nafziger, Lewis, & Pearson, 1996). An alternative strategy employed in prior studies is to operationalize T2D based on medication use, which can also be imprecise. On the one hand, individuals with T2D may not report taking medication due to inadequate clinical care. On the other hand, empirical evidence showing certain oral hypoglycemics reduce incident T2D (Knowler et al., 2002) has led to a rise in their prescription (though not in a uniform manner) for those at risk for diabetes (Aroda & Ratner, 2018). Yet another alternative strategy is to operationalize T2D based on objective assessments of blood-based biological markers, for which hemoglobin A1c is the gold standard measure. However, one limitation of relying solely on laboratory-based markers to determine T2D diagnosis is that some patients categorized as T2D may be unaware of this diagnosis. Of note, in the current study, sensitivity analyses revealed that 423 (3.42%) participants with HbA1c data at T1 (2006/2008; sample size=12,333) who did not report a diagnosis of T2D met the HbA1c criterion (≥ 6.5%) for a diagnosis. Individuals who are unaware of their diagnosis may experience negative physical and cognitive health effects from untreated T2D; however, they may also avoid the potential adverse psychological effects of having a T2D diagnosis and resulting T2D treatment demands. Indeed, a previous study showing that T2D confers risk of depressive symptoms found that the prevalence of depression was increased only in participants with diagnosed T2D but not in participants whose T2D was undiagnosed (Knol et al., 2007). While the current study's use of self-reported T2D may not provide a wholly accurate estimation of T2D in the HRS, the current study's inclusion criteria also considers HbA1c. Furthermore, statistical analyses were adjusted for medication adherence,

and sensitivity analyses showed that patterns of association were similar when HbA1c was the sole determinant for T2D diagnosis.

The current study controlled for self-reported medication adherence as treatment non-adherence may influence levels of HbA1c, depressive symptoms, and/or memory function (Gonzalez et al., 2013). Notably, 98.50% of the current sample reported regularly taking their prescription medication, which contrasts prior work suggesting a lower rate of medication adherence in T2D samples (Gonzalez et al., 2013). Future studies should employ additional strategies (e.g., clinical chart review and/or informant report) in medication adherence data collection. Another potential limitation of the current study is its use of episodic memory as the outcome variable. Although processing speed and executive functioning are more frequently implicated as T2D-related cognitive decrements, the HRS has not routinely included measures of these cognitive domains. Therefore, episodic memory was selected as the cognitive performance measure because it is sensitive to diabetes-related cognitive decrements (Ryan & Geckle, 2000) and age-related cognitive decline, and it is a well-documented primary determinant of dementia risk (Backman et al., 2001). Given that HRS initiated two commonly used measures of processing speed/executive function (phonemic and semantic verbal fluency) in 2010, future research will be able to test the current study's hypotheses using different cognitive outcomes.

Strengths

Strengths of this current study include its use of six years of episodic memory data in order to characterize HbA1c associations with memory change. The current study also featured a relatively large sample size of older adults with T2D and a comprehensive set of covariates. Furthermore, the current study conducted a broad set of sensitivity analyses to test the robustness of results which provide a higher degree of confidence for interpreting observed patterns of

association. A particularly important strength of the current study is its rigorous methodological analyses that examined longitudinal mediation within a structural equation modelling framework.

Conclusion

In conclusion, this U.S.-wide longitudinal study provides first evidence that depressive symptoms may represent a mechanism linking poorer glycemic control to T2D-related cognitive decrements. Reducing depressive symptoms may represent one potential method to decrease the adverse effects of hyperglycemia on memory aging in older adulthood. Given the significant burden of managing T2D, clinicians should consider encouraging their older adult patients with T2D to more frequently engage in activities that facilitate emotional support as it is a nonpharmacological strategy that may confer broad benefits to mental and cognitive health. Taken together, findings from the current study as well as this dissertation highlight the relevance of psychosocial factors as targets for reducing the significant psychiatric and cognitive morbidity prevalent in the rapidly growing population of older adults with T2D.

Chapter 5

Integration and Conclusion

This dissertation sought to advance existing evidence on potential physiological and psychosocial risk and protective factors associated with Type 2 Diabetes (T2D)-related cognitive decrements in older adulthood. The overarching goals across all three studies in older adults with T2D were two-fold: (1) to characterize the associations between markers of cardiometabolic function related to T2D severity (Hemoglobin A1c (HbA1c) and homocysteine) and cognitive outcomes, and (2) to test the role of emotional support as a potential buffer against cardiometabolic-related risk for cognitive morbidity. A summary of findings and their implications are discussed below.

Study 1 examined associations among glycemic control, depressive symptoms, emotional support, and processing speed. While it did not provide evidence that HbA1c was associated with depressive symptoms or episodic memory, Study 1 showed that the adverse impact of depressive symptoms on cognition found in those with low support was attenuated in those with higher levels of emotional support, independent of T2D disease severity. Study 2 tested the associations between homocysteine and four domains of cognition in a sample of older adults with uncontrolled T2D, as well as the role of emotional support in moderating homocysteine-cognition relationships. Study 2 showed that the negative association between homocysteine and cognition was strongest for frontally mediated cognitive domains (specifically, executive function and working memory) but that homocysteine-cognition associations did not vary levels of support. Study 3 investigated

longitudinal associations between glycemic control and memory decline through depressive symptoms and tested the buffering role of emotional support in attenuating patterns of association. Study 3 found that the negative effect of glycemic control on episodic memory six years later operated in part through four-year increases in depressive symptoms (i.e., longitudinal mediation). Additionally, Study 3 showed that higher levels of emotional support attenuated the negative cross-sectional associations between glycemic control and both depressive symptoms and memory performance. Findings from this dissertation provide support for the relevance of psychosocial factors, specifically depressive symptoms and emotional support, as potential targets for reducing disease-related effects on cognitive performance in the context of advancing T2D in older adulthood. All three studies also provided evidence for potential mechanisms underlying T2D-related cognitive decrements.

Although Study 2 featured a small sample size, its inclusion of well-established neuropsychological measures to assess four separate domains of cognitive function represents an important strength. Study 2 provided greater clarity into the nature of cognitive effects most strongly impacted by homocysteine, extending prior work in T2D which has been limited to global cognitive screening measures. The negative associations between homocysteine and executive function as well as homocysteine and working memory suggest that homocysteine may confer particularly deleterious effects on frontally mediated cognitive domains. The domain specificity of this finding is in line with the 'vascular hypothesis of cognitive aging' (Spiro & Brady, 2008) and has implications for frontal lobe dysfunction as a potential mechanism underlying T2D-related cognitive decrements. Although future research with larger and more representative samples are needed to replicate these findings, results from Study 2 provide preliminary evidence that the adverse effects of homocysteine on frontal cognitive functions may help explain why older adults

with uncontrolled T2D have a substantially higher risk for dementia compared with older adults with controlled T2D (Xu et al., 2009). Findings from this study also point to the potential utility of predicting the everyday impact of physiological dysregulation in uncontrolled T2D, as executive functions are critical for behaviors that maintain functional independence (Cahn-Weiner et al., 2007). Importantly, high levels of homocysteine may represent a marker of potential difficulties with managing the significant demands of T2D treatment.

Study 3 provided first evidence in the available literature for the role of depressive symptoms as one potential mechanism linking HbA1c to episodic memory declines in T2D. Prior studies have conducted separate investigations into the link from T2D/HbA1c to depressive symptoms and the link from depressive symptoms to cognition, which limit interpretation regarding the inter-relationships between these variables. Given the findings from Study 2 showing stronger associations between homocysteine and frontally mediated versus hippocampally dependent cognitive functions, future studies should examine whether the mediating role of depression in hyperglycemia-related memory decline can be extended to changes in executive function. Greater understanding into the role of depressive symptoms in declining memory versus executive function in T2D may reveal important information into potentially shared behavioral pathways that may be targeted to reduce T2D-related risk for cognitive morbidity.

A primary focus of this dissertation was to examine the role of emotional support as a buffer against the impact of health-related stress on cognition (Studies 1, 2, and 3), and whether emotional support exerted buffering effects through interactions with depressive symptoms (Studies 1 and 3). The theoretical framework of the stress-buffering model of support (Cohen & Wills, 1985) and empirical evidence in T2D samples (e.g., Baek et al., 2014; Okura et al., 2009; Strom & Egede, 2012) provide justification for examining emotional support to dampen the

adverse consequences of T2D-related stress on various health outcomes. More importantly, examining psychosocial factors such as emotional support as intervention targets may be particularly relevant for older adults with T2D who already have significant treatment burden associated with managing T2D and T2D-related health complications.

Despite diverging patterns of association, Studies 1 and 3 underscored the salience of emotional support as a psychosocial resource to buffer against the impact of health-related stress on cognitive and mental health outcomes in older adults with T2D. On the one hand, Study 1 suggests that higher levels of emotional support may buffer against depression-related decreases to cognitive function, independent of T2D severity. On the other hand, Study 3 suggests that emotional support may be beneficial for reducing the adverse impact of HbA1c on depressive symptoms and memory performance. Indeed, that emotional support attenuated the adverse impact of depressive symptoms on cognition in Study 1 versus the impact of HbA1c on both depressive symptoms and cognition in Study 3 warrants additional study. Differences in observed associations between the two studies may be due to differences in cognitive outcomes (processing speed in Study 1 versus episodic memory in Study 3), emotional support questionnaires, sampling strategy (regional-based in Study 1 versus population-based in Study 3), and sample size. Although additional research is needed to clarify the discordant associations found in Study 1 versus Study 3, it is notable that emotional support was found to exert beneficial effects in both. Future research using experimental designs are needed to isolate the unique mechanisms associated with emotional support's stress-buffering effects on various outcomes.

In sum, the findings of this dissertation provide clarity into physiological and psychosocial pathways that may confer risk for and protection against poor cognitive outcomes in older adults with T2D. Poor cognitive outcomes related to T2D may stem from poor glycemic control resulting

in worse mental health, which may erode memory functions. Furthermore, for older adults with uncontrolled T2D, poor cognitive outcomes may arise from the neurotoxic effects associated with high levels of homocysteine, which may explain the higher dementia risk found in uncontrolled versus controlled T2D. Emotional support may reduce the impact of physiological dysregulation on mental health and cognitive health and/or the impact of depression on cognitive function. This dissertation provides evidence that may help clarify reasons underlying T2D-related cognitive decrements and contribute to future research aimed at developing nonpharmacological interventions to improve the health of a rapidly growing older adult population with T2D. It is hoped that the current dissertation provides rationale for complementary research on behavioral and biological mechanisms underlying T2D-related cognitive morbidity, as well as modifiable factors that may potentially protect against cognitive decline and dementia.

APPENDICES

APPENDIX A

Center for Epidemiological Studies Depression Scale, 10-item Version

Question	Answer
1. I felt depressed	(YES/NO)
2. I felt that everything I did was an effort	(YES/NO)
3. My sleep was restless	(YES/NO)
4. I was happy	(YES/NO)
5. I felt lonely	(YES/NO)
6. People were unfriendly	(YES/NO)
7. I enjoyed life	(YES/NO)
8. I felt sad	(YES/NO)
9. I felt that people disliked me	(YES/NO)
10. I could not get going	(YES/NO)

APPENDIX B

Emotional Support Measure from the NIH Toolbox

	Never	Rarely	Sometimes	Usually	Always
I have someone who understands my problems	□ 1	□ 2	□ 3	□ 4	□ 5
I have someone who will listen to me when I need to talk.....	□ 1	□ 2	□ 3	□ 4	□ 5
I feel there are people I can talk to if I am upset.....	□ 1	□ 2	□ 3	□ 4	□ 5
I have someone to talk with when I have a bad day.....	□ 1	□ 2	□ 3	□ 4	□ 5
I have someone I trust to talk with about	□ 1	□ 2	□ 3	□ 4	□ 5

my problems					
I have someone I trust to talk with about my feelings.....	□ 1	□ 2	□ 3	□ 4	□ 5
I can get helpful advice from others when dealing with a problem	□ 1	□ 2	□ 3	□ 4	□ 5
I have someone to turn to for suggestions about how to deal with a problem.....	□ 1	□ 2	□ 3	□ 4	□ 5

APPENDIX C

Study 2 Eligibility Criteria

Inclusion Criteria

1 Aged 65 to 75 years old

2. Self-reported non-Hispanic Black or White race

3. Diagnosed with Type 2 Diabetes Mellitus (T2DM)

4. Most recent HbA1c level ³ 8.0%

5. Stable T2DM treatment in the last 3 months

6. No major surgery or trauma within the last month

Exclusion Criteria

1. Unable or unwilling to provide informed consent

2. History of Type 1 diabetes

3. History of significant non-vascular neurological disorders or conditions (e.g., dementia, epilepsy, brain tumor, and multiple sclerosis)

4. History of loss of consciousness for 20 minutes or longer

5. Diagnosed intellectual disability

6. Use of antipsychotic medication within the last year

7. Recent changes in memory interfering with the ability to complete independent activities of daily living (e.g., managing finances and medications)

8. Having a legal guardian

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