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Title: Does Hemoglobin A1c Influence the Relationship between Stressful Life Events and Cognition in Later Life? Findings from the VA Normative Aging Study

Abstract approved:

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With Type 2 diabetes sharply growing in prevalence around the world, there has been an increased interest in adverse health outcomes resulting from excessively high blood sugar and the associated damage to blood vessels, increasing the risk of a variety of chronic illnesses and mortality. If untreated, high blood sugar can result in increased hemoglobin A1c (HbA1c), which can damage veins and arteries for the duration of these erythrocytes' lifespan, resulting in accumulative damage and loss of efficiency of the circulatory system. Both HbA1c and stressful life events (SLEs) have demonstrated independent effects on cognition in late life, with higher levels of both stress and HbA1c impairing cognition. SLEs can influence a variety of physiological pathways, including HbA1c, thus it is possible that HbA1c can moderate the

influence of SLEs on cognitive function. The present study investigated the mediating and moderating effects of HbA1c on the relationship between SLEs and cognitive outcomes in late life. Both global and fluid cognitive measures to investigate general and domain-specific declines associated with both SLEs and HbA1, and then age stratified these same analyses to examine whether the old-old (75+) are more vulnerable, will be used to investigate the potential relationships between these variables. The sample consisted of older adult males (N = 578) from the VA Normative Aging Study (M_{age} = 74.3 years, SD = 6.5). Structural equation models showed that both SLE and HbA1c exhibited direct effects that varied depending upon the cognitive outcome and type of analysis. However, SLE and HbA1c were unrelated in this sample, therefore no mediation effects were found. One moderation effect was found for the pattern recognition task in the general sample; however the interaction was in the opposite effect of the direct effects, and further investigation suggested a multicollinearity problems, potentially nullifying this result. The analyses stratified by age (< 75 and 75+) yielded some interesting results. Within age group, age was consistently an inversely associated with MMSE and word list total recall, but no significant relationship to verbal fluency and pattern recognition in the old-old group, suggesting either plateau effects, survivor effects, or potentially a specific vulnerability. Further, education appeared to be more protective against cognitive deficits in the old-old group when compared to the young-old group, and HbA1c was more consistently inversely related to cognition in the old-old group, while

stress was more likely to have a significant relation in the young-old group. One moderation model for verbal fluency was significant for the old-old group, and results suggested that those high in HbA1c and SLE had lower scores for verbal fluency. Future research should be conducted with more diverse samples, and better aligning the timing of the stress and HbA1c assays. The implications of this work include, bolsters our understanding of how joint effects of physiology and stress may influence specific domains of cognitive function in aging, perhaps resulting in accelerated aging.

Does Hemoglobin A1c Influence the Relationship between Stressful Life Events and Cognition in Later Life? Findings from the VA Normative Aging Study.

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I understand that my thesis will become part of the permanent collection of Oregon State University libraries. My signature below authorizes release of my thesis to any reader upon request.

Austin Brockmann, Author

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DEDICATION

Dedicated to Colin Davis.

A cherished friend, brilliant scholar, and a gentle soul. It is with great regret that I could not send you the final product as we promised, but I still cannot wait to tell you all about it next we meet.

Rest in peace until I can see you again

CHAPTER 1

OVERVIEW

There is a wealth of literature examining diabetes as a risk factor for accelerated aging, including declines in cognition and mortality (Arvanatakis et al., 2004; Morley, 2008; Shrethsa et al., 2019). Current trends in diabetes worldwide indicate that the number of diabetics is poised to increase sharply due to changes in diet and exercise which will pose imminent threats to healthy aging and strain healthcare systems worldwide. Alzheimer's disease and other dementias are strongly intercorrelated with diabetes, with a 65% percent increase in likelihood to have dementia in those that are diabetic, with some scholars even coining the term type 3 diabetes to describe Alzheimer's (Arvanatakis et al., 2004). Currently, a variety of potential mechanisms linking diabetes and dementia have been identified in the literature. Most notably, shrinkage to blood vessels and oxidative damage, impaired oxygen transport, and by extension of these promotion of tau clusters and amyloid plaques in the brain, which may impair organ function and are often credited as the most likely sources of neurodegeneration (for review, see Wang & Michaelis, 2010). The specific area of focus for this thesis is on the blood biomarker HbA1c, which is often used as a method of assessing presence of diabetes, and its influence on cognition in later life.

DIABETES

Type 1 versus Type 2

Diabetes is defined by an inability to regulate blood sugar via the pancreas. There are two types, type 1 which is often congenital and type 2 which can manifest at any point during the lifespan, usually related to obesity. In type 1 diabetes, the pancreas

does not produce insulin properly or in the necessary quantities, often requiring an external pump to supply a proper dosage of insulin (WHO, 2020). In type 2 diabetes, there is a level of resistance in which the body is no longer able to regulate free floating glucose in the bloodstream due to a failure to efficiently produce insulin (WHO, 2020), resulting in glycosylated hemoglobin, which can cause damage to both vascular and neural structures. Thus, diabetes is associated with heart disease, stroke, neural destruction, lower cognitive function, and many other medical conditions, accounting for an increasingly large burden on pharmaceutical and medical expenses in the United States (Shrethsa et al., 2019; WHO, 2020). Notably, a 2017 report by the CDC suggests that currently the United States has approximately 100 million individuals that are at a diagnosable or pre-diagnosable levels of blood sugar for diabetes, with current projections indicating that this number will increase with current trends (CDC, 2017).

One method of diagnosing diabetes is using hemoglobin A1c (HbA1c) as an indicator of sugar intake over the past few months (Ghazanfar et al., 2010). Notably, HbA1c differs from a standard blood sugar test because it measures the percent glycohemoglobin rather than the raw detected metric for free floating glucose molecules in the blood stream (Ghazanfar et al., 2010). However, today both often see use in assessing diabetic status, often in tandem.

Causes of Diabetes and Its Long-Term Health Effects

On a physiological level, type 2 diabetes is initiated by the desensitization of glucagon receptors that are unable to respond appropriately to the presence of sugars and impair the production of insulin to properly regulate it. More precisely, glucagon responds to low levels of blood sugar and causes the liver to begin breaking down

glycogen and releasing it into the blood stream. Following this, once the need for increased blood sugar has passed, insulin is released in response to excessive blood sugar to break down and dispose of the sugar in the blood stream. The dysregulation of insulin production and glucagon receptors can have large effects on neural structure and consequent brain development, thus the risk posed by unregulated diabetes is significant (Bree et al., 2009). Due to the inability to remove glucose from the bloodstream with efficiency, oxidative damage accumulates and can cause destruction of blood vessels, neural synapses, and generally hinder organ function (Marden et al., 2017). Notably, there are both short and long-term physical health detriments in diabetes, and it is possible that this could leave the body in a vulnerable state to the influences of other negative health correlates such as SLEs. SLEs may also modify metabolic behaviors related to glucose receptors and insulin production that accentuates the negative influences of HbA1c (WHO, 2020). With the rates of type 2 diabetes increasing at especially pronounced rates in developed countries (WHO, 2020), this represents a multifaceted public health problem with increased medical costs, compounded adverse health effects, and long-term consequences of weakened organ systems that may further hinder bodily functions that are active in the maintenance of homeostasis.

Diabetes and Cognition

There are direct adverse effects of the high saturation of free-floating glucose in the blood stream. At higher blood sugar levels, hemoglobin is significantly more likely to undergo passive glycation where the glucose binds to the same receptor used to transport oxygen to the brain (Bree et al., 2009). Lack of oxygen transport can have

adverse effects on the brain such as neuronal death (Ergul et al., 2012), oxidative damage (Ahmad et al., 2014), and lower nutrient transport (Marden et al., 2017). Where these smaller effects may not have direct effects instantaneously, neglecting to combat high blood sugar over the long term can allow for continued damage that is strongly linked with lower cognitive scores and problems in brain function. Notably, there are measurable effects for both diabetic and prediabetic levels of HbA1c, and once the healthy levels are surpassed, effects will manifest themselves dependent on the amount of HbA1c present (Marden et al., 2017).

The Present Study

Both hemoglobin A1c (HbA1c) and stressful life events (SLEs) have been associated with impaired cognition across the lifespan using delayed recall memory tasks (Marden et al., 2017), with more pronounced effects on general cognition in later life (for a review, see Feinkohl et al., 2015). In addition to these direct effects on cognition, there is a potential for mediating or moderating effects since SLEs have been shown to further affect numerous pathways related to HbA1c and its damage to the cells, physiological wellbeing, and neural structures (Marden et al., 2017). There have been noted effects on Mini Mental Status Exam performance (Folstein, Folstein, & McHugh, 1975); however, these effects may be contingent upon level of education and age group (Tschanz et al., 2012). Accumulated damage to neurons has the capability to impair an individual's ability to perform Activities of Daily Living (ADL's) as well as Instrumental Activities of Daily Living (IADL's) by reducing cognitive capabilities required to perform these functions. With noted domain-specific and global declines associated with accumulated neural damage, both SLEs and HbA1c in excessive amounts

represent specific concerns for healthy cognitive aging (Gobbens & Assen, 2014). High levels of both stress and HbA1c are associated with development of Alzheimer's disease (Barbagallo & Dominguez, 2014; Smith et al., 2000) and other associated dementias (Feil et al., 2011; Magri et al., 2006), making both areas of interest for preventive care in older adult populations. To the researcher's knowledge however, no one has examined whether HbA1c moderates or mediates the impact of SLEs on cognition in an older adult population.

The proposed study seeks to examine the joint influence of SLEs and HbA1c on cognition in a sample of older adult men using a cross-sectional design. The proposed study will aim to establish main effects on general cognition and individual cognitive abilities. Because there are theoretical justifications to considering HbA1c as a mediator and as a moderator for SLE's influence on cognition, both a mediated and moderated model will be tested and compared for best fit. Using structural equation modeling, the proposed study seeks to investigate the influence of SLEs and HbA1c on cognition, as well as on fluid cognitive abilities, through both mediated and moderated approaches.

CHAPTER 2

REVIEW OF LITERATURE

The literature below pertains to various veins of research focused on cognition across the lifespan, stressful life events and broader varieties of stress, as well as HbA1c and its influence on cognitive outcomes. To best represent the various perspectives relevant to the present work, the literature below covers each of these topics in broader contexts individually, as well as compiling the research done on multiple variables pertinent to the current work (e.g., stress and HbA1c together) initially beginning by addressing the literature on stress and the various ways it is related to age and cognitive outcomes, and then moves into work on stress and HbA1c, as well as work on neuropsychological elements related to HbA1c.

STRESS, COGNITION, AND AGING

Stress and Aging

There are multiple approaches to defining stress, such as a strain (a physiological state) or a stressor (an external event). Stress can best be defined as a transaction between individual resources and environmental demands with the individual experience defined by the joint transaction between these (Aldwin, 2007).There are also different ways of measuring stress, including SLEs and hassles or daily stressors, as well as trauma and chronic role strain. How these various types of stress change with age is remarkably complex and multifaceted (for reviews, see Aldwin et al., 2011; Almeida et al., 2011). Additionally, research on acute stress displays a level of inconsistency between longitudinal and cross-sectional designs in research examining age change versus age differences in hassles (Stawski et al., 2008).

Most work to date has focused on the relationship between aging and life events, which generally show a decrease with age (Aldwin et al., 2011). Early research on SLEs and age found a negative correlation (for reviews see Aldwin, 1990; 1991), however, these measures were more likely to use life events primarily experienced by younger adults and are not as inclusive of the kinds of stressful events that may occur in late life. Newer measures have since been developed to include events that middle-aged and older adults are more likely to experience, and have modest correlations with age (Aldwin, 1990). An early qualitative study found that younger adults are more likely to report positive and negative life events than their midlife and older counterparts, but notably reports did not differ between midlife and late life (Chiriboga, 1997), suggesting that the decline in report is nonlinear. However, a longitudinal study by Aldwin et al. (2011) found that, in general, life events decrease with age. The exception to this rule includes both health-related events (Aldwin, 1991) and loss-related events, which may increase with age (George & Lynch, 2003; Lynch & George, 2002). Thus, it is important to utilize measures of stress that are sensitive to older adults' experiences in later life to more accurately reflect the kinds of stressors they experience in this stage of life.

Cognition and Aging

Cognitive function encompasses a variety of skills and capabilities rooted in brain function, and is often assessed using pen and pencil tests, such as the MMSE (Folstein, et al., 1975), or batteries administered by a researcher in laboratories such as the Neurobehavioral Evaluation System 2 (NES2) (White et al., 1996) and CERAD (Consortium to Establish a Registry for Alzheimer's Disease) (Morris et al., 1989).

Cattell (1963) proposed two broad categories of intelligence: fluid reasoning, which is used in navigating novel problems and new situations, and crystallized intelligence, which relies upon experience and previously learned knowledge. Early work by Baltes & Lindenberger (1997) found gains in crystallized abilities with age and decreases in fluid intelligence, which is consistent with the early work by Horn and Cattell (1967). A comprehensive review by Harada, Love, and Triebel (2013) has since reconfirmed this early finding of stability or modest improvements in crystallized intelligence in normally aging individuals, with declines in fluid cognitive abilities, specifically noting declines in processing speed, attention, memory, visuospatial abilities, and executive functioning in normal aging.

On a global level, declines in cognition are typical, as demonstrated by a wealth of longitudinal research dedicated to the topic. Despite this, specific domains may experience deficits while other faculties remain highly functional and further research continues to assert that fluid cognition generally decline while crystallized cognition modestly improves with age (Salthouse, 2009). Due to the highly individualized nature of cognitive aging, it is important to separate the various facets of cognition when researching cognitive abilities in later life. In normal aging, it is typical to see gains and losses in ability, cognition being no exception. Accumulated experiences may present a substantial benefit to older adults in their crystallized intelligence, however, modest declines in fluid reasoning and ability to navigate novelty are typical in older adults (Schaie & Willis, 2010, p. 376).

Although there are high levels of heterogeneity in cognitive decline, overall cognition is likely to decrease gradually in late life, with more pronounced effects

towards the end of life (Glisky, 2007). Aging research currently suggests that there is an overall decline in MMSE scores in later life, which is additionally supported by modest declines in most areas associated with and representation in the MMSE (e.g., memory and visuospatial abilities) (Schaie, Willis, & Caskie, 2006). These trends in impairment are consistent with other reviews looking specifically at neuroanatomy of the prefrontal cortex and global cognition (for a review, see Gunning-Dixon, Faith, & Raz, 2000).

Despite declines in MMSE scores with age, it is noteworthy that specific domains encompassed by fluid abilities are the primary area of decline, and MMSE scores alone may not always be representative of the specific nature of cognitive decline outside of use as a screening tool (Tschanz et al., 2012). Because the MMSE is used to assess overall cognition using a variety of tasks, it retains high utility as a screening tool which could potentially be used in tandem with specific fluid cognition tasks to better assess the cognition while also emphasizing the areas of most noteworthy decline in fluid abilities.

Importantly, aging is heterogenous and cognition represents a powerful example of this in which one individual may display an entirely different trajectory than a peer; thus, these trends do not hold universally across all people (Salthouse, 2009). Some individuals may maintain high levels of function and ability throughout their entire lifespan leading into later life, whereas others may face declines and impairment throughout their aging or even before old age. Importantly, gains and losses are not universally distributed and thus we can see highly distinct patterns of aging based upon the individual and a variety of biological, cognitive, and psychosocial factors, but remain unable to entirely predict the individualized nature of cognitive aging (Salthouse, 2010).

Thus, this thesis will include both global and domain-specific measures of cognition in order to better reflect where some of these critical gains and losses may specifically exist due to the effects of SLE and HbA1c.

MMSE. The MMSE (Folstein et al., 1975) is a widely used and well-validated assessment of global cognition across several domains (memory, attention, visuospatial skills, orientation, and language.) This test has primarily been used in assessing cognitive decline associated with Alzheimer's or other dementias in older adults and is still widely used today as a marker of cognition or screen for dementia (Farooqui et al. 2017). When cognition is considered as a single trait in global metrics, modest declines are observed with age (for a review, see Karr et al., 2018). Some declines in MMSE scores are normal with aging, but larger declines are often rooted in pathologies such as Alzheimer's Disease or other dementias (Pradier et al., 2014). In general, declines in MMSE scores with age are modest, and are associated with lower levels of overall cognitive function.

Memory. Declines in both working and episodic memory are typical in older adults, although they are modest unless pathologically rooted, with most individuals retaining similar scores across their adult lifespan using lab-administered tasks (Nyberg et al., 2012). In normal aging, an older adult will retain most of their memory. Experiments on human anatomical structures indicate that the decline of specific regions in aging can explain substantial portions of the deficits faced by those with pathological decline, including the lateral prefrontal cortex, the cerebellum, medial–temporal structures, the insula, and the basal ganglia, and white matter volume (Raz et al., 2010). Thus, decline in specific brain regions may constitute a mechanism

by which memory loss occurs. Additionally, longitudinal studies indicate that routine experience of acute stress is associated with declines in self-reported memory capabilities (Stawski, Mogle, & Sliwinski, 2013). Though some individuals are able to retain high levels of function in memory faculties with age, research indicates that memory is an especially vulnerable area for declines in later life when compared to other specific domains of cognitive function (Stawski, Mogle, & Sliwinski, 2013; Nyberg et al., 2012). Due to memory being specifically vulnerable during aging, some decline is expected with advanced age.

Visuospatial abilities. Reduced visuospatial abilities are typically seen in aging, with very pronounced differences between normally aging adults and those with neurodegenerative disorders, as demonstrated by both experiments and performance-based assessments (Karr et al., 2018). Compensatory mechanisms, or cognitive reserves, are unlikely to overcome declines in visuospatial abilities in studies using lab assessments and in fMRI research (Piefke et al., 2012), as well as in research focused on neural connectivity (Pelliciari et al., 2009). In normal aging, these declines are modest but retain significance in their capability to reduce functionality and performance of daily tasks (Karr et al., 2018), potentially posing challenges for older adults in navigating ADL's and IADL's. Individuals may find it more difficult to compensate for visuospatial declines since S1 cortex functionality, one of the primary regions responsible for visuospatial abilities, is unlikely to be compensated for by functionality in another region of the brain (Pelliciari et al, 2009).

Language. Language skills remain intact with modest and often nonsignificant declines with age in ecological assessments (Gilsky, 2007). In instances of

neurodegenerative disorders and dementia, it is common to see declines in language, sometimes accompanied by development of speech disorders. In normal aging, these modest declines may explain lower scores on language-based cognitive assessments, but particularly in recall tasks (for a review, see Karr et al., 2018). It is unlikely that language abilities decline with normal aging, as declines are very modest or nonsignificant.

To the author's knowledge based upon the reviewed literature, there is currently no literature examining the interaction between stress and HbA1c, though there is a wealth of literature dedicated to influences of HbA1c on cognition, stress on cognition, and further literature on HbA1c and stress in a non-interactive context.

Hemoglobin A1c and Cognition

HbA1c is a measure of blood sugar over the past two to three months (for review see Ghazanfar et al., 2010). Specifically, HbA1c is a measure of the percentage of red blood cells in a drawn sample that have glycosylated. Once red blood cells have undergone glycosylation, no known organic compound is capable of severing the bond between hemoglobin and glucose, meaning that it will last until the blood cell dies, hence its ability to for estimating blood sugar over a sustained period (Ghazanfar et al., 2010).

There may be age differences in what levels of HbA1c are considered healthy in maintenance of neural function. In normal aging, an older adult is likely to need slightly higher levels of HbA1c than younger adults do in order to better maintain organ health and function (Pani et al., 2008). When broader measures of organ system function were used, age differences were observed with older adults requiring higher levels of HbA1c

than younger adults. This trend of older adults requiring more HbA1c has been observed in studies looking at smaller specific organs as well and is largely credited to decreased erythrocyte count and lower rates of erythrocyte replacement (Bae et al., 2014). Notably, having lower erythrocyte count with lower replacement means that there is likely to be more glycosylated hemoglobin present in the blood stream at any given moment assuming a similar diet.

There are a variety of demonstrated and proposed mechanisms by which HbA1c influences cognition; some are rooted in oxygen deprivation due to the glycosylation of the erythrocytes. One of the most direct mechanisms is by limiting the ability of the red blood cells to transport oxygen to the brain, resulting in oxygen deficits that impair functioning. Further bolstering the model of oxygen deficits causing impaired cognitive abilities, a meta-analysis found a 65% increased risk for developing dementia in those with diabetes, credited largely to inability to transport adequate oxygen for brain function and repair (Arvanitakis et al., 2004). These findings are particularly relevant to diabetes and HbA1c since they represent another mechanism by which higher levels of glycosylated red blood cells create damage and inhibit brain function on an anatomical level, which can promote tau cluster tangles and amyloid plaque formation (for review on Amyloid plaques, Tau cluster tangles, and additional biological pathways, see Wang & Michaelis, 2010). Though the amyloid plaque and tau cluster tangle hypothesis is supported by compelling evidence, it remains limited to correlational designs, and the mechanisms underlying these effects are not well understood (Roberts et al., 2014), though current literature suggests they represent a key area for future research. Furthermore, there is still heterogeneity to the development of these plaques and

tangles, and there remains potential third variables that make the direct mechanisms unclear. With impaired neural functioning, performance on cognitive tasks is expected to decline based on previous findings using paper-based cognitive tasks (Bishop, Lu, & Yankner, 2010), with heterogeneity in specific domains that are known to typically decline.

Another mechanism by which high HbA1c may be associated with cognitive decline is due to the damage to blood vessels through glyco-oxidative processes, or glucose-related oxidative reactions in the bloodstream. Specifically, higher HbA1c levels are strongly associated with increases in glycosylation and consequent oxidation damage to the blood vessels in processes that have been known to potentially be precursors to development of Alzheimer's and heart disease. By impairing neural functioning and accelerating cell death, cognitive faculties are further hindered, and prolonged exposure to high levels of HbA1c can result in substantial damage to blood vessels and organs that inhibit their ability to function normally as damage accrues (Ahmad et al., 2014). Following glyco-oxidative damage, there may be shrinkage in blood vessels and brain volume, problems in neuronal communication, arteriole clogging, heighted levels of inflammation, and hindered neurogenesis (Ergul et al., 2012) suggesting additional prospects as a mechanism behind cognitive decline. Not only does glycoxidation impaired neurons by weakening synapses and causing cell death (Ahmad et al., 2014), but the restriction of blood flow through shrinkage and clogging prevents oxygen transport to impair the neurons (Ergul et al., 2012), creating further damage and decreased cognitive function. These factors jointly create

decreased functionality in already existing networks, while also impairing repair and replacement processes that may further exacerbate damage from high levels of HbA1c.

The literature on HbA1c levels and cognition has demonstrated an inverse relationship between HbA1c levels and cognition (for review see Feinkohl et al., 2015), with exacerbated effects at higher levels due to insulin resistance (Roriz-Filho et al., 2009; Mayeda et al., 2015). HbA1c has a variety of demonstrated pathways by which it can influence cognition and health. Juster, McEwen, and Lupien (2009) reviewed the current state of research using allostatic load to predict cognition. In this review, every article that used HbA1c as a factor in allostatic load and reported a correlation matrix demonstrated a significant influence of HbA1c on cognition, with higher HbA1c levels associated with lower cognitive performance. Newer literature on allostatic load has demonstrated an effect consistent with Juster, McEwen, and Lupien, using a population of older adults (Booth et al., 2015). Further, fluctuations in HbA1c also affected variability in cognitive function, as demonstrated in a study by Marden and colleagues (2017) using ecological measures of general cognitive function.

Much of the literature to date has focused specifically on the influence of diabetic or prediabetic levels of HbA1c and cognitive scores, although effects have been observed regardless of a diabetes diagnosis (Marden et al., 2017), indicating that the relationship exists independent of a diagnosis. Specific research has noted that experimentally-assessed abilities in attention and the ability to focus, as well as memory and learning processes, suffer as a result of higher HbA1c levels in younger, middle aged, and older adults (Brismar et al., 2007; Marden et al., 2017), further demonstrating an association with impaired performance throughout the lifespan and in old age.

Current literature published on HbA1c and cognition converges on an inverse relationship by which increases in HbA1c will impair cognitive function in global measures, as well as in attention, visuospatial skills, memory, and learning-based tasks.

Perhaps the most widely credited mechanisms for this relationship include stress and destruction of neural pathways associated with these cognitive constructs. Research utilizing cognitive batteries that incorporate language and visuospatial elements as a component of general cognitive functioning indicate that these constructs decline in the face of heightened HbA1c levels (Rawlings et al., 2014; Talarowska et al., 2009).

Research on stress and HbA1c maintains impressive consistency in demonstrating an inverse relationship between HbA1c and cognitive performance. Accumulated brain damage and poor neuron maintenance can promote Tau clusters and Amyloid plaques (Wang & Michaelis, 2010) with additional damage caused by apoptosis of brain cells due to lack of oxygen (Arvanitakis et al., 2004). Furthermore, blood vessels accumulate damage and loss of efficient function through oxidative damage (Ahmad et al., 2014), which can further promote clogs and shrinkage of blood vessels and arterioles which are crucial in transporting nutrients to the brain and preventing neural death (Ergul et al., 2012). The primary outcomes of these accumulated damages most notably include death of neurons, and prevention of neural maintenance and nutrients to function.

Stress and Cognition

Much of the emerging literature on stressful life events and cognition has been focused on early childhood, especially on adverse childhood experiences (ACEs) and

traumatic stress. Generally, the literature on traumatic stress has shown a significant influence in a variety of both experimental and ecological studies, and for a variety of cognitive domains (Schalinkski et al., 2018). However, the present review will focus on research in later life.

Using the MMSE, both acute and chronic stressors are associated with impaired cognitive performance in several age and demographic groups, with protective effects found from increased time spent in a formal educational setting. Older adults were less likely to return to previous levels of cognitive ability following a stressful life event (Tschanz et al., 2012; for review see Qureshi et al., 2011). Continued acute stress is additionally associated with declines and impaired cognitive health using broad indicators such as Response Time Inconsistency (RTI), though marked differences exist dependent upon how one responds to the stress and ability to cope (Stawski et al., 2019).

Despite these trends, there are inconsistencies in the literature that are further complicated by small samples and a lack of longitudinal studies that go beyond short frames of observation which limit current understanding of the developmental influence of stress on cognition. Early studies showed no effects for generalized stress measures on cognitive performance (Amster & Krauss, 1974) but others showed an inverse relationship in which declines in fluid and crystallized intelligence were associated with SLEs (Sands, 1981). Additionally, some research has found no effect for number of SLEs, but significant effects of loss-related SLEs exclusively (Grimby & Berg, 1995). The relationship becomes less clear, as some research found that SLEs are associated with improved cognitive function (Comijs et al. 2011; Rosnick et al., 2007). However, the

exact relationship between SLEs in older adults can be challenging to assess because most of the literature to date has not focused on older adult experiences with SLEs using an age sensitive metric, which limits our current understanding due to a lack of utilization of age specific scales for SLEs.

Another possible explanation for this variability in findings of SLEs and cognition that there may be important moderating effects which underlie the heterogeneity in results across different cases in addition to the inconsistency present between different measurements. For example, one study found that SLEs were associated with lower MMSE scores, but only in instances in which the individual was already impaired (Peavy et al., 2009). The association between SLEs and lower MMSE scores has since been replicated, though newer findings have shown that this only holds true for those who are also facing decreases in social support (Dickinson et al., 2011). Physiological factors may also be important moderators. Some emerging research has shown that effects of SLEs are moderated by presence of expressed ApoE4 genotypes, with carriers experiencing greater cognitive impairment in the face of SLEs (Comijs et al., 2011).

To address these inconsistent results, Tschanz and colleagues (2012) examined both moderators of the relationship between SLEs and cognition, as well as exploring non-linear relationships using a large longitudinal sample with a longer frame of observation. Using a revised MMSE reduced to two items representing each domain, they found evidence of an interaction between education and SLEs, in which higher education groups displayed less vulnerability to the negative effects of SLEs on cognition and would recover at a faster rate. These effects were more pronounced in

older adults than in their younger counterparts, with an age-graded effect, indicating that the older an individual was, the more likely the interaction was to predict decline.

Contrary to previous findings, no moderation effects of the ApoE4 genotype were found (Tschanz et al., 2012), which could potentially be influenced by the heterogeneity in aging between subjects. Current reviews on ApoE4 genotype and cognition demonstrate an inverse relationship, although the specific cognitive facets that decline demonstrate no significant consistency (Banning et al., 2019), further supporting the importance of individual trajectories in research on genetic influences.

Tschanz et al. (2012) also explored the non-linear relationship between SLEs and cognition. Laboratory studies often find an inverted U shape reminiscent of the model put forth by the Yerkes-Dodson Law (Teigen, 1994). However, Tschanz and colleagues found modestly U-shaped curves, indicating that stress was associated with cognitive decline for an initial period, but individuals were able to recover and regain previous levels of cognitive function after the period of decline. This might explain inconsistencies in findings of a positive, negative, or no relationship between SLEs & cognition – perhaps the timing of the measures reflected the different slopes on the U-shaped curve, indicating that timing of SLEs may be an especially salient factor that is not reflected in most current literature. While most experimental studies display stress patterns reminiscent of the Yerkes-Dodson Curve, SLEs appear to display an opposite trajectory, indicating that the Yerkes-Dodson might not pertain to SLEs, and may provide useful insight in experimental results that do not translate to ecological studies. Because of potential nonlinear effects found by Tschanz and colleagues, one may instead expect that the effect of stress will be dependent upon the timing of the stressful

event relative to cognitive assessment. Age effects were noted where older participants were less likely to recover to previous levels of cognitive ability than the younger groups of participants.

The effects of SLEs on the brain and associated pathways are well documented, and overwhelmingly converge on the conclusion that they are detrimental (for review see Wager-Smith & Markou, 2011). Among these pathways are increased apoptosis of neurons and dendritic atrophy (Woolley et al., 1990), decreased neuroplasticity and neurogenesis (Smith et al., 1995), and a reduction of dendritic spines (Chen et al., 2008c). Noted decreases occur at global levels (Vaidya et al., 1999), however there are also potential regional differences that disproportionately effect brain derived neurotrophic factor levels in the hippocampus (Czeh et al., 2002; Aleisa et al., 2006), nucleus accumbuns (Eisch et al., 2003), median eminence (Givalois et al., 2004), dentate gyrus attenuates (Adachi et al., 2008) and the prefrontal cortex which is further associated with impaired function and smaller overall volume (Arnsten, 2009). Most of this work also supports differential effects based on the individual (Wager-Smith & Markou, 2011), however on a broader level these trends hold with adequate consistency and across the brain there are observed decreases in brain derived nuerotropic factors (Vaidya et al., 1999). Various cognitive faculties are associated with the areas impacted by SLEs. For example, the prefrontal cortex which is thought to be a specific area of interest to a variety of cognitive abilities such as language production, visuospatial skills, and memory (Bruehl et al., 2009; Ansell et al., 2012), as well as the hippocampus which is strongly associated with memory capabilities (Papagni et al,. 2010), as well as global change with noted individual differences (Wager-Smith &

Markou, 2011) which highlight the importance of considering multiple aspects of cognitive function when considering overall cognitive capability and the hazards they face in older age.

Hemoglobin A1c and Stress

Previous literature has indicated that a variety of mechanisms may create co-actional effects between stress and HbA1c, with current research suggesting ample justification for both mediating and moderating influences, at least in animal models (McFall et al., 2010). Some research has indicated that stress, especially SLEs, may change eating behaviors and cause an individual to gravitate towards foods high in sugar increasing HbA1c levels, and stress of any type is correlated to higher levels of HbA1c and lower engagement in health behaviors (Sinha & Jastreboff, 2013). Stress eating, and especially dysregulation of standard eating patterns, poses specific risk for heightened levels of blood glucose (Hucklebridge et al., 1999; Ortiz & Wiley, 2018), and consequent HbA1c formation. To the author's knowledge, there is no research focused specifically on HbA1c levels and stressful life events as they pertain to cognitive outcomes, although some health behavior literature has found effects for both acute and chronic stressors, as well as a wealth of literature dedicated to increased sugar intake following SLEs (Soo & Lam, 2009). One specific study found that acute stress was not related to glycemic control unless it was examined using specific categories for stress, where the authors found that older adults were specifically at risk if the daily stress was relational or physical health-related (Walker et al., 2019). High levels of stress and HbA1c additionally cause destruction to neurons, weakening of synapses, and in excess can impair cognitive performance (Miller & Spencer, 2014). Soo & Lam (2009)

found that chronic stress created spikes in key hormones that mechanistically regulate HbA1c levels, causing higher levels of HbA1c as a direct result of heightened stress, indicating that stress may play an important role in the regulation of HbA1c levels indirectly via blood glucose levels. To the author's knowledge, however, previous publications have not looked at the interaction between HbA1c and stress as a predictor for cognitive outcomes.

Hemoglobin A1c, Stress, and Neurophysiology

High levels of HbA1c have been associated with deficits in specific areas of the brain, specifically the frontal lobe (Bruehl et al., 2009), associated with deficits in executive functioning and memory, the superior longitudinal fasciculus (van Bloemendaal et al., 2016), associated with language, and the uncinate fasciculus (Kim et al., 2016), associated with memory and global function. Additionally, stressful life events have similarly been associated with deficits in brain areas such as the frontal lobe (Ansell et al., 2012), the hippocampus and the anterior cingulate (Papagni et al., 2010) which are both associated with memory. Accordingly, the selected cognitive tests reflect the skills associated with these functions, including the MMSE (Folstein et al., 1975) for global functioning, total word recall from the CERAD (Morris et al., 1989) for memory, the pattern recognition task from the NES2 (White et al., 1996) for visuospatial abilities, and the verbal fluency task from the CERAD (Morris et al., 1989) to represent language abilities.

The relationship between HbA1c and SLEs leaves room for potential mediating or moderating pathways. For example, if a stressful life event causes higher levels of HbA1c, as demonstrated by Sinha & Jastreboff (2013), these accumulated damages

may begin to impair brain function and promote neural apoptosis in a similar way to that of SLEs themselves which are associated with impaired neural function and poorer neural maintenance (Wager-Smith & Markou, 2011), representing a potential mechanism by which SLEs are able to induce change in HbA1c that can impair cognition. Additionally, it is possible that the strength of the relationship between SLEs and cognition could be exacerbated or reduced by the level to which HbA1c impairs neural repair or otherwise creates harmful structural changes such as clusters and plaques (Wang & Michaelis, 2010). For these reasons, the present study will focus on the potential for mediating and moderating pathways of influence, considering HbA1c as a mediator and then as a moderator for the relationship between SLEs and various cognitive outcomes.

Summary

The literature reviewed above suggests that there will be significant and differential impairment to various domains of cognition with increases in HbA1c and SLEs. With current trends in diabetes worldwide and especially in the US, one can expect that these exacerbating influences on normal aging processes will prove costly and burdensome for the healthcare system. By differentiating between the various cognitive domains, the proposed study seeks to investigate the coaction of SLEs and level of HbA1c across a variety of cognitive measures. This approach considers them not only as separate, direct effects, but in an interactive and mediating context. To the researcher’s knowledge, this would be the first study to examine such multidimensional effects in a field setting.

Due to the complex interrelationships between SLEs and HbA1c as they affect various neural pathways and impair brain repair and maintenance, the present study will consider these effects in tandem as they may offer insight in models of mediation and moderation. Furthermore, due to potential differences in brain regions that are vulnerable and their associated cognitive faculties, various cognitive task will be used to best represent the areas that are critically impacted.

Present Study

A conceptual model representing the proposed pathways in the present study can be found in Figure 2-1. Based upon previous research, it is expected that higher SLE and higher HbA1c levels will be associated with lower levels of cognitive function across the various domains, with the most pronounced differences found in visuospatial function. Preliminary analyses will first examine be intercorrelations among SLEs, HbA1c, and the various cognitive measures. These intercorrelations will be more salient for more fluid cognitive factors as well as MMSE scores, visuospatial skills, and less pronounced in memory and language abilities. Additionally, these relationships may be more pronounced among the old-old (75+) as compared to the young-old (<75). The present study will investigate three hypotheses:

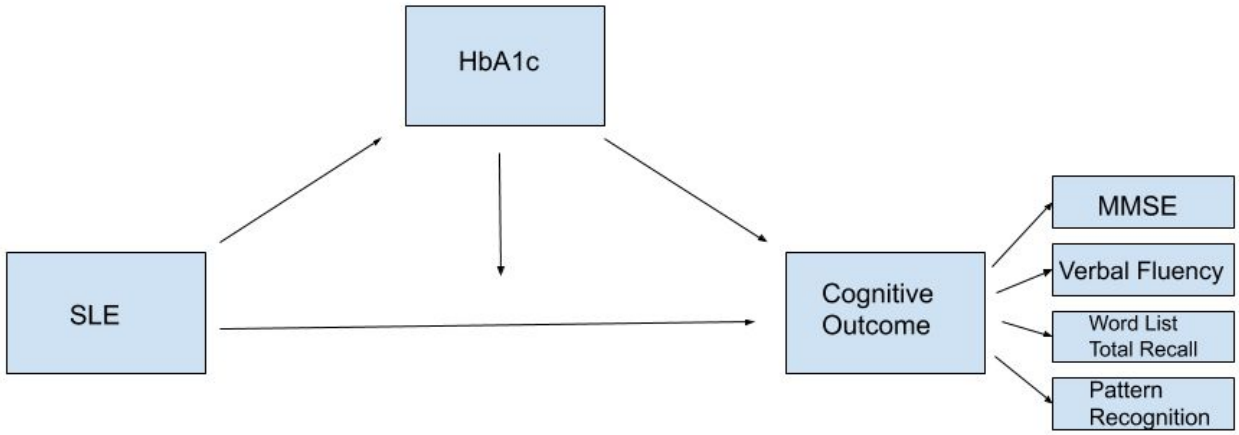
1. Does HbA1c mediate the relationship between SLEs and global cognitive impairment, language, memory, and visuospatial abilities?

2. Does HbA1c moderate the relationship between SLEs and global cognitive impairment, language, memory, and visuospatial abilities?

3. Are there differences in the strength of directions of the analyses for Hypothesis 1 and 2 when the sample is stratified by age and education?

Figure 2-1.

Conceptual Model for the Present Study



CHAPTER 3

METHODS

Sample and Procedure

The VA Normative Aging Study (NAS) began in 1963 as a cohort study of 2,280 aging men who were screened for good health, defined as the absence of chronic conditions and blood pressure of 140/80 or lower (Bell, Rose, & Damon, 1972). Since 1986, NAS participants report every three years for a medical examination, at which time a fasting blood draw is done by a board-certified internist (Bossé, Ekerdt, & Silbert, 1986). Prior to reporting for the medical examination, the NAS men completed the Health and Social Behavior (HSB) survey, which contains demographics, self-rated physical health, and stress measures (Aldwin et al., 2011). The first wave of the cognitive assessments used in the present study were administered individually between 2002 and 2006, using measures from standard neuropsychological batteries (see Brady, Spiro & Graziano, 2005).

Between 2002 to 2006, 578 NAS participants completed assessments of HbA1c and SLEs. During this time, demographic variables were updated as appropriate (e.g., marital status) to reflect the current status of the participants. The present study utilized data from 578 participants (M_{age} = 74.5 years, SD = 6.5 years) who completed the neuropsychological battery, as well as the HSB survey, and who had HbA1c assays. Of these participants, individuals with a diagnosis of dementia (32 participants) or history of stroke (33 participants) were removed, leaving a retained sample of 527. Of the retained sample of 527, 424 of them had spouses. They were highly educated: 352 (67%) had at least some college education ($M_{education}$ = 14.7 years, SD = 2.7 years) and fairly healthy.

Only 14 had a diagnosis of diabetes and 16 had a history of smoking. Participants with a diabetes diagnosis were not removed from the participant pool, as the present study was interested in the interaction between HbA1c and SLEs, thus diabetes did not constitute a concern as the reason for higher HbA1c levels was not of interest to the present study.

Due to substantial missingness in the data set, structural equation models using maximum likelihood estimation through the Lavaan package (Rosseel, 2019) was employed to maintain sample size across all analyses. Due to this, no participants were excluded on the basis of missing data. However, sample size varied slightly across analyses due to removal of outliers by specific cognitive outcome.

Measures

Global cognition. For a measure of global cognition, the Mini Mental Status Exam (MMSE) (Folstein et al., 1975) was used. The MMSE briefly assesses multiple areas of fluid and crystallized cognitive function, and thus can effectively represent impairment in a general way to quickly screen a participant for dementia or deficits in cognitive performance. Because this test utilizes a variety of fluid domains to create a composite score of overall impairment, it was considered as an outcome separate from the specific domains as a means to better reflect general impairment in functioning versus potential domain specific effects. A standard MMSE scale would have a maximum score of 30, however the item indicating participants' ZIP code was committed due to concerns over relevance and meaning since counties in Massachusetts have little political meaning and are not well known (Weisskopf et al., 2004, and thus the maximum score was 29 (M

= 27.40, SD = 1.65, range = 20-29, skewness = 1.26, kurtosis = 1.83, 16 missing values); a higher score indicates better cognitive functioning.

Language. Verbal fluency was measured through a semantic task drawn from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) (Morris et al., 1989). The specific task used for verbal fluency was category fluency (animal naming), in which participants were given 60 seconds and asked to generate a list of animal names. Following the 60 seconds, participants were scored based on the number of unique animal names generated in the given time frame, with a higher score indicative of more unique names produced (M = 18.38, SD = 5.10, range = 2 - 34, skewness = 0.25, kurtosis = 0.00, 94 missing values).

Memory. The CERAD (Morris et al.,1989) uses word list tasks to test immediate, delayed, and cued recall, which is the ability to recognize words when presented with a list to which respondents were previously exposed. Given the high intercorrelations among these measures, word list total recall was used to represent memory to best avoid concerns of multicollinearity throughout the analyses (M = 18.75, SD = 4.01, range = 4 - 30, skewness = -0.20, kurtosis = 0.22, 58 missing values.)

Visuospatial. Computerized pattern recognition tasks, as used in the Neurobehavioral Evaluation System 2 (NES2) (White et al., 1996), are frequently employed to represent visuospatial capabilities. The pattern recognition tasks consist of participants being presented with three patterns on 10x10 matrices (two of these patterns will be identical, with one differing). Participants are then asked to identify the pattern that is different from the two identical ones. Due to the computerized nature of the NES2, it is easy for it to collect a variety of measures, such as response time, and

score for correct versus incorrect responses. For purposes of the present study, number of correct responses was used to represent visuospatial skills (M = 23.76, SD = 1.62, range = 14 - 25, skewness = -1.94, kurtosis = 5.4, 219 missing values).

Stressful life events. SLEs were measured using the Elder Life Stress Inventory (ELSI; Aldwin et al., 2014). The ELSI is a 30-item scale that aims to capture daily events that older adults are more likely to experience. This scale reflects events that span a variety of domains, such as health problems, stressful social happenings, and familial stress (Aldwin, 1990). For purposes of the present study, a composite score of all non-health related items from the ELSI was used due to concerns over the confounding of the health items on the scale for biomedical and cognitive outcomes. Initial assessment of the SLE variable displayed substantial skewness (M = 1.11, SD = 1.61, range = 0 - 17, skewness = 4.22, kurtosis = 29.84, 125 missing values) that created potential problems for analyses, especially regarding possible collinearity concerns with an interaction term. Thus, SLE was square root transformed to provide a more normal distribution that could be used in the regression models to alleviate some concerns of highly correlated predicters. The descriptive statistics for the square root transformed variable are as follows (M = 0.76, SD = 0.73, range = 0-4.12, skewness = 0.59, kurtosis = 0.43, 125 missing values). A comparison of the non-transformed and transformed SLE variable can be found in Figure 3-1. Following a square root transformation, the SLE variable was closer to a normal distribution but remained highly skewed in the same direction. The distribution following transformation was still far from normal, but it was closer by a substantial margin and thus it was maintained for analyses.

Hemoglobin A1c. HbA1c assays were done using fasting blood draws. These tests represent the level of glycosylated hemoglobin in the red blood cells at the time of blood draw. Prior to reporting to the NAS, participants underwent an overnight fast. Upon arrival, respondents report to the medical laboratory for a fasting blood draw, and then undergo a post-challenge glucose test (100g). Assays were collected using a Tosoh-G8 glycohemoglobin analyzer, a specialized HbA1c analysis instrument (www.diagnostics.eu.tosohbioscience.com). The descriptive statistics for HbA1c are as follows: M = 5.67, SD = 0.69, range = 3.6 - 9.4, skewness = 2.03, kurtosis = 7.85, 13 missing values.

Covariates. Age and education were used as covariates in the SEM models, with age represented as chronological years and education as number of complete years of formal education.. Previous literature (e.g., Baltes & Lindenberger, 1997; Harada, Love, & Triebel, 2013; Moye et al., 2011) indicated that advanced age is associated with declines in fluid intelligence and modest increases in crystallized intelligence. Education on the other hand, is associated with higher levels of cognitive performance and potentially acts as a protective factor against cognitive decline and dementia in later life. The descriptive statistics for the covariates are as follows: M_{age} = 74.34 years, SD = 6.5 years, range = 59-97, skewness = .27, kurtosis = .01. $M_{education}$ = 14.7 years, SD = 2.7 years, range = 6-25, skewness = 5.34*(e^-1), kurtosis = .11.

Analyses

Structural equation models (SEMs) were computed for both mediating and moderating models (Hypothesis 1 and 2, respectively, as well as the within age group analyses in Hypothesis 3). SEM was chosen due t the substantial flexibility it offers in

using a variety of variable types (observed variables, index variables, and task oriented at representing a broader construct). Specifically, SEM is able to estimate multiple dependent relationships simultaneously which provides utility for the covariates of age and education, as well as perform mediation analyses more effectively for the direct, indirect, and total effect, which can be computed within the model. Maximum likelihood estimation (MLE) was performed using a common seed value as a reference for the MLE to obtain reproduceable values. The Lavaan package for R (Rosseel, 2019) was used for all analyses to construct SEMs and estimate missing values.

Outliers. Several approaches were utilized to assess outliers pertaining to specific models and on a multivariate level. All assessments of outliers were performed using the FAoutlier package for R studio (Chambers, 2015) to obtain general Cook's distance values for all participants in each model, as well as Mahalanobis distances to assess multivariate outliers. However, the Mahalanobis distances appeared to find multiple groups and thus it overestimated the number of outliers to be trimmed based on distance from a presumed singular cluster, which did not represent a good fit for the data. Due to this, Mahalanobis distances were not pursued in the removal of outliers.

To assess model specific outliers, General Cook's Distance values were produced for each case on a per model basis to determine how far the value was from each regression line. This approach had greater utility in assessing the outliers to be trimmed, and as a result General Cook's Distance was used as the criteria to remove cases. To determine which cases should be treated as outliers for each model, a cutoff of three times the mean general Cook's distance (Kutner et al., 2005) was used to remove cases that bear disproportionate influence on the model relative to the other cases.

Other methods utilizing General Cook's Distance were considered, including trimming all values below 1 (Cook, 1977), as well as using four divided by the sample size to produce a cutoff point (Fox, 1991). Both of these methods were deemed less useful, as trimming values below 1 was typically used in smaller sample sizes to reflect a more lenient cutoff criteria and for this data it was far too conservative in consideration of values to trim which was not particularly high utility. Alternatively, the criteria of 4 divided by the sample size appeared to overestimate the amount of cases to be removed perhaps due to the multiple clusters where it was not able to account for the distribution of the data in a meaningful way. Due to this, the first cutoff criteria of 3 times the mean (Kutner et al., 2005) was used as it was able to better account for multiple clusters by using the data as a reference point rather than absolute values that were not as applicable to the present data, as this one considered the average in a way that could factor in the multiple clusters and better reflect the trends in the data as per the specific model. Under the selected criteria, 26 cases were removed for MMSE models, 34 cases were removed for Verbal Fluency models, 30 cases were removed for Word List models, and 15 cases were removed for Pattern Recognition models. Generally speaking, outliers did not overlap substantially, and only 3 cases were outliers across all cognitive outcomes, 7 cases were outliers on three or more cognitive outcomes, 21 cases were outliers on two cognitive outcomes, and 40 cases were unique to one cognitive outcome. Due to the difference in number of outliers per analysis, participant pools will vary modestly by analysis. After the removal of outliers, MMSE analyses had 501 participants, verbal fluency analyses had 493 participants, word list analyses had 497 participants, and pattern recognition analyses had 512 participants.

Outlier *t*-test results. Upon removing outliers, *t*-tests were used to determine whether there were significant differences between the outliers and the maintained sample for the covariates age and education. All t-tests used were calculated using a Welch's t-test, which provided non integer degrees of freedom due to the non-equal variance between the groups compared. For MMSE scores, verbal fluency, and pattern recognition, there were no significant differences for age or education. However, word list total recall displayed a significant difference in age between outliers and the maintained sample where the outliers were significantly younger than the maintained sample (p = .004), with no significant differences by education. Results from the initial *t*-tests are displayed in Tables 3-1 and 3-2.

Additional *t*-tests were used to compare mean scores for the cognitive outcomes for the removed outliers and the retained sample (see Table 3-3). The outliers did not substantially differ from the retained sample except for the analyses for the pattern recognition task, where the outliers scored lower than their retained counterparts (p = .008).

Hypothesis 1, mediation. The first hypothesis predicted that HbA1c will mediate the relationship between SLE and the cognitive outcomes. To assess this, structural equation models were used to incorporate covariates, using MLE to account for missing data, as well as a 1000 iteration bootstrapping procedure to estimate parameters as well as determining significance of the mediating effect. For estimation and bootstrapping, a preselected anchor seed of 1337 will be used to maintain replicable results for all estimated values. Covariates for these models will include age and education.

Hypothesis 2, moderation. The second hypothesis predicted that HbA1c will moderate the effect of SLEs on the cognitive outcomes. To examine this, structural equation models using MLE were used to handle missing data. A computed interaction term between HbA1c and SLE was use as a predicter in a regression model after the main effects of HbA1c and SLE with covariates of age and education were entered.

Hypothesis 3, age stratification. The third hypothesis will explore whether there are differences in hypothesis 1 and 2 by age using a median split stratified sample (median splits: 59-74 years, N = 273, and 75-94 years, N = 254). Due to the possibility that a specific demographic may be especially vulnerable, these exploratory analyses will be used to inform possible directions for improving the analyses in hypotheses 1 and 2. Where some of the previous literature has explored this by stratifying the sample into three age categories (e.g., Tschanz et al., 2012), the present study will utilize a median split of age to provide balanced and meaningful groups that were useful for analysis.

Ideally, a three-way interaction model using age, HbA1c, and SLE would have been computed for these analyses. However, due to high skewness there were concerns of multicollinearity, and models were not able to converge due to high intercorrelations among the various interaction terms. Due to this, age groups were stratified and a single interaction term of HbA1c and SLE was used in order to assess Hypothesis 3.

Table 3-1.

Comparison of Age between the Outliers and the Retained Sample

Variable	Outlier	Retained	*t*	df	*p*	95% CI
MMSE						
N	26	501	-1.15	28.56	.260	-3.67, 1.03
Mean	73.08	74.40				
Verbal Fluency						
N	34	493	-1.33	39.17	.190	-3.44, 0.71
Mean	73.06	74.42				
Word List Total Recall						
N	40	487	-2.98	49.45	.004	-4.41, -0.86
Mean	71.9	74.54				
Pattern Recognition						
N	15	512	-0.37	14.85	.720	-4.22, 2.98
Mean	73.73	74.35				

Table 3-2.

Comparison of Education between the Outliers and the Retained Sample

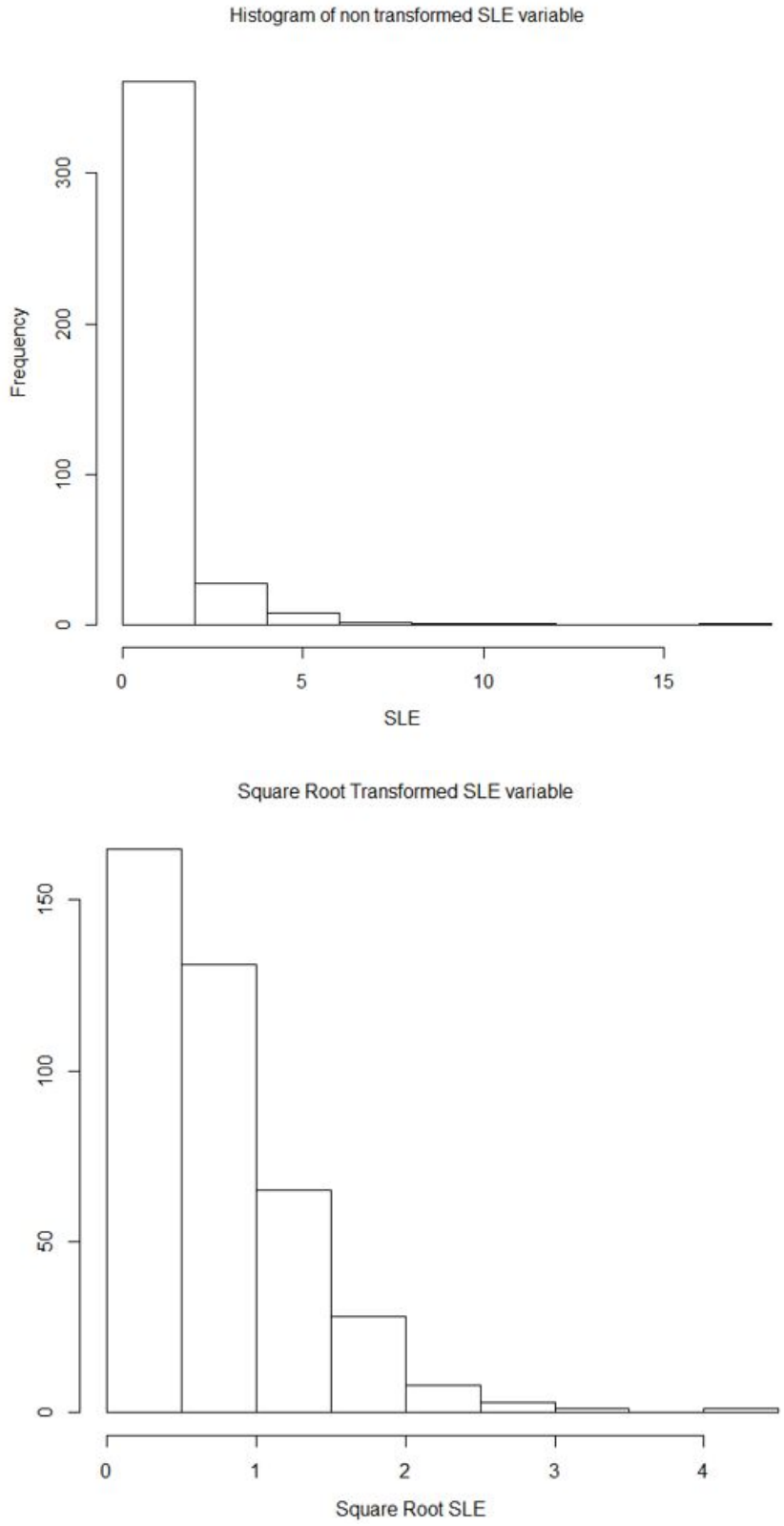
Variable	Outlier	Retained	*t*	df	*p*	95% CI
MMSE						
N	26	501	-0.93	27.03	.360	-1.85, 0.70
Mean	14.15	14.15				
Verbal Fluency						
N	34	493	1.32	35.87	.190	-0.42, 2.00
Mean	15.44	14.65				
Word List Total Recall						
N	40	487	-0.66	47.11	.510	-1.11, 0.56
Mean	14.45	14.72				
Pattern Recognition						
N	15	512	-0.04	14.41	.970	-2.16, 2.08
Mean	14.67	14.7				

Table 3-3.

Comparison of Cognitive Outcomes in Outliers and the Retained Sample

Variable	Outlier	Retained	*t*	df	*p*	95% CI
MMSE						
N	26	501	1.70	26.30	.101	-0.161, 1.696
Mean	26.69	27.46				
Verbal Fluency						
N	34	493	-0.01	35.13	.988	-2.81, 2.77
Mean	18.47	18.45				
Word List Total Recall						
N	40	487	-0.34	41.71	.736	-2.40, 1.71
Mean	19.08	18.73				
Pattern Recognition						
N	15	512	3.05	14.20	.008	0.82, 4.64
Mean	21.20	23.93				

Figure 3-1.
Comparison and Stressful Life Events Variable Pre and Post Transformation



CHAPTER 4

RESULTS

The NAS men in this subsample were relatively healthy. With the cases of dementia and stoke removed, the average MMSE score was 27.42 out of 29; only 12 (approximately 2% under a composite of 24) met the criteria for cognitive impairment. Similarly, HbA1c scores were also largely in the normal range; only 58 participants met the criteria for diabetes using HbA1c as the primary metric. Stress levels were low, with a mean score of 1.1; 31% reported no stressors in the past year.

For ease of reading and interpreting the analyses for each hypothesis, a summary table denoting any significant effects, or in the case of Hypothesis 3, any significant differences by age, is included at the end of the results section. However, the detailed outputs for each model are provided for reference in Appendices A-C. For clarity of communication, this section will exclusively use the summary tables while referencing the information from the various models.

Preliminary Analyses

An initial pairwise correlation matrix is presented in Table 4-1. Results indicated that age was significantly correlated to all cognitive outcomes, and education was correlated to all cognitive outcomes except for the pattern recognition task, and thus they will be used as covariates in all the models. The cognitive variables were strongly correlated with MMSE scores, as well as each other, with the only exception being pattern recognition and verbal fluency, which were not significantly correlated to each other but still demonstrated strong correlations to the other variables. Additionally, stressful life events and HbA1c were not correlated at the zero-order level in this

sample. However, age and education were correlated/confounded with these two variables, and it is possible that a relationship may emerge in multivariate analyses.

Hypothesis 1: Does HbA1c Mediate the Relationship between Life Events and Cognition?

SEM analyses for Hypothesis 1 are presented in Table 4-2 for MMSE, verbal fluency, word list total recall, and pattern recognition. Full tables, including model fit statistics, are presented in Appendix A. For all analyses, 1000 iterations of bootstrapping were done to provide estimates of confidence intervals. Significance of the mediation effect was assessed using the indirect pathway produced through the bootstrapping procedure. Briefly, results indicated that this hypothesis was not supported for any of the outcomes, as there was no significant relationship between SLE and HbA1c in any of the multivariate analyses. Nonetheless, the pattern of direct effects for the different analyses was instructive, and thus the results will be discussed in some detail.

MMSE. For MMSE scores, both age and education were significant, with lower scores at older ages and higher scores with higher education levels. SLE showed a significant relationship with MMSE, with higher levels of stress being associated with lower MMSE scores. HbA1c was marginally related to MMSE scores, $p = .058$, with higher HbA1c scores associated with lower MMSE levels. However, there was no significant relationship between SLE and HbA1c, and thus no significant indirect pathway. the mediation hypothesis was not supported.

Verbal Fluency. For verbal fluency, both age and education were significant predictors, with lower scores at older ages and higher scores with higher education

levels. SLE had no significant relationship with verbal fluency. Additionally, SLE was not related to HbA1c, and thus the indirect pathway was also insignificant. The mediation hypothesis was not supported for verbal fluency scores.

Word List Total Recall. For the word list task, both age and education were significant predictors, with lower scores at older ages and higher scores with higher education levels. SLE had no significant relationship with word list total recall. nor with HbA1c. Thus, the mediation hypothesis is not supported for word list total recall scores.

Pattern Recognition Number Correct. For the pattern recognition task, once again, age was a significant predictor, with lower scores at older ages. Education, however, was not related to pattern recognition scores. Further, SLEs had no significant relationship with pattern recognition or HbA1c. Thus, the mediation hypothesis was not supported for pattern recognition scores.

Hypothesis 2: Does HbA1c Moderate the Relationship between Life Events and Cognition?

A summary table for all moderation analyses is presented in Table 4-5. Complete tables, including model fit statistics, can be found in Appendix B.

MMSE. For MMSE, the final model found significant effects for age, $p < .001$, and education, $p = .004$, as well as the main effect for HbA1c, $p = .044$. However, SLE and the interaction term between HbA1c and SLEs failed to reach significance. Thus, Hypothesis 2 was not supported for MMSE scores.

Verbal Fluency. For verbal fluency, the final model found significant effects for age, $p < .001$, and education, $p = .005$. However, SLEs, HbA1c, and the interaction term

between HbA1c and SLEs failed to reach significance. Due to this, Hypothesis 2 was not supported for verbal fluency scores.

Word List Total Recall. In the final model, moderation analyses for word list total recall demonstrated significance for age, $p < .001$, and education, $p < .001$. However, SLEs, HbA1c, and the interaction term between HbA1c and SLEs failed to reach significance. Due to this, Hypothesis 2 was not supported using word list total recall as an outcome.

Pattern Recognition Number Correct. In this model, the age coefficient was significant, $p < .001$, but education was not significant. However, the main effects for SLE and HbA1c were significant, $p = .041$, and $p = .012$, respectively, with the interaction term also demonstrating significance, $p = .047$. Due to this, Hypothesis 2 was supported using for Pattern Recognition. For pattern recognition, results indicated that those with higher HbA1c or SLEs would perform worse on the task, however the interaction term was positive, associated better performance on the pattern recognition task with higher levels of stress and HbA1c. Thus, there were concerns about possible multicollinearity for the interaction terms, which is discussed below.

Hypothesis 3: Relations among Stress, HbA1c, and Cognitive Outcomes by Age Group

Hypothesis 3 is an exploratory research question to determine whether there are differences in the models by age and education. Previous literature had found age effects when separating analyses into a three-way stratification by age and education (such as the work by Tschanz et al., 2012). However, the present study first attempted to assess the viability of using three age groups and found that the sample sizes were

likely to be too small for reliable comparison. Using three categories for age, the groups would have been heavily unbalanced at 131 individuals below 70, 298 individuals in the range 70-79, and 98 individuals 80 and above. For education, using a group analysis was less viable as only 16 individuals had lower than 9 years of education, 186 individuals had 9-13 years of education, and 325 individuals had 13 years or higher. Due to the high skewness of education, it was not viable to pursue analyses that split participants into meaningful groups that are reflected in other studies (Tschanz et al., 2012), as use of even a median split yielded uneven group sizes (lower than 13 years [n = 175], greater than 12 years [*n* = 352]). Due to this, a median split by age was pursued as an alternative to still reflect potential group differences as outlined in Hypothesis 3. The young-old group members were less than 75 *n* =273a), while the old-old group were 75 and older (*n* =254). Age groups were created after the elimination of outliers for each outcome individually. Significant mediation effects were noted in the summary Table 4-5 , and moderation in effects in Table 4-6, to easily compare between age groups. Again, tables with the full models are presented in Appendix C.

MMSE mediation. Comparing mediation models between young-old and old-old participants, both failed to reach significance. For the young-old, the direct pathway for SLE demonstrated significance at the $p < .001$ level, while the old-old showed no significant direct effect. Further, the pathway from HbA1c to MMSE demonstrated no significance for in those below 75 and only trended significance for those 75+, $p = .081$. For both groups, the indirect pathways failed to reach significance with no significant pathway for SLE as a predictor for HbA1c for either group. Neither group showed a mediating effect for HbA1c.

MMSE moderation. For both age groups, there was no significant main effect for SLE. However, HbA1c had a significant effect in the younger group only, $p = .027$, but not in the older group. Neither group showed significant interaction effects, and thus the moderation models was not supported in either group.

Verbal Fluency mediation. Results from mediation analyses by age group failed to reach significance. For both groups, none of the direct or indirect pathways reached significance.

Verbal Fluency moderation. In comparing interaction models between the two age groups, those under 75 found no significance for the main effect of SLE and HbA1c or for the interaction term. For those older than 75+, no significance was found for main effect of HbA1c, however there was a significant effect for both SLE and the interaction term in the older group, $p = .034$ and $p = .042$, respectively. Further details of the interaction effect are provided below in the assessment of multicollinearity.

Word List mediation. Results from mediation analyses failed to reach any significance. For both groups, none of the direct or indirect paths were significant.

Word List moderation. For both age groups, the moderation hypothesis was not supported. In comparing interaction models between the two age groups, those under 75 found no significance for the main effect of SLE and HbA1c or for the interaction term. For those 75+, trending significance was found for main effect of HbA1c $p = .065$, with additional nonsignificant effects for both SLEs and the interaction term. Thus, both groups were similar in their failure to reach significance for the moderating effect.

Pattern Recognition mediation. Comparing mediation models between participants under 75 and 75+, both failed to reach significance. For participants under

75, the direct pathway failed to reach significance, which is the same as the trend in participants 75+ which also failed to reach significance. For both groups, the indirect pathways failed to reach significance with no significant pathway for SLE as a predictor for HbA1c, with the pathway from HbA1c to Pattern Recognition demonstrating no significance for the young-old group, with a significant pathway for the old-old group, p = .031. Due to the nonsignificant mediating and direct pathways, both groups were similar in demonstrating a nonsignificant mediating effect for HbA1c with a nonsignificant indirect pathway for both age groups.

Pattern Recognition moderation. For both age groups, the moderation hypothesis was not supported. In comparing interaction models. For the under 75 group, both main effects were not significant as well as for the interaction term. For those older than 75+, the main effect of HbA1c was significant, p = *.015*, however both SLE and the interaction term were not significant. Due to this, there was no significant moderation effect for either group.

Multicollinearity Assessment

One concern during the analyses was the possible presence of multicollinearity, which posed a potential problem to the estimates in the moderation models. Both the full sample analysis for pattern recognition in Hypothesis 2 and the verbal fluency moderation model in those above 75+ found significant interaction terms between SLE and HbA1c. However, graphing the results suggested that those high in HbA1c and SLE had better cognitive scores, which is contradictory to the literature and counterintuitive. Thus, additional testing was conducted for suspected collinearity.

Using Variable Inflation Factor (VIF), tolerance values, and Klein's Rule (Klein, 1962) as a secondary confirmation of the VIF and tolerance interpretation, both models demonstrated substantial collinearity, with all indices reaching agreement that there were concerns for collinearity within the model. Because collinearity in interactions can be complicated to properly interpret, additional figures were relied upon inclusive of the charted interaction plots and then additional scatterplots that were used to visualize the non-covariate adjusted correlations between terms that were dichotomized as high and low HbA1c for the respective groups and outcomes.

For significant findings in the interaction term, interaction plots were produced which are contained in Figures 4-1 and 4-2, with the additional scatterplots in Figures 4-3 to 4-4 for pattern recognition in hypothesis 2, and Figures 4-5 through 4-8 for the verbal fluency task in hypothesis 3 to assess the significant finding for the interaction in the older group.

For the pattern recognition moderation model in hypothesis 2 significant results for the interaction were positive, indicating that those with higher HbA1c and higher numbers of SLEs performed better, which is counterintuitive. The VIF score was exceptionally high (above 90), thus the scatterplots were also used to try and interpret the interaction. In both scatterplots using samples split by HbA1c levels, SLE was nor correlated to the pattern recognition task (p = .37 in the low HbA1c group, p = .27 in the high HbA1c group.) Due to this, it was concluded that the effect was most likely spurious.

Following this, the same procedure was conducted for the verbal fluency moderation model in hypothesis 3. The VIF score was exceptionally high (above 90),

thus the scatterplots were also used to try and interpret the interaction. In both scatterplots using samples split by HbA1c levels for the younger group, SLE was nor correlated to the verbal fluency task though it was marginal for the higher HbA1c groups (p = .31 in the low HbA1c group, p = .06 in the high HbA1c group.) Following this, the same plots were produced for the older group, which found that there was a significant result for the high HbA1c group (p = .03) but not in the low HbA1c group (p = .31). Due to this significant correlation, it was concluded that this interaction was significant, indicating that those who were older and higher in HbA1c were more affected by SLEs for the verbal fluency task.

Table 4-1.

Correlation Matrix

	1	2	3	4	5	6	7
1. MMSE							
2. Verbal Fluency	0.307***						
3. Word List Total Recall	0.395***	0.373***					
4. Pattern Recognition Number Correct	0.283***	0.096	0.269***				
5. HbA1c	-0.102*	-0.015	-0.082	-0.088			
6. SLE	-0.102*	-0.139*	-0.046	-0.007	0.034		
7. Age	-0.283***	-0.291***	-0.342***	-0.209***	0.087*	0.039	
8. Education	0.162***	0.123*	0.185***	0.096	-0.004	0.035	-0.053

* $p<.05$; ** $p<.01$; *** $p<.001$

Table 4-2.

Summary Table of Results for Hypothesis 1: Does HbA1c Mediate the Relationship between Stressful Life Events and Cognition?

Cognitive Outcome	Age	Education	HbA1c	SLE	Indirect Effect
MMSE	-0.300***	0.122**		-0.181***	
Verbal Fluency	-0.286***	0.129**			
Word List Total Recall	-0.367***	0.170***			
Pattern Recognition	-0.210***				

* $p<.05$; ** $p<.01$; *** $p<.001$

Table 4-3.

Summary Table of Results from Hypothesis 2: Does HbA1c Moderate the Relationship between Stressful Life Events and Cognition?

Cognitive Outcome	Age	Education	HbA1c	SLE	Interaction
MMSE	-0.301***	0.125**	-0.197*		
Verbal Fluency	-0.284***	0.130**			
Word List Total Recall	-0.364***	0.170***			
Pattern Recognition	-0.199***		-0.317*	-1.639*	1.638*

* $p<.05$; ** $p<.01$; *** $p<.001$

Table 4-4.

Comparison of Cognitive Outcomes in the Younger and Older Age Groups

Variable	Younger	Older	*t*	df	*p*	95% CI
MMSE						
N	252	249	6.09	431.02	.001	0.57, 1.12
Mean	27.88	27.03				
Verbal Fluency						
N	248	245	5.35	393.88	.001	1.58, 3.42
Mean	19.71	17.2				
Word List Total Recall						
N	243	244	7.75	413.69	.001	2.00, 3.37
Mean	20.06	17.37				
Pattern Recognition						
N	260	252	3.54	274.10	.001	0.23, 0.82
Mean	24.19	23.66				

Table 4-5.

Summary Table of Results for Hypothesis 3: Do Age-Related Differences Exist for the Analyses in Hypothesis 1?

Cognitive Outcome	Age Group	Age	Education	HbA1c	SLE
MMSE	Young Participants	-0.206***	ns		-0.264***
	Old Participants	-0.184**	0.194***		ns
Verbal Fluency	Young Participants	-0.194*	ns		
	Old Participants	ns	0.151*		
Word List Total Recall	Young Participants	-0.151*	ns		
	Old Participants	-0.225***	0.216***		
Pattern Recognition	Young Participants	-0.203**		ns	
	Old Participants	ns		-0.230*	

* $p<.05$; ** $p<.01$; *** $p<.001$

Table 4-6.

Summary Table of Results for Hypothesis 3: Do Age-Related Differences Exist for the Analyses in Hypothesis 2?

Cognitive Outcome	Age Group	Age	Education	HbA1c	SLE	Interaction
MMSE	Young Participants	-0.204***	ns	ns		
	Old Participants	-0.182**	0.191**	-0.307*		
Verbal Fluency	Young Participants	-0.207**	ns		ns	ns
	Old Participants	ns	0.153*		-0.116*	2.781*
Word List Total Recall	Young Participants	-0.150*	0.131*			
	Old Participants	-0.211*	0.204**			
Pattern Recognition	Young Participants	-0.201**		ns		
	Old Participants	ns		-0.442*		

* $p<.05$; ** $p<.01$; *** $p<.001$

Figure 4-1.
Interaction Plot for Effects of Stress on Pattern Recognition by three levels of HbA1c

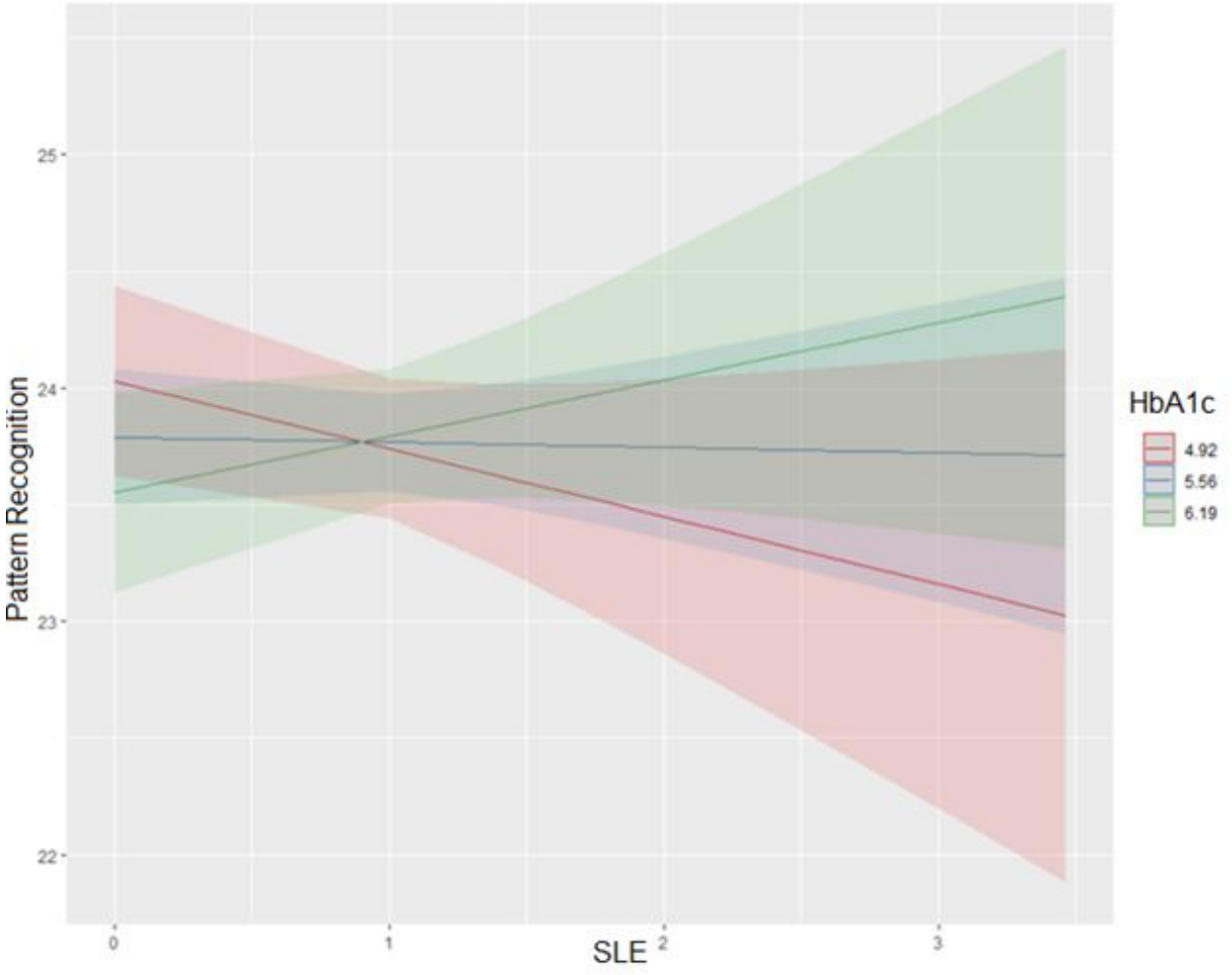


Figure 4-2.
Interaction Plot for Effects of Stress on Verbal Fluency by three levels of HbA1c in Adults Aged 75+

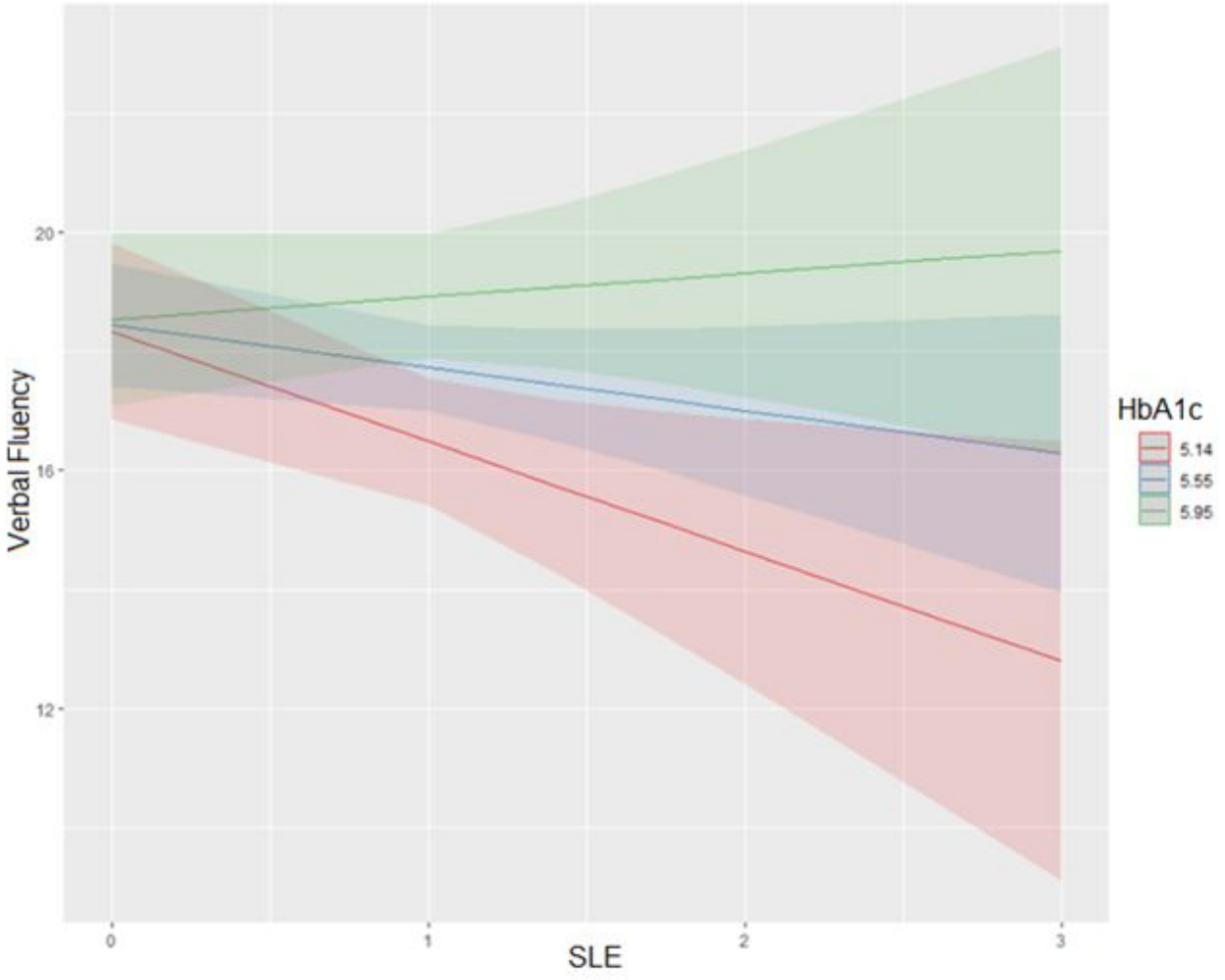
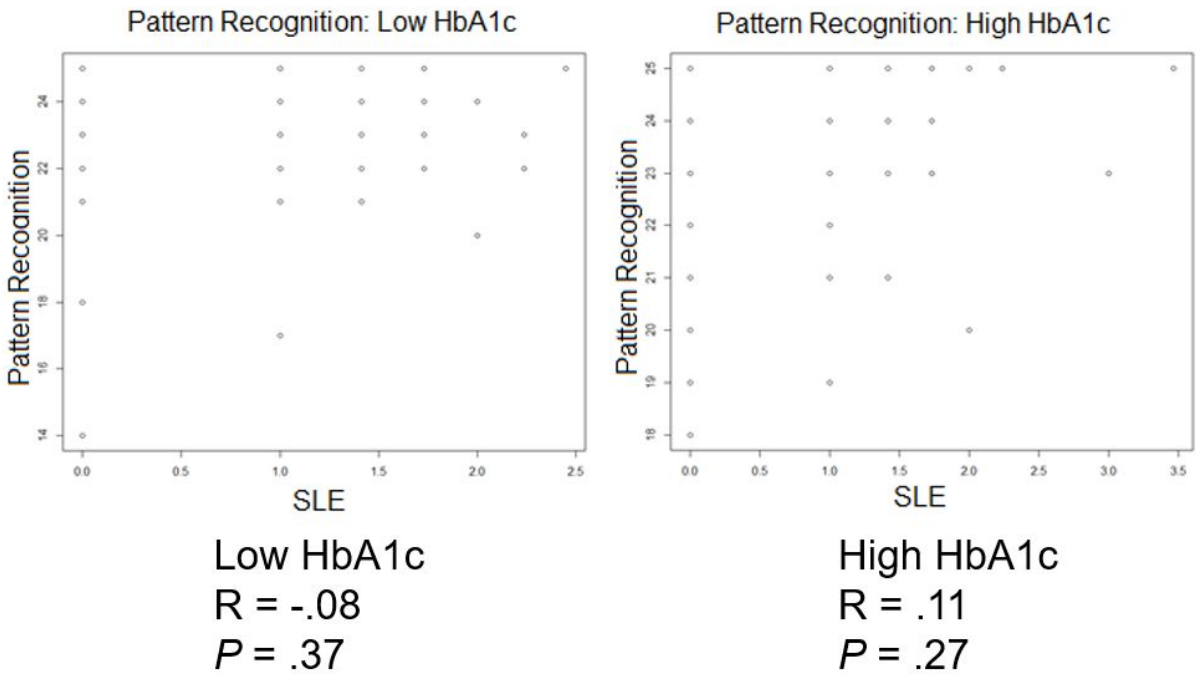


Figure 4-3.

Hypothesis 2 Scatterplots Displaying Non-Covariate Adjusted Values by HbA1c Group: Pattern Recognition

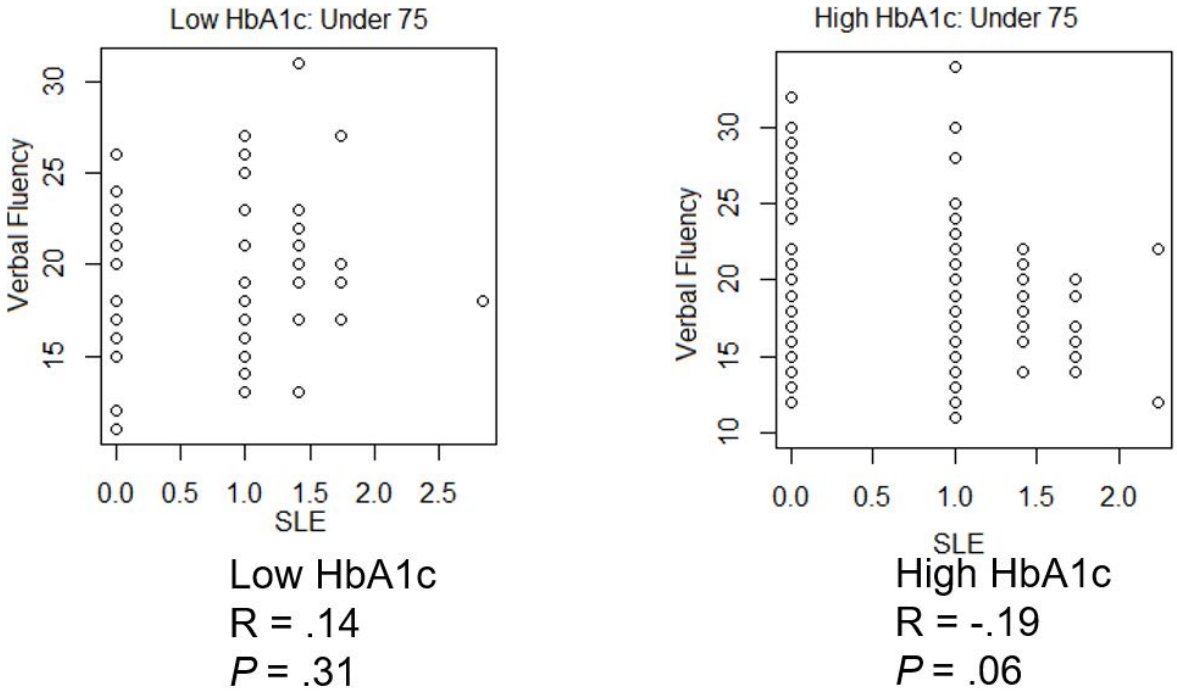


Low HbA1c
R = -.08
P = .37

High HbA1c
R = .11
P = .27

Figure 4-4.

Hypothesis 3 Scatterplots Displaying Non-Covariate Adjusted Values by HbA1c Group: Verbal Fluency in Participants Aged less than 75

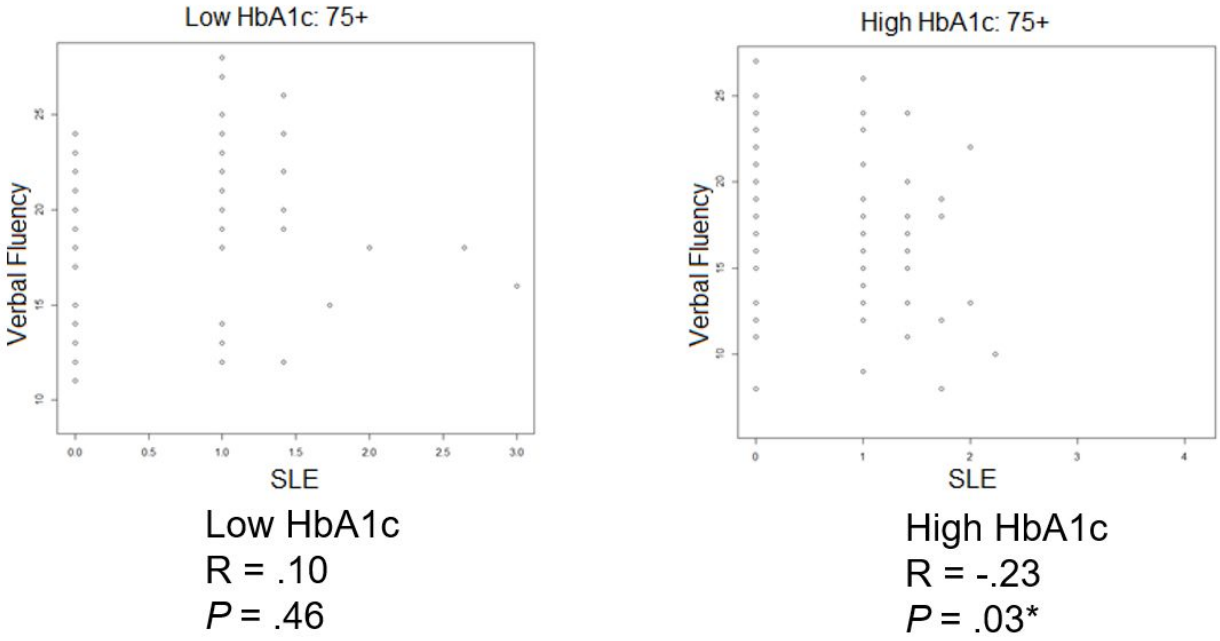


Low HbA1c
R = .14
P = .31

High HbA1c
R = -.19
P = .06

Figure 4-5.

Hypothesis 3 Scatterplots Displaying Non-Covariate Adjusted Values by HbA1c Group: Verbal Fluency in Participants Aged 75 and Over



Low HbA1c
R = .10
P = .46

High HbA1c
R = -.23
P = .03*

**p* < .05

CHAPTER 5

DISCUSSION

Some of the present findings did provide support for an association between impaired cognition in later life and both SLEs and HbA1c. However, there is a lack of research on the co-actional influences of SLE and HbA1c, thus the present study aimed to examine models of both mediation and moderation to better understand this relationship. Hypothesis 1 examined whether HbA1c mediated the effect of SLE on both overall cognition (MMSE) and domain-specific functioning (verbal fluency, wordlist recall, and pattern recognition). Hypothesis 2, on the other hand, examined whether HbA1c moderated SLE's effect on these same cognitive outcomes. These hypotheses were largely not supported, and instead appeared to show both SLE and HbA1c having modest and independent relationships to the cognitive outcomes. Following these analyses, Hypothesis 3 aimed to investigate potential age differences by median splitting the participants into groups of those under 75 (young-old group) and those 75+ (old-old group). Despite several interesting differences between the age groups for these analyses, the mediation and moderation hypotheses remained largely unsupported. Despite potential co-actional influences remaining underrepresented in current literature, there are still several discrepancies in approaches used and analyses which may help better explain differences in results.

Generally speaking, there were no differences in comparing the *t*-test results comparing the outliers and retained sample across analyses. For the given models, only two models saw significant differences between outliers and the retained sample: word

list total recall, where the retained sample was significantly older, $p = .004$, and the pattern recognition task where the retained sample was significantly higher performing, $p = .008$. In the *t*-test results comparing older and younger participants for the various cognitive outcomes, the younger group consistently outperformed the older group on all assessments, all significant on the $p < .001$ level, which is consistent and to be expected based upon previous work (Salthouse, 2010).

Hypothesis 1: Mediation

Using structural equation models, age and education were generally related to the cognitive outcomes with age associated with lower scores and education associated with higher scores. In the correlation matrix, both SLE and HbA1c were inversely related to MMSE scores, while SLE was also inversely related to verbal fluency. However, in the structural equation models for mediation, SLE was only inversely related to MMSE scores, and HbA1c was not associated with any of the cognitive outcomes. Further, SLE was not significantly associated with HbA1c preventing the possibility of any mediation effects being significant.

Functionally, this means that HbA1c is not likely to represent a path by which SLE is able to influence cognition, and the results indicate that the influence of HbA1c on cognition may be independent of that of SLE entirely for these outcomes. Previous work by McFall and colleagues (2019) indicated that there were significant co-actional effects of stress on blood sugar levels and by proxy HbA1c, however a critical element in this work provided by this study was timing consistency. Specifically, measurements for stress and HbA1c were done with proper frequency to capture HbA1c in response to

an SLE. In the NAS data, HbA1c was measured at the physical examination, while the SLE inventory was assessed by requesting a participant recall stress in the past year. Problematically for these analyses, this difference in time scale means the values for HbA1c are potentially not representative of values during the occurrence and acute ramifications of an SLE, as HbA1c is beneficial for measurement of up to three months prior but not beyond that frame (Ghazanfar et al., 2010).

In addition to the work by Marden and colleagues, Soo and Lam (2009) studied HbA1c levels directly following stressful events and found that following an SLE, one could see increased HbA1c associated with the occurrence of the stressful event. However, their timing was also more precise in observing the changes as they happened rather than applying the HbA1c measurement to a time beyond its meaningful utility. Potentially the reason the results using NAS data were not in alignment with previous work was due to timing, which ultimately represents a constraint in the use of this data to measure the relationship between HbA1c and SLEs.

Hypothesis 2: Moderation

Structural equation models for moderation analyses for Hypothesis 2 showed a slightly different pattern of results. For the moderation models HbA1c was inversely associated with MMSE scores and the pattern recognition task, while SLE was only inversely associated with pattern recognition. The interaction term between SLE and HbA1c was not significant for MMSE, verbal fluency, and word list total recall, however, results indicated that for the pattern recognition task, an interaction model was significant for all main effects and the interaction term. For the pattern recognition task, the main effects indicated that those with lower HbA1c and lower SLEs scored higher

on pattern recognition tasks, while the interaction term was positively associated with task performance. However, further analysis revealed a significant problem with multicollinearity, and thus this result was discounted. Thus, Hypothesis 2 was not supported.

For MMSE, verbal fluency, and word list total recall scores the insignificance indicates that the strength of the relationship between SLEs and the cognitive outcomes is not dependent upon the level of HbA1c and remains independent in these models. On the other hand, the results for pattern recognition displayed significance for the main effects as well as the interaction term between them. Specifically, SLE and HbA1c had no significant relationship on the pattern recognition task until the introduction of the interaction term in Model 3. This potentially indicates that the strength of the relationship between SLE and pattern recognition tasks not only depends on HbA1c, but additionally that the consideration of the interaction between the two is especially crucial in understanding of how the main effects relate to the task. However, due to the contradictory relationships between the main effects and interaction terms, this is more likely an instance where multicollinearity makes the results difficult to interpret, thus these estimates may be unreliable.

Previously, literature has indicated that there are caveats underlying effects of stress on general cognitive performance suggesting potential mediating or moderating effects such as social support (Dickinson et al., 2011) or prior impairment (Peavy et al., 2009). Based on these factors, the respective studies found differentiated effects suggesting there may be further moderating influences that fundamentally change the relationship between SLEs and cognitive performance. Similar to hypothesis 1, it is

possible timing issues again could have posed a constraint that complicates the study of any potential relationship in moderation, or potentially that some additional caveats that apply were not considered or included in the model.

An additional concern for interpretation of the moderation analyses is the potential presence of collinearity. Specifically, the SLE variable was very highly skewed, and while a square root transformation helped to make the distribution more normal, it remained skewed despite this. In translating this into an interaction term, there was a very large correlation between the SLE value and the interaction term. Due to the collinearity, it is possible that some of these results were warped to the point of being uninterpretable due to difficulties in the estimation of values and standardized betas. Collinearity testing was used to address the significant findings for the pattern recognition model, and across all indices the model was found to be subject to substantial collinearity concerns, specifically between the interaction term and main effects. While the significant findings for pattern recognition are not void of value, and may be indicative of some trend, collinearity does pollute our understanding of these findings. Due to the contradictory findings with the effect of the interaction term, it is difficult to ascertain the utility of the given significant results.

Hypothesis 3: Age-Stratified Mediation and Moderation

There were some differences observed by grouping the underlying structural equation models in the age analyses. In the MMSE and verbal fluency analyses, education was significantly associated with higher scores for the older groups, but not for the younger ones, suggesting that education may become more important for

maintaining cognition in very late life. However, for pattern recognition, there was no significant association for either group.

There were no significant effects for the indirect pathway in either group, due to SLE having an insignificant effect on HbA1c, but furthermore an insignificant effect of HbA1c on MMSE was observed across models. However, the HbA1c to MMSE pathways established significance in the older population only. In moderating models for MMSE, HbA1c and education significantly predicted MMSE scores in the younger group only. Potentially, these differences between the mediation and moderation models can be explained by the procedure for fitting structural equation models. One distinction between the models was the use of bootstrapping, which was only applied to the mediation model. It is possible that due to the resampling process in bootstrapping that the estimated standard errors produced differing results, specifically by producing asymmetrical distributions in the resampling due to the non-normal distribution of the variables. In mediation analysis, bootstrapping was used a method for estimating values by resampling, but also as a means to better handle the skewed distribution of the variables and produce values for total and indirect mediation effects. Had bootstrapping been used for the moderation models, it is possible that the confidence intervals and thus the values computed from these would change (Efron & Tibshirani, 1986). Bootstrapping was not used for the moderation models because it was not needed to estimate the moderation effect.

Age. Notably, age was one of the effects that was quite differentiated across the analyses. Specifically, age was a significant covariate for all the analyses in the younger age group, but only for the MMSE and word list recall in the older adults. Age was not

significantly associated with either pattern recognition or verbal fluency. Between the two groups the results indicated that age was a salient predictor in the younger participants, but selectively useful in predicting the results for the older participants. In the younger group, perhaps this is relevant to vulnerable periods of decline. For example, the range of the younger participants was 59-74, which is still within bounds of the average lifespan for an adult male in the United States. Potentially, this is due to a normal decline in fluid intelligence, especially in older populations (Glisky, 2007), however this still fails to explain the nonsignificance for verbal fluency and pattern recognition in the older participants. A possible factor in considering age is survivor effects– this group had approximately half of the cases aged over the average lifespan for an adult male in the US, thus there may be more complicated confounding factors that underlie the results for the older age group, and age may be a less salient factor.

There are several viable reasons for why age may have been differentially effective as a covariate in the given models. Notably, the consistent significance in models for the younger adults may be sensible, given that many of them are beginning to reach the ages that are most associated with declines in cognitive test scores (Tschanz et al., 2013). Due to this, it is possible that the younger participants saw larger associations for age due to the onset of some of the processes that underlie longer term neurodegeneration. On the other hand, the older adults only saw significance in age effects for the MMSE and word list task, which is additionally sensible. MMSE scores are expected to decline with age, and as such the strong association is to be expected with this specific task (Folstein et al., 1975). In the case of the word list task, which represented memory, it would be expected to decline because memory is an especially

vulnerable faculty in aging (Stawski et al., 2013), which again would support the significant finding for age in this task but not others. It is more difficult to speak to the older demographic because they also have confounds associated with advancing age in a bracket that already surpasses the average lifespan in the United States, however the observed effects do remain consistent with prior literature.

Education. Another prevalent trend in the age analyses was the protective influence of education, but only in the older participants. Previous literature has found buffering effects for higher education against SLEs for shortened MMSE scales (Tschanz et al., 2012), and this may explain why it was so consistently significant for the older adults. The previous work by Tschanz and colleagues found that age not only acted as a buffering effect, where higher education protected against declines in cognition in the face of SLEs, but additionally the effect in older populations was far more pronounced and having higher education provided far greater protection against declines in advanced age. In the work by Tschanz, there was a modest protective effect for those with higher education in their younger-old group, however it was small and mostly detected for those with education below high school level. Potentially these age effects were not detected due to the highly educated sample in the NAS data, where approximately two thirds had some college and the distribution of education was rather compact. Since the effect of education appears to be especially pronounced in later life, it is probable that it failed to be significant in the younger group because it was a tight distribution, where it was detected in the older group where more pronounced differences appear to exist for each additional year of education.

These trends in age for the analyses may be reflective of various past studies, which have found that the most pronounced declines happen in later life (Glisky, 2007), which is also when the protective influence of education is most salient (Tschanz et al., 2013). This could potentially explain why there was complete consistency to the protective influence of education in the older population as well as the inconsistent results in the younger population. The one instance of a significant effect of education in the younger population was for the word list task that was used to represent memory. This is additionally in line with previous work that has established memory as a critically vulnerable faculty in late life (Stawski et al., 2013), thus this effect may become more pronounced earlier in the face of any declines.

Hemoglobin A1c. A final point of note in the trends by age difference was the significance of HbA1c along three analyses for the older population where it was consistently insignificant for the younger population. As people age, very slightly elevated levels of HbA1c may be necessary to maintain organ function, however in these cases it was always negatively associated. The mean and standard deviation for both age groups did not differ substantially, and the range was larger in the younger group. Research by Huang and colleagues (2011) corroborates some of the present findings where they found no significant effect on the same word list and verbal fluency tasks, but a significant effect of HbA1c on a global assessment. More recent work on the English longitudinal study by Zheng and colleagues (2018) demonstrated that older adults with higher HbA1c did in fact see accelerated decline in global fluid measures, executive function, and orientation tasks. Notably, Zheng and colleagues used the same verbal fluency and word list task as the present study but additionally they used a

subset of the questions from the MMSE, all of which were negatively associated with higher HbA1c. Where this study presents a contradiction to the findings of the present study, it also corroborates the significance of HbA1c as an influence on global cognition.

There are a few potential explanations for the disagreement with the work by Zheng and colleagues where there is agreement with Huang and her colleagues. One of the largest differences between Zheng and Huang's work is the inclusion of women in the work by Zheng. Due to the available sample, analyses by gender were not possible for this work, but potentially there are differentiated effects by gender or other demographics, which is further bolstered by the findings in Huang's work which is a male only veteran sample. Additionally, the present study uses a much older sample than Zheng's work, which had a mean age of 65. In the present work, no significant effects were found for HbA1c on cognitive outcomes in the younger participants, which is in agreement with Zheng's work to an extent. In Huang's work, the primary focus was older adults which were similarly aged to the older participant group in the present study, and despite not using a pattern recognition task in her study, her results are in perfect alignment with the ones present here: verbal fluency and word list total recall were not significantly associated with HbA1c, but a global measure was significantly associated in an old, male, veteran sample.

Potentially, the discrepancies between the present results and those found in Zheng's work could be due to demographics. Despite Zheng using a younger-old sample, her sample was on average much younger, had a larger range, and included females. It is difficult to ascertain why the findings are different, however due to a large

difference in demographics it is possible that there are important differences to be considered in more diverse populations.

Similar to Hypothesis 2, there was a significant interaction term in the analyses for the older participants in the verbal fluency moderation model. However, for reasons like the pattern recognition model in Hypothesis 2, it is difficult to interpret due to the high collinearity. For these results, additional testing for collinearity indicated that the model experienced especially high collinearity, and notably the direction of effect between the main effects and interaction term were not consistent, with the main effects demonstrating a negative effect on cognition and the interaction term showing a positive effect. Additionally, HbA1c was not significantly associated with the verbal fluency score.

SLE. Splitting the sample into two age groups weakened the relationships between SLE the cognitive outcomes. SLE had an inverse relationship with cognition in the younger group for MMSE (mediation model) and with verbal fluency in the older group (moderation model).

Limitations

In all research, limitations hinder the utility of results with this study being no exception. Notably, there was a lack of diabetic participants which presents merit in some ways, but additionally problems. Specifically, participants with a diabetes diagnosis were used in the present analyses due to research consistently indicating that HbA1c at any level beyond the safe threshold presents danger to the body along similar pathways (Ghazanfar et al., 2010; Pani et al., 2008), however some of the treatment options for diabetes may present unique differences in participants. Medications that are

targeted to reduce HbA1c levels are not uncommon in treatment for diabetes, and it remains possible that some of the medications used, especially those that may target the hemoglobin, may influence cognition or oxygen transport as well. In the present analyses, those with a diabetes diagnosis were included since they were few (14), and in no instances were they on medication, thus they were included to further bolster the findings.

However, one of the difficult problems remains in those with higher HbA1c levels that were not diagnosed. HbA1c rarely functions as a sole indicator of diabetic status though in some contexts it is used to make a diagnosis (Ghazanfar et al., 2010). Without more information and additional tests, the researcher could not state with certainty that these participants were diagnosable.

This problem was similar to that present in the MMSE. Participants were excluded if they had a diagnosis of dementia, but some remaining participants displayed MMSE scores indicative of a likely case of dementia (under 24 on the revised 29 item scale) where substantial impairment appeared to be present. For similar reasons to the inclusion of those with high HbA1c levels indicative of diabetes, the researcher was not qualified to make a dementia diagnosis without additional information, but nonetheless all of these participants but one were removed in the trimming of outliers. Still, this remains an important point of consideration for future work about how they can consider values that fit within the critical margins of screening for dementia, but do not have a diagnosis.

One of the most substantial limitations to the present analyses was the problem of timing. HbA1c offers a look at the past 2-3 months of blood glucose levels, and the

measure of SLEs asked participants to look back on the last year. In longitudinal work it is often most efficient to ask participants to report once a year or every few years, and in this case, participants reported every three years. Due to this, problems of timing represented a very significant constraint placed upon the data used, and potentially this mismatch contributed to the lack of correlation between SLEs and HbA1c. In order to circumvent this, relying on data that uses time synchronized measures may be able to find a clearer relationship or lack thereof by relying on more measures in a shorter amount of time, such as in a BURST design.

Another limitation of the current analyses was the inability to produce additional age categories for analyses that could better reflect theoretically justified age stratification. Some previous work has made efforts to split participants into more groups in order to better reflect trends at different places in the aging process. Initially splitting the participants into three age groups as per previous findings was considered, but the data was not amenable to being split this way while maintaining power and meaningful groups for comparison. Due to this, a median split approach was employed. The median split approach represented an attempt to look for any differences by age as the proposal had aimed to investigate, and approximately represented the distinction among the young-old (<75) and old-old (75+) for practical purposes for these analyses. This is functionally a limitation as the data was not able to reflect a theoretically supported categorization of age, and thus even the differences that were found could be smaller pieces of the larger trends a better divided grouping could reflect. To overcome this, data with greater diversity by age and education could prove useful in identifying

trends across the various analyses by age and in providing the means to meaningfully stratify by education.

The sample had further limitation in both its gender and ethnic diversity. It is possible that samples that include women and individuals from other ethnic groups may show different results.

One other crucial direction for consideration is the use of bootstrapping. For the mediation analyses, the bootstrapping procedure represented a powerful way to compute effects and handle the non-normal distributions in the data. However, having the moderation analyses run without bootstrapping produced some contradictory findings between the two models, which could potentially be caused by asymmetry due to the resampling because of the non-normal distribution. While some of the findings were consistent across models, it is likely worth considering bootstrapping the moderation models in the future to maintain consistency and to produce results that are theoretically closer to the population effects.

Lastly, a potential reason for the differences in main effects across analyses was the incorporation of an interaction term in the moderation models. The variables used in the mediation and moderation analyses may have been the same, but the incorporation of an interaction term with the main effects in the moderation model may have changed the main effects' strength and significance in the various models. In the case of the present study, one of the crucial considerations is in the high collinearity between terms in the interaction model, and thus post hoc analyses could potentially benefit interpretation of the results. However, in the present results the assessments of collinearity and inclusion of scatterplots and interaction plots targeted at the significant

interaction terms offer some insight into the interpretation of the interactions in the face of high collinearity. These are not without limitation themselves, as the scatterplots do not include covariates, but the models in the interactions plots do contain these. In summary, there is no shortage of nuance to consider in interpreting moderation analyses, which is then exacerbated by issues related to collinearity of independent variables.

Thus, future work would do best to consider incorporating a bootstrapping procedure which includes all of the model variables, and then build on the results of this using an interaction plot that is sensitive to the covariates of the model. Though it is less likely that a covariate could provide undue influence and modify the effect of the main effects and interaction, these are still important inclusions in the model that ideally should not be left out. Perhaps one of the best ways to handle this is to use an SEM approach where the covariates have pathways to each of the variables in the model, and additionally the simultaneous assessment of variables and flexibility in model constraints may prove useful in avoiding undue burden from a single variable while avoiding potentially inflated *p* values.

Future Directions

Several avenues could be important for furthering research into SLEs and HbA1c and their influence on cognitive performance. For example, in these analyses a present limitation was the mismatch of timing for measures where HbA1c provides a context for blood sugar over the past months, where SLEs were surveyed for the last year. Due to this, it is entirely possible having these measures be in sync could be important for demonstrating a clearer relationship. Potentially one method of doing this could be a

BURST design, where participants undergo intensive repeated measures for a given time frame periodically so as to obtain micro level data without inducing overwhelming participant burden for a long period of time. This could, for example, allow a researcher to collect data on SLEs as they are occurring and additionally maintain a meaningful time frame for HbA1c changes following the event. It is entirely possible that there are changes in HbA1c as a result of SLEs, but due to timing this may have been lost in the present work.

Another direction that future work could consider pursuing is the inclusion of diverse age groups and other demographics. The present analyses were incapable of considering a broad variety of age categories due to the restricted age range, and though splitting the sample into additional age categories was considered, it was effectively limited to a median split in order to preserve power and maintain meaningful analyses. Where a median split is perhaps functional in attempting to observe if there was any trend, it was not theoretically founded and where sample demographics limited the present analyses. It is possible that other work could more fully pursue meaningful categories of different age groups that are bolstered by theory, which would be ideal to see in further research. Despite this, some differences were still found by age group, but having a theoretically founded method of stratification could undoubtedly shed greater light on these trends. For other demographics, the participants used in these analyses were all male, and additionally overwhelmingly white (504 of the 527 participants.) Due to how homogenous the sample was, it is difficult to extrapolate these results to broader demographic categories, and thus it may be especially useful to pursue future analyses with diverse samples.

Additionally, further work could more fully pursue the influence of education. Where the present analyses were restricted to use of education as a covariate due to a very well educated sample, previous work by Tschanz and colleagues (2012) found compelling evidence for the protective effect of education, where recovery to previous levels of cognition post SLE were more likely and quicker in those with a higher education. Due to the skewed distribution of education, the present analyses were unable to reflect this in a meaningful way, and thus this could not be adequately pursued. To build upon any work attempting to assess co-actional influences, it would likely be beneficial to incorporate both age and education stratified models to see specific vulnerabilities or resilience in part due to the variables that were used as covariates.

To the author's knowledge, this work is the first to explore potential relationships between stressful life events and HbA1c in tandem as they affect cognition, and the first to consider these variables in tandem using an age-sensitive SLE scale. Specifically, in using the ELSI, this study incorporated an index of questions that are specifically tailored and selected for their relevance to older persons. This is important because research on SLEs and blood biomarkers is sparse, and additionally even less is dedicated to older adults. Notably, this is the time that an older adult may begin to experience the ramifications of high levels of HbA1c as they begin experiencing more pronounced cognitive decline in later life. Considering aging is an especially vulnerable time for cognitive faculties, this work can further bolster our understanding of where deeper-seated underlying cognitive decline can begin to occur due to physiological

stress and its relationship to psychosocial stressor, which is essential for promotion of healthy aging both now and in the future.

Conclusions

Despite data constraints and apparent shortcomings in design, the current study is valuable because it reveals some of the intricacies of the relationship between psychosocial variables (age, education, and stress) and biomedical variables (HbA1c) as they relate to cognitive outcomes. Notably, whether the results can be extrapolated to diabetes or not, the levels of HbA1c are continually rising around various parts of the world and having this work to better understand the implications of this for the general public's cognition in late life can still be very important. However, larger trends do not consistitute the entire picture, and work to better reflect individual differences and group differences in HbA1c and stress should be reflected in future work. Future research should examine whether age group differences in age and education effects are replicable, and explicate in greater detail the pattern differences between global and domain-specific cognition.

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APPENDIX A

Fully Tabled Results for Hypothesis 1

Mediation Results for MMSE scores Hypothesis 1: *Does HbA1c Mediate the Relationship between Stressful Life Events and Cognition?*

	Outcome Variable	Predictor Variable	*B*	SE	β	*p*	95% CI
Covariates							
	MMSE	Age	-0.072	0.012	-0.300	.001	-0.096, -0.050
		Education	0.072	0.025	0.122	.004	0.020, 0.119
Direct Pathway							
	MMSE	Stressful Life Events	-0.413	0.108	-0.181	.001	-0.624, -0.191
Indirect Pathway							
	HbA1c	Stressful Life Events	0.016	0.041	0.019	.698	-0.065, 0.101
	MMSE	HbA1c	-0.246	0.130	-0.092	.058	-0.513, -0.027
Total Effect							
			-0.417	0.109	-0.183	.001	-0.625, -0.191

MMSE refers to the Mini Mental Status Examination

Model AIC: 9065.567

X2 (7, N = 501) = 82.893, p < .001

Mediation Results for verbal fluency scores Hypothesis 1: *Does HbA1c Mediate the Relationship between Stressful Life Events and Cognition?*

	Dependent Variable	Independent Variable	*B*	SE	β	*p*	95% CI
Covariates							
	Verbal Fluency	Age	-0.211	0.035	-0.286	<.001	-0.281, -0.146
		Education	0.235	0.089	0.129	.008	0.057, 0.411
Direct Pathway							
	Verbal Fluency	Stressful Life Events	-0.598	0.389	-0.086	.125	-1.378, 0.159
Indirect Pathway							
	HbA1c	Stressful Life Events	0.031	0.044	0.037	.481	-0.053, 0.124
	Verbal Fluency	HbA1c	0.121	0.331	0.015	.715	-0.509, 0.809
Total Effect							
			-0.594	0.387	-0.085	.124	-1.367, 0.158

Model AIC: 9523.766

X2 (7, N = 493) = 48.045, p < .001

Mediation Results for word list total recall scores Hypothesis 1: *Does HbA1c Mediate the Relationship between Stressful Life Events and Cognition?*

	Dependent Variable	Independent Variable	*B*	SE	β	*p*	95% CI
Covariates							
	Word List Total Recall	Age	-0.214	0.025	-0.367	.001	-0.265, -0.164
		Education	0.240	0.067	0.170	.001	0.097, 0.364
Direct Pathway							
	Word List Total Recall	Stressful Life Events	-0.274	0.269	-0.050	.307	-0.781, 0.249
Indirect Pathway							
	HbA1c	Stressful Life Events	0.008	0.049	0.01	.864	-0.094, 0.100
	Word List Total Recall	HbA1c	-0.438	0.240	-0.07	.068	-0.906, 0.050
Total Effect							
			-0.278	0.270	-0.051	.303	-0.798, 0.252

Model AIC: 9443.595

X2 (7, N = 487) = 95.162, p < .001

Mediation Results for pattern recognition scores Hypothesis 1: *Does HbA1c Mediate the Relationship between Stressful Life Events and Cognition?*

	Dependent Variable	Independent Variable	*B*	SE	β	*p*	95% CI
Covariates							
	Pattern Recognition	Age	-0.042	0.010	-0.210	.001	-0.061, -0.020
		Education	0.040	0.028	0.083	.147	-0.014, 0.096
Direct Pathway							
	Pattern Recognition	Stressful Life Events	-0.083	0.118	-0.046	.482	-0.315, 0.152
Indirect Pathway							
	HbA1c	Stressful Life Events	0.052	0.041	0.061	.203	-0.029, 0.136
	Pattern Recognition	HbA1c	-0.196	0.163	-0.093	.230	-0.535, 0.101
Total Effect							
			-0.093	0.118	-0.052	.427	-0.221, 0.137

Model AIC: 8516.923

X2 (7, N = 512) = 23.574, p = .001

APPENDIX B

Fully Tabled Results for Hypothesis 2

Moderation Results for MMSE scores Hypothesis 2: *Does HbA1c Moderate the Relationship between Stressful Life Events and Cognition?*

	B	SE	β	*p*	95% CI
Model 1: Covariates					
Age	-0.080	0.010	-0.320	.001	-0.098, -0.057
Education	0.074	0.026	0.126	.004	0.024, 0.125
Model 2: Independent Effects					
Age	-0.072	0.010	-0.300	.001	-0.093, -0.052
Education	0.072	0.025	0.122	.005	0.022, 0.121
Stressful Life Events	-0.413	0.113	-0.181	.001	-0.634, -0.192
HbA1c	-0.246	0.115	-0.092	.032	-0.471, 0.021
Model 3: Interaction Effects					
Age	-0.073	0.010	-0.301	.001	-0.093, -0.053
Education	0.074	0.025	0.125	.004	0.024, 0.123
Stressful Life Events	-2.312	1.590	-1.015	.146	-5.428, 0.803
HbA1c	-0.527	0.261	-0.197	.044	-1.040, -0.015
Interaction	0.344	0.287	0.846	.231	-0.219, 0.908

Model 1 AIC: 7410.596; X2 (2, N = 501) = 61.275, $p < .001$
Model 2 AIC: 9065.567; X2 (4, N = 501) = 79.083, $p < .001$
Model 3 AIC: 9179.075; X2 (5, N = 501) = 80.528, $p < .001$

Moderation Results for verbal fluency scores Hypothesis 2: *Does HbA1c Moderate the Relationship between Stressful Life Events and Cognition?*

	B	SE	β	*p*	95% CI
Model 1: Covariates					
Age	-0.217	0.036	-0.293	.001	-0.287, -0.147
Education	0.237	0.085	0.129	.005	-0.070, 0.403
Model 2: Independent Effects					
Age	-0.211	0.036	-0.286	.001	-0.282, -0.141
Education	0.235	0.085	0.129	.006	-0.069, 0.402
Stressful Life Events	-0.598	0.408	-0.086	.143	-1.398, -0.203
HbA1c	0.121	0.417	0.015	.772	-0.695, 0.937
Model 3: Interaction Effects					
Age	-0.210	0.036	-0.284	.001	-0.281, -0.140
Education	0.238	0.085	0.130	.005	0.072, 0.404
Stressful Life Events	-8.080	5.494	-1.159	.141	-18.847, 2.688
HbA1c	-0.961	0.894	-0.115	.282	-2.713, 0.791
Interaction	1.343	0.984	1.083	.172	-0.585, 3.270

Model 1 AIC: 7896.997; X2 (2, N = 493) = 42.832, $p < .001$
Model 2 AIC: 9523.766; X2 (4, N = 493) = 45.009, $p < .001$
Model 3 AIC: 9663.333; X2 (5, N = 493) = 46.850, $p < .001$

Moderation Results for word list total recall scores Hypothesis 2: *Does HbA1c Moderate the Relationship between Stressful Life Events and Cognition?*

	B	SE	β	*p*	95% CI
Model 1: Covariates					
Age	-0.221	0.025	-0.378	.001	-0.270, -0.171
Education	0.238	0.060	0.170	.001	0.120, 0.356
Model 2: Independent Effects					
Age	-0.214	0.025	-0.367	.001	-0.264, -0.165
Education	0.240	0.060	0.170	.001	0.122, 0.357
Stressful Life Events	-0.274	0.290	-0.050	.344	-0.842, 0.294
HbA1c	-0.438	0.288	-0.070	.128	-1.002, 0.127
Model 3: Interaction Effects					
Age	-0.213	0.026	-0.364	.001	-0.263, -0.163
Education	0.238	0.060	0.170	.001	0.121, 0.356
Stressful Life Events	-2.932	3.224	-0.536	.363	-9.250, 3.387
HbA1c	-0.753	0.477	-0.120	.114	-1.689, 0.182
Interaction	0.475	0.574	0.490	.408	-0.650, 1.601

Model 1 AIC: 7794.352; X2 (2, N = 487) = 86.309, $p < .001$
Model 2 AIC: 9443.595; X2 (4, N = 487) = 89.559, $p < .001$
Model 3 AIC: 9693.607; X2 (5, N = 487) = 90.248, $p < .001$

Moderation Results for pattern recognition scores Hypothesis 2: *Does HbA1c Moderate the Relationship between Stressful Life Events and Cognition?*

	B	SE	β	*p*	95% CI
Model 1: Covariates					
Age	-0.043	0.011	-0.217	.001	-0.065, -0.022
Education	0.038	0.029	0.079	.187	-0.019, 0.095
Model 2: Independent Effects					
Age	-0.042	0.011	-0.210	.001	-0.063, -0.020
Education	0.040	0.029	0.083	.162	-0.016, 0.097
Stressful Life Events	-0.083	0.120	-0.046	.489	-0.319, 0.153
HbA1c	-0.196	0.124	-0.093	.113	-0.439, 0.046
Model 3: Interaction Effects					
Age	-0.040	0.011	-0.199	.001	-0.061, -0.018
Education	0.041	0.029	0.085	.151	-0.015, 0.097
Stressful Life Events	-2.967	1.454	-1.639	.041	-5.817, -0.118
HbA1c	-0.666	0.265	-0.317	.012	-1.185, -0.147
Interaction	0.520	0.261	1.638	.047	0.008, 1.032

Model 1 AIC: 6735.404; X2 (2, N = 512) = 17.429, $p < .001$
Model 2 AIC: 8516.923; X2 (4, N = 512) = 20.676, $p < .001$
Model 3 AIC: 8780.987; X2 (5, N = 512) = 24.560, $p < .001$

APPENDIX C

Fully Tabled Results for Hypothesis 3

Mediation Results for MMSE scores in adults less than 75 years old Hypothesis 3:

Do Age-Related Differences Exist for the Analyses in Hypothesis 1 and Hypothesis 2?

	Dependent Variable	Independent Variable	*B*	SE	β	*p*	95% CI
Covariates							
	MMSE	Age	-0.070	0.020	-0.206	.001	-0.110, -0.031
		Education	0.015	0.033	0.03	.656	-0.05, 0.076
Direct Pathway							
	MMSE	Stressful Life Events	-0.487	0.119	-0.264	.001	-0.731, -0.268
Indirect Pathway							
	HbA1c	Stressful Life Events	0.008	0.050	0.010	.866	-0.085, 0.110
	MMSE	HbA1c	-0.128	0.157	-0.061	.413	-0.461, 0.154
Total Effect							
			-0.488	0.120	-0.264	.001	-0.728, -0.266

MMSE refers to the Mini Mental Status Examination

Model AIC: 4167.643

X^2 (7, N = 252) = 34.067, p < .001

Mediation Results for MMSE scores in adults 75+ years old Hypothesis 3: *Do Age-Related Differences Exist for the Analyses in Hypothesis 1 and Hypothesis 2?*

	Dependent Variable	Independent Variable	*B*	SE	β	*p*	95% CI
Covariates							
	MMSE	Age	-0.077	0.030	-0.184	.012	-0.137, -0.02
		Education	0.122	0.038	0.194	.001	0.052, 0.198
Direct Pathway							
	MMSE	Stressful Life Events	-0.305	0.186	-0.123	.101	-0.680, 0.076
Indirect Pathway							
	HbA1c	Stressful Life Events	0.026	0.076	0.031	.737	-0.124, 0.184
	MMSE	HbA1c	-0.390	0.223	-0.13	.081	-0.841, 0.023
Total Effect							
			-0.315	0.189	-0.127	.095	-0.699, 0.066

MMSE refers to the Mini Mental Status Examination

Model AIC: 4374.750

X^2 (7, N = 249) = 23.337, p = .001

Moderation Results for MMSE scores in adults less than 75 years old Hypothesis 3:

Do Age-Related Differences Exist for the Analyses in Hypothesis 1 and Hypothesis 2?

	B	SE	β	*p*	95% CI
Model 1: Covariates					
Age	-0.081	0.021	-0.236	.001	-0.123, -0.039
Education	0.017	0.031	0.035	.580	-0.043, 0.078
Model 2: Independent Effects					
Age	-0.070	0.021	-0.206	.001	-0.111, -0.029
Education	0.015	0.030	0.030	.627	-0.044, 0.073
Stressful Life Events	-0.487	0.125	-0.264	.001	-0.732, -0.242
HbA1c	-0.128	0.130	-0.061	.324	-0.383, 0.127
Model 3: Interaction Effects					
Age	-0.070	0.021	-0.204	.001	-0.111, -0.029
Education	0.014	0.030	0.028	.648	-0.045, 0.073
Stressful Life Events	-0.029	1.643	-0.016	.986	-3.249, 3.192
HbA1c	-0.055	0.291	-0.026	.849	-0.626, 0.516
Interaction	-0.084	0.300	-0.252	.780	-0.671, 0.504

Model 1 AIC: 3332.900; X2 (2, N = 252) = 14.312, p = .001
Model 2 AIC: 4167.643; X2 (4, N = 252) = 29.437, p < .001
Model 3 AIC: 4241.701; X2 (5, N = 252) = 29.530, p < .001

Moderation Results for MMSE scores in adults 75+ years old Hypothesis 3: *Do Age-Related Differences Exist for the Analyses in Hypothesis 1 and Hypothesis 2?*

	B	SE	β	*p*	95% CI
Model 1: Covariates					
Age	-0.074	0.027	-0.177	.006	-0.127, -0.021
Education	0.124	0.041	0.196	.002	0.044, 0.204
Model 2: Independent Effects					
Age	-0.077	0.027	-0.184	.004	-0.129, -0.024
Education	0.122	0.040	0.194	.002	0.044, 0.201
Stressful Life Events	-0.305	0.188	-0.123	.105	-0.673, 0.063
HbA1c	-0.390	0.190	-0.130	.040	-0.762, -0.017
Model 3: Interaction Effects					
Age	-0.076	0.027	-0.182	.005	-0.128, -0.023
Education	0.121	0.040	0.191	.002	0.043, 0.199
Stressful Life Events	-4.541	2.956	-1.833	.125	-10.334, 1.253
HbA1c	-0.923	0.417	-0.307	.027	-1.741, -0.105
Interaction	0.760	0.530	1.728	.151	-0.278, 1.799

Model 1 AIC: 3544.029; X2 (2, N = 249) = 14.910, p = .001
Model 2 AIC: 4374.750; X2 (4, N = 249) = 21.760, p < .001
Model 3 AIC: 4406.921; X2 (5, N = 249) = 23.782, p < .001

Mediation Results for verbal fluency scores in adults less than 75 years old

Hypothesis 3: *Do Age-Related Differences Exist for the Analyses in Hypothesis 1 and Hypothesis 2?*

	Dependent Variable	Independent Variable	*B*	SE	β	*p*	95% CI
Covariates							
	Verbal Fluency	Age	-0.258	0.103	-0.194	.012	-0.480, -0.058
		Education	0.205	0.133	0.107	.123	-0.067, 0.451
Direct Pathway							
	Verbal Fluency	Stressful Life Events	-0.479	0.562	-0.066	.394	-1.499, 0.607
Indirect Pathway							
	HbA1c	Stressful Life Events	0.035	0.053	0.041	.504	-0.068, 0.141
	Verbal Fluency	HbA1c	-0.371	0.424	-0.044	.382	-1.265, 0.446
Total Effect							
			-0.492	0.558	-0.068	.378	-1.508, 0.586

Model AIC: 4487.993

X^2 (7, N = 248) = 15.606, p = .029

Mediation Results for verbal fluency scores in adults 75+ years old Hypothesis 3: *Do Age-Related Differences Exist for the Analyses in Hypothesis 1 and Hypothesis 2?*

Covariates	Dependent Variable	Independent Variable	*B*	SE	β	*p*	95% CI
	Verbal Fluency	Age	-0.107	0.071	-0.101	.135	-0.248, 0.041
		Education	0.247	0.118	0.151	.036	0.032, 0.480
Direct Pathway							
	Verbal Fluency	Stressful Life Events	-0.725	0.564	-0.116	.199	-1.782, 0.382
Indirect Pathway							
	HbA1c	Stressful Life Events	0.024	0.078	0.030	.757	-0.139, 0.179
	Verbal Fluency	HbA1c	0.728	0.568	0.095	.200	-0.218, 2.113
Total Effect							
			-0.707	0.549	-0.114	.197	-1.718, 0.387

Model AIC: 4555.951

X^2 (7, N = 245) = 11.870, p = .105

Moderation Results for verbal fluency scores in adults less than 75 years old

Hypothesis 3: *Do Age-Related Differences Exist for the Analyses in Hypothesis 1 and Hypothesis 2?*

	B	SE	β	*p*	95% CI
Model 1: Covariates					
Age	-0.276	0.096	-0.207	.004	-0.463, -0.088
Education	0.214	0.133	0.112	.107	-0.046, 0.475
Model 2: Independent Effects					
Age	-0.258	0.097	-0.194	.008	-0.448, -0.068
Education	0.205	0.133	0.107	.125	-0.057, 0.466
Stressful Life Events	-0.479	0.603	-0.066	.427	-0.166, 0.702
HbA1c	-0.371	0.594	-0.044	.533	-1.535, 0.794
Model 3: Interaction Effects					
Age	-0.262	0.097	-0.197	.007	-0.452, -0.072
Education	0.212	0.133	0.111	.112	-0.049, 0.474
Stressful Life Events	-6.209	7.514	-0.851	.409	-20.935, 8.518
HbA1c	-1.267	1.314	-0.150	.335	-3.482, 1.309
Interaction	1.027	1.343	0.793	.444	-1.606, 3.660

Model 1 AIC: 3674.971; X2 (2, N = 248) = 9.847, p = .007
Model 2 AIC: 4487.993; X2 (4, N = 248) = 10.884, p = .028
Model 3 AIC: 4608.396; X2 (5, N = 248) = 11.462, p = .043

Moderation Results for verbal fluency scores in adults 75+ years old Hypothesis 3:

Do Age-Related Differences Exist for the Analyses in Hypothesis 1 and Hypothesis 2?

	B	SE	β	*p*	95% CI
Model 1: Covariates					
Age	-0.118	0.076	-0.111	.123	-0.267, -0.032
Education	0.250	0.110	0.153	.023	0.035, 0.466
Model 2: Independent Effects					
Age	-0.107	0.076	-0.101	.161	-0.255, 0.042
Education	0.247	0.110	0.151	.024	0.032, 0.461
Stressful Life Events	-0.725	0.560	-0.116	.196	-1.823, 0.373
HbA1c	0.728	0.586	0.095	.214	-0.419, 1.876
Model 3: Interaction Effects					
Age	-0.092	0.076	-0.087	.222	-0.240, 0.056
Education	0.233	0.109	0.142	.032	0.020, 0.466
Stressful Life Events	-17.895	8.443	-2.875	.034	-34.444, -1.347
HbA1c	-1.394	1.182	-0.181	.238	-3.710, 0.923
Interaction	3.084	1.515	2.781	.042	0.115, 6.053

Model 1 AIC: 3730.664; X2 (2, N = 245) = 7.188, p = .027
Model 2 AIC: 4555.951; X2 (4, N = 245) = 10.244, p = .037
Model 3 AIC: 4568.171; X2 (5, N = 245) = 14.233, p = .014

Mediation Results for word list recall scores in adults less than 75 years old

Hypothesis 3: *Do Age-Related Differences Exist for the Analyses in Hypothesis 1 and Hypothesis 2?*

	Dependent Variable	Independent Variable	*B*	SE	β	*p*	95% CI
Covariates							
	Word List Total Recall	Age	-0.138	0.063	-0.151	.028	-0.261, -0.011
		Education	0.167	0.088	0.133	.058	-0.018, 0.335
Direct Pathway							
	Word List Total Recall	Stressful Life Events	-0.245	0.371	-0.050	.509	-1.008, 0.485
Indirect Pathway							
	HbA1c	Stressful Life Events	0.044	0.055	0.051	.431	-0.060, 0.161
	Word List Total Recall	HbA1c	-0.370	0.316	-0.064	.242	-0.970, 0.275
Total Effect							
			-0.261	0.370	-0.053	.480	-1.017, 0.462

Model AIC: 4372.263

X^2 (7, N = 243) = 19.522, p = .007

Mediation Results for word list recall scores in adults 75+ years old Hypothesis 3:

Do Age-Related Differences Exist for the Analyses in Hypothesis 1 and Hypothesis 2?

	Dependent Variable	Independent Variable	*B*	SE	β	*p*	95% CI
Covariates							
	Word List Total Recall	Age	-0.203	0.059	-0.225	.001	-0.314, -0.084
		Education	0.298	0.093	0.216	.001	0.104, 0.468
Direct Pathway							
	Word List Total Recall	Stressful Life Events	-0.352	0.409	-0.066	.390	-1.218, 0.466
Indirect Pathway							
	HbA1c	Stressful Life Events	-0.043	0.078	-0.049	.578	-0.199, 0.119
	Word List Total Recall	HbA1c	-0.588	0.393	-0.097	.135	-1.395, 0.142
Total Effect							
			-0.326	0.412	-0.061	.428	-1.206, 0.512

Model AIC: 4589.454

X^2 (7, N = 244) = 23.603, p = .001

Moderation Results for word list recall scores in adults less than 75 years old

Hypothesis 3: *Do Age-Related Differences Exist for the Analyses in Hypothesis 1 and Hypothesis 2?*

	B	SE	β	*p*	95% CI
Model 1: Covariates					
Age	-0.153	0.060	-0.168	.011	-0.271, -0.035
Education	0.173	0.081	0.138	.033	0.014, 0.332
Model 2: Independent Effects					
Age	-0.138	0.061	-0.151	.024	-0.258, -0.018
Education	0.167	0.081	0.133	.040	0.008, 0.326
Stressful Life Events	-0.245	0.374	-0.050	.513	-0.977, 0.488
HbA1c	-0.370	0.392	-0.064	.346	-1.138, 0.399
Model 3: Interaction Effects					
Age	-0.137	0.061	-0.150	.025	-0.258, -0.017
Education	0.165	0.081	0.131	.043	0.005, 0.325
Stressful Life Events	0.559	4.166	0.114	.893	-7.606, 8.724
HbA1c	-0.257	0.693	-0.045	.710	-1.615, 1.100
Interaction	-0.145	0.749	-0.166	.846	-1.613, 1.323

Model 1 AIC: 3582.007; X2 (2, N = 243) = 10.546, p = .005
Model 2 AIC: 4372.263; X2 (4, N = 243) = 10.546, p = .018
Model 3 AIC: 4496.866; X2 (5, N = 243) = 11.942, p = .036

Moderation Results for word list recall scores in adults 75+ years old Hypothesis 3:

Do Age-Related Differences Exist for the Analyses in Hypothesis 1 and Hypothesis 2?

	B	SE	β	*p*	95% CI
Model 1: Covariates					
Age	-0.204	0.060	-0.226	.001	-0.321, -0.086
Education	0.288	0.089	0.209	.001	0.114, 0.462
Model 2: Independent Effects					
Age	-0.203	0.060	-0.225	.001	-0.319, -0.086
Education	0.298	0.089	0.216	.001	0.124, 0.472
Stressful Life Events	-0.352	0.444	-0.066	.428	-1.222, 0.519
HbA1c	-0.588	0.423	-0.097	.164	-1.417, 0.241
Model 3: Interaction Effects					
Age	-0.190	0.060	-0.211	.002	-0.308, -0.072
Education	0.282	0.089	0.204	.002	0.106, 0.457
Stressful Life Events	-6.610	5.155	-1.242	.200	-16.714, 3.494
HbA1c	-1.187	0.645	-0.197	.065	-2.450, 0.076
Interaction	1.112	0.913	1.176	.223	-0.677, 2.901

Model 1 AIC: 3721.621; X2 (2, N = 244) = 20.201, $p < .001$
Model 2 AIC: 4589.454; X2 (4, N = 244) = 22.652, $p < .001$
Model 3 AIC: 4708.346; X2 (5, N = 244) = 24.132, $p < .001$

Mediation Results for pattern recognition scores in adults less than 75 years old

Hypothesis 3: *Do Age-Related Differences Exist for the Analyses in Hypothesis 1 and Hypothesis 2?*

	Dependent Variable	Independent Variable	*B*	SE	β	*p*	95% CI
Covariates							
	Pattern Recognition	Age	-0.061	0.021	-0.203	.003	-0.102, -0.021
		Education	0.021	0.043	0.050	.620	-0.065, 0.103
Direct Pathway							
	Pattern Recognition	Stressful Life Events	-0.069	0.132	-0.044	.600	-0.354, 0.170
Indirect Pathway							
	HbA1c	Stressful Life Events	0.055	0.054	0.060	.313	-0.051, 0.166
	Pattern Recognition	HbA1c	0.065	0.152	0.037	.670	-0.265, 0.332
Total Effect							
			-0.066	0.131	-0.042	.616	-0.351, -0.170

Model AIC: 3991.801

X^2 (7, N = 260) = 11.984, p = .101

Mediation Results for pattern recognition scores in adults 75+ years old Hypothesis 3: *Do Age-Related Differences Exist for the Analyses in Hypothesis 1 and Hypothesis 2?*

	Dependent Variable	Independent Variable	*B*	SE	β	*p*	95% CI
Covariates							
	Pattern Recognition	Age	-0.026	0.031	-0.076	.399	-0.870, 0.033
		Education	0.061	0.04	0.118	.128	-.0170, 0.146
Direct Pathway							
	Pattern Recognition	Stressful Life Events	-0.117	0.214	-0.06	.586	-0.544, 0.289
Indirect Pathway							
	HbA1c	Stressful Life Events	0.041	0.078	0.05	.597	-0.114, 0.204
	Pattern Recognition	HbA1c	-0.552	0.256	-0.23	.031	-1.009, -0.003
Total Effect							
			-0.139	0.221	-0.071	.529	-0.568, -0.139

Model AIC: 4013.894

X^2 (7, N = 252) = 10.871, p = .144

Moderation Results for pattern recognition scores in adults less than 75 years old

Hypothesis 3: *Do Age-Related Differences Exist for the Analyses in Hypothesis 1 and Hypothesis 2?*

	B	SE	β	*p*	95% CI
Model 1: Covariates					
Age	-0.061	0.023	-0.201	.009	-0.106, -0.015
Education	0.020	0.037	0.047	.587	-0.053, 0.093
Model 2: Independent Effects					
Age	-0.061	0.024	-0.203	.009	-0.107, -0.015
Education	0.021	0.037	0.050	.566	-0.052, 0.095
Stressful Life Events	-0.069	0.138	-0.044	.614	-0.339, 0.200
HbA1c	0.065	0.141	0.037	.646	-0.212, 0.342
Model 3: Interaction Effects					
Age	-0.061	0.023	-0.201	.009	-0.107, -0.015
Education	0.023	0.037	0.052	.546	-0.051, 0.096
Stressful Life Events	-1.577	1.548	-0.999	.309	-4.611, 1.458
HbA1c	-0.211	0.316	-0.122	.504	-0.831, 0.408
Interaction	0.273	0.279	0.989	.328	-0.274, 0.820

Model 1 AIC: 3062.145; X2 (2, N = 260) = 7.074, $p < .001$
Model 2 AIC: 3991.801; X2 (4, N = 260) = 7.465, $p = .113$
Model 3 AIC: 4170.918; X2 (5, N = 260) = 8.411, $p = .135$

Moderation Results for pattern recognition scores in adults 75+ years old

Hypothesis 3: *Do Age-Related Differences Exist for the Analyses in Hypothesis 1 and Hypothesis 2?*

	B	SE	β	*p*	95% CI
Model 1: Covariates					
Age	-0.017	0.028	-0.050	.545	-0.071, -0.037
Education	0.048	0.044	0.095	.270	-.0370, 0.134
Model 2: Independent Effects					
Age	-0.026	0.027	-0.076	.345	-0.079, -0.028
Education	0.061	0.043	0.118	.161	-.0240, 0.145
Stressful Life Events	-0.117	0.197	-0.060	.553	-0.502, 0.269
HbA1c	-0.552	0.212	-0.230	.009	-0.967, -0.136
Model 3: Interaction Effects					
Age	-0.026	0.027	-0.076	.345	-0.079, -0.028
Education	0.058	0.043	0.113	.177	-.0260, 0.142
Stressful Life Events	-4.108	3.026	-2.110	.175	-10.039, 1.823
HbA1c	-1.059	0.434	-0.442	.015	-1.909,-0.208
Interaction	0.717	0.543	2.095	.186	-0.347, 1.781

Model 1 AIC: 3152.277; X2 (2, N = 252) = 1.453, p = .484
Model 2 AIC: 4013.894; X2 (4, N = 252) = 8.489, p = .075
Model 3 AIC: 4098.057; X2 (5, N = 252) = 10.255, p = .068