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The Interaction of Type II Diabetes and Gonadal Steroids on Cognition in Middle-Aged Women

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**The Interaction of Type II Diabetes and Gonadal Steroids on Cognition in
Middle-Aged Women**

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Honors College Thesis

Undergraduate Neuroscience Program

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Abstract

Diabetes is not commonly thought to be a women's health issue, however, it appears to have an association with increased cognitive impairment in women during menopause as compared to women without diabetes (Espeland et al., 2011). The present study investigated the effects of type II diabetes and menopause on cognition in women between the ages of 46 and 55 years. To assess cognition, participants performed the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph 1998), Letter Number Sequencing Test (Wechsler, 1997), Trail Making Test (Delis, 2001), Verbal Fluency Test (Delis, 2001), Wechsler Test of Adult Reading (Wechsler, 2001), and the Buschke Selective Reminding and Delayed Recall Tests (Buschke, 1974). Participants also answered questionnaires on mood, diabetes, and hormone and reproductive history. No premenopausal women or perimenopausal women with diabetes participated. Women were divided into the following groups to examine the interactions of diabetes and hormones on cognition: perimenopausal women without diabetes, postmenopausal women with diabetes, and postmenopausal women without diabetes. It was predicted that women with diabetes would score lower on all tests, with an emphasis on difficulties with executive function and memory. Postmenopausal women with diabetes showed lower scores in working memory, executive control, visual attention, task switching, and episodic memory as seen in data from the Letter Number Sequencing Test, Verbal Fluency Test, Trail Making Test, and Buschke Selective Reminding and Delayed Recall Tests, respectively. Perimenopausal women without diabetes showed lower scores than postmenopausal women with and without diabetes on verbal memory and executive control. The sample of eight women was small, though there were indications of differences between groups highlighting the need for further research.

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I. Introduction and Previous Work

Recent research has shown that metabolic diseases and cardiovascular risk factors, such as obesity, insulin resistance, and type II diabetes, may lead to an increased risk for cognitive decline and even Alzheimer's disease or vascular dementia (Neth, 2017). While diabetes may not commonly be viewed as a women's health issue, there are data to suggest that it may negatively impact women during reproductive aging. Women are at higher risk than men for cardiovascular disease, hypertension, stroke, and coronary artery disease, all of which are associated with diabetes as reviewed by Coker (2003). Due to the cognitive impairment associated with diabetes and menopause independently, women may also be at higher risk for peripheral vascular disease, dementia, and Alzheimer's disease (Mcneill et al., 2018). Thus far, research has focused on cognitive impairment in older women with diabetes and there are very few studies examining how diabetes interacts with menopause to affect cognition. This study attempted to take a closer examination of the relationships between cognition, menopause, and diabetes in middle-aged women to see how diabetes affects the brain in women at different stages of the menopause transition. This could allow for researchers to determine which stage of menopause is associated with the most adverse effects and potentially mitigate cognitive decline in the future.

Menopause and Cognition

Menopause affects all women and has many effects on the brain. Understanding the menopause transition is important for examining the health effects in middle-aged women. A woman is considered postmenopausal after 12 months of amenorrhea due to permanent cessation of ovarian function (Greendale et al., 1999). The menopause transition typically occurs around 51 years. Three important phases include premenopause, perimenopause, and postmenopause. Premenopause refers to women still experiencing regular menstrual cycles (Davis et al., 2015).

Menstrual cycles are considered regular if they last 25 to 35 days (Casper, 2017). Perimenopause refers to women experiencing irregular menstrual cycles due to changes in ovarian function (Greendale et al., 1999). Menstrual cycles are considered irregular if they last more than 60 days (Davis et al., 2015). Additionally, a woman is perimenopausal if she has had at least one period in the last 12 months (Cheung et al., 2004). Lastly, postmenopause refers to women who have not experienced menstrual cycles for 12 months (Dalal et al., 2015). Various symptoms may be experienced throughout the menopausal transition including hot flashes, urinary incontinence (sensations of frequency and urgency), vaginal atrophy (signs may include vaginal dryness, itching, and irritation), reduced sexual dysfunction, and depression (Greendale et al., 1999).

The menopause transition can have negative effects on the brain, especially in terms of memory and thinking related to the changing hormone levels. Common symptoms associated with menopause involve confusion, forgetfulness, and fuzzy thinking (Mitchell et al., 2001). Schaafsma et al. (2010) found subjective cognitive complaints to be associated with measurable declines in verbal memory and attention, which was specifically notable in the perimenopausal group as compared to premenopausal and postmenopausal groups. Additionally, a review by Weber et al. (2014), found for a measure of executive function, postmenopausal women performed significantly worse than perimenopausal women on verbal fluency tasks. On measures of verbal memory, postmenopausal women also performed significantly worse than perimenopausal women on immediate memory as well as immediate and delayed verbal recall. This shows that the menopause transition has negative effects on cognition. Greendale et al. (2009) found a different pattern of results in a longitudinal study of cognitive performance across the menopause transition. This large-scale (n=2,362), longitudinal study consisted of four follow up visits over the course of four years. Slopes of cognitive scores were calculated using the data

collected from women to predict their scores across hormone changes. The perimenopausal women experienced the most memory difficulties while improvement to premenopausal levels was noted in their postmenopausal states. These data suggest that cognitive impairment may only occur for a period of time during the fluctuating hormone phase before a woman is postmenopausal (Greendale et al., 2009). Similarly, in a cross-sectional study (n=103), Weber et al. (2013) found that women in their first year of postmenopause performed significantly worse than premenopausal and late-postmenopausal women on tasks including verbal learning, verbal memory, and attention/working memory. These data also suggest that the brain may have the ability to adjust and compensate for hormone changes later in life.

When women go through menopause, whether they do so naturally or via surgery, there are decreased levels of 17β -estradiol (E2; Au et al., 2016). E2 decline during menopause is associated with cognitive functioning decline and an increase in depressive problems (Weber et al., 2014). A previous menstrual cycle study showed that when estrogen levels are high, women excel on tests including verbal articulation, fluency, and perceptual speed (Mitchell et al., 2001). Additionally, the use of estrogen hormone therapy, which is used to control menopause symptoms, can reduce aging effects on cognition and assist prefrontal mechanisms if taken during early-postmenopause (Girard et al., 2017). However, when given to older women it may result in slight decreases in cognitive functioning that lasts for a few years post-medication termination (Espeland et al., 2017). Estrogen's apparent protective effect on cognitive functioning is lost at menopause (Morgan et al., 2018). Estrogen can stimulate neurotransmitters and blood flow to the brain as well as promote neuronal and synaptic growth within the hippocampus and cortex, all of which are important for learning, memory, and cognition

(Morgan et al., 2018). How estrogen protects the brain is still not fully understood. However, data show that middle-aged women are at risk for cognitive impairment due to hormone changes.

Diabetes and Cognition

Type II diabetes is becoming increasingly more prevalent in the United States as obesity rates and sedentary lifestyles rise. Overall prevalence of diagnosed diabetes based on the NHIS 2011-2015 was 21.8 million individuals in the United States (Cowie et al., 2018). The current diabetes epidemic shows increased necessity for research in how this disease affects all aspects of health. Understanding the toll that diabetes has on the brain is important because these effects may be worsened in women during the menopause transition.

Individuals with type II diabetes are incapable of normal regulation of glucose metabolism, meaning they are insulin resistant (Kahn et al., 2013). Insulin resistance, the body's inability to use insulin properly, is when there is an impaired response to insulin leading to the body's inability to remove glucose from the bloodstream. This leads to hyperglycemia, which is an abnormal rise in blood glucose levels. A feedback loop between β -cells and insulin sensitive tissues is crucial to glucose homeostasis in the body (Kahn et al., 2013). If β -cells cannot properly control insulin output to regulate glucose levels, there will be an increase in glucose (Kahn et al., 2013).

Research suggests that chronic type II diabetes can negatively impact the brain via accelerated cognitive dysfunction and increased risk for dementia (Klein et al., 2003). This exact mechanism is not fully understood. It is hypothesized that impaired metabolic processes in individuals with diabetes lead to insulin resistance, poor glycemic control, and inflammation, which may cause the secondary end-organ damage seen in the brain (Yoon et al., 2017). Klein et al. (2003) proposed another mechanism of pathogenesis in which there may be changes in the

gene expression of neurons. These changes in neuronal structure and function may lead to disruptions in cognitive processes in the brain, resulting in the notable cognitive impairment seen in individuals with diabetes.

Prior research studies examined cognition via cognitive batteries in men and women aged 40 to 80 years and found significant impairments in memory and executive function in the participants with diabetes. In a study conducted by Knopman et al. (2001) cognitive assessments including Delayed Word Recall, the Digit Symbol Subtest of the Wechsler Adult Intelligence Scale, and a First-Letter Word Fluency Test were administered to individuals between the ages of 47 and 70 years with and without diabetes. Both subjects with diabetes younger than 58 years and older than 58 years performed significantly worse on the Digit Symbol Subtest as well as the First-Letter Word Fluency Test as compared to subjects without diabetes (Knopman, 2001). The Digit Symbol Subtest measures processing speed, working memory, and attention while the Verbal Fluency Test measures executive control, which are all components of executive function. Diabetes was a risk factor for cognitive decline in even the younger age group.

Imaging studies found similar results in that adults with diabetes showed increased temporal horn volume thus leading to deficits in memory and executive function (DeBette, 2011). This study also examined vascular risk factors in relation to how they may accelerate structural brain aging and cognitive decline. MRIs of middle-aged individuals, a mean age of 54 years, with diabetes showed a far more rapid increase in temporal horn volume, an indicator of hippocampal atrophy. These degenerative changes in brain structure were correlated with cognitive decline including deficits in memory and executive function. This study examined longitudinal change of various quantitative MRI markers of cognitive decline as well as longitudinal change in cognitive test scores (DeBette, 2011). Another study conducted by Heijer

et al. (2003) also examined this relationship using MRIs to examine atrophy of medial temporal lobe structures. The one important difference in this study compared to others is that they questioned whether diabetes simply increased the risk of Alzheimer's disease due to its vascular components or if diabetes directly caused Alzheimer neuropathology to develop (Heijer et al. 2003). Their results yielded more hippocampal and amygdalar atrophy on MRI in the subjects with diabetes. However, in individuals without diabetes, insulin resistance was associated with only amygdalar atrophy on MRI. Hippocampal and amygdalar atrophy was used in this study as a marker of preclinical Alzheimer's disease, as this was also associated with memory impairment and development of other symptoms of dementia later in life (Heijer et al. 2003). These findings indicate that diabetes influenced neurodegeneration and that this influence changed across the age span (Knopman, 2001).

There have been inconsistencies across results of similarly designed studies. Scott et al. (1998) did not find an association between diabetes and cognitive function in older subjects. This study utilized 12 cognitive tests and no significant results were found. The researchers suggested that subjects in studies where cognitive decline was found may have been experiencing temporary deficits due to ischemia or injury to the brain, which occurs in patients with diabetes. Additionally, subjects in these prior studies may have suffered from repeated, severe hypoglycemic episodes, explaining the impairment in cognition (Scott, 1998). The researchers did note, however, that women with diabetes performed worse on all cognitive tests but not at a significant level. It is clear that the association between diabetes and cognition is not fully understood and further studies are needed.

Diabetes, Menopause, and Cognition

No study described above explicitly examined the role of sex on cognitive changes in diabetes, though data suggested that females with diabetes experienced more cognitive impairment than males with diabetes (Knopman, 2001). Women with type II diabetes tend to be significantly younger at menopause as compared to women without diabetes (Mauvais, 2017). Menopause is associated with increased visceral fat, a decrease in lean body mass, and changes in body composition that can lead to impaired insulin sensitivity, which are risk factors for type II diabetes in postmenopausal women (Mauvais, 2017). As mentioned earlier, estrogen seems to have a protective effect on cognition. Therefore, this increased risk for cognitive decline caused by the reduction of protective effects of estrogen paired with increased vascular disease associated with diabetes, such as hypertension, obesity, and high cholesterol, may affect cognitive functioning.

There seems to be an interaction between estrogen via hormone therapy and insulin and the delayed onset of diabetes (Mauvais, 2017). Menopausal hormone therapy may improve islet β -cell function, insulin secretion, noninsulin-dependent glucose disposal, and glucose effectiveness in postmenopausal women, though it is not approved by the FDA specifically for the use of diabetes prevention due to complex possible risks and benefits (Mauvais, 2017). Research by Espeland et al. (2015) found that older postmenopausal women with diabetes showed brain atrophy via decreased gray matter volumes when taking hormone therapy in a randomized clinical trial. Espeland et al. (2015) also noted that high levels of estrogen via postmenopausal hormone therapy may increase the risk of cognitive impairment in diabetes. The effects of estrogen hormone therapy on diabetes is still unclear though studies are currently being

conducted to examine the potential for protective mechanisms of postmenopausal hormone treatment in women with diabetes (Mauvais, 2017).

Prior studies have examined the effect of diabetes on cognitive impairment in older women. Studies conducted by Logroscino et al. (2004) and Gregg et al. (2000) administered multiple cognitive tests to women with and without diabetes. Logroscino et al. (2004) included women between 70 and 81 years who completed a baseline interview of their cognitive state and the women with diabetes performed significantly worse on all cognitive tests. The cognitive tests were Immediate and Delayed Recall, Verbal Fluency Tests, and a Digit Span Backwards Test. A global score was made from the results of these tests. These results suggested impairments in working memory and attention which are components of executive functioning. It was also noted that women who had a longer duration of diabetes had evidence of further impaired cognition. Women utilizing oral hypoglycemic agents, which are medications that decrease blood glucose levels like metformin, performed in a similar manner to women without diabetes, however, women not taking these medications displayed the poorest performance of all groups. Those experiencing improved glucose control via oral medications were found to have better cognitive performance, memory, and orientation, suggesting that oral therapy may benefit the cognitive health of individuals with diabetes. Logroscino et al. (2004) did not offer reason as to why this was the case, though it may be that the oral medications were able to control glucose levels and prevent the secondary end-organ damage seen in the brain. Gregg et al. (2000) had similar findings in that women with diabetes who were 65 years and older performed significantly worse on the Digit Symbol Test, Trail B Test, and Mini Mental State Examination. This indicated that women with diabetes showed declines in concentration, language, and memory as measured by the Mini Mental State Examination. Additionally, their scores on the Digit Symbol Test

suggested declines in attention, psychomotor performance, and perceptual organization. Lastly, their scores on the Trail B Test suggested declines in attention and visual scanning. Women who were not taking insulin had a significantly higher risk of cognitive decline than those who were. These data are similar to that of Logroscino et al. (2004) in that medication aiding glucose tolerance, in the form of insulin, seemed to assist in the prevention of the negative effects of diabetes on the brain. In other words, medications that help regulate glucose metabolism, thus preventing hyperglycemic events in individuals with diabetes, may prevent some of the cognitive impairment individuals not taking these medications may experience. Memory problems were reported with a higher frequency in the group with diabetes as compared to the group without diabetes. Similar to the previous study, the cognitive decline increased with duration of diabetes. Gregg et al. (2000) did not assess the presence of other components of diabetes including oral medications, glycemic control, and neuropathies. Due to this limitation, our study included an assessment of such components for the subjects with diabetes. Neither of these studies examined brain structure via imaging nor did they attempt to examine the mechanism by which diabetes affected cognition.

The Current Study

In the Dumas Lab, menopause and cognition have been studied extensively. The aim of this thesis was to examine the effect of diabetes on cognition in women at different stages of the menopause transition. This study attempted to investigate the relationship between menopause and diabetes and their combined effect on cognition. While Gregg et al. (2000) found significant cognitive decline in older postmenopausal women with type II diabetes, no studies have examined middle-aged women with diabetes. This age group is important to study because

cognitive decline may start in middle adulthood in subjects with diabetes and the role of sex and menopause on diabetes and cognition has not yet been examined.

I hypothesized that women with diabetes would score lower on all cognitive tests due to decreased executive functioning and that this decreased cognitive functioning would be greater in women who are further along the menopause transition. I hypothesized that executive functioning, specifically, would show notable decline and this hypothesis is supported by the prior research (Knopman et al. 2001; Logroscino et al. 2004; Gregg et al. 2000). Within the group of women with diabetes, I hypothesized that premenopausal women would show the least cognitive deficits while postmenopausal women would show the most cognitive deficits. Within the group of women without diabetes, I hypothesized, again, that premenopausal women would show the least cognitive deficits while postmenopausal women would show the most cognitive deficits.

II. Methodology

Participants

Recruitment flyers were placed in the city of Burlington and surrounding towns. Diabetes clinics and doctors' offices across the state of Vermont were contacted and given flyers. An ad for subjects with diabetes ran in Seven Days for two weeks. Participants were required to complete a brief phone screening interview to determine their eligibility for the study. Once determined eligible, an appointment was scheduled for a two-hour study visit at the University Health Center where subjects were consented and asked to complete various cognitive tests and questionnaires regarding their medical history. Inclusion criteria included women between the ages of 45 and 55 years who were either healthy or had type II diabetes. There were no other

exclusion criteria for the pilot study apart from women who could not complete the cognitive tasks and questionnaires. Eight women were recruited for the study.

Measures

General Cognitive Health Assessments: Subjects completed interview-based assessments or questionnaires to assess the presence of dementia, depressed feelings, sleep quality, and IQ. These cognitive and behavior assessments are standardized tests designed to identify women with significant cognitive or behavioral impairment. The Mini Mental State Exam is a dementia assessment instrument (Folstein et al., 1975). To evaluate current depression, subjects completed the Beck Depression Rating Scale (Beck et al. 1961). The Pittsburgh Sleep Quality Index was used to assess sleep quality over a one-month interval (PSQI; Buysse et al. 1989). Lastly, subjects performed the Wechsler Test of Adult Reading (WTAR) to estimate IQ (Wechsler, 2001).

Diabetes. In order to determine if subjects had type II diabetes, their medical records were examined and they were classified as having diabetes if they had been officially diagnosed by a physician. Subjects with diabetes were required to complete a Diabetes History Form (Columbia Medical Associates, 2016) to obtain more information regarding disease duration, physical activity, complications, and diabetes care.

Reproductive Hormone History. Women were asked various questions about their menstrual cycle history to classify them as pre-, peri-, and postmenopausal. Women were considered premenopausal if they still had regular menstrual cycles and were not yet menopausal (Davis et al., 2015). Regular menstrual cycles refer to menstrual cycles lasting 25 to 35 days (Casper, 2017). Women were considered perimenopausal if they had been experiencing irregular menstrual cycles and at least one period in the past 12 months (Cheung et al., 2004). Irregular

menstrual cycles refer to a menstrual cycle lasting more than 60 days (Davis et al., 2015).

Women were considered postmenopausal if it had been 12 months since their last menstrual cycle (Dalal et al., 2015). All women completed the Indices of Estrogen Exposure Questionnaire (Lord et al. 2009). This questionnaire is a measure of life time estrogen exposure and inquired about menstrual cycles, motherhood, menopause, and history of hormone therapy. Additionally, all women completed a Menopause Symptom Checklist (Newhouse and Sargent 2002).

Neuropsychological Testing. The cognitive measures for this study included the following: Repeatable Battery for the Assessment of Neuropsychological Status, Letter Number Sequencing Test, Buschke Selective Reminding and Delayed Recall Tests, Trail Making Test, and Verbal Fluency Test. To assess general neuropsychological functioning, all women performed the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph 1998). The RBANS assessed five cognitive domains including immediate memory, language, visuospatial/constructional ability, attention, and delayed memory and provides a global total measure. The Letter Number Sequencing Test was used as a measure of working memory ability, in which subjects were asked to reorder sequences of numbers first numerically and letters second alphabetically to the researcher. The Buschke Selective Reminding and Delayed Recall task involved the subject listening to 16 words and then recalling as many words as they could. The researcher then reminded the subject of the words she was unable to recall and the task was to try to recall the whole list again (Buschke, 1974). The Trail Making Test and Verbal Fluency subtests from the Delis-Kaplan Executive Function System (D-KEFS) were included. The Trail Making Test required subjects to connect circles that are distributed over a sheet of paper as quickly as possible. There were four parts to this test, each involving different conditions to assess visual attention and task switching. The Verbal Fluency subtests required

subjects to produce as many words as possible from a given category in one minute to examine executive control and verbal ability.

Statistical Analysis

Due to the difficulty in recruitment of this age group of women, means and standard deviations are presented to begin to examine cognitive performance in women with and without diabetes at different stages of the menopausal transition. We did not compute statistics on this sample as parametric analyses that assume normal distributions of the data will be unreliable with such a small sample size. In addition, while non-parametric analyses can be conducted on data with non-normal distributions, the groups in this study are still too small to produce reliable results.

III. Results

Demographics

The total number of participants acquired for this study was eight, consisting of two women with diabetes and six women without diabetes. The two women with diabetes were postmenopausal with a mean age of 52.5 ($SD=3.5$). Of the six women without diabetes, three were perimenopausal with a mean age of 49.3 ($SD=3.9$) and three were postmenopausal with a mean age of 51.0 ($SD=4.8$). No premenopausal women participated in the study. All of these subjects were high functioning women with at least a high school degree or more.

Table 1: *Demographic data of all subjects included in the study including their age ($M=50.6$, $SD=3.5$), stage of menopause, diabetes diagnosis, and education level.*

	Diabetes <i>Postmenopausal</i>	No Diabetes <i>Perimenopausal</i> <i>Postmenopausal</i>	
<i>Number of Subjects</i>	2	3	3
<i>Age in years (M, SD)</i>	52.5 (3.5)	49.3 (2.9)	51.0 (4.8)
<i>Education, Years (M, SD)</i>	16.0 (2.0)	16.7 (1.2)	14.0 (2.8)

Menopause: Of the postmenopausal women, one had surgical menopause via a hysterectomy while the rest had natural menopause. The mean menopause duration in postmenopausal women with diabetes was 6 years ($SD= 1.4$). The mean menopause duration in postmenopausal women without diabetes was 7.5 years ($SD= 7.5$). One postmenopausal woman without diabetes was on a low dose topical progesterone hormone therapy for 12 months about two years prior to her study visit. No other women reported use of hormone therapy.

Women varied greatly in number and severity of menopause symptoms experienced. The pattern of the means showed that postmenopausal women with diabetes reported high frequency and severity of menopause symptoms ($M=59.5, SD=3.5$). Postmenopausal women without diabetes reported a higher frequency and severity of menopause symptoms ($M= 44.3, SD=36.7$) than perimenopausal women without diabetes ($M=32.7, SD=39.3$). Symptoms experienced by more than half of the subjects included irritability, mood swings, worrying needlessly, constipation, leg cramps, intestinal gas, fatigue, early awakening, and muscle stiffness.

Diabetes: The duration of diabetes varied amongst the two subjects with diabetes. One woman was diagnosed 13 years ago and the other was diagnosed three years ago. Both subjects were taking metformin and insulin to control their sugar levels. Both subjects reported not exercising regularly. One subject experienced a hypoglycemic event that was treated with glucose tablets. Neither subject had been hospitalized for their diabetes.

Global Cognitive Health

Overall, all subjects displayed scores on the MMSE, WTAR, Beck Depression Rating Scale, and PSQI that did not indicate severe cognitive problems. The postmenopausal group with diabetes showed the highest scores on the Beck Depression Rating Scale and PSQI indicating higher rates of depressive symptoms and decreased sleep quality.

Table 2: Means and standard deviations from MMSE, WTAR, Beck Depression Rating Scale, and PSQI that assessed general cognitive health of the subjects. Overall, all eight subjects did not show severe cognitive problems.

Test	Diabetes		No Diabetes	
	Post	Peri	Peri	Post
MMSE	29.5 (0.7)	29.3 (0.6)	29.3 (0.6)	30.0 (0.0)
WTAR	110.5 (17.7)	118.0 (7.6)	118.0 (7.6)	123.3 (1.5)
Beck	9.0 (5.7)	3.7 (5.5)	3.7 (5.5)	7.0 (4.6)
PSQI	7.5 (2.1)	5.3 (2.5)	5.3 (2.5)	3.7 (1.5)

Neuropsychological Data

RBANS: Postmenopausal women with diabetes showed higher scores than both perimenopausal and postmenopausal women without diabetes on the total scale. Postmenopausal women with diabetes also showed higher scores than both groups on immediate memory, visuospatial/constructional, language, and delayed memory. However, postmenopausal women with diabetes showed lower scores than perimenopausal and postmenopausal women without diabetes in the attention conditions, which included a digit span and a coding task, where subjects had to match symbols to their corresponding numbers as quickly as possible. Additionally, perimenopausal women without diabetes showed lower scores than postmenopausal women without diabetes on most conditions except attention and visuospatial/constructional conditions, which included figure copying and line orientation.

Table 3: Means and standard deviations from RBANS. Women with diabetes performed better than women without diabetes. The perimenopausal group showed slightly lower scores on all tasks except attention and visuospatial/constructional.

Test	Diabetes		No Diabetes	
	Post	Peri	Peri	Post
Immediate Memory	116.0 (14.1)	106.3 (18.2)	106.3 (18.2)	109.7 (4.0)
Visuospatial/Constructional	112.5 (4.9)	111.7 (8.3)	111.7 (8.3)	111.3 (17.5)
Language	114.0 (24.0)	106.0 (6.1)	106.0 (6.1)	110.7 (9.1)
Attention	108.0 (24.0)	117.7 (10.2)	117.7 (10.2)	108.7 (26.5)
Delayed Memory	114.5 (13.4)	106.7 (1.5)	106.7 (1.5)	110.0 (5.0)
Total Scale	119.5 (19.1)	113.7 (8.0)	113.7 (8.0)	114.3 (15.3)

Letter Number Sequencing: Perimenopausal women ($M=13.0$, $SD=7.1$) and postmenopausal women with diabetes ($M=13.3$, $SD=2.9$) showed similar scores on the Letter Number Sequencing Test. Postmenopausal women without diabetes ($M=11.0$, $SD=1.7$) showed lower scores than both groups suggesting differences in working memory.

Trail Making: Postmenopausal women with diabetes had lower contrast scores than perimenopausal and postmenopausal women without diabetes. Low contrast scores indicate possible cognitive problems specifically in visual scanning and attention. Additionally, perimenopausal women without diabetes scored slightly lower on contrast scores as compared to postmenopausal women without diabetes.

Table 4: Means and standard deviations from the Trail Making Test. The composite score is the sum of the scaled number sequencing and letter sequencing scores. VS Contrast is the difference between the scaled switching score and scaled visual scanning score. NS Contrast is the difference between the scaled switching score and the scaled number sequencing score. LS Contrast is the difference between the scaled switching score and the letter sequencing score. Com Contrast is the difference between the scaled switching score and the composite score. Postmenopausal women with diabetes scored lower than peri- and postmenopausal women without diabetes on most measures.

Test	Diabetes		No Diabetes	
	Post	Peri	Peri	Post
Composite	12.5 (3.5)	12.3 (0.6)	12.3 (0.6)	12.7 (2.5)
VS Contrast	6.0 (7.1)	11.3 (1.5)	11.3 (1.5)	12.3 (1.2)
NS Contrast	5.5 (3.5)	11.0 (1.0)	11.0 (1.0)	11.7 (0.6)
LS Contrast	6.0 (7.1)	11.3 (1.2)	11.3 (1.2)	11.3 (2.5)
Com Contrast	5.5 (6.4)	10.0 (0.0)	10.0 (0.0)	13.0 (5.2)

Buschke Selective Reminding and Delayed Recall: Postmenopausal women without diabetes recalled more words in both the immediate and delayed recall conditions as compared to perimenopausal women without diabetes. Postmenopausal women with diabetes showed better scores than perimenopausal women without diabetes in all conditions. Postmenopausal women without diabetes showed better scores than postmenopausal women with diabetes in all

conditions. These patterns show differences in episodic memory in postmenopausal women with diabetes compared to postmenopausal women without diabetes.

Table 5: Means and standard deviations from Buschke. Postmenopausal women without diabetes showed better scores on all tasks as compared to perimenopausal women and postmenopausal women with diabetes.

Test	Diabetes		No Diabetes	
	Post	Peri	Post	Peri
Total Recall	89.5 (17.7)	77.3 (0.6)	95.0 (9.9)	
Total Consistency	60.5 (23.3)	44.0 (5.3)	66.0 (16.1)	
Total Recall Failure	11.5 (12.0)	16.7 (3.2)	6.3 (4.5)	
Total Delayed Recall	12.5 (3.5)	8.0 (1.0)	12.3 (3.1)	

Verbal Fluency: Perimenopausal women without diabetes showed lower scores than postmenopausal women without diabetes on all conditions. Perimenopausal women without diabetes also showed lower scores than postmenopausal women with diabetes on all conditions except condition 1, letter fluency. Additionally, postmenopausal women with diabetes showed lower scores than postmenopausal women without diabetes on all conditions except condition 3a, total correct responses in category switching.

Table 6: Means and standard deviations from Verbal Fluency Test. Condition 1 is letter fluency, condition 2 is category fluency, condition 3a is total correct responses in category switching, and condition 3b is total switching accuracy in category switching. Perimenopausal women showed lower scores than postmenopausal women with and without diabetes on all tasks except letter fluency. Postmenopausal women with diabetes showed lower scores than postmenopausal without diabetes on all tasks except total correct responses in category switching.

Test	Diabetes		No Diabetes	
	Post	Peri	Post	Peri
Condition 1	9.5 (3.5)	12.0 (4.4)	14.7 (3.1)	
Condition 2	13.0 (1.4)	13.0 (1.0)	15.0 (3.6)	
Condition 3a	13.0 (2.8)	7.7 (7.6)	12.7 (4.7)	
Condition 3b	12.0 (1.4)	7.0 (7.2)	12.3 (4.2)	

IV. Discussion

The aims of this study were to examine how cognition differs between women with diabetes and women without diabetes who are at different stages of the menopause transition. It was predicted that women farther along in reproductive aging would experience the most cognitive impairment, in that postmenopausal women would perform worse than perimenopausal women. It was also hypothesized that type II diabetes would cause increased cognitive impairment as compared to women without diabetes. Due to the small sample size, we chose not to compute statistics on the data, thus we could not tell if the differences between the groups were due to chance or not. However, the data show some interesting trends that are both similar to and different from the previous research, highlighting the need for further investigation.

Postmenopausal women with diabetes showed higher scores than women without diabetes on components of the RBANS, including immediate memory, language, delayed memory, and the total scale. Women with diabetes also showed better scores than perimenopausal women without diabetes on the episodic memory via the Buschke Selective Reminding and Delayed Recall Tests. These results differ from my hypothesis. This may be due to the small sample size, or it may be possible that diabetes may be associated with better cognition on these cognitive domains. This suggestion, however, is not supported by previous research.

Perimenopausal women without diabetes showed lower scores than postmenopausal women without diabetes on parts of the RBANS and Verbal Fluency Tests that show differences in working memory, executive function, language, and visuospatial/constructional ability. This is different from previous research by Weber et al. (2014) in that postmenopausal women showed measurable declines in verbal memory and immediate and delayed recall as compared to

perimenopausal women. These results could be a random pattern due to the small sample. Perimenopausal women also showed better scores than both groups of postmenopausal women on the attention component of the RBANS Test, as predicted. Perimenopausal women also showed similar scores as postmenopausal women without diabetes on the Trail Making Test, which measures attention and visual acuity. Both perimenopausal and postmenopausal women without diabetes also showed similar scores on the Letter Number Sequencing Test.

It is possible that the postmenopausal women without diabetes in this study, who had a mean duration of menopause of 7.5 years, may have been postmenopausal long enough for their bodies to begin to compensate for the loss of estrogen. Weber et al. (2013) and Greendale et al. (2009) noted that women who are late-postmenopausal may begin to experience improved verbal learning, verbal memory, and attention/working memory back to their baseline, premenopausal state. Early-postmenopause was defined as less than 12 months postmenopausal by Weber et al. (2013). Using this definition, all postmenopausal women in our study could be classified as late-postmenopausal as they have been postmenopausal for 6.75 years on average. This may support our findings in that perimenopausal women showed lower scores than postmenopausal women in verbal fluency and working memory tasks. Perhaps younger postmenopausal women would have shown lower scores than perimenopausal women on these tasks, as in research by Weber et al. (2013), where women only in their first year of menopause performed significantly worse than late-postmenopausal women on similar cognitive tasks. The initial loss of estrogen during the menopause transition is an extreme disruption in women that leads to various symptoms and cognitive changes. Therefore, cognitive impairment may begin in the perimenopausal stage, when menstrual cycles begin to become irregular. When women lose estrogen and menstrual cycles, there may be even greater changes in cognition during this initial time period of

postmenopause. Thus, after a few months, women may develop abilities to compensate for this drastic hormone change and regulate back to normal cognitive functioning. This demonstrates that cognition may not decline linearly across the menopause transition and women may experience both declines and improvements.

Both postmenopausal women with diabetes and without diabetes had higher ratings of depression, as noted by Table 2. Additionally, these women reported feelings of mood swings, worrying needlessly, and fatigue with high frequency on the Menopause Symptom Checklist, as noted in the results section. These data align with previous research by Weber et al. (2014) in that perimenopausal and postmenopausal women were at a significantly increased risk for having depressive symptoms and being diagnosed with clinical depression as compared to premenopausal women. Individuals with diabetes also seemed to have increased risk for depression when considering risk factors such as diabetic complications, education level, poor glycemic control, and sex (Andreoulakis et al., 2012). Therefore, the postmenopausal women with diabetes in this study may have been experiencing the additive risks for depression from both menopause and diabetes.

As predicted, postmenopausal women with diabetes showed lower scores than both perimenopausal and postmenopausal women without diabetes on the Letter Number Sequencing Test and the Trail Making Test. This suggests differences in working memory as well as attention and task switching. Postmenopausal women with diabetes showed lower scores than postmenopausal women without diabetes but showed higher scores than perimenopausal women without diabetes on the Verbal Fluency Test, which was not predicted. This suggests differences in executive control between postmenopausal women with and without diabetes, but not between perimenopausal women and postmenopausal women with diabetes. This may be due to the small

sample size or it may be that diabetes' effects on cognition have a more significant effect on women later in the menopause transition. In other words, the effects of diabetes may not be as measurable during the perimenopausal stage. There is no previous research on how diabetes may affect cognition in the stages of menopause differently. Gregg et al. (2000) did note, however, that cognitive impairment worsened as duration of diabetes increased. This study did not examine estrogen as it presented both men and women, but cognitive decline was greatest in women who had been diagnosed with diabetes for at least 15 years (Gregg et al., 2000). Of the two subjects with diabetes in our study, the subject who had been diagnosed with diabetes 13 years ago showed worse scores on all tests as compared to the other subject who had been diagnosed three years ago. Long-term type II diabetes has many negative consequences on the brain in that high blood glucose can impact the brain's functional connectivity (Klein et al., 2003). The effects this has on cognition may worsen with time, as high glucose levels continue to disrupt brain tissue. The changes in neuronal structure that negatively impact cognition could also be worsened if these glucose levels were not continuously monitored and controlled. Interestingly, the subject who had a longer disease duration reported that she did not properly monitor her glucose levels, nor did she know her typical morning and night levels. The other subject, however, did report properly monitoring and managing her glucose levels adequately. This may also be important to note when examining the differences between their scores on the cognitive measures. If an individual does not adequately manage her sugar levels, they may rise or fall to numbers that are dangerous for the brain. It would be interesting to examine the differences in cognition due to diabetes care, management, and duration of diabetes to examine how menopause is related as previous research by Mauvais et al. (2017) suggested that estrogen

may delay the onset of type II diabetes. From this information, it is hypothesized that diabetes may cause additive cognitive impairment over time, as the disease takes a toll on the brain.

Limitations

The current study has multiple limitations that are important to note. The sample size was small, with only eight subjects total. Subject recruitment was difficult due to the age range of women being studied. Middle-aged women are likely working. We had minimal response to the advertisements hung around town and in Seven Days newspaper. Subject recruitment may have also been hindered by the short period of time for data collection.

Due to the small sample size, these data do not provide a representative sample. There were only two subjects with diabetes versus six subjects without diabetes, preventing statistical analyses between groups. The women in the current study were all high functioning women that all received high school degrees and seven received a bachelor's degree or higher. All women were well educated, Caucasian, and fulltime employees. Therefore, these data may not be generalized to all populations.

Lastly, the current study was a short cross-sectional design in which participation in the study required one study visit without any follow-ups. A cross-sectional design still allows for comparisons between groups, if a large sample size is present. However, it does not allow for the observation of changes in individuals across the menopause transition.

Future Research

There is a clear need for further research in this field to not only examine the relationships between menopause, diabetes, and cognition in middle-aged women but also to examine the mechanisms underlying the interactions between diabetes and menopause.

As mentioned in the limitations, the present study was conducted over a few short months with a one-time study visit for each subject. Longitudinal studies that follow women with diabetes through their menopause transition, from premenopause to late-postmenopause, would allow researchers to examine when and how cognitive decline begins in women with diabetes. It may then be possible to approximate the stage of menopause that is associated with the highest cognitive decline when linked with diabetes, so that future studies examining ways to mitigate cognitive change can target this group at increased risk for cognitive decline.

Additionally, there are few studies in the field utilizing imaging techniques to assess where in the brain structural changes are seen and how these changes may relate to the cognitive decline. Weber et al. (2013) noted that estrogen can influence hippocampal and prefrontal cortex functions, which indicates that these structures may be involved in the cognitive impairment associated with menopause. Additionally, the study described earlier by Heijer et al. (2003) noted more hippocampal and amygdalar atrophy on MRI in subjects with diabetes. Thus, it may be possible to see structural change in the hippocampus in menopausal women with diabetes as compared to women without diabetes on MRI. Such a study would allow researchers to examine where changes in the brain occur and how that relates to cognitive decline. Studies may then begin to investigate the mechanistic properties underlying combined influence of menopause and diabetes on cognition. Understanding these mechanisms could allow researchers to examine therapies that target degeneration in the impacted regions of the brain.

Final Conclusions

While we did not compute statistical comparisons on these data because of the small sample size, it is still important to highlight the need for further research in this field. This was the first study to attempt to examine the effects of diabetes in middle-aged women to determine how these effects differ at various stages of the menopause transition. Though interesting trends were found, future large scale, longitudinal studies with imaging and cognitive assessments are needed to begin to fully understand the interactions between diabetes, menopause, and cognition.

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