MEDWIN PUBLISHERS
Committed to create value for Researchers

Alzheimer's Research & Therapy Open Access

The Effect of Diabetes and Hypertension on Cognition: Mechanisms that Impair & Protect

Turk K*

University of Massachusetts Boston, USA

***Corresponding author:** Kristina Turk, University of Massachusetts Boston, 704 Goldenrod Drive Chatham, IL 62629, USA, Tel: 2178366775; Email: kristinaturk82@gmail.com

Research Article

Volume 2 Issue 1

Received Date: September 04, 2019

Published Date: September 23, 2019

Abstract

Comorbid hypertension and diabetes adversely impact memory, increase cognitive decline, and increase risk of developing dementia of the Alzheimer's type. Given population aging and rising obesity rates, both conditions are expected to increase in the near future. The cognitive reserve hypothesis suggests that education may buffer negative effects of hypertension or diabetes on cognition. In line with this hypothesis, the goal of this study was to determine whether educational attainment moderates the effect of diabetes and hypertension on cognition, using the 2008 wave of the Health and Retirement Study (n=10,258 adults aged 65 and above). Further, this study seeks to elucidate the deleterious mechanisms on the brain caused by hypertension and diabetes. The mean age of the sample was 74.6 years; 58% were female, and average education was 12.26 years. Hierarchical ordinary least squares multiple regression techniques were used. Results show diabetics who take oral medications (especially in combination with insulin) score lower on cognition than non-diabetics. The analyses controlled for age, sex, race, self-rated health, ADLs, smoking status, alcohol use, income, and exercise. The study found that education (measured in years but not in degree categories) moderates the effect of diabetes on cognition for diabetics using both oral medications and insulin ($t=2.13$, $p>.038$). Thus, it lends very limited if any support to the cognitive reserve hypothesis. It also raises concerns about potential cognitive side effects diabetes medications.

Keywords: Alzheimer's disease; Blood pressure; Hypertension; Diabetes

Introduction

Hypertension and diabetes are two very common conditions among the older population. Thus, for public health purposes, it is important to understand their impact. Explicitly, 73 million Americans have hypertension, and incidence increases with age, affecting more than two-thirds of American adults aged 65 years and older [1]. Moreover, current estimates indicate that 23% of people aged 60 and older have type 2 diabetes, and its prevalence is rising, with the most significant increases seen in individuals 65 and older [2]. These conditions are also extremely costly to our healthcare system. Specifically, over $47 billion were spent on diabetes care within the older population in 2002, with

costs for hypertension accumulating to over $93.5 billion in 2010 [3,4].

Both hypertension and diabetes are health conditions that have been linked to deficits in brain function that adversely affect cognition [5,6]. The incidence of dementia and cognitive impairment are increasing, so understanding how diabetes and hypertension may contribute to cognitive impairment is important to policymakers and public health professionals. Furthermore, previous research has indicated the sharpest declines in cognitive ability are seen in those who have comorbid hypertension and diabetes [5-8]. Specifically, studies have shown that comorbid hypertension and diabetes affect memory, [9] recall, [5] increase the rate of cognitive decline, and increase the risk of developing Alzheimer's and the other dementias [7]. This is a concern because dementia is a progressive loss of brain function with severe consequences on health status, quality of life, and financial wellbeing for the person with the disease and his or her family and caregivers. Currently approximately 5.2 million people are living with Alzheimer's and other dementias in the United States; approximately one out of eight older adults have Alzheimer's disease [10]. By 2025, this is expected to increase by 30% when 6.7 million older Americans will be living with Alzheimer's disease and other dementias [11]. Moreover, payments for dementia care services to health providers are estimated to be around $200 billion in the United States, including $140 billion in costs to Medicare and Medicaid [11]. Thus, discovering how to prevent cognitive decline and dementia is a major focus of researchers, policymakers, and stakeholders.

One potential buffer of cognitive decline documented in the literature is educational attainment [12,13]. The effects of hypertension and diabetes on the brain have been previously explored, but not how educational attainment may moderate the effect of hypertension and diabetes on the brain. Thus, this study will highlight how educational attainment, a potential protective factor, moderates the effects of hypertension and diabetes on cognition. Further, this study seeks to elucidate the mechanism of pharmacological interventions used in treating hypertension and diabetes and the physiological effects of hypertension and diabetes on cognition.

Literature Review

Cognitive Decline Overview

The effects of diabetes and hypertension on cognition have been previously explored in scientific literature [6,14-21]. However, the exact mechanisms by which diabetes and hypertension affect cognition are not well understood, nor are potential protective mechanisms such as educational attainment that may buffer against cognitive decline. Previous research has discovered some possible biological effects that may lead to cognitive decline such as atrophy of gray and white matter in the prefrontal lobes and increased plaque formation in the hippocampus area of the brain [3,8,14,22-25]. Additionally, some oral medications used to control hypertension and diabetes have been linked to enhanced cognitive decline [23,26]. Conversely, achieving a high level of education is documented in the literature as a protective factor in helping slow the rate of cognitive decline [12,13,27-29].

Hypertension/Diabetes & Relationship to Cognitive Decline

Physiological Factors: Uncontrolled and controlled hypertension have an adverse biological effect on cognitive function that is independent of normal aging [6,14-21]. Hypertension has been shown to accelerate the effects of aging on brain structures [25] and is associated with a faster rate of progression of cognitive decline [14]. The decline in cognitive function among individuals with hypertension can be somewhat attributed to physical effects on the brain resulting from hypertension, which include lower brain weight [14] due to atrophy of gray and white matter in the prefrontal lobes [25], increased plaque formation in the hippocampus area from elevated systolic blood pressure in middle age, increased neurofibrillary tangles in the hippocampus area from elevated diastolic blood pressure in middle age, and atrophy in the hippocampus [14].

Similar to studies on hypertension and cognitive decline, there are a number of studies that focus on the relationship of diabetes to cognitive decline [8,3,22,23]. Specifically, diabetes is associated with lower Mini Mental Status Exam scores, impairments in executive function, inability to use organizational and planning skills appropriately, younger age of onset of cognitive decline, and more rapid cognitive decline [3,8]. Some researchers hypothesize that the cognitive declines associated with diabetes occur via the mechanism of formation of advanced glycation end products (AGEs) [22]. "Advanced glycation end products (AGEs) are proteins or lipids that become glycated after exposure to sugars" [30]. Advanced glycation end products form during the normal aging process, but diabetes is known to accelerate the process of formation of these products, causing the development of atherosclerosis [22,30]. Furthermore, some studies indicate that diabetes is associated with extensive sub-cortical atrophies and white matter lesions impeding

cognitive processes [8,31]. Research also indicates that a possible mechanism by which hypertension and diabetes lead to cognitive decline by causing small vessel disease. Small vessel disease can lead to the development of infarcts that cause formations in neural pathways, thereby creating deficits in cognitive ability [27,31].

Medication Use: Diabetics using oral medications may experience adverse effects, including greater impairments in cognition [23,26]. Specifically, some oral diabetes medications have long half-lives and may contribute to an increased risk of falls, hypoglycemia, and noticeable cognitive impairment in all domains [26]. Also, some studies have reported that the use of medications that reduce blood glucose level can raise the risk of cognitive impairment in older adults [23].

Conversely, other studies about hypertension and diabetes medication use have reported improvements in cognition [32]. Plastino, et al. (2010) [32] found that insulin therapy for diabetics could be effective in slowing cognitive decline in people with Alzheimer's disease. Furthermore, Chang-Quan, et al. (2011) [33] found that those with hypertension who take antihypertensive medication had a lower incidence of dementia than those who do not take antihypertensive medications. Wu, et al. (2003) [34] found that among older Mexican-Americans with diabetes, diabetic medications slow and even prevent decline in cognitive functioning, particularly for individuals with a longer disease duration.

Other Factors that Affect Cognitive Decline: Age is one of the most common risk factors associated with cognitive decline [35]. Most people with Alzheimer's disease or other dementias are 65 or older; the odds of developing dementia double approximately every five years beyond age 65 [10]. After reaching age 85, there is a 50% risk of developing Alzheimer's disease or other dementia [11].

Gender is a factor that enhances the risk for cognitive decline. Several studies have reported that cognitive decline and dementia are more prevalent in women than in men [10,36,37]. This finding is thought to be related to longevity, as women tend to live longer than men on average, giving them more time to develop cognitive impairment and Alzheimer's disease [36].

Race is another risk factor for cognitive decline. Studies have indicated that there is an increased risk of Alzheimer's disease and the other dementias for both African-Americans and Hispanics compared to whites [10,11,36,37]. African-Americans and Hispanics have elevated incidence of vascular disease. Therefore, the risk of Alzheimer's disease and other dementias increases [10,11]. African-Americans are four times more likely to develop Alzheimer's disease or another type of dementia by age 90, while Hispanics are twice as likely to develop Alzheimer's disease or another type of dementia by age 90 compared to whites [36,37]. Asian-American prevalence rates of dementia are similar to those of whites [36].

Some risk factors for cognitive decline, such as alcohol consumption can be modified to maximize health benefits. Some studies on alcohol consumption have shown that light to moderate consumption (2-4 drinks or less per day) reduces the risk of cognitive impairment, dementia, and Alzheimer's disease [38], improves cognition [39], and improves subjective wellbeing [25]. Researchers hypothesize moderate alcohol consumption improves cognition because it provides a protective effect on cardiovascular risk factors [25]. However, this protective effect found may be restricted only to the effects of resveratrol found in red wine [38]. Alcohol consumption has also been linked to the risk of cognitive decline [25,38,39]. Research indicates that excessive alcohol consumption over time may increase the risk for dementia, stroke, and mortality [10,38,]. Science suggests this might be due to the inability of older adults to metabolize alcohol properly and their increased sensitivity to the effects of alcohol [25].

Cigarette smoking has also been linked with decline in cognitive function [38]. Recent prospective cohort studies have shown connections between those who smoke and increased risk for Alzheimer's disease [38]. Results of one study found that heavy smoking predicted a younger age of onset of developing Alzheimer's disease [38]. Further research in this area is necessary to determine causal influence.

Lifestyle factors, such as nutrition/diet and regular exercise have been studied as risk factors for cognitive decline [25,10]. Consumption of fruits and vegetables, and foods rich in antioxidants, is known to lower the risk of cardiovascular disease, thus lowering the risk of cognitive decline [25,10]. Studies have evaluated vegetables and fruits containing the antioxidants of vitamins C and E, flavonoids, and carotenoids; these findings suggest that consuming leafy green vegetables such as spinach and kale is strongly associated with maintaining and even improving cognition [25]. Conversely, diets high in saturated fats and low-density lipoprotein (LDL) cholesterol can clog arteries, cause cardiovascular disease, and thus increase the risk for Alzheimer's disease and other dementias [10].

A positive relationship between exercise and cognition in older adults has also been well established [25,40]. Exercise is defined as physical activity that keeps the heart rate up consistently for at least 30 minutes [25]. Exercise increases cognitive capacity in older adults by building up greater levels of cognitive reserve, which helps reduce the risk for Alzheimer's disease and the other degenerative dementias [40].

Gaps in the Literature

Although there has been a lot of research about the effects of hypertension and diabetes on the brain, none of it addresses the potential moderating factor of educational attainment on hypertension and diabetes and its relationship to cognition. Notably, some studies only focus on hypertension and cognition [14-20,25], while other studies only focus on diabetes and cognition [8,3,22-24], not the two conditions together. Furthermore, there is limited literature on the effects of diabetes and hypertension medication on cognition, though the literature also establishes some degree of a relationship between these factors [23,26,41,42].

Conceptual Model

Model Summary

The conceptual framework for this study was developed from the literature that was reviewed. Both hypertension and diabetes have been linked to deficits in brain function in the literature, demonstrating a direct effect on cognitive function. Furthermore, diabetic medication use has also been reviewed as a potential factor in cognitive impairment, demonstrating a direct effect of medication use on the brain. Alternatively, the literature highlights that educational attainment may protect the brain against cognitive decline. Thus, the model predicts that educational attainment will moderate the effect of hypertension and diabetes on the brain and educational attainment will have a direct effect on cognition. Race/ethnicity, age, gender, BMI, income, smoking status, alcohol use, exercise, activities of daily living index, and self-reported health are all known to affect cognition, thus all are used as covariates in this model.

Theories

Hypertension, Diabetes, Medications, and Cognitive Decline

Both hypertension and diabetes are known to affect the brain adversely by causing small vessel disease leading to infarcts, brain atrophy, and white matter lesions as discussed in the literature review [8,27,31]. Based on this, I hypothesize that hypertension and diabetes will have a direct effect on cognition, by decreasing total cognition score.

Medication management for diabetics is a vital element of living with the disease. Large clinical trials have demonstrated the need for glycemic control among diabetics [43]. Effective glycemic control involves eating healthy, managing weight, regular exercise, blood sugar monitoring, and proper medication management, which may include oral medication and/or insulin treatment [43]. However many older diabetics do not maintain glycemic control effectively. Some earlier work has demonstrated that poor glycemic control leads to poorer cognitive function, whereas some other studies suggest that cognitive function and education level affects the ability to achieve proper glycemic control [43]. Theory is still being developed in these areas, as most studies have made conclusions based on small samples and limited methodology.

Given limited theoretical background regarding why diabetes and hypertension medications impair or improve cognition, some explanations have been offered. One explanation why medication use may impair cognition is that some oral diabetes medications have long half-lives, staying in one's system for an extended period of time, thus contributing to noticeable cognitive impairment in all domains [26]. Furthermore, some researchers hypothesize that medication effects may just be a temporary side effect. For example, Sommerfield, et al. (2004) [44] found that diabetics experienced impaired cognitive function and deterioration in mood during acute hyperglycemic episodes. After critically reviewing the limited available literature, I hypothesize that diabetics taking both oral medications and insulin to treat their diabetes will have lower cognition scores compared to non-diabetics.

Education as a Buffer for Cognitive Decline

The literature highlights two main theories on the role of educational attainment on cognition. The most widely recognized hypothesis about educational attainment and cognition is the cognitive reserve hypothesis [12,13,27-29,45,46]. The cognitive reserve hypothesis states that people with dementia who have high levels of educational attainment have higher functioning levels of cognitive resources such as memory and problem solving skills [12]. These resources can offset the effects of declines in brain structure [29] and lessen the impact of neuropathological lesions on cognition [46] better than in

those individuals with lower levels of educational attainment [13]. The literature indicates that this is because education promotes greater levels of neural network connectivity [29] and higher synaptic density and efficiency that allow for better coping with cognitive decline during the neurodegenerative processes [13,27]. Moreover, clinical manifestation of cognitive impairment will occur later among people who have high levels of educational attainment [13]. Supporting the cognitive reserve hypothesis, Fritsch, et al. (2002) [12] found that high educational attainment slows the rate of decline in people who have Alzheimer's disease, and Stern, et al. (1995) [28] found that education provides a reserve against the clinical presentation of pathology in Alzheimer's disease.

Based on the literature reviewed, I believe that the cognitive reserve hypothesis will be confirmed within this study. The cognitive reserve hypothesis explains why individuals with higher levels of educational attainment are at lower risk of developing cognitive impairment. Therefore, the effects of hypertension and diabetes on cognition should vary by educational attainment level, indicating higher cognition scores for those with higher levels of education. Educational attainment should have a significant moderating effect on hypertension and diabetes' effects on cognition as the conceptual model predicts.

A second theory about the relationship between educational attainment and cognitive decline is the brain-battering hypothesis, sometimes also referred to as the "socioeconomic hypothesis" [12,13,27]. The brain-battering hypothesis asserts that individuals with higher levels of educational attainment have been subjected to fewer toxins [12], have fewer cardiovascular risk factors [12,13], have superior access to quality health care [12,13,27], and lead healthier lifestyles by eating more nutritiously and engaging in exercise more often than individuals with low educational attainment levels [12,27]. Brain-battering suggests that these factors may protect the brain from pathological lesions that cause cognitive decline [12,13,27].

Supporting the brain-battering hypothesis, Del Ser, et al. (1999) [27] and colleagues studied autopsied brains of those with Alzheimer's disease and found that people with less educational attainment had a higher presence of vascular lesions than those with higher levels of educational attainment. If this theory is confirmed in the study, there will be a parallel effect showing a direct effect of education on cognition as the conceptual model figure shows. Therefore, my hypothesis that higher levels of educational attainment reflect higher cognition scores will be supported. Based on the model, it will mean that, holding all covariates constant, there will still be a relationship present, showing that educational attainment is predictive of better cognitive performance. This is consistent with the brain-battering hypothesis.

Controls

Common risk factors for diabetes and hypertension demonstrate the need to control for specific variables in the statistical model. Weight (measured by BMI), lack of physical activity, race/ethnicity, and age are the most common risk factors for diabetes and hypertension [25,36,40,47]. African-Americans and Hispanics are more likely to develop type 2 diabetes than whites. Similarly, hypertension is more common among African-Americans than whites [36,37]. Tobacco use and excess consumption of alcohol are risk factors for hypertension [36,37,47,48].

Hypotheses

H_1: Hypertension and diabetes will negatively impact cognition by decreasing total cognition score.
H_2: Education will moderate the effect of hypertension and diabetes on cognition. Hypertension and diabetes will impact cognition by decreasing total cognition score among those with lower levels of education.
H_3: Those with higher levels of educational attainment will have higher total cognition scores.
H_4: Diabetics taking oral medications and insulin will have lower cognition scores than non-diabetics.

Methods

Sample

The sample for this study was from the 2008 wave of the Health and Retirement Study (HRS). The HRS is a biennial longitudinal panel study surveying a nationally representative sample of Americans over age 50. The HRS uses households in the United States to gain a national area probability sample and oversamples blacks, Hispanics, and Florida residents. Data about many aspects of aging, including health, family, and economics, are included in the HRS. The total sample of respondents in the 2008 core wave was 17,217. Proxy respondents and all missing cases were excluded. After excluding the proxy respondents a total of 16,077 cases remained. Cases with missing data were also excluded dropping a total of 5,819 cases, thus, the final analytic sample was n=10,258.

Measures

Dependent variable: The dependent variable, total cognition score, is a continuous variable with scores ranging from 0 to 35, with 35 indicating the highest possible total cognition score and 0 indicating the lowest possible total cognition score. The score includes a series of questions about immediate recall (count from 0-10 with 0 indicating the lowest score and 10 indicating the highest score); delayed recall (count from 0-10 with 0 indicating the lowest score and 10 indicating the highest score); serial 7s (count from 0-5 with 0 indicating the lowest score and 5 indicating the highest score); backwards count from 20 (count from 0-2 with 0 indicating the lowest score and 2 indicating the highest score); object naming (scissors & cactus; count from 0-2 with 0 indicating the lowest score and 2 indicating the highest score); president naming (count from 0-1 with 0 indicating the lowest score and 1 indicating the highest score); vice president naming (count from 0-1 with 0 indicating the lowest score and 1 indicating the highest score); and date naming (month, day, year, day of week; count from 0-4 with 0 indicating the lowest score and 4 indicating the highest score) (HRS, 2008).

Independent variables: One of the two main independent variables used in the study is hypertension. The HRS question about hypertension is self-reported and asks, "Has a doctor ever told you that you have high blood pressure or hypertension?" Hypertension was coded first as a dummy variable for whether or not someone had high blood pressure (coded 1 has high blood pressure, or 0=no high blood pressure). A variable was then created for whether someone takes high blood pressure medications based on responses to the question: "In order to lower your blood pressure, are you now taking any medication?" The hypertension and hypertension medication variables were used to create a variable for those with hypertension taking medications where 1= has high blood pressure and taking high blood pressure medications and 0=not taking high blood pressure medications/doesn't have high blood pressure. Then, this variable was used to create another variable for those with high blood pressure not taking medication (where 1= has high blood pressure but not taking medications and 0= doesn't have high blood pressure /has high blood pressure and taking medications. People who do not have high blood pressure are the reference group for this variable.

The second main independent variable in the study is diabetes. Diabetes status is self-reported and was determined by responses to the question: "Has a doctor ever told you that you have diabetes or high blood sugar"? First, dummy variables were created for whether or not someone has diabetes (1= has diabetes, 0=no diabetes). Then categorical dummy variables were created for whether someone has diabetes and takes no medication, whether someone has diabetes and takes only oral medications (based on responses to: "In order to treat or control your diabetes, are you now taking medication that you swallow?"), whether someone has diabetes and takes only insulin (based on responses to: "Are you now using insulin shots or a pump?"), and finally whether someone has diabetes and takes both oral medications and insulin as medications. The reference group is non-diabetics.

Moderating variable: Education was used as a moderator in this study in two ways. First, education was used as a continuous variable (education years) based on the number of years the respondent was in school. The range of scores for this variable is 0-17 years. Alternatively, the HRS variable degree, denoting highest level of education, was coded into four categories. First, the categorical variable 'grammar school' was created for those who only had an eighth grade education or less. Second, the categorical variable 'high school' was created for those who had a high school education. Third, the categorical variable of 'college' was created for those who had a college education. Finally, 'grad school' was created for those who had a graduate school education. 'Grammar school' was used as the reference group in the analyses.

Control variables: There was several control variables used in the study. First, race was coded into the categories of non-Hispanic black, non-Hispanic white, non-Hispanic other race, and Hispanic. Non-Hispanic white was used as the reference group for this variable. Gender was coded as a dummy variable (female=1 and male=0), and age was measured as a continuous variable. Income was transformed into the log of income so that it would be less skewed. Body mass index (BMI) is a continuous variable used as a control and was calculated as weight divided by height squared. Smoking was coded into two categories, one for 'current smoker' and one for 'former smoker' if they had smoked in the past, but were not currently smokers, or if they were non-smokers. 'Former smoker' was used as the reference group. Alcohol was coded first as a dummy for those who drink and those who do not drink. Alcohol use was coded 1 if the respondent drank alcohol and alcohol use was coded 0 if the respondent did not drink alcohol. The alcohol use variable was used to create categorical variables for how many drinks were consumed per day. 'Light drinking' was created for those who drank 1-2 drinks per day. 'Moderate drinking' was created for those who drank 3-4 drinks per day. Finally 'heavy drinking' was created for those who drank more

than 4 drinks per day. Those who do not drink were used as the reference group. Exercise was coded based on regular exercise (more than 1 time per week was considered regular). Dummy variables were created for whether or not someone did regular vigorous, regular moderate or regular light exercise. Everyone who did not regularly exercise was given a 0. The categories are mutually exclusive, and each respondent was placed in the highest category of exercise. For example, if someone did regular light exercise twice a week and also did regular vigorous exercise twice a week then they were put into the regular vigorous category. 'No regular exercise' was the reference group.

Self-rated health was coded into dummy variables based on the HRS question asking, "Would you say your health is excellent, very good, good, fair, or poor?" (Excellent, very good, good=1 fair, poor=0). The activities of daily living variable were coded into an index using the count command for difficulty dressing, difficulty walking, difficulty bathing, difficulty eating, difficulty getting out of bed, and difficulty toileting to reflect an ADL index score of 0-6.

Analyses

The dependent variable, cognition score, is normally distributed. This was determined by using the kernel density function in STATA 12. Therefore, this study used hierarchical ordinary least squares regression to analyze the various models required for analysis. The regressions were adjusted for complex survey design (using svy commands in STATA 12). First, bivariate regressions were run separately for hypertension and diabetes to show their separate effects on cognition. Additionally, both hypertension and diabetes were used together in a regression model to show their collective effect on cognition. After running the bivariate regression models, education moderators were added to the model to show how levels of education affect variance in cognition. The continuous centered education variable, denoting number of years in school, was used first for the moderator models with only the main independent variables of hypertension and diabetes. Separate models with the moderators and only main independent variables using the categorical education variables of high school, college, graduate school, with the reference being grammar school were also run. Following the moderator models, models with both hypertension and diabetes and all the control variables were also run. Control variables included age, race, gender, BMI, income, exercise, smoking, alcohol use, activities of daily living index, and self-rated health.

Interaction terms were then created and added to the models to show interactions of the continuous centered education variable with diabetes and with hypertension. Two interaction terms were created for hypertension and education (high blood pressure with no medications*education and high blood pressure with medications*education) and four interaction terms were created for diabetes and education (diabetes with no medications*education, diabetes with oral medications*education, diabetes with insulin*education, and diabetes with both insulin and oral medications*education). None of the hypertension interaction terms were significant, thus only categorical interaction terms were created for the diabetes variables and degree of education. Twelve categorical interaction terms for diabetes and education were created and used in models (diabetes with no medications*high school, diabetes with no medications*college, diabetes with no medications*graduate school, diabetes with oral medications*high school, diabetes with oral medications*college, diabetes with oral medications*graduate school, diabetes with insulin*high school, diabetes with insulin*college, diabetes with insulin*graduate school, diabetes with both insulin and oral medications*high school, diabetes with both insulin and oral medications*college, and diabetes with both insulin and oral medications*graduate school). Several models were run using these interaction terms, including models with just hypertension and diabetes and the education moderator variables, and additionally models with hypertension and diabetes, the education moderators, and all of the control variables. The change in R-squared value was analyzed when variables were added to the models, showing how the additional variables explained the variance in cognition scores. Wald tests were computed to show significance for categorical variables of interest (Table 1).

Variance inflation factor was used to test for multicolinearity. The average variance inflation (VIF) was 1.74; suggesting multicolinearity was not a problem in the models. Sensitivity analysis was conducted because some cognition scores in the sample were determined to be outliers if they were at least three standard deviations below the mean. Sensitivity analysis showed no changes in the results after dropping all cognition scores that were three standard deviations below the mean cognition score of the sample, so the original sample including all reported cognition scores was used for final analysis.

Characteristics		Total sample (n = 10,258)	
		Mean	sd
Cognition		21.56	5.24
Hypertension	High blood pressure with medications	61.24%	
	High blood pressure no medications	5.26%	
Diabetes	Diabetes with no medications	0 3.77%	
	Diabetes with oral medications	14.61%	
	Diabetes with insulin use	2.45%	
	Diabetes with both insulin & oral medications	2.97%	
Education	Education Years (Continuous)	12.26%	3.22
	Grammar School (reference)	23.90%	
	High School	53.64%	
	College	14.40%	
	Graduate School	8.06%	
Control variables			
Age		74.60%	7.46
Gender	Male (reference)	41.68%	
	Female	58.32%	
Self-Rated Health	Good Health	69.55%	
	Fair/Poor Health (reference)	30.45%	
Logged Income		9.894	1.11
Race & Ethnicity	White (reference)	77.47%	
	Black	13.21%	
	Hispanic	7.98%	
	Other	1.34%	
Smoker		9.91%	
Former Smoker/non-smoker (reference)		90.09%	
Light Exercise		17.39%	
Moderate Exercise		49.70%	
Vigorous exercise		20.91%	
Light Drinking		25.02%	
Moderate Drinking		4.02%	
Heavy Drinking		0.0103	
BMI		27.11%	5.54
Activities of Daily Living		-0.41%	1.05

Table 1: Descriptive Characteristics of the Sample.

Results

Results for the ordinary least squares regression models are shown in Table 2. Throughout all models, diabetics who took both insulin and oral medications, compared to non-diabetics, showed decreased cognition scores. This somewhat confirms the hypothesis that diabetics taking oral medications and insulin will have lower cognition scores, showing that diabetes medications might be associated with impaired cognition. Those with hypertension taking no medications had lower total cognition scores compared to those without hypertension in all models.

Bivariate regression results indicate lower cognition scores for both those with hypertension taking medications ($p< .01$, $t= -6.80$) and those who do not take medications ($p< .01$, $t= -6.16$), compared to those who do not have hypertension. Similarly, bivariate regression results indicate lower cognition scores for diabetics who take oral medications ($p< .01$, $t= -6.65$), diabetics using insulin ($p< .01$, $t= -5.32$), and diabetics using both insulin and oral medications ($p< .01$, $t= -8.93$), compared to non-diabetics. The bivariate regression model with both hypertension and diabetes explains 0.01% of the variance in total cognition scores.

The moderator, years of education, was significant when added in the model with the hypertension and diabetes variables, explaining 20% of the variance in cognition scores. This finding shows that cognition scores were higher based on number of education years, confirming the hypothesis that education has a direct effect on cognition. When interactions among hypertension and education and diabetes and education were added into the model, no significant effects were seen, still explaining 20% of the variance in total cognition scores.

Dependent Variable Cognition	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7	Model 8	Model 9	R sq.
Hypertension										
Hypertension with meds	0.05		0	0.67		0.09	0.05		0.08*	
Hypertension with no meds	-0.75		-0.78	-0.67		-0.7	-0.68**		-0.71**	
Diabetes										
Diabetes oral meds		-0.25	-0.28		-0.2	-0.24*		-0.19	-0.23**	
Diabetes no meds		-0.26	-0.29		-0.19	-0.22*		-0.19	-0.22**	
Diabetes insulin		-0.43	-0.44		-0.56*	-0.58*		-0.59	-0.6	
Diabetes both meds		-0.95	-1		-0.98	-1.02**		-0.84	-0.88**	0.01
Moderator										
Education years				-0.51	-0.51	-0.51**	-0.48	-0.50**	-0.48**	0.2
Interactions										
Hypertension-education							-0.04		-0.39	0.2
Hypertension no meds-education							-0.03		-0.39	0.2
Diabetes oral meds-education								-0.03	-0.02	0.2
Diabetes no meds-education								-0.06	-0.04	0.2
Diabetes insulin- education								-0.03	-0.03	0.2
Diabetes both meds-education								-0.18**	-0.18	0.2
Controls										
Race										
Black	-3.24**	-3.19	-3.20**	-2.79**	-2.74**	-2.75**	-2.75**	-2.75**	-2.76**	0.36
Other Race	-1.04**	-1.03**	-1.02**	-1.22**	-1.21*	-1.21*	-1.22*	-1.23**	-1.22**	0.36
Hispanic	-2.67**	-2.65**	-2.63**	-0.81**	-0.80**	-0.79*	-0.81	-0.78**	-0.77**	0.36
Gender-female	-1.02**	-0.99**	-0.99**	-0.95	-0.93**	-0.92**	-0.95**	-0.94**	-0.94	0.36
Activities of Daily Living	-0.59**	-0.58**	-0.57**	-0.56**	-0.55**	-0.55**	-0.56**	-0.55**	-0.54**	0.36
Self-rated health-good health	-1.00**	-0.95**	-0.95**	-0.67**	-0.62**	-0.62**	-0.67	-0.62**	-0.62**	0.36
Smoking	-0.49**	-0.53**	-0.51**	-0.24	-0.27	-0.25	-0.24	-0.28	-0.26	0.36
Alcohol use-light drinking	-0.77**	-0.75**	-0.75**	-0.33**	-0.30**	-0.30**	-0.33**	-0.31**	-0.31**	0.36
Moderate drinking	0.67**	0.64**	0.63**	0.45	0.42*	0.41**	0.45**	0.42**	0.42**	0.36
Heavy Drinking	-0.06**	-0.16	-0.14	-0.12	-0.22	-0.22	-0.14	-0.22	-0.21	0.36
Exercise- Regular light exercise	0.61**	0.62**	0.61**	0.66**	0.66**	0.65**	0.66**	0.65**	0.64**	0.36
Regular moderate exercise	0.74**	0.73**	0.73**	0.67**	0.66**	0.66**	0.67**	0.65**	0.66**	0.36
Regular vigorous exercise	0.49**	0.47**	0.47**	0.31**	0.29**	0.29**	0.31**	0.29**	0.30**	0.36
BMI	0.00**	0.00**	0.00**	0.00**	0.00**	0.00**	0.00**	0.00**	0.00**	0.36
Logged income	0.70**	0.70**	0.70**	0.33**	0.33**	0.33**	0.33**	0.34**	0.33**	0.36
Age	-0.19**	-0.19**	-0.19**	-0.18**	-0.18**	-0.18**	-0.18**	-0.18**	-0.18**	0.36

Table 2: Effect of Hypertension and Diabetes: Predictors of Total Cognition Scores Using Ordinary Least Squares Regression HRS 2008.

Figure 1 show interactions among the varying degrees of diabetics (diabetics who take no medications, diabetics who take oral medications, diabetics who take insulin and diabetics who take both insulin and oral medications) and how their expected cognition scores vary based on education level. Interaction terms were added into the model to test the hypothesis that for those with lower levels of education, hypertension and diabetes will decrease total cognition score, compared to non-diabetics and those without hypertension. The only significant

interaction in the final model was for diabetics taking both oral medications and insulin. These diabetics taking both oral meds and insulin had higher total cognition scores compared to non-diabetics and all other diabetes groups, suggesting that education bolsters cognition more among those with dual meds than among the other groups. This aligns with the cognitive reserve hypothesis. Alternatively, perhaps people with higher socioeconomic status (SES) seek treatment earlier than those with lower SES, before the damaging effects of diabetes can affect cognition. All other interaction terms between hypertension and education and diabetes and education were not significant.

Diabetics with education levels one standard deviation below the mean and taking oral medications or taking insulin had lower expected cognition scores compared to non-diabetics and diabetics taking no medications showing the general effect of education. This confirms the study hypothesis that for those with lower levels of education, diabetes will decrease total cognition score, compared to non-diabetics. Figures 1 & 2 also indicates that diabetics taking no medications, diabetics taking oral medications, and diabetics taking both oral meds and insulin had higher total cognition scores compared to non-diabetics. Based on these findings, some support can be lent to the cognitive reserve hypothesis.

As expected, several control variables were significant when added to the model. Compared to whites, blacks and Hispanics had lower total cognition scores. Gender was significant in the final model for females compared to males, showing lower total cognition scores for females. Total cognition scores were lower for the activities of daily living index, indicating that those with higher scores on the index had lower cognition scores. Those with self-rated good health had higher cognition scores compared to those with self-rated fair or poor health. Total cognition scores were lower for smokers compared to non-smokers and former smokers. Both light drinkers and moderate drinkers have higher cognition scores compared to those who do not drink. Regular light exercisers, regular moderate exercisers, and regular vigorous exercisers have higher cognition scores, compared to those who do not exercise regularly. Total cognition scores were higher for those with higher income. Age was significant, indicating that as age goes up, total cognition scores decrease. Adding education years to the control model showed that 36% of the variance in total cognition could be explained by the main independent variables, control variables, and moderator variable of education.

Wald tests showed significant differences (F=0.013, p < .05) among diabetics taking no medications, diabetics taking oral medications, diabetics taking insulin, and diabetics taking both insulin and oral medications. Additionally, Wald tests showed significant differences (F=0.0006, p < .05) between those with hypertension who take medications and those with hypertension who do not take medications. For models using the categorical education variables, Wald tests indicated significant differences (F = 0.0000, p < .05) among those who had a high school education, college education, and graduate school education.

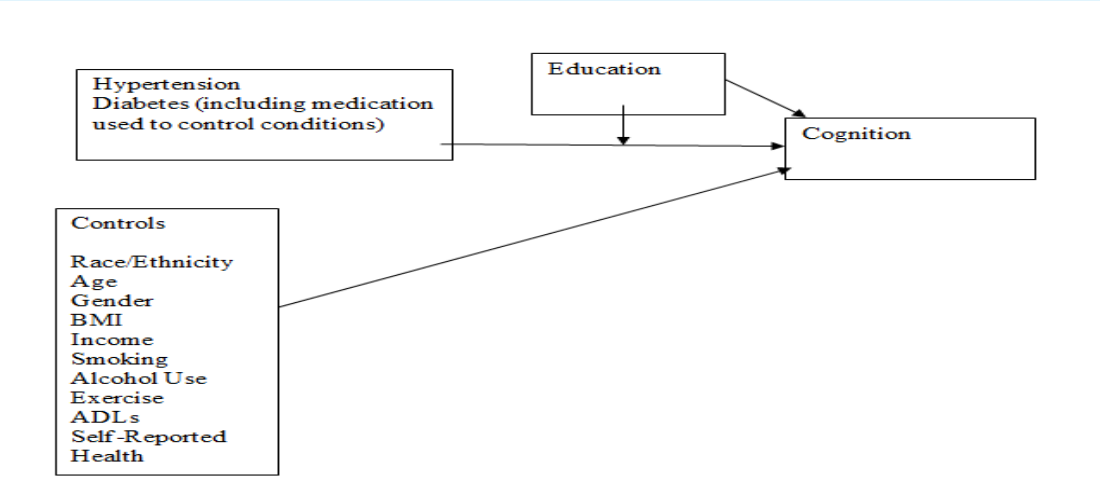

Figure 1: Conceptual Model: Education as a Moderator of the Effect of Hypertension and Diabetes on Cognition.

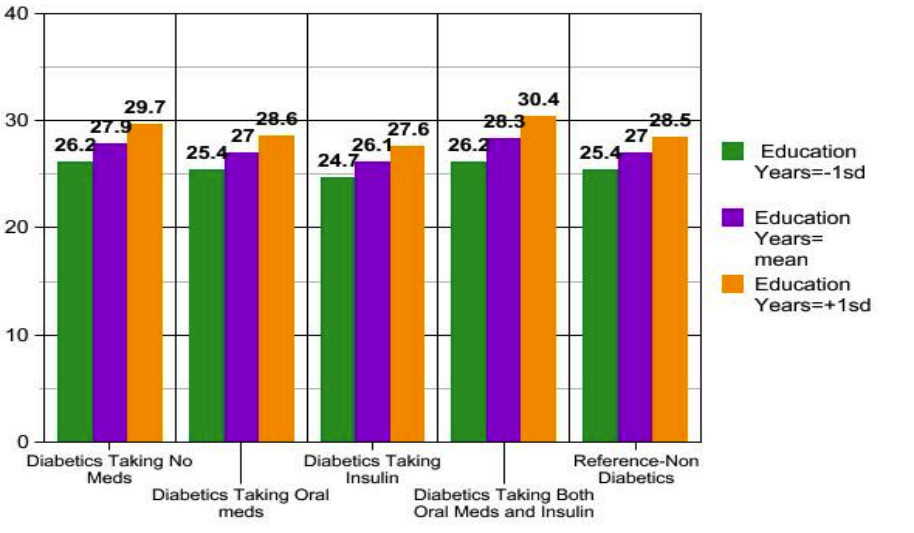

Figure 2: Cognition Scores Based on Education Years and Diabetic Medication Use Compared to Non-Diabetics.

Discussion

Many previous studies have looked at the effects of hypertension and/or diabetes on the brain and cognition. Some studies look at physiological factors affecting cognition, whereas others look at factors that can protect the brain from cognitive impairment. This study delved into understanding how diabetes and hypertension affect cognition: examining the deleterious mechanisms of hypertension and diabetes on cognition using a large nationally representative sample. Additionally, this research sought to highlight the protective mechanism of educational attainment on cognition, and how and if educational attainment moderates the effects of hypertension and diabetes on cognition. The effects of diabetic medication on the brain were also examined.

Four hypotheses were tested within this study. The first hypothesis was that hypertension and diabetes negatively impact cognition by decreasing total cognition score. This hypothesis was supported within the study, as cognition scores were lower for diabetics and those with hypertension compared to non-diabetics and those without hypertension. This fits with the literature indicating that diabetes is associated with lower Mini Mental Status Exam scores, impairments in executive function, inability to use organizational and planning skills appropriately, younger age of onset of cognitive decline, and more rapid cognitive decline [3,8]. Further, this also supports literature reviewed showing that hypertension accelerates the effects of aging on brain structures [25] and is associated with a faster rate of progression of cognitive decline [14].

The second hypothesis was that education will moderate the effect of hypertension and diabetes on cognition. The literature reviewed indicates that education promotes greater levels of neural network connectivity [29] and higher synaptic density and efficiency that allows for better coping with cognitive decline during the neurodegenerative processes [13,27]. Thus, hypertension and diabetes will impact cognition by decreasing total cognition score, among those with lower levels of education. There was only one significant interaction effect among all interactions testing this hypothesis. This interaction was the interaction between continuous education years and the group of diabetics taking both oral medication and insulin. This finding suggests that education level has an effect that boosts cognition scores despite insulin use and oral medications use among diabetics. Furthermore, this lends some support to the idea that educational attainment acts as a protector against some cognitive complications of diabetes and diabetes medications. This outcome is consistent with the literature around the cognitive reserve hypothesis as it relates to education level and cognition.

Conversely, an extensive number of interaction effects were not significant. Conceivably, this may be because educational attainment is only protective for severe diabetics who take both oral medications and insulin for

diabetes. It is also possible that diabetes and hypertension are unique in their mechanisms on brain injury, causing the protective effects to be null in most cases. This could be attributed to the fact that diabetes and hypertension are known to affect the hippocampus and the prefrontal lobes of the brain and in these areas the protective effects of educational attainment may go undetected. Additionally, another theory that could explain this finding is that people with higher levels of education usually have higher socioeconomic statuses, thus obtaining earlier access to better health care and managing their conditions better. Self-management of diabetes and hypertension is complex, suggesting that people with a higher SES who take their meds correctly have an advantage compared to groups of people with diabetes and hypertension and lower SES. This could be due to a greater understanding of diabetes management and consistent changes in positive lifestyle behaviors, such as engaging in healthy diets and regular exercise.

The third hypothesis tested was that those with higher levels of educational attainment will have higher total cognition scores. The results of the study confirmed this hypothesis, showing that those with higher levels of education, had higher total cognition scores overall. This outcome supports the findings from other literature discussing the protective effects of education on cognition and the cognitive reserve hypothesis [12,27-29,45,46]. Furthermore, supporting the results of the study, the literature evaluated indicates that high educational attainment slows the rate of decline in people who have Alzheimer's disease and other cognitive impairments [12]. Additionally, one study evaluated found that education provides a reserve against the clinical presentation of pathology in Alzheimer's disease and cognitive decline [28]. This is consistent with the results of this study.

The fourth hypothesis, diabetics taking oral medications and insulin will have lower cognition scores than non-diabetics, was somewhat confirmed within the study. Moreover, those just taking oral medications also had lower cognition scores than non-diabetics. These findings support other work around medication effects on cognition that show that the use of oral medications and insulin impair cognition [23,26]. Specifically, Spain, et al. (2009) [26] noted that some oral medication use, such as use of the glucose-lowering drug Diabinise, could lead to cognitive impairment in the older population. Saczynski, et al. (2008) [23] also highlighted that medications for glucose control may increase the risk for cognitive impairment. The mechanism by which oral medications impair cognition is still not well known, but this study somewhat supported the finding that oral medications combined with insulin do have negative effects on total cognition scores. However, this finding could illustrate clinical impact of the diabetes, rather than the medication effects meaning diabetics who are clinically severe and require use of medications have impaired cognition. This highlights that it may not be the treatment regimen that affects cognition, but that the treatment regimen is indicative of the disease severity. The physiological brain injury in severe diabetics combined with use of both oral medications and insulin might be a lethal combination on cognition, only protected by education level.

Heavy consumption of alcohol had no significant effect on cognition compared with those who do not drink alcohol. This does not support the other literature highlighting that alcohol consumption has been linked to the risk of cognitive decline [25,38]. Previous research has indicated that excessive alcohol consumption over time may increase the risk for dementia, stroke, and mortality [10,38]. However, the contradictory finding is likely to do with how the variable was coded, and could be considered a limitation of the study. Some studies use a coding strategy of heavy alcohol consumption considered to be more than two drinks per day, rather than greater than four drinks per day, as it was coded in this study. Also, this study could not assess alcohol use over time because it was not longitudinal.

The medication effects found within this study lend support to the idea that diabetics taking both insulin and oral medications have more impaired cognition than non-diabetics. There is little literature around this area of research, so a major strength of this study is that it highlighted a unique finding about medication use among diabetics. Strength of this study is that a large nationally representative sample was used for data analysis. However, some limitations should be noted too. One limitation is that the study uses cross sectional data, not longitudinal data that would show effects over time. Additionally, after completing this research, there are still some questions of which mechanisms really cause cognitive decline in those with hypertension and diabetes. For example, the medication effect on diabetics using both insulin and oral medications may be limited to only those that are considered severe diabetics.

The medication effects seen in this study raised questions that may lead to further research to help build on the literature and theory about medication use among diabetics. Expanding the findings from this study would be valuable to see if results can be replicated, thus improving generalizability to the older population in the

United States. Attempting to isolate what it is about a diabetic taking both oral medications and insulin together that causes cognitive deficits compared to non-diabetics may help clarify the findings study. Similarly, future research could focus on educational attainment and diabetes. Though this study found very limited moderating effects of education on diabetes, exploring the effect that diabetics taking both insulin and oral medications had higher cognition scores for those that are better educated may be useful since the literature is limited.

Some practical implications could be considered based on this study. Physicians should be aware of what medications they prescribe to older adults for diabetes and hypertension as they may negatively impact cognition, especially in severe diabetics taking both oral meds and insulin. Knowing that a patient is a severe diabetic, physicians should monitor cognitive status regularly at visits, because one can assume severe diabetics take more medications than less severe diabetics and that cognitive decline is more extensive in severe diabetics. Further, there could be polypharmacy issues that cause cognitive decrements in older patients taking both oral diabetes medications and insulin in conjunction with medications for other chronic conditions. Moreover, in some situations physicians should consider oral diabetes medications in conjunction with insulin as a possible explanation for cognitive decline, as opposed to other explanations, or in combination with other explanations such as physiological damage that occurred during the life course due to the aging process.

References

1. Biskupiak J, Kim J, Phatak H, Wu D (2010) Prevalence of high-risk cardiovascular conditions and the status of hypertension management among hypertensive adults 65 years and older in the United States: Analysis of a primary care electronic medical records database. J Clin Hypertens 12(12): 935-944.

2. Zhang X, Decker FH, Luo H, Geiss LS, Pearson WS, et al. (2010) Trends in the Prevalence and Comorbidities of Diabetes Mellitus in Nursing Home Residents in the United States: 1995–2004. J Am Geriatr Soc 58(4): 724-730.

3. Okura T, Heisler, M, Langa KM (2009) Association Between Cognitive Function and Social Support with Glycemic Control in Adults with Diabetes Mellitus. J Am Geriatr Soc 57(10): 1816-1824.

4. Centers for Disease (2011) Vital signs: prevalence, treatment, and control of hypertension—United States, 1999-2002 and 2005-2010. MMWR 60(4): 103-108.

5. Stewart S, Zelinski E, Wallace R (2000) Age, medical conditions, and gender as interactive predictors of cognitive performance: The effects of selective survival. J Gerontol B Psychol Sci Soc Sci 55(6): 381-383.

6. van den Berg E, Kloppenborg RP, Kessels RP, Kappelle LJ, Biessels GJ (2009) Type 2diabetes mellitus, hypertension, dyslipidemia, and obesity: A systematic comparison of their impact on cognition. Biochemia et Biophysica Acta 1792(5): 470-481.

7. Musicco M, Palmer K, Salamone G, Lupo F, Perri A, et al. (2009) Predictors of progression of cognitive decline in Alzheimer's disease: The role of vascular and sociodemographic factors. J Neurol 256(8): 1288-1295.

8. Yeung SE, Fischer AL, Dixon RA (2009) Exploring effects of type 2 diabetes on cognitive functioning in older adults. Neuropsychology 23(1): 1-9.

9. Savopoulos C, Hatzitolios A, Apostolopoulou M, Mirou A, Baltatzi M, et al. (2005) Correlation between clinical and imaging findings concerning cognitive dysfunction in and after stroke hypertensive patients with type 2 diabetes mellitus. Annals of General Psychiatry 5(1): S127.

10. Thies W, Bleiler L (2012) Alzheimer's disease facts 2012. Alzheimer's & Dementia 8: 131-168.

11. Fredman L, James B, Johnson T, Scholz K, Weuve J (2012) 2012 Alzheimer's disease facts and figures. Alzheimers Dement 8(2): 131-168.

12. Fritsch T, McClendon MJ, Smyth KA, Ogrocki PK (2002) Effects of educational attainment and occupational status on cognitive and functional decline in persons with Alzheimer-type dementia. Int Psychogeriatr 14(4): 347-363.

13. Bruandet A, Richard F, Bombois S, Maurage C, Masse I, et al. (2007) Cognitive decline and survival in Alzheimer's disease according to education level. Dement Geriatr Cogn Disord 25(1): 74-80.

14. Sakurai H, Hanyu H, Sato T, Kanetaka H, Shimizu S, et al. (2011) Vascular risk factors and progression in

Alzheimer's disease. Geriatr Gerontol Int 11(2): 211-214.

15. Knopman D, Mosley T, Catellier D, Coker L (2009) Fourteen-year longitudinal study of vascular risk factors, apoe4 genotype, and cognition: The aric mri study. Alzheimer's & Dementia 5(3): 207-214.

16. Luchsinger J, Reitz C, Patel B, Tang M, Manly J, et al. (2007) Relation of diabetes to mild cognitive impairment. Archives of Neurology 64(4): 570-575.

17. Verdelho A, Madureira S, Ferro JM, Basile AM, Chabriat H (2007) Differential impact of cerebral white matter changes, diabetes, hypertension and stroke on cognitive performance among non-disabled elderly. The LADIS study. J Neurol Neurosurg Psychiatry 78(12): 1325-1330.

18. Mount D, Lambert M (2009) Mental ability performance among adults with type 2 diabetes in primary care. Mental Health in Family Medicine 6: 99-106.

19. Reitz C, Luchsinger J, Patel B, Tang M, Manly J, et al. (2007) Relation between vascular risk factors and neuropsychological test performance among elderly persons with Alzheimer's disease. J Neurol Sci 257: 194-201.

20. Bruehl H, Wolf O, Sweat V, Tirsi A, Richardson S, et al. (2009) Modifiers of cognitive function and brain structure in middle-aged and elderly individuals with type 2 diabetes mellitus. Brain Res 1280: 186-194.

21. Tiehuis A, van den Berg E, Kappelle L, Biessels G (2007) Cognition and dementia in type 2 diabetes: Brain imaging correlates and metabolic and vascular risk factors. Aging Health 3(3): 361-373.

22. Yaffe K, Lindquist K, Schwartz AV, Vitartas C, Vittinghoff E, et al. (2011) Advanced glycation end product level, diabetes, and accelerated cognitive aging. Neurology 77(14): 1351-1356.

23. Saczynski J, Jónsdóttir M, Garcia M, Jonsson P, Peila R, et al. (2008) Cognitive impairment: an increasingly important complication of type 2 diabetes: the age, gene/environment susceptibility--Reykjavik study. Am J Epidemiol 168(10): 1132-1139.

24. Saczynski J, Siggurdsson S, Jonsson P, Eiriksdottir G, Olafsdottir E, et al. (2009) Glycemic status and brain injury in older individuals: the age gene/environment susceptibility-Reykjavik study. Diabetes Care, 32(9): 1608-1613.

25. Myers J (2008) Factors associated with changing cognitive function in older adults: Implications for nursing rehabilitation. Rehabil Nurs 33(3): 117-123.

26. Spain M, Edlund, BJ (2009) Pharmacological management of type 2 diabetes in newly diagnosed older adults. J Gerontol Nurs 35(7): 16-21.

27. Del Ser T, Hachinski V, Merskey H, Munoz D (1999) An autopsy-verified study of the effect of education on degenerative dementia. Brain 122(Pt 12): 2309-2319.

28. Stern Y, Tang M, Denaro J, Mayeux R (1995) Increased risk of mortality in Alzheimer's disease patients with more advanced educational and occupational attainment. Annals of Neurology 37(5): 590-595.

29. Meijer W, van Boxtel M, Van Gerven P, van Hooren S, Jolles J (2009) Interaction effects of education and health status on cognitive change: A 6-year follow-up of the Maastricht aging study. Aging Ment Health 13(4): 521-529.

30. Goldin A, Beckman J, Schmidt A, Creager MA (2006) Advanced glycation end products sparking the development of diabetic vascular injury. Circulation 114(6): 597-605.

31. Alladi S, Kaul S, Mekala S (2010) Vascular cognitive impairment: current concepts and Indian perspective. Ann Ind Acad Neurol 13(Suppl2): 104-108.

32. Plastino M, Fava A, Pirritano D, Cotronei P, Sacco N, et al. (2010) Effects of insulinic therapy on cognitive impairment in patients with Alzheimer disease and Diabetes Mellitus type-2. J Neurol Sci 288(1-2): 112-116.

33. Chang Quan H, Hui W, Chao Min W, Zheng Rong W, Jun Wen G, et al. (2011) The association of antihypertensive medication use with risk of cognitive decline and dementia: a meta-analysis of longitudinal studies. Int J Clin Pract 65(12): 1295-1305.

34. Wu JH, Haan MN, Liang J, Ghosh D, Gonzalez HM, et al. (2003) Impact of Antidiabetic medications on physical and cognitive functioning of older Mexican Americans with diabetes mellitus: a population-based cohort study. Ann Epidemiol 13(5): 369-376.

35. van der Vorm A, van der Laan AL, Borm G, Vernooij Dassen M, Olde Rikkert M, et al. (2010) Experts' opinions on ethical issues of genetic research into alzheimer's disease: Results of a delphi study in the Netherlands. Clin Genet 77(4): 382-388.

36. Gies C, Lessick M (2009) Alzheimer's disease in women: a clinical and genetics perspective. Nurs Womens Health 13(4): 312-324.

37. Laws S, Hone E, Gandy S, Martins RN (2003) Expanding the association between the APOE gene and the risk of alzheimer's disease: possible roles for APOE promoter polymorphisms and alterations in apoe transcription. J Neurochemistry 84(6): 1215-1236.

38. Harwood DG, Kalechstein A, Barker WW, Strauman S, St George Hyslop P, et al. (2010) The effect of alcohol and tobacco consumption, and apolipoprotien e genotype, on the age of onset in alzheimer's disease. Int J Geriatr Psychiatry 25(5): 511-518.

39. Espeland M, Gu L, Masaki K, Langer R, Coker L, et al. (2005) Association between reported alcohol intake and cognition: results from the Women's Health Initiative Memory Study. Am J Epidemiol 161(3): 228-238.

40. Hong Kim S, Minjeong Kim, Yu Bae Ahn, Hyun Kook Lim, Sung Goo Kang, et al. (2011) Effect of dance exercise on cognitive function in elderly patients with metabolic syndrome: A pilot study. J Sports Sci Med 10(4): 671-678.

41. Muldoon M, Waldstein S, Ryan C, Jennings J, Polefrone J, et al. (2002) Effects of six anti-hypertensive medications on cognitive performance. J Hypertens 20(8): 1643-1652.

42. Shorr R, de Rekeneire N, Resnick H, Yaffe K, Somes G, et al. (2006) Glycemia and cognitive function in older adults using glucose-lowering drugs. J Nutr Health Aging 10(4): 297-301.

43. Nguyen HT, Grzywacz JG, Arcury TA, Chapman C, Kirk JK, et al. (2010) Linking Glycemic Control and Executive Function in Rural Older Adults with Diabetes Mellitus. J Am Geriatr Soc 58(6): 1123-1127.

44. Sommerfield AJ, Deary IJ, Frier BM (2004) Acute Hyperglycemia Alters Mood State and Impairs Cognitive Performance in People With Type 2 Diabetes. Diabetes Care 27(10): 2335-2340.

45. Scarmeas N, Albert M, Stern Y (2006) Education and rates of cognitive decline in incident Alzheimer's disease. J Neurol Neurosurg Psychiatry 77(3): 308-316.

46. Wilson RS, Li Y, Aggarwal NT, Barnes LL, McCann JJ, et al. (2004) Education and the course of cognitive decline in Alzheimer disease. Neurology 63(7): 1198-1202.

47. Gao S, Jin Y, Unverzagt FW, Liang C, Hall KS, et al. (2009) Hypertension and cognitive decline in rural elderly chinese. J Am Geriatr Soc 57(6): 1051-1057.

48. Giltay E, Zitman S, Komhout D (2008) Cardiovascular risk profile and subsequent disability and mental well-being: The zutphen elderly study. Am J Geriatr Psychiatry 16(11): 874-882.