University of Alabama at Birmingham
UAB Digital Commons

All ETDs from UAB | UAB Theses & Dissertations

2016

Dietary Patterns, Insulin Resistance, and Cognitive Outcomes in a Cohort of Black and White Americans

Keith Pearson
University of Alabama at Birmingham

Follow this and additional works at: https://digitalcommons.library.uab.edu/etd-collection

Recommended Citation

Pearson, Keith, "Dietary Patterns, Insulin Resistance, and Cognitive Outcomes in a Cohort of Black and White Americans" (2016). *All ETDs from UAB*. 2690.
https://digitalcommons.library.uab.edu/etd-collection/2690

This content has been accepted for inclusion by an authorized administrator of the UAB Digital Commons, and is provided as a free open access item. All inquiries regarding this item or the UAB Digital Commons should be directed to the UAB Libraries Office of Scholarly Communication.

DIETARY PATTERNS, INSULIN RESISTANCE, AND COGNITIVE OUTCOMES IN A COHORT OF BLACK AND WHITE AMERICANS

by

KEITH E. PEARSON II

SUZANNE E. JUDD, COMMITTEE CHAIR
PAULA CHANDLER-LANEY
BARBARA A. GOWER
GEORGE HOWARD
VIRGINIA G. WADLEY

A DISSERTATION

Submitted to the graduate faculty of The University of Alabama at Birmingham,
in partial fulfillment of the requirements for the degree of
Doctor of Philosophy

BIRMINGHAM, ALABAMA

2016

DIETARY PATTERNS, INSULIN RESISTANCE, AND COGNITIVE OUTCOMES IN A COHORT OF BLACK AND WHITE AMERICANS

KEITH E. PEARSON II

NUTRITION SCIENCES

ABSTRACT

As life expectancy continues to increase and the number of elderly Americans rises, public health initiatives are seeking to identify modifiable risk factors to preserve cognitive function and increase quality of life in advanced ages. The primary objective of this dissertation was to investigate dietary patterns, carbohydrate consumption, and insulin resistance as modifiable risk factors that may contribute to the development of cognitive impairment and cognitive decline. Three separate studies were performed in the REasons for Geographic And Racial Differences in Stroke study, a prospective cohort containing 30,239 black and white participants. Cognitive impairment was defined using the Six-Item Screener. Verbal learning, memory, and executive function were assessed using the word list learning, word list delayed recall, and animal fluency test. Dietary intake was measured by the Block98 food frequency questionnaire (FFQ). Principal component analysis was utilized to derive dietary patterns and estimates for glycemic index (GI), glycemic load (GL), and available carbohydrate intake (CHO) were assigned when analyzing the FFQs. The homeostatic model assessment of insulin resistance was used to estimate insulin resistance. In a cohort of participants without stroke at baseline, we found that the alcohol/salads dietary pattern was associated with lower odds of incident cognitive impairment and higher verbal learning, memory, and executive function. The plant-based pattern was associated with higher verbal learning and memory, and the Southern pattern was associated with lower verbal learning, memory,

and executive function. Higher GL and CHO were associated with higher odds of incident cognitive impairment. Additionally, we observed a significant racial difference in the associations between both GL and CHO and change in verbal learning over time. Lastly, an inverse association was observed between insulin resistance and incident cognitive impairment. Although no significant racial difference was detected, the association was predominantly present in black participants. In conclusion, dietary patterns consisting of plant-based foods, alcohol intake, lower GL, and lower CHO may contribute to more favorable cognitive outcomes in advanced ages. The relationship between insulin resistance and cognitive outcomes is less clear, and further studies are warranted to elucidate potential racial differences in the effects of insulin resistance on cognitive health.

Keywords: dietary patterns, insulin resistance, carbohydrate, cognitive function, cognitive impairment, cognitive decline

ACKNOWLEDGEMENTS

I am indebted to a number of individuals who have loved, supported, and encouraged me, and thereby share in the completion of this degree. First, I must thank my family, who is largely responsible for molding me into the person I am today. Mom and Dad, you are the hardest working people I know. Thank you both for all of the sacrifices you have made over the years and for encouraging me to excel academically. Jon, you are my younger brother but in many ways I look up to you. Thank you for listening and setting a great example by striving for holiness in all that you do. Leaving you three in West Virginia has been more difficult than I originally thought, but in a strange way I feel closer to each of you and no longer take our times together for granted. Kandice, my wife, thank you for the constant love and support and for the sacrifices you have made to make this possible. I can't imagine completing this without your help. I look forward to many more fun-filled years with you that don't involve graduate school.

I must also acknowledge the incredible support I have received from my dissertation committee: Drs. Suzanne Judd, Paula Chandler-Laney, Barbara Gower, George Howard, and Virginia Wadley. Suzanne, you have been a great mentor, advisor, and advocate. Thank you for being willing to take in a young nutrition student with little prior research experience. The patience, advice, and training you have provided will always be appreciated. Paula, the conversations we have had about academia and life have been more helpful to me than you realize. Thank you for always making time for me, even when I randomly stop by your office. Dr. Gower, your constant quest for finding mechanisms has shaped the way that I think about research and data. Thank you

for the numerous conversations we've had about low carbohydrate diets. George, there are so many things I could thank you for. Thank you for dreaming up the REGARDS study, which has funded me and been an integral part of my training the past several years. I feel like I have developed so much as a scientist just by participating in REGARDS analyst meetings and watching you interpret data. Dr. Wadley, thank you for the patience and guidance you have provided to a nutrition student with an interest in cognitive function. Your expertise has been greatly appreciated.

Big thanks are owed to a number of graduate students and post-docs who have befriended me and made this process much more enjoyable. First, many thanks to Kenneth for all of the guidance and support you provided, especially during my first year in Birmingham. You directly/indirectly are responsible for me finding my wife, my church, and most of my friends here, and the advice you offered in the initial stages of this PhD process spared me from many mistakes and embarrassment. I'll be forever grateful for those things. Nate, thank you for being a great office-mate and friend who may be one of the few people I know who loves food as much or more than I do. Our conversations about reactive oxygen species and uncoupling have been extremely helpful. Also, thanks for teaching me how to properly make hot chicken. Daniella, you are such a big dreamer in the best way possible, and because of that I know you will be a successful scientist. Thank you for inspiring me through your hard work and perseverance. Annie, being 1-2 years behind you in this program, you have been a great help and example as I have navigated this process. However, I still think I can beat you and Daniel in a foot race. Sindhu, thank you for providing wisdom and advice from a post-doc perspective. You have always been great at encouraging and listening to me.

Because of the large size of the REGARDS study and the potential for IRB violations, I cannot acknowledge all 30,239 REGARDS participants by name, but without the willingness of these people to participate in the REGARDS study, none of this research would be possible. Also, the REGARDS staff has been incredibly helpful over the past several years. Special thanks to David Rhodes, the Coordinating Center, and the Survey Research Unit, for all of the hard work you put in every day. Additionally, Aleena and Ya, the help you have provided from a statistical and programming perspective has been invaluable.

Lastly, I am eternally indebted to God, who has sustained me and given me hope throughout this process. Because of him, I am reminded daily that this life is about much more important things than making my name great or obtaining this PhD. Thank you for your love and providence.

TABLE OF CONTENTS

Page

LIST OF TABLES

Table *Page*

DIETARY PATTERNS ARE ASSOCIATED WITH COGNITIVE FUNCTION IN THE REGARDS COHORT

GLYCEMIC LOAD AND CARBOHYDRATE INTAKE ARE ASSOCIATED WITH INCIDENT COGNITIVE IMPAIRMENT IN THE REASONS FOR GEOGRAPHIC AND RACIAL DIFFERENCES IN STROKE (REGARDS) COHORT

INSULIN RESISTANCE, COGNITIVE IMPAIRMENT, AND COGNITIVE DECLINE IN THE REASONS FOR GEOGRAPHIC AND DIFFERENCES IN STROKE (REGARDS) COHORT

LIST OF FIGURES

Figure *Page*

DIETARY PATTERNS ARE ASSOCIATED WITH COGNITIVE FUNCTION IN THE REGARDS COHORT

INTRODUCTION

Cognitive Health: A Public Health Priority in the 21st Century

In what has been labeled the "graying of America"[1], the proportion and total number of elderly Americans (65 years of age and older) are rising and expected to increase for the next several decades. As of 2012, the elderly comprised approximately 43.1 million people or 13.7% of the total US population, and this number is projected to grow to 21.0% of the population by 2040[2]. There are several reasons behind this expected growth, including the continual rise in life expectancy as well as the Baby Boom generation of Americans, born following World War II between 1946 and 1964, now beginning to turn the age of 65. Regardless of the cause, the number and proportion of elderly Americans will continue to increase for the foreseeable future, and public health initiatives are seeking to discover interventions to improve the health and quality of life of this population[3].

A key component of preserving quality of life in advanced ages is the maintenance of cognitive health. As the number of elderly increase, the number of Americans living with Alzheimer's disease, other dementias, and cognitive impairment is expected to concomitantly rise and nearly triple by year 2050[4]. These diseases manifest themselves clinically with a decline in cognitive function, contributing to a lower quality of life for many elderly. Far beyond the mild memory loss typically associated with aging, the latter stages of these diseases often leave the individual dependent on the care of others for basic activities of daily living such as bathing and feeding. This places a profound emotional burden on family and caregivers, who are forced to watch loved ones

go through major personality changes, lose the ability to communicate effectively or remember familiar faces, and in severe cases fail to perform rudimentary tasks such as walking or swallowing. There is additionally a large financial burden placed on families and the health care system at large to provide the extensive care that these individuals require. It is estimated that health care, long-term care, and hospice expenditures will exceed $236 billion in 2016 for the care of people with Alzheimer's disease and other dementias, with some studies reporting that the costs of dementia care are comparable to the health care expenditures of heart disease and far surpass those of cancer[4,5].

Clearly, identifying modifiable risk factors that contribute to cognitive decline is a growing public health priority and could aid in the preservation of cognitive function and quality of life in older ages. However, despite the notable advances in the primary prevention of other chronic diseases, comparably little is known about the brain and applicable lifestyle modifications that can be implemented to preserve cognitive function.

Diet: A Modifiable Risk Factor to Preserve Cognitive Function?

Of the potentially modifiable risk factors, the interest in the modification of diet to promote cognitive health has grown in recent decades. Traditional research approaches have sought to examine individual foods that may be targeted for intervention and have successfully identified several foods that may be beneficial to cognitive function. Fish is one of the foods that have been previously associated with higher cognitive function and slower cognitive decline in a number of studies[6-10]. Fatty fish such as salmon, trout, and tuna possess relatively large amounts of ω-3 fatty acids, a polyunsaturated fat with a well-documented role in brain development[11,12]. Several studies have suggested that

potential anti-inflammatory and cardioprotective effects of these fatty acids may explain the associations with slower decline in cognitive function observed with higher fish consumption[9,10]. Vegetable intake has also been consistently associated with improved cognitive function and slower cognitive decline[13-15]. Vegetables contain several antioxidant nutrients such as Vitamins C and E, beta carotene, and flavonoids, which could improve cognitive health through the reduction of oxidative stress induced neurodegeneration[16,17]. Fish and vegetables are just two of the numerous foods that have been associated with cognitive function. Although these studies have provided a beneficial perspective on the topic of diet and cognition, solely examining foods in isolation fails to reflect true eating behavior. Humans typically consume multiple foods together in meals that collectively make up an overall dietary pattern, and analysis involving individual foods may be ignoring the interactions and correlations among foods and nutrients that collectively contribute to health. By taking advantage of the potential interactions and the collective effects of multiple foods, dietary patterns may be more predictive of cognitive decline than foods or nutrients in isolation and have become increasingly popular among nutritional epidemiologists studying the role of diet in cognitive health[18].

Two widespread methods utilized in dietary pattern analysis are the use of dietary indices and principal component analysis (PCA). Dietary indices are defined *a priori* by the investigator and are typically created to reflect adherence to a predetermined set of nutrition criteria, such as nutrition guidelines or a dietary philosophy hypothesized to be beneficial for a particular health outcome[19]. One such dietary index with evidence of a protective effect in cognitive decline is the Mediterranean diet. The Mediterranean diet

score was created to reflect the traditional diet of the Mediterranean region and, while there are many variations, typically consists of a high consumption of fruits, vegetables, legumes, fish, nuts, olive oil, and whole grains; and low consumption of red meat, processed meats, and dairy; and moderate alcohol intake[20]. The Mediterranean diet score has been associated with decreased risk of Alzheimer's disease and cognitive impairment and a slower decline in cognitive function in several cohort studies[21-23]. Another dietary index that was recently created with possible cognitive benefits is the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet. The criteria that define the MIND dietary pattern are taken from both the Mediterranean and the Dietary Approaches to Stop Hypertension (DASH) dietary patterns, with specific modifications to include foods that have been previously associated with cognitive function. The MIND diet consists of 10 foods that have been positively associated with cognitive health (green leafy vegetables, nuts, berries, beans, whole grains, fish, poultry, olive oil, and wine) and 5 foods that have been negatively associated with cognitive health (red meats, butter and stick margarine, cheese, pastries/sweets, and fried/fast food). Higher scores representing higher adherence to the MIND diet have been associated with reduced risk of Alzheimer's disease and slower cognitive decline[24,25]. Dietary pattern analyses using dietary indices have provided valuable insight into the types and combinations of foods that may benefit cognitive function. However, this type of analysis is limited because defining dietary patterns with nutrition criteria selected a *priori* may not reflect true or realistic dietary patterns within a population.

Alternatively, another method of deriving dietary patterns is through the use of principal component analysis (PCA), which uses correlations between food items to

reduce the dietary data into underlying factors describing food consumption known as dietary patterns[18,19]. This method does not rely on prior dietary recommendations or guidelines and instead allows the dietary patterns to emerge from the dietary data, usually collected through Food Frequency Questionnaires (FFQ)[18,19]. Several studies in the nutritional epidemiology literature have employed PCA to derive dietary patterns and have evaluated their associations with cognitive function. However, most have possessed small sample sizes generalizable to only one race[26-32] and further studies are needed in large, diverse cohorts to better understand this relationship.

Carbohydrates, Insulin Resistance, and Cognition

Given the observation that individuals with diabetes have nearly twice the risk of developing dementia and other cognitive impairments[33], dietary carbohydrate intake has gained interest as another potential modifiable risk factor that may have implications in cognitive health. Both the quality and quantity of dietary carbohydrate influence the development of type 2 diabetes and directly impact post prandial glycemia, glycemic control, and insulin resistance[34,35]. The quality of carbohydrate is often measured using the glycemic index (GI), which ranks foods according to their relative post-prandial glucose response[36]. Still, despite the utility of the GI, several studies have suggested that the quality of carbohydrate in conjunction with the amount of carbohydrate is a better predictor of post-prandial glucose levels than GI alone[34,35]. Thus, the GI may be limited in that it only considers the quality of carbohydrate, irrespective of the quantity of carbohydrate in a typical portion of that food. For this reason, the glycemic load (GL) was developed and is a more appropriate tool to estimate the post-prandial glucose

response of carbohydrate-containing foods[37]. Contrary to GI, GL includes both the quality and quantity of carbohydrate and is calculated by taking the product of a food's GI and the available carbohydrate in a serving and dividing the total by 100[38].

Of the existing studies that have investigated the effects of carbohydrate intake on cognitive function, the vast majority have been clinical interventions examining the acute cognitive changes following a carbohydrate-containing meal. Two literature reviews completed in 2009 and 2014 have reported inconsistent results in existing studies and concluded that further investigations need to address limitations in methodology before recommendations can be made[39,40]. Fewer studies have examined the role of chronic carbohydrate consumption on cognitive function, and several researchers have highlighted the need for epidemiologic research to examine the impact of carbohydrate intake on cognitive decline in human populations[41]. Only a handful of cohort studies have previously evaluated this relationship, and even fewer in a racially diverse cohort, thereby warranting further study[42-44].

Most of the existing literature report that diets high in GL are associated with a decline in cognitive performance and have hypothesized that this relationship may be at least partially mediated through insulin resistance. Indeed, over the past two decades, insulin resistance has been progressively implicated in the etiologies of several neurodegenerative diseases, such as Alzheimer's disease, other dementias, and cognitive impairment[45-47]. Evidence suggests that chronic peripheral insulin resistance and hyperinsulinemia may contribute to cognitive decline through a number of mechanisms, including reduced insulin transport into the brain and increased brain levels of Aβ, tau phosphorylation, inflammation, oxidative stress, and mitochondrial dysfunction[48,49].

Although insulin resistance has been previously associated with cognitive outcomes in a number of cohort studies, similar to the carbohydrate literature, many of these studies took place in relatively small samples or in samples only representing one race[50-53].

The fact that nearly all previous studies studying chronic carbohydrate intake, insulin resistance, and cognitive outcomes have taken place in samples representing only one race is particularly concerning given the emerging body of evidence suggesting that insulin resistance may contribute more to chronic disease development in white populations compared to black populations. Previous studies have reported racial differences in the associations between insulin resistance and blood pressure[54], carotid atherosclerosis[55,56], and incident stroke[57,58], collectively suggesting that insulin resistance may contribute more to cardiovascular disease in white individuals than black individuals. Given the vascular pathway in cognitive decline[59], it is reasonable to hypothesize that there may also be racial differences in the associations between carbohydrate intake, insulin resistance, and cognitive decline. To date, no studies have thoroughly investigated this hypothesis and studies are necessary in large cohorts containing a sufficient number of both black and white participants to adequately assess racial differences.

Objectives and Hypotheses

The overall objectives of this dissertation were two-fold: 1) to evaluate the associations between PCA-derived dietary patterns, cognitive impairment, and cognitive function. It was our hypothesis that these dietary patterns would predict cognitive outcomes in our sample; and 2) to examine the relationship between carbohydrate intake,

insulin resistance, and cognitive outcomes. It was our hypothesis that carbohydrate intake and insulin resistance would be associated with increased cognitive impairment and faster cognitive decline, and that the relationship between carbohydrate intake, insulin resistance, and cognitive outcomes would be stronger in white participants than black participants. This dissertation is comprised of a series of three studies using the REasons for Geographic And Racial Differences in Stroke (REGARDS) study sample, a racially diverse cohort of 30,239 participants living throughout the continental United States. The large number of black participants (approximately 42% of the original sample) as well as the extensive data collected on dietary intake, insulin, and cognitive function made the REGARDS study an ideal sample to address some of the methodological limitations of previous studies.

DIETARY PATTERNS ARE ASSOCIATED WITH COGNITIVE FUNCTION IN THE REGARDS COHORT

by

KEITH E. PEARSON II, VIRGINIA G. WADLEY, LESLIE A. MCCLURE, JAMES M. SHIKANY, FRED W.UNVERZAGT, SUZANNE E. JUDD

Submitted to the Journal of Nutritional Sciences

Format adapted and errata corrected for dissertation

Abstract

Identifying factors that contribute to the preservation of cognitive function is imperative to maintaining quality of life in advanced years. Of modifiable risk factors, diet quality has emerged as a promising candidate to impact cognition. The objective of this study was to evaluate associations between empirically-derived dietary patterns and cognitive function. This study included 18,080 black and white participants aged 45 and older from the REGARDS cohort. Principal component analysis on data from the Block98 FFQ yielded five dietary patterns: convenience, plant-based, sweets/fats, Southern, and alcohol/salads. Incident cognitive impairment was defined as shifting from intact cognitive status (score >4) at first assessment to impaired cognitive status (score ≤4) at latest assessment, measured by Six-Item Screener. Learning, memory, and executive function were evaluated with the word list learning, word list delayed recall, and animal fluency assessments. In fully-adjusted models, greater consumption of the alcohol/salads pattern was associated with lower odds of incident cognitive impairment (Q5 vs Q1: OR 0.68; 95% CI 0.56, 0.84; p for trend 0.00050). Greater consumption of the alcohol/salads pattern was associated with higher scores on all domain-specific assessments and greater consumption of the plant-based pattern was associated with higher scores in learning and memory. Greater consumption of the Southern pattern was associated with lower scores on each domain-specific assessment (all $p < 0.05$). In conclusion, dietary patterns including plant-based foods and alcohol intake were associated with higher cognitive scores, and a pattern including fried food and processed meat typical of a Southern diet was associated with lower scores.

Introduction

As average life expectancy continues to increase due to progressive advances in the prevention and treatment of chronic disease[1], Americans are enjoying the benefits of a prolonged life while simultaneously discovering the consequences of an aging population, particularly those related to a decline in cognitive function. In the United States, where the prevalence of Alzheimer's disease and other dementias is expected to triple by 2050[2], identifying modifiable risk factors that contribute to cognitive function is a growing area of research and could aid in the preservation of quality of life in older ages.

Several studies have evaluated the contributions of specific foods and nutrients to cognitive function, and some evidence suggests that regular consumption of foods such as fatty fish, nuts, and berries, among others, could be related to more favorable cognitive outcomes[3-8]. Although these studies have provided valuable information, one limitation is that this type of approach does not accurately reflect the way people consume foods. Rather than individual foods or nutrients, people generally consume a combination of foods in meals that fall within an overall dietary pattern. By taking advantage of the potential interactions and collective effects of multiple foods, dietary patterns may be more predictive of cognitive function than foods or nutrients in isolation[9].

Previous studies using investigator-defined dietary pattern analysis have demonstrated that adherence to a Mediterranean diet pattern or the Mediterranean-Dash Intervention for Neurodegenerative Delay (MIND) dietary pattern was associated with a reduced risk of cognitive impairment and slower cognitive decline[10-12]. However, these dietary patterns are typically defined a priori by investigators and may not reflect true or

realistic patterns of food consumption within a population. As an alternative, this study aimed to use principal component analysis to employ an empirical approach to identify dietary patterns that may more accurately represent the dietary habits of our sample. A number of studies have used similar methodology but have possessed smaller sample sizes generalizable to only one race[13-19]. This study utilized the REasons for Geographic And Racial Differences in Stroke (REGARDS) cohort, which consists of 30,239 black and white participants dispersed throughout the continental United States. Within the REGARDS cohort, we have previously identified five dietary patterns[20]: convenience, plant-based, sweets/fats, Southern, and alcohol/salads. The objective of this study was to examine the associations between empirically-derived dietary patterns, incident cognitive impairment, and cognitive performance on three domain-specific assessments in a large cohort of black and white adults over the age of 45. Our hypotheses were that the convenience, sweets/fats, and Southern dietary patterns would be associated with poorer cognitive outcomes and that the plant-based and alcohol/salads dietary patterns would be associated with more favorable cognitive outcomes.

Experimental methods

Study sample

The REasons for Geographic And Racial Differences in Stroke (REGARDS) study is a national cohort of 30,239 community-dwelling black and white participants aged 45 and older at baseline. Participants were recruited from 2003-2007 using lists purchased from Genesys, Inc. that were selected to oversample both black Americans and residents of the region of the Southeast United States known as the stroke belt. Upon

entry into the study, the full cohort of participants had a mean age of 64.8 years (ranging from 45 to 98 years) and was approximately 42% black, 55% female, and 56% living in the stroke belt. Exclusion criteria included belonging to a race other than white or black, currently undergoing active treatment for cancer or another medical condition that could affect long-term study participation, nursing home residence, or the inability to communicate in English.

The data from this analysis were collected primarily by using computer assisted telephone interviewing and an in-home medical examination. The initial telephone call collected data regarding demographics, socioeconomic status, and medical history. An in-home examination by a trained medical professional followed where anthropometrics, blood and urine samples, blood pressure measurements, and an ECG were collected. Additionally, several self-administered questionnaires were left with the participant to complete and mail back to the REGARDS coordinating center. Additional details of the study design have been described in depth elsewhere[21]. This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects were approved by the institutional review boards of all participating institutions. Written informed consent was obtained by all participants included in this study.

Assessment of dietary patterns

Dietary intake of the participants was assessed using the Block98 food frequency questionnaire (FFQ), which aims to assess usual dietary intake over the past year by including questions about both frequency and portions of various foods. The Block98

FFQ assesses food frequency by asking participants how often they consume each food item, with the following possible answers: never, a few times per year, once per month, 2-3 times per month, once per week, 2 times per week, 3-4 times per week, 5-6 times per week, or every day. The Block98 FFQ additionally assesses the usual quantity of food consumed by asking the participant how much of each food item they consume, on average, each time they consume that food item. For foods consumed in individual units such as eggs, bacon, and doughnuts, participants were asked to choose the number that represents the usual quantity of that food they consume (i.e. 1 egg, 2 eggs, 3 eggs, or 4 eggs). To help estimate usual quantity consumed for other items such as spinach or ice cream, participants were provided a photo that illustrated several common portions of foods (1/4 cup, 1/2 cup, 1 cup, or 2 cups of foods on plates or 1/2 cup, 1 cup, or 2 cups of foods in bowls). Block FFQs have been previously validated using multiple food records[22-24]. The FFQs were left with the participant during the in-home examination, mailed back by the participant to the REGARDS coordinating center, and sent to NutritionQuest for analysis.

The dietary patterns used in these analyses were derived previously[20] and have been associated with incident stroke[25], incident coronary artery disease[26], sepsis[27], and progression to end-stage renal disease in individuals with chronic kidney disease[28]. The 107 food items from the FFQ were combined into 56 food groups for use in principal component analysis (PCA). Using a random split sample technique to ensure validity and replication of the patterns, PCA with varimax rotation was utilized in the first half of the sample. Factor solutions were examined for interpretability and separate PCA analyses were conducted to test for congruence by region, sex, and race. Congruence coefficients

were obtained to examine whether the dietary patterns could represent the entire sample or should be derived separately for these sub-groups. In the second half of the sample, a confirmatory factor analysis including only the food groups with absolute value loadings ≥0.20 was used to independently validate the results from the PCA and test for model fit. After considering the scree test using eigenvalues >1.5 and examining the congruence coefficients to achieve optimal congruence across region, sex, and race subgroups, this analysis retained five factors, and a final PCA with varimax rotation was performed in the full sample. In total, the five factors explained approximately 24% of the total variance in dietary intake in the REGARDS sample, which is similar to other dietary pattern analyses reported in the literature[29]. Factor scores were calculated for each participant for each dietary pattern by multiplying the factor loading of each food group by each participant's average consumption of each food group.

The five dietary patterns were named according to the types of foods that loaded highly in each of them. Factor one was named the convenience pattern and consisted of mixed dishes with meat, pizza, Chinese food, and Mexican dishes; factor two was named the plant-based pattern and consisted of vegetables, fruits, fish, and beans; factor three included high factor loadings for miscellaneous sugars, desserts, candy, sweetened breakfast foods, and added fats and was named the sweets/fats pattern; factor four was named the Southern pattern because of its high loadings of added fats, fried food, eggs and egg dishes, organ meats, processed meats, and sugar-sweetened beverages; and factor five was named the alcohol/salads pattern and loaded highly in green-leafy vegetables, tomatoes, salad dressing, wine, and liquor. Full factor loadings for each pattern are shown in Table 1.

Assessment of cognitive function

Given the large, nation-wide distribution of the REGARDS study, the cognitive assessment of its participants required a brief assessment that was able to be delivered over telephone. Beginning December 2003, the Six-Item Screener (SIS)[30] was administered during baseline telephone calls and subsequently in annual intervals. The SIS is a brief screening assessment that consists of a three-item word recall and three-items pertaining to temporal orientation. Intact cognitive function was defined as having a score of 5 or 6 correct, and incident cognitive impairment was defined as shifting from intact cognitive function on the first cognitive assessment to impaired cognitive function (a score $\leq$4) on the most recent cognitive assessment[30]. Using a combined endpoint of dementia and mild cognitive impairment in a diverse community-based sample, the cut-point of 4 or fewer correct on the SIS has a sensitivity and specificity of 74% and 80%, respectively[30].

In January 2006, a three-test battery of domain-specific assessments was administered by telephone to participants and has been subsequently administered every two years. To assess verbal learning and memory domains, the Word List Learning (WLL) and Word List Delayed Recall (WLDR) from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery[31] were administered. These assessments involved a set of three learning trials of a list of 10 words followed by a five minute delay that preceded a free recall trial. For WLL, the scores from the three trials were summed and produced a score ranging from zero to 30. For WLDR, the score reflects the number of words the participant could recall after a five minute delay and ranges from zero to 10. For both measures, repetitions and intrusions were excluded, and

a procedure was implemented to exclude non-standard performance patterns (occurring in <2% of the sample). To assess executive function, the animal fluency test (AFT)[31] was administered. This test required participants to name as many animals as they could in one minute, yielding a raw score that was then adjusted for repetitions and intrusions.

For this analysis, the primary outcome is incident cognitive impairment as measured by the SIS. Due to the limited number of participants with multiple assessments for the domain-specific cognitive measures, we will be examining cross-sectional cognitive performance by including only the first measure of the WLL, WLDR, and AFT assessments for each participant who possessed dietary data and were free of stroke at baseline.

Covariate assessment

Age (continuous in years), race (dichotomous: black/white), sex (dichotomous: male/female), region of residence (categorical: stroke-belt, stroke-buckle, non-belt or buckle), income (categorical: <$20,000/year, $20,000-$34,999/year, $35,000-$74,999/year, >$75,000/year, and refused to provide income information), and education (categorical: less than high school, high school graduate, some college, college graduate) were self-reported at baseline. Total energy intake (continuous in kilocalories) was estimated from the FFQ administered at baseline. Height and weight were obtained from the in-home examination and used to calculate body mass index (BMI) (continuous in kilograms/meters^2). Physical activity defined by exercise frequency (categorical: none, 1-3x/week, 4+ x/week) and smoking status (categorical: current, past, never) were self-reported at baseline. History of heart disease (dichotomous: yes/no) was defined as self-

reported myocardial infarction, coronary artery bypass graft, angioplasty, stenting, or evidence of myocardial infarction from an ECG performed during the in-home examination. Participants were defined as hypertensive (dichotomous: yes/no) if systolic blood pressure was ≥140 mmHg or diastolic blood pressure was ≥90 mmHg or if they self-reported current medication use to control blood pressure. Diabetes status (dichotomous: yes/no) was defined as having a fasting glucose ≥126 mg/dL or non-fasting blood glucose ≥200 mg/dL or if the participant reported taking medication or insulin for the management of diabetes. Depressive symptoms (continuous in CESD-4 item score units) were evaluated at baseline over the telephone using the Center for Epidemiological Studies – Depression – 4 item version[32].

Statistical analysis

Likelihood-ratio chi-squared tests and t-tests were used to calculate unadjusted means of demographic characteristics by quintile of each dietary pattern. Logistic regression was utilized to examine the relationship between quintiles of dietary pattern scores and odds of incident cognitive impairment via the SIS. Three models incrementally adding covariates were evaluated in this analysis. Model 1 included adjustment for age, race, sex, region, and total energy intake. Model 2 additionally adjusted for socioeconomic variables previously shown to effect cognitive function: income and education. Model 3 added adjustments for other known cognitive risk factors: physical activity, smoking status, BMI, hypertensive status, diabetes status, history of cardiovascular disease, and depressive symptoms. Participants with non-missing values for all covariates were included in each model, resulting in 0%, 0.03%, and 7.5% missing

data for each model, respectively. Effect modification for race and sex was examined by placing an interaction term in the model for each pattern. Tests for linear trend across quintiles of dietary patterns were evaluated by including each dietary pattern in quintiles as a continuous, ordinal variable in each model. Multiple regression was utilized to evaluate mean differences between quintiles of dietary patterns and each of the three domain-specific cognitive assessments, including all of the covariates listed previously to adjust for confounding. Analyses for the AFT also included a covariate to adjust for the participants who received assistance from someone in their home environment or was given a disallowed prompt by the interviewer (~3.4% of sample).

Results

Of the 30,239 original REGARDS participants, 72% of the cohort returned a usable FFQ. This analysis excluded participants not returning a usable FFQ (n=8,603), defined as the following: did not return a FFQ (17% of full sample), returned a blank FFQ (3%), possessing >15% missing data on FFQ (5%), or estimated to consume implausible energy intakes on FFQ (3%) [20,26].

Of the dietary sub-sample of REGARDS, participants were excluded if they did not possess at least two SIS assessments (n=1,191) or were cognitively impaired at baseline (n=1,447). Participants who self-reported history of stroke at baseline or had an incident stroke prior to first cognitive assessment (n=905) were also excluded. Finally, participants lacking an in-home medical assessment were excluded from these analyses (n=13). These exclusions resulted in a final sample of 18,080 participants. Additionally, cross-sectional analysis of cognitive performance on domain-specific assessments was

performed in REGARDS participants possessing at least one WLL, WLDR, and AFT assessment, dietary data, and no history of stroke prior to cognitive assessment (n=14,247). Participants excluded from the longitudinal analyses were more likely than included participants to be older, male, black, less educated, and have lower income. Excluded participants were also more likely to report no weekly physical activity, currently smoke, have a higher BMI, have a history of hypertension, diabetes, and cardiovascular disease, and exhibit more depressive symptoms.

Descriptive statistics of participants who were included in this analysis are provided in Table 2. Compared to participants in the lowest quintile (Q1), participants in the highest quintile (Q5) of consumption of the convenience pattern tended to be younger, white, male, live outside the stroke belt, and have a higher income and a higher education level. Participants in Q5 of the plant-based pattern tended to be older, a higher proportion black, female, and possess a higher education level than participants in Q1. Participants in the Q5 of the sweets/fats pattern tended to be more white, male, stroke-belt residents, with a lower income and education than participants in Q1. For the Southern pattern, Q5 participants were more likely to be black, male, residing in the stroke-belt, and possess a lower income and education level than participants in Q1. Finally, participants in Q5 of the alcohol/salads pattern tended to be more likely to be younger, white, male, residing outside the stroke-belt, with a higher income and education level.

Of the 18,080 participants included in this analysis, 1,486 cases of incident cognitive impairment were identified over an average follow up of 6.8 years. Odds of incident cognitive impairment by quintile of each dietary pattern are displayed in Table 3.

After adjustment for demographic factors and total energy intake, participants in the highest quintile of the Southern dietary pattern had higher odds of incident cognitive impairment (Q5 vs Q1: OR 1.46; 95% CI 1.19, 1.78; p for trend = <0.0001) compared to participants in the lowest quintile. Additionally, participants in the highest quintile of the plant-based and alcohol/salads dietary patterns had lower odds of incident cognitive impairment (Plant-based - Q5 vs Q1: OR 0.81; 95% CI 0.67, 0.98; p for trend = 0.016; Alcohol/salads - Q5 vs Q1: OR 0.65; 95% CI 0.54, 0.79; p for trend = <0.0001). After further adjustment for socioeconomic status and other cognitive risk factors, the observed associations with the plant-based and Southern patterns were attenuated and no longer statistically significant, but the association with the alcohol/salads pattern remained (Q5 vs Q1: OR 0.68; 95% CI 0.56, 0.84; p for trend = 0.00050). No significant associations between the convenience and sweets/fats dietary patterns and incident cognitive impairment were observed, and tests for interactions by race and sex were non-significant for each pattern.

In the assessments of learning, memory, and executive function, participants in the highest quintile of the alcohol/salads patterns had higher scores on all measures of cognitive function compared to participants in the lowest quintile. Likewise, participants with the highest consumption of the plant-based pattern scored higher on the WLL and WLDR assessments compared to participants with the lowest consumption. There were no differences in scores on the AFT between the extreme quintiles of the plant-based pattern, but a significant linear trend was observed (see Figure 3). Additionally, scoring in the highest quintile of the Southern dietary pattern was associated with significantly lower scores in the learning, memory, and executive function domains. Scoring in the

highest quintile of the convenience dietary pattern was also associated with higher performance on the WLL ($p < 0.05$). No other differences were detected on any domain-specific assessments between any of the quintiles for the convenience and sweets/fats patterns, although a significant linear trend was observed on the WLL for the convenience and sweets/fats patterns and for the convenience pattern on the AFT. Domain-specific results for the plant-based, Southern, and alcohol/salads patterns are displayed in Figure 1, Figure 2, and Figure 3, and further details are provided in Table 4.

Discussion

In this study of 18,080 black and white participants aged 45 and older, we found that greater consumption of the alcohol/salads dietary pattern was associated with lower odds of incident cognitive impairment and higher performance on several cognitive measures assessing learning, memory, and executive function. Additionally, greater consumption of a plant-based dietary pattern was associated with higher cognitive performance while greater consumption of a Southern dietary pattern was associated with lower cognitive performance on these domain-specific measures. Our findings strengthen the body of literature that collectively suggests that dietary patterns may impact cognitive function, and this particular study provides a unique perspective by utilizing empirically-derived dietary patterns in a large, diverse sample of black and white adults living throughout the country.

As expected, greater consumption of the plant-based dietary pattern that loaded highest in many different types of vegetables, fruits, and legumes was associated with higher cognitive performance on the WLL and WLDR assessments. This is consistent

with previous studies, both cross-sectional and longitudinal, that have demonstrated an association between higher levels of fruit or vegetable intake and more favorable cognitive outcomes[33-36]. Many researchers have hypothesized that this observation could be related to higher intakes of fruits and vegetables contributing to higher levels of antioxidants, resulting in lower levels of oxidative stress. In a cross-sectional study of 193 healthy adults aged 45-102 years, Polidori et al.[34] tested this hypothesis and found that adults who reported consuming higher intakes of fruits and vegetables had higher cognitive performance, higher levels of circulating antioxidant micronutrients, and lower levels of oxidative stress biomarkers compared to adults consuming lower amounts of fruits and vegetables. Additionally, higher fruit and vegetable intake has been associated with lower blood pressure[37] and cardiovascular disease incidence[38], which are both known risk factors for cognitive impairment[39,40] and may be mediating these associations despite attempts to adjust for confounding.

Interestingly, greater consumption of the alcohol/salads dietary pattern was associated with lower odds of incident cognitive impairment and higher cognitive performance on all cognitive assessments analyzed in this study. This pattern loaded highest on salad dressings/sauces and green leafy vegetables, and also contained a high factor loading for tomatoes. Green leafy vegetables and tomatoes are vegetables that are particularly high in antioxidants and could be contributing to cognitive function in similar ways described for the plant-based dietary pattern. This pattern also consisted of higher intakes of both wine and liquor. Several previous epidemiological studies have demonstrated an association between moderate alcohol consumption and more favorable cognitive outcomes, most citing the potential cardiovascular benefits of moderate alcohol

consumption to be contributing to the increased cognitive performance[41-44]. Although previous studies utilizing similar methodology have yielded dietary patterns comparable to the plant-based and Southern dietary patterns[13,29,45], the alcohol/salads pattern appears to be unique to our cohort. We believe that the size and racial diversity of REGARDS participants geographically distributed throughout the United States provides the opportunity for our analysis to yield unique patterns that may not reflect the dietary patterns previously derived in participants of smaller, less diverse cohorts.

The Southern dietary pattern was associated with poorer cognitive performance on the WLL, WLDR, and AFT assessments in this study. This was not surprising given the pattern's high factor loadings of fried food, processed meats, sugar sweetened beverages, and refined white bread. A similar "processed food pattern" was identified by Torres et al.[45] and also consisted of fried foods, processed meat, and sugar beverages in 249 people aged 65-90 years with mild cognitive impairment. In that study, the highest intake of the processed food pattern was associated with the lowest cognitive performance on a global cognitive examination.

The results of this analysis must be interpreted with consideration of the study's limitations. Three of the five dietary patterns were associated with cognitive performance on multiple domain-specific assessments, but only the alcohol/salads pattern was associated with incident cognitive impairment on the SIS. This discrepancy may reflect a higher sensitivity of the domain-specific assessments to detect cognitive differences relative to the Six-Item Screener. Additionally, through our use of multivariable modeling, we attempted to minimize the influence of several confounders on the associations between dietary patterns and cognitive function. Regardless of our efforts,

the possibility of residual confounding still remains. The correlation between socioeconomic status and cognition is well established, and several studies have reported attenuations in associations between dietary patterns and various cognitive outcomes after the adjustment of socioeconomic measures[13,46]. However, it is notable that many of the associations between dietary patterns and cognitive function in this analysis remained significant even after adjustment for income and education. One final limitation is the possibility for recall bias to exist in the measurement of our dietary data by FFQ. It is reasonable to suggest that participants with lower cognitive function would have more difficulty providing accurate dietary data via recall of food frequency. However, we attempted to minimize the potential of recall bias by excluding participants with cognitive impairment at baseline from the longitudinal analysis of incident cognitive impairment. Despite these limitations, we believe this study provides a unique perspective of the diet-cognition relationship in a very large cohort of geographically-dispersed black and white Americans. Utilizing empirically-derived dietary patterns with no pre-specification of diet quality, we identified a plant-based and alcohol/salads dietary pattern associated with higher cognitive performance and a Southern dietary pattern associated with lower cognitive performance. Findings from this study, in conjunction with previous literature, could be used to develop interventions to maintain the cognitive function of older Americans.

References

1. Ortman JM, Velkoff VA, Hogan H (2014) An aging nation: the older population in the United States. *Washington, DC: US Census Bureau*, 25-1140.

2. Alzheimer's Association. 2016 Alzheimer's disease facts and figures. *Alzheimer's & Dementia.* 2016;12(4):459-509.

3. Kalmijn S, Feskens EJM, Launer LJ *et al.* (1997) Polyunsaturated fatty acids, antioxidants, and cognitive function in very old men. *American Journal of Epidemiology* **145**, 33-41.

4. Morris MC, Evans DA, Tangney CC *et al.* (2005) Fish consumption and cognitive decline with age in a large community study. *Archives of Neurology* **62**, 1849-1853.

5. Pribis P, Bailey RN, Russell AA *et al.* (2012) Effects of walnut consumption on cognitive performance in young adults. *The British Journal of Nutrition* **107**, 1393-1401.

6. Solfrizzi V, Panza F, Capurso A (2003) The role of diet in cognitive decline. *Journal of Neural Transmission* **110**, 95-110.

7. Subash S, Essa MM, Al-Adawi S *et al.* (2014) Neuroprotective effects of berry fruits on neurodegenerative diseases. *Neural Regeneration Research* **9**, 1557-1566.

8. Devore EE, Kang JH, Breteler MM *et al.* (2012) Dietary intakes of berries and flavonoids in relation to cognitive decline. *Annals of Neurology* **72**, 135-143.

9. Hu FB (2002) Dietary pattern analysis: a new direction in nutritional epidemiology. *Current Opinion in Lipidology* **13**, 3-9.

10. Psaltopoulou T, Sergentanis TN, Panagiotakos DB *et al.* (2013) Mediterranean diet, stroke, cognitive impairment, and depression: A meta-analysis. *Annals of Neurology* **74**, 580-591.

11. Morris MC, Tangney CC, Wang Y *et al.* (2015) MIND diet slows cognitive decline with aging. *Alzheimer's & Dementia*.

12. Morris MC, Tangney CC, Wang Y *et al.* (2015) MIND diet associated with reduced incidence of Alzheimer's disease. *Alzheimer's & Dementia.*

13. Akbaraly TN, Singh-Manoux A, Marmot MG *et al.* (2009) Education attenuates the association between dietary patterns and cognition. *Dementia and Geriatric Cognitive Disorders* **27**, 147-154.

14. Kesse-Guyot E, Andreeva VA, Jeandel C *et al.* (2012) A healthy dietary pattern at midlife is associated with subsequent cognitive performance. *The Journal of Nutrition* **142**, 909-915.

15. Ashby-Mitchell K, Peeters A, Anstey KJ (2015) Role of dietary pattern analysis in determining cognitive status in elderly Australian adults. *Nutrients* **7**, 1052-1067.

16. Kim J, Yu A, Choi BY *et al.* (2015) Dietary patterns and cognitive function in Korean older adults. *European Journal of Nutrition* **54**, 309-318.

17. Sugawara N, Yasui-Furukori N, Umeda T *et al.* (2015) Relationship between dietary patterns and cognitive function in a community-dwelling population in Japan. *Asia-Pacific Journal of Public Health* **27**, NP2651-NP2660.

18. Shakersain B, Santoni G, Larsson SC *et al.* (2015) Prudent diet may attenuate the adverse effects of Western diet on cognitive decline. *Alzheimer's & Dementia*.

19. Qin B, Adair LS, Plassman BL *et al.* (2015) Dietary patterns and cognitive decline among chinese older adults. *Epidemiology* **26**, 758-768.

20. Judd SE, Letter AJ, Shikany JM *et al.* (2014) Dietary patterns derived using exploratory and confirmatory factor analysis are stable and generalizable across race, region, and gender subgroups in the REGARDS study. *Frontiers in Nutrition* **1**, 29.

21. Howard VJ, Cushman M, Pulley L *et al.* (2005) The reasons for geographic and racial differences in stroke study: objectives and design. *Neuroepidemiology* **25**, 135-143.

22. Boucher B, Cotterchio M, Kreiger N *et al.* (2006) Validity and reliability of the Block98 food-frequency questionnaire in a sample of Canadian women. *Public Health Nutrition* **9**, 84-93.

23. Block G, Woods M, Potosky A *et al.* (1990) Validation of a self-administered diet history questionnaire using multiple diet records. *Journal of Clinical Epidemiology* **43**, 1327-1335.

24. Caan BJ, Slattery ML, Potter J *et al.* (1998) Comparison of the Block and the Willett self-administered semiquantitative food frequency questionnaires with an interviewer-administered dietary history. *American Journal of Epidemiology* **148**, 1137-1147.

25. Judd SE, Gutierrez OM, Newby PK *et al.* (2013) Dietary patterns are associated with incident stroke and contribute to excess risk of stroke in black Americans. *Stroke* **44**, 3305-3311.

26. Shikany JM, Safford MM, Newby P *et al.* (2015) Southern dietary pattern is associated with hazard of acute coronary heart disease in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study. *Circulation*, CIRCULATIONAHA. 114.014421.

27. Gutierrez OM, Judd SE, Voeks JH *et al.* (2015) Diet patterns and risk of sepsis in community-dwelling adults: a cohort study. *BMC Infectious Diseases* **15**, 231.

28. Gutierrez OM, Muntner P, Rizk DV *et al.* (2014) Dietary patterns and risk of death and progression to ESRD in individuals with CKD: a cohort study. *American Journal of Kidney Diseases* **64**, 204-213.

29. Newby P, Tucker KL (2004) Empirically derived eating patterns using factor or cluster analysis: a review. *Nutrition Reviews* **62**, 177-203.

30. Callahan CM, Unverzagt FW, Hui SL *et al.* (2002) Six-item screener to identify cognitive impairment among potential subjects for clinical research. *Medical Care* **40**, 771-781.

31. Welsh KA, Butters N, Mohs RC *et al.* (1994) The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part V. A normative study of the neuropsychological battery. *Neurology* **44**, 609-614.

32. Kohout FJ, Berkman LF, Evans DA *et al.* (1993) Two shorter forms of the CES-D (Center for Epidemiological Studies Depression) depression symptoms index. *Journal of Aging and Health* **5**, 179-193.

33. Chan R, Chan D, Woo J (2013) A cross sectional study to examine the association between dietary patterns and cognitive impairment in older Chinese people in Hong Kong. *The Journal of Nutrition, Health & Aging* **17**, 757-765.

34. Polidori MC, Pratico D, Mangialasche F *et al.* (2009) High fruit and vegetable intake is positively correlated with antioxidant status and cognitive performance in healthy subjects. *Journal of Alzheimer's Disease* **17**, 921-927.

35. Kang JH, Ascherio A, Grodstein F (2005) Fruit and vegetable consumption and cognitive decline in aging women. *Annals of Neurology* **57**, 713-720.

36. Morris MC, Evans DA, Tangney CC *et al.* (2006) Associations of vegetable and fruit consumption with age-related cognitive change. *Neurology* **67**, 1370-1376.

37. John JH, Ziebland S, Yudkin P *et al.* (2002) Effects of fruit and vegetable consumption on plasma antioxidant concentrations and blood pressure: a randomised controlled trial. *Lancet* **359**, 1969-1974.

38. He FJ, Nowson CA, Lucas M *et al.* (2007) Increased consumption of fruit and vegetables is related to a reduced risk of coronary heart disease: meta-analysis of cohort studies. *Journal of Human Hypertension* **21**, 717-728.

39. Breteler MM, Claus JJ, Grobbee DE *et al.* (1994) Cardiovascular disease and distribution of cognitive function in elderly people: the Rotterdam Study. *British Medical Journal* **308**, 1604-1608.

40. Kilander L, Nyman H, Boberg M *et al.* (1998) Hypertension is related to cognitive impairment: a 20-year follow-up of 999 men. *Hypertension* **31**, 780-786.

41. Stampfer MJ, Kang JH, Chen J *et al.* (2005) Effects of moderate alcohol consumption on cognitive function in women. *The New England Journal of Medicine* **352**, 245-253.

42. Lang I, Wallace RB, Huppert FA *et al.* (2007) Moderate alcohol consumption in older adults is associated with better cognition and well-being than abstinence. *Age and Ageing* **36**, 256-261.

43. Hendrie HC, Gao S, Hall KS *et al.* (1996) The relationship between alcohol consumption, cognitive performance, and daily functioning in an urban sample of older black Americans. *Journal of the American Geriatrics Society* **44**, 1158-1165.

44. McGuire LC, Ajani UA, Ford ES (2007) Cognitive functioning in late life: the impact of moderate alcohol consumption. *Annals of Epidemiology* **17**, 93-99.

45. Torres SJ, Lautenschlager NT, Wattanapenpaiboon N *et al.* (2012) Dietary patterns are associated with cognition among older people with mild cognitive impairment. *Nutrients* **4**, 1542-1551.

46. Parrott MD, Shatenstein B, Ferland G *et al.* (2013) Relationship between diet quality and cognition depends on socioeconomic position in healthy older adults. *The Journal of Nutrition* **143**, 1767-1773.

Table 1. Factor loadings for each dietary pattern derived in the REasons for Geographic And Racial Differences in Stroke (REGARDS) cohort 2003-2014

	Dietary Patterns				
	Convenience	**Plant-based**	**Sweets/Fat**	**Southern**	**Alcohol Salad**
Food group					
100% fruit juice	-0.051	0.25	0.041	0.17	-0.17
Added fats	0.11	0.053	0.40	0.38	0.25
Beans	0.36	0.38	-0.0026	0.09	-0.13
Beer	0.14	-0.16	-0.10	0.11	0.23
Bread	0.11	-0.05	0.47	0.37	-0.070
Bread - whole grain	-0.0025	0.30	0.18	-0.098	0.070
Butter	0.017	-0.016	0.17	0.13	0.32
Candy	0.085	-0.038	0.40	-0.10	-0.072
Cereal	-0.012	0.38	0.074	0.049	-0.20
Cereal - high fiber	0.068	0.24	0.048	-0.25	-0.044
Chinese food	0.44	0.029	-0.04	-0.022	0.15
Chocolate	0.13	-0.079	0.46	-0.12	-0.013
Coffee	0.0084	-0.063	0.22	-.16	0.30
Condiments	0.25	0.060	0.31	0.15	0.29
Dairy - high fat	0.18	-0.067	0.37	0.043	0.21
Dairy - low fat	0.079	0.20	0.042	-0.19	-0.012
Desserts	0.20	0.040	0.53	0.11	-0.17
Eggs and egg dishes	0.012	-0.0087	0.11	0.42	0.29
Fish	0.27	0.38	-0.11	0.067	0.21
Fried food	0.24	0.023	0.10	0.56	-0.0067
Fried potatoes	0.37	-0.13	0.28	0.16	0.066
Fruit	-0.065	0.58	0.0077	-0.095	-0.029
Liquor	0.050	-0.10	-0.14	0.096	0.31

Margarine	0.041	0.045	0.37	0.10	-0.035
Mexican dishes	0.48	-0.090	0.048	-0.067	0.10
Milk alternatives	-0.012	0.18	-0.073	-0.027	-0.020
Milk - high fat	-0.10	0.012	0.18	0.24	-0.052
Milk - low fat	0.10	0.16	0.032	-0.42	0.0015
Miscellaneous sugar	-0.11	0.0042	0.54	0.19	0.00080
Mixed dishes with meat	0.61	0.13	0.050	0.053	0.026
Nuts and seeds	0.10	0.26	0.19	-0.098	0.19
Organ meat	0.17	0.068	-0.062	0.47	-0.087
Pasta dishes	0.59	0.089	0.17	-0.029	0.026
Pizza	0.45	-0.18	0.20	-0.12	0.074
Potatoes	0.36	0.12	0.26	0.031	0.025
Poultry	0.29	0.31	-0.045	0.034	0.13
Processed meats	0.25	-0.061	0.26	0.45	0.22
Red meat	0.45	-0.077	0.18	0.26	0.26
Refined grains	0.31	0.17	0.20	0.20	-0.0016
Salad dressing/sauces	0.12	0.30	0.045	-0.13	0.55
Salty snacks	0.32	-0.072	0.30	0.081	0.10
Shell fish	0.28	0.090	-0.080	0.23	0.24
Soda	0.096	-0.23	0.15	0.24	0.022
Soup	0.44	0.32	-0.0092	0.030	-0.15
Sugar-sweetened beverages	-0.023	0.064	0.068	0.37	-0.15
Sweet breakfast foods	0.19	-0.028	0.39	0.13	-0.14
Tea	-0.072	0.091	0.31	-0.024	0.054
Vegetable - cruciferous	0.067	0.59	-0.053	0.11	0.062
Vegetable - dark yellow	0.0098	0.41	0.055	0.13	-0.17
Vegetable - green leafy	0.16	0.49	-0.077	-0.22	0.48
Vegetable - other	0.052	0.48	0.041	-0.040	0.039

Vegetable - tomato	0.015	0.32	-0.026	0.018	0.27
Vegetable mixed dishes	0.35	0.31	-0.033	0.13	-0.25
Water	-0.093	0.32	-0.056	-0.024	0.086
Wine	0.062	0.021	-0.14	-0.14	0.36
Yogurt	0.075	0.31	0.035	-0.25	-0.040

Table 2. Baseline characteristics by quintile of dietary pattern in the REasons for Geographic And Racial Differences in Stroke (REGARDS) cohort 2003-2014

	Plant-based		Southern		Alcohol/Salads	
	Q1	Q5	Q1	Q5	Q1	Q5
Age	61.9 (8.8)	65.3 (8.9)	64.2 (9.1)	63.1 (8.8)	65.8 (9.4)	63.1 (8.7)
Race						
Black	887 (24.5)	1296 (35.8)	276 (7.6)	2146 (59.4)	1731 (47.9)	613 (17.0)
White	2729 (75.5)	2320 (64.2)	3340 (92.4)	1470 (40.7)	1885 (52.1)	3003 (83.1)
Sex						
Male	1935 (53.5)	1281 (35.4)	1315 (36.4)	1961 (54.2)	1264 (35.0)	1874 (51.8)
Female	1681 (46.5)	2335 (64.6)	2301 (63.6)	1655 (45.8)	2352 (65.0)	1742 (48.2)
Region						
Stroke Belt	1245 (34.4)	1198 (33.1)	1020 (28.2)	1469 (40.6)	1263 (34.9)	1083 (30.0)
Stroke Buckle	775 (21.4)	792 (21.9)	695 (19.2)	906 (25.1)	868 (24.0)	740 (20.5)
Non-belt	1596 (44.1)	1626 (45.0)	1901 (52.6)	1241 (34.3)	1485 (41.1)	1793 (49.6)
Total energy intake (kcal)	1568 (686)	2088 (741)	1719 (624)	2188 (789)	1649 (745)	2031 (726)
Income						
< $20,000/yr	502 (13.9)	507 (14.0)	268 (7.4)	815 (22.5)	881 (24.4)	246 (6.8)
$20,000 - $34,999	844 (23.3)	800 (22.1)	658 (18.2)	984 (27.2)	991 (27.4)	654 (18.1)
$35,000 - $74,999	1188 (32.9)	1193 (33.0)	1251 (34.6)	1054 (29.2)	945 (26.1)	1263 (34.9)
>$75,000	696 (19.3)	678 (18.8)	969 (26.8)	378 (10.5)	345 (9.5)	1073 (29.7)
Refused	386 (10.7)	438 (12.1)	470 (13.0)	385 (10.7)	454 (12.6)	380 (10.5)
Education						
Less than high school	333 (9.2)	233 (6.5)	114 (3.2)	564 (15.6)	483 (13.4)	129 (3.6)
High school graduate	1077 (29.8)	713 (19.7)	680 (18.8)	1122 (31.0)	1046 (28.9)	684 (18.9)
Some college	1027 (28.4)	979 (27.1)	906 (25.1)	1037 (28.7)	1003 (27.8)	921 (25.5)
College graduate	1177 (32.6)	1690 (46.8)	1915 (53.0)	892 (24.7)	1083 (30.0)	1880 (52.0)

Means and standard deviations are shown for continuous variables. Number of participants and row percentages are shown for categorical variables.

Table 3. Odds of incident cognitive impairment by quintile of dietary pattern in the REasons for Geographic And Racial Differences in Stroke cohort 2003-2014

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P_{Trend}
Convenience						
impaired/total	386/3616	318/3616	321/3616	249/3616	212/3616	
Model 1	1	0.92 (0.79, 1.09)	1.05 (0.89, 1.24)	0.85 (0.71, 1.02)	0.85 (0.69, 1.04)	0.098
Model 2	1	0.95 (0.80, 1.11)	1.10 (0.93, 1.29)	0.88 (0.74, 1.06)	0.88 (0.72, 1.09)	0.25
Model 3	1	0.96 (0.81, 1.14)	1.06 (0.89, 1.26)	0.86 (0.71, 1.03)	0.87 (0.70, 1.08)	0.14
Plant-based						
impaired/total	272/3616	298/3616	336/3616	288/3616	292/3616	
Model 1	1	0.89 (0.74, 1.06)	0.94 (0.79, 1.12)	0.80 (0.66, 0.96)	0.81 (0.67, 0.98)	0.016
Model 2	1	0.93 (0.78, 1.11)	1.00 (0.84, 1.19)	0.86 (0.72, 1.04)	0.91 (0.75, 1.11)	0.25
Model 3	1	0.92 (0.77, 1.11)	0.98 (0.81, 1.18)	0.87 (0.71, 1.05)	0.89 (0.73, 1.10)	0.23
Sweets/Fats						
impaired/total	271/3616	311/3616	305/3616	295/3616	304/3616	
Model 1	1	1.07 (0.90, 1.28)	1.06 (0.89, 1.27)	1.07 (0.89, 1.29)	1.23 (1.00, 1.53)	0.12
Model 2	1	1.05 (0.88, 1.25)	1.04 (0.87, 1.25)	1.03 (0.85, 1.25)	1.14 (0.92, 1.41)	0.38
Model 3	1	1.07 (0.89, 1.28)	1.05 (0.87, 1.27)	1.02 (0.84, 1.25)	1.19 (0.95, 1.49)	0.31
Southern						
impaired/total	217/3616	254/3616	297/3616	348/3616	370/3616	
Model 1	1	1.03 (0.85, 1.25)	1.14 (0.94, 1.38)	1.29 (1.07, 1.56)	1.46 (1.19, 1.78)	<0.0001
Model 2	1	1.01 (0.83, 1.22)	1.09 (0.90, 1.32)	1.18 (0.97, 1.43)	1.23 (1.00, 1.52)	0.016
Model 3	1	0.97 (0.79, 1.19)	1.07 (0.88, 1.31)	1.16 (0.95, 1.42)	1.16 (0.93, 1.45)	0.053

Alcohol/Salads						
impaired/total	397/3616	343/3616	271/3616	270/3616	205/3616	
Model 1	1	0.94 (0.80, 1.11)	0.78 (0.66, 0.93)	0.83 (0.70, 0.98)	0.65 (0.54, 0.79)	<0.0001
Model 2	1	0.98 (0.83, 1.15)	0.83 (0.70, 0.99)	0.91 (0.77, 1.08)	0.76 (0.62, 0.92)	0.0046
Model 3	1	0.94 (0.80, 1.12)	0.81 (0.68, 0.97)	0.88 (0.73, 1.05)	0.68 (0.56, 0.84)	0.00050

Model 1 adjusts for demographic variables (age, race, sex, region, and total energy intake). Model 2 additionally adjusts for socioeconomic variables (income and education). Model 3 additionally adjusts for cognitive risk factors and co-morbidities (physical activity, smoking status, BMI, hypertensive status, diabetes status, history of CVD, and score on the CESD.

Table 4. Least squares means and mean differences between quintiles of dietary pattern adherence on the Word List Learning, Word List Delayed Recall, and Animal Fluency Test in the REasons for Geographic And Racial Differences in Stroke (REGARDS) cohort 2003-2014

		Word List Learning			Word List Delayed Recall			Animal Fluency Test		
		LS mean	**Mean diff.**	**P value**	**LS mean**	**Mean diff.**	**P value**	**LS mean**	**Mean diff.**	**P value**
Convenience										
	Q1	16.11	0	N/A	6.02	0	N/A	15.39	0	N/A
	Q2	16.14	0.037	0.99	6.09	0.068	0.63	15.32	-0.070	0.98
	Q3	16.34	0.23	0.27	6.09	0.069	0.63	15.56	0.17	0.73
	Q4	16.34	0.23	0.28	6.10	0.079	0.52	15.56	0.17	0.74
	Q5	16.48	0.37	0.033	6.10	0.085	0.56	15.71	0.32	0.23
Plant-based										
	Q1	15.98	0	N/A	5.95	0	N/A	15.33	0	N/A
	Q2	16.12	0.14	0.73	6.02	0.074	0.55	15.41	0.079	0.98
	Q3	16.29	0.31	0.049	6.12	0.17	0.0047	15.61	0.28	0.24
	Q4	16.48	0.50	0.00010	6.14	0.19	0.0015	15.52	0.20	0.62
	Q5	16.53	0.55	<0.0001	6.18	0.24	<0.0001	15.63	0.30	0.26
Sweets/Fats										
	Q1	16.27	0	N/A	6.05	0	N/A	15.42	0	N/A
	Q2	16.45	0.18	0.49	6.14	0.089	0.36	15.53	0.12	0.91
	Q3	16.30	0.027	0.99	6.06	0.0041	0.99	15.39	-0.027	0.99
	Q4	16.28	0.0040	0.99	6.10	0.043	0.91	15.69	0.27	0.30
	Q5	16.01	-0.26	0.30	6.03	-0.020	0.99	15.42	0.0037	0.99
Southern										
	Q1	16.72	0	N/A	6.21	0	N/A	15.95	0	N/A
	Q2	16.48	-0.24	0.22	6.15	-0.059	0.75	15.94	-0.011	0.99
	Q3	16.39	-0.33	0.029	6.14	-0.075	0.55	15.49	-0.46	0.0078
	Q4	16.23	-0.50	0.00030	6.06	-0.16	0.021	15.43	-0.52	0.0023

	Q5	15.96	-0.76	<0.0001	5.97	-0.25	0.00020	15.18	-0.76	<0.0001
Alcohol/Salads										
	Q1	15.91	0	N/A	5.97	0	N/A	15.22	0	N/A
	Q2	16.07	0.16	0.61	6.01	0.042	0.91	15.42	0.19	0.60
	Q3	16.29	0.38	0.0066	6.09	0.12	0.10	15.68	0.46	0.0072
	Q4	16.57	0.66	<0.0001	6.15	0.18	0.0027	15.57	0.35	0.086
	Q5	16.68	0.77	<0.0001	6.20	0.23	0.0001	15.63	0.41	0.035

LS means adjusted for age, race, sex, region, total energy intake, income, education, physical activity, smoking status, BMI, hypertensive status, diabetes status, history of CVD, and score on the CESD. LS means for the Animal Fluency Test also adjusted for disallowed help/prompting. Mean differences represent the mean difference in cognitive performance between participants in each dietary pattern quintile compared to participants in quintile 1.

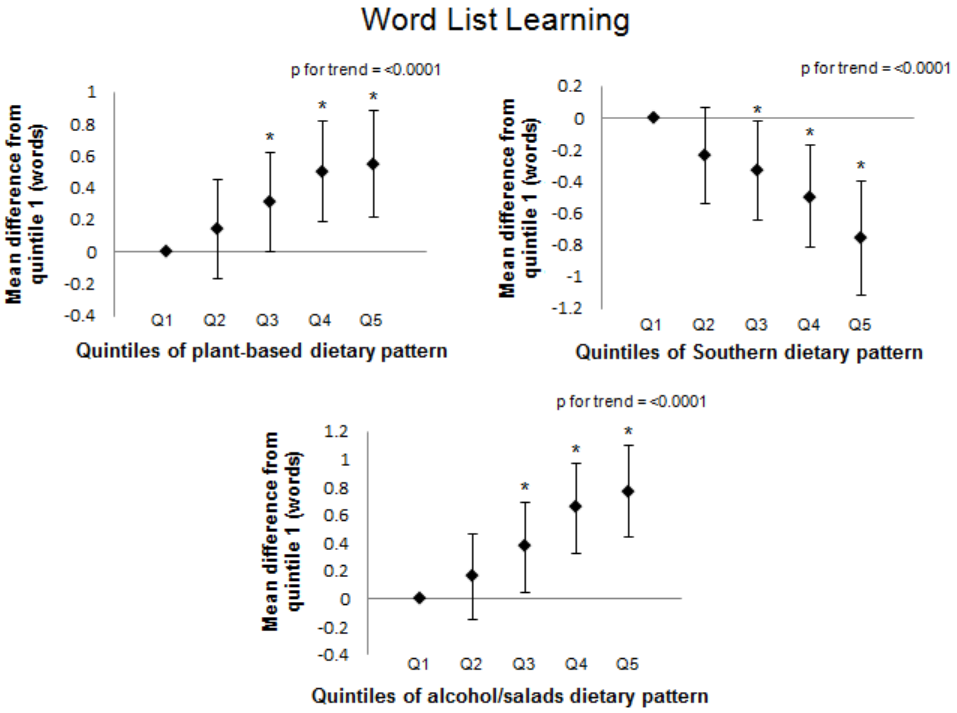

Figure 1. Multivariable-adjusted mean differences and 95% confidence intervals on the Word List Learning assessment. Adjusted for age, race, sex, region, total energy intake, income, education, physical activity, smoking status, body mass index, hypertensive status, diabetes status, history of cardiovascular disease, and depressive symptoms. Example interpretation: Participants with factor scores in quintiles 3, 4, and 5 of the Southern dietary pattern scored significantly lower on the Word List Learning assessment than participants in quintile 1.

* Mean differences are statistically significant ($p<0.05$)

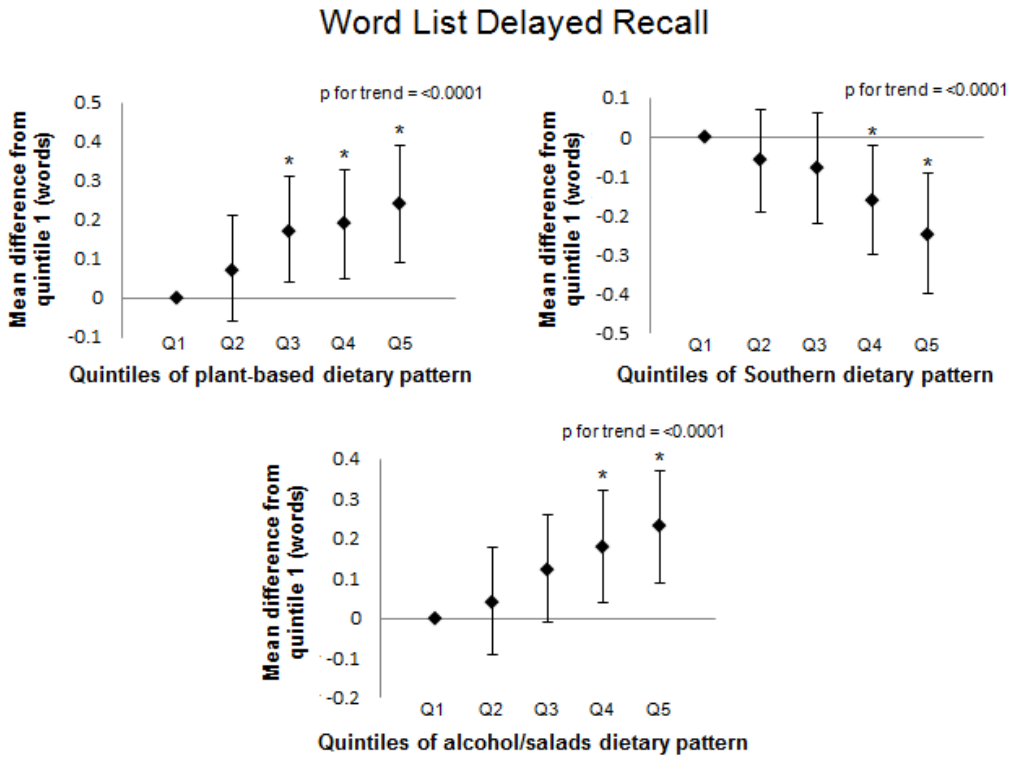

Figure 2. Multivariable-adjusted mean differences and 95% confidence intervals on the Word List Delayed Recall assessment. Adjusted for age, race, sex, region, total energy intake, income, education, physical activity, smoking status, body mass index, hypertensive status, diabetes status, history of cardiovascular disease, and depressive symptoms. Example interpretation: Participants with factor scores in quintiles 4 and 5 of the Southern dietary pattern scored significantly lower on the Word List Delayed Recall assessment than participants in quintile 1.

* Mean differences are statistically significant ($p<0.05$)

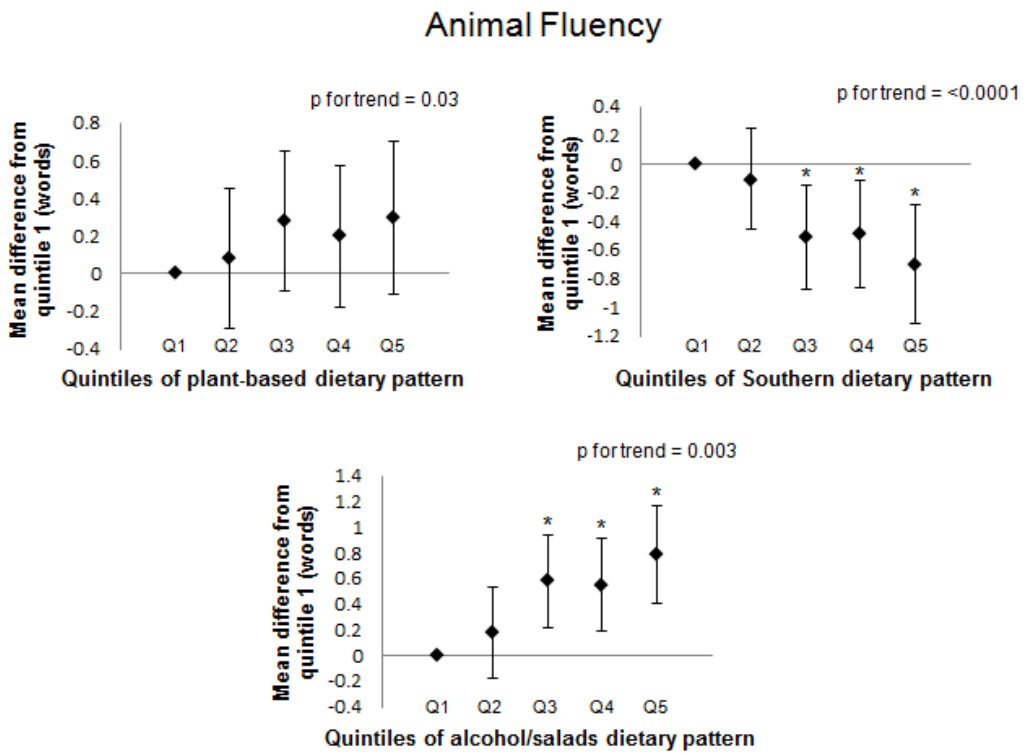

Figure 3. Multivariable-adjusted mean differences and 95% confidence intervals on the Animal Fluency Test. Adjusted for age, race, sex, region, total energy intake, income, education, physical activity, smoking status, body mass index, hypertensive status, diabetes status, history of cardiovascular disease, depressive symptoms, and disallowed help/prompting. Example interpretation: Participants with factor scores in quintiles 3, 4, and 5 of the Southern dietary pattern scored significantly lower on the Animal Fluency Test than participants in quintile 1.

* Mean differences are statistically significant ($p<0.05$)

GLYCEMIC LOAD AND CARBOHYDRATE INTAKE ARE ASSOCIATED WITH INCIDENT COGNITIVE IMPAIRMENT IN THE REASONS FOR GEOGRAPHIC AND RACIAL DIFFERENCES IN STROKE (REGARDS) COHORT

by

KEITH E. PEARSON II, BARBARA A. GOWER, VIRGINIA G. WADLEY, GEORGE HOWARD, PAULA CHANDLER-LANEY, LESLIE A. MCCLURE, JAMES M. SHIKANY, FRED W. UNVERZAGT, SUZANNE E. JUDD

Prepared for submission to the American Journal of Clinical Nutrition

Format adapted for dissertation

Abstract

Carbohydrate quality and quantity have been associated with several chronic diseases, but few studies have investigated associations with cognitive impairment. The objective of this study was to test the hypothesis that higher glycemic index (GI), glycemic load (GL), and available carbohydrate (CHO) intakes may be associated with higher odds of incident cognitive impairment and faster cognitive decline in a large prospective cohort. This study utilized the REGARDS cohort, consisting of 30,239 black and white participants aged 45 years and older. Dietary intake was assessed by the Block98 food frequency questionnaire, from which values for GI, GL, and CHO were estimated and split into quintiles. Incident cognitive impairment was defined as shifting from intact cognitive status (score >4) at baseline to an impaired cognitive status (score <5) at most recent cognitive assessment, measured by an annual Six-Item Screener. Cognitive decline was assessed by word list learning/delayed recall and the animal fluency test administered every two years. Logistic regression and repeated measures analysis were used to analyze the data. This analysis included 17,654 participants free of stroke and cognitive impairment at baseline. A total of 1,564 cases of incident cognitive impairment were observed over a median follow up of 8.1 years. After adjustment for covariates, participants in the highest quintile of GL and CHO had higher odds of incident cognitive impairment than those in the lowest quintile (GL – OR: 1.53; 95% CI: 1.15, 2.05; p for trend = 0.0030; CHO – OR: 1.66; 95% CI: 1.23, 2.24; p for trend = 0.0026). No significant associations were observed with GI. A significant racial interaction was present with GL and CHO for the word list learning assessment. In conclusion, a dietary pattern lower in GL and CHO may aid in the preservation of cognitive function in older ages.

Introduction

Average life expectancy continues to increase, and the number of Americans aged 65 and older is projected to rise from approximately 40 million in 2010 to over 88 million by year 2050[1]. Because age is the greatest risk factor for cognitive impairment, identifying lifestyle modifications that contribute to slower cognitive decline is a primary concern of many public health initiatives. The relationship between carbohydrate intake and cognitive decline has garnered much attention primarily due to the observation that individuals with diabetes have nearly twice the risk of developing dementia and other cognitive impairments compared to individuals without diabetes[2]. Both the quality and quantity of carbohydrate, often measured by GI and GL, influence the development of type 2 diabetes and directly impact post prandial glycemia, overall glycemic control, and the development of insulin resistance[3,4]. Because it is believed that glycemic control and insulin resistance may be mediating the relationship between diabetes and cognitive decline[5], it has been hypothesized that diets high in carbohydrate, particularly refined high-glycemic carbohydrate, may contribute to the cognitive decline observed in older ages[6].

Although the acute effects of carbohydrate ingestion on cognitive function have been well-documented in the literature[7,8], few prospective studies have observed the effect of chronic carbohydrate intake on cognitive decline. Cohort studies investigating associations between GL, a measure reflecting both carbohydrate quality and quantity, and cognitive function have reported conflicting results and possess significant methodological limitations such as small sample size, cross-sectional design, inadequate estimation of GL, or have represented only one race or sex[9-11]. The fact that most

previous studies have included only one race is particularly limiting because these studies have not been able to adequately address potential racial differences in this relationship. Given the growing body of literature reporting racial differences in the associations between insulin resistance and vascular disease[12-17], it is reasonable to hypothesize racial differences may also be present in the associations between carbohydrate intake and cognitive outcomes.

The objective of this study was to examine the associations between both quantity and quality of carbohydrate, incident cognitive impairment, and cognitive decline in 17,654 black and white participants throughout the continental United States from the REasons for Geographic And Racial Differences in Stroke (REGARDS) study. Our hypotheses were two-fold: 1) higher GI, GL, and available carbohydrate intake (CHO) would be associated with higher odds of incident cognitive impairment and larger declines in cognitive function; and 2) the strength of the association between GI, GL, and CHO would be larger in white participants compared to black participants.

Methods

Study Design and Data Collection

From 2003-2007, the REGARDS study recruited 30,239 black and white participants aged 45 years and older, dispersed throughout the continental United States, to investigate the reasons behind observed ethnic and regional disparities in stroke incidence and stroke mortality. To help achieve this aim, the study oversampled both black participants (approximately 42% of sample) and residents living in the southeast part of the United States known as the Stroke Belt (approximately 56% of sample).

Exclusion criteria included belonging to a race other than white or black, currently undergoing active treatment for cancer or another medical condition that could affect long-term study participation, nursing home residence, or the inability to communicate in English.

Data were collected in REGARDS using a combination of computer-based telephone interviewing, an in-home medical examination, and self-administered questionnaires. Participants were initially informed of the study via commercial mailing and were subsequently contacted by telephone. After verbal consent was given, information was collected on demographic characteristics, socioeconomic status, and medical history. Trained medical personnel then went to the participants' homes and completed a medical examination during which anthropometrics, blood pressure and ECG measurements, and blood and urine samples were collected. The medical personnel also left several questionnaires with the participants to complete and mail back to the REGARDS coordinating center. Written informed consent was obtained during this visit. Additionally, follow-up telephone interviews with participants occur every six months to collect information on medical events and other longitudinal data. A more detailed description of the methodology of the REGARDS study has been published previously[18]. The study was approved by all participating institutional review boards.

Cognitive Assessment

The cognitive assessment of REGARDS participants used in this analysis was administered over the telephone to achieve the collection of longitudinal cognitive data in the large, national distribution of study participants. Starting in December 2003, the Six-

Item Screener (SIS) was administered during the baseline telephone calls and in annual intervals thereafter. The SIS is a brief screening assessment that aims to identify participants with cognitive impairment[19]. It consists of three questions related to temporal orientation and a three item word recall, with scores ranging from zero to six. The following definition of incident cognitive impairment was utilized in these analyses: a participant with intact cognitive function at first SIS assessment (score of 5 or 6) shifting to impaired cognitive function on the most recent SIS assessment (score of 4 or less). This cutoff of scoring 4 or less on the SIS to define cognitive impairment has been validated in both black and white samples and found to have a sensitivity of 74% and a specificity of 80% when compared to a combined endpoint of clinically diagnosed dementia and mild cognitive impairment[19].

In addition to the SIS measurement, beginning in January 2006, a three-test battery of domain-specific assessments has been administered to REGARDS participants over the telephone every two years. The word list learning (WLL) and word list delayed recall (WLDR) assessments from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery[20] were utilized to measure decline in verbal learning and memory domains, respectively. To implement these assessments, the participants were given a set of three learning trials of a list of 10 words followed by a five minute delay that precedes a free recall trial. For the WLL, the sum of the scores from the three trials produces a score ranging from 0 to 30 that represents the participants' verbal learning performance. For the WLDR, the number of words that the participant could recall after the delay produces a score ranging from 0 to 10 that represents the participants' verbal memory. The third test included in the battery was the animal fluency test (AFT)[20], used

to measure executive function. This test asked participants to name as many animals as they could in one minute, yielding a score that reflects the number of valid responses.

Dietary Assessment

The Block98 Food Frequency Questionnaire (FFQ) was given to participants during the in-home medical examination and has been validated using multiple food records and in diverse populations[21-23]. The FFQ asks questions regarding frequency of consumption and portion size on 110 different food items to estimate usual dietary intake over the previous year. After completing the FFQ, participants mailed the completed forms back to the REGARDS Coordinating Center, which were subsequently sent to NutritionQuest (Berkeley, CA) for scoring and analysis. The three dietary exposures of interest in this analysis were GI, GL, and CHO.

The GI was developed by Jenkins et al.[24] in the early 1980's and functions as a system to rank foods according to the quality of carbohydrate the food contains. The GI of a particular food is determined by the post-prandial glucose response to a standard portion of that food relative to the glucose response following consumption of a control food (usually glucose or white bread)[25]. Values for commonly consumed foods that contain carbohydrate have been previously documented in the literature[26]. In our study, GI values using glucose as a control were assigned by NutritionQuest to each carbohydrate containing food item measured by the FFQ. The GI variable used in this analysis was calculated by taking the product of each food's assigned GI value and the grams of CHO per serving and multiplying this by each participant's average daily servings of each food. This value was summed for all foods and then divided by average

daily grams of CHO to yield a value representing the weighted average GI of the carbohydrates consumed by each participant. This calculation was performed by NutritionQuest and has been used in several epidemiologic studies in relation to chronic disease risk.[27]

Although GI functions as a qualitative measure of dietary carbohydrate, GL differs from GI by taking both carbohydrate quality and quantity into consideration[28]. A food's GL is calculated by multiplying its GI by the grams of CHO in a standard serving of that food and then dividing this value by 100. The GL variable used in this analysis was calculated by taking each food's individual GL value and multiplying it by each participant's average daily servings of each food, and then summing for all foods to yield a value representing the average daily total GL for each participant.

To estimate average daily CHO intake, total carbohydrate intake and dietary fiber intake were estimated from the Block98 FFQ at baseline. CHO was calculated by subtracting the dietary fiber from total carbohydrate intake. This value excludes dietary fiber because of the minimal blood glucose response following dietary fiber intake.

Covariate Assessment

Age, race, region, sex, income, and education were collected by self-report at the beginning of the study. The FFQ administered at baseline was used to estimate total energy intake. Height and weight were measured during the in-home examination and used to calculate body mass index (BMI). Physical activity, defined by exercise frequency, and smoking status were self-reported at baseline. History of heart disease was defined as self-reported myocardial infarction, coronary artery bypass graft, angioplasty,

stenting, or evidence of myocardial infarction from an ECG performed during the in-home examination. Participants were defined as hypertensive if systolic blood pressure was at or above 140 mmHg or diastolic blood pressure was at or above 90 mmHg or if they self-reported current medication use to control blood pressure. Diabetes status was defined as having a fasting glucose greater than or equal to 126 mg/dL or non-fasting blood glucose greater than or equal to 200 mg/dL or if the participant reported taking medication or insulin for the management of diabetes. Depressive symptoms were evaluated at baseline over the telephone using the Center for Epidemiological Studies – Depression (CESD) – 4 item version[29].

Statistical Analysis

Likelihood-ratio chi-squared tests and t-tests were used to calculate unadjusted means of sociodemographic characteristics by quintile of GI, GL, and CHO. To examine the relationship between quintiles of the dietary exposures and odds of incident cognitive impairment on the SIS, logistic regression was employed, and four models incrementally adding covariates were evaluated in this analysis. Model 1 included adjustment for age, race, sex, region of residence, total energy intake, and interval between most recent SIS assessment and baseline telephone interview. Model 2 adds adjustments for income and education, and model 3 includes adjustments for exercise frequency, body mass index, and smoking status. Finally, model 4 additionally adjusts for history of heart disease, hypertensive status, diabetes status, and depressive symptoms. Tests for linear trend across quintiles of dietary exposures were evaluated by including each exposure in

quintiles as a continuous, ordinal variable in each model. Racial interactions were examined in separate models for each dietary variable.

For REGARDS participants possessing at least two cognitive assessments on the domain-specific tests, repeated measures analysis was used to evaluate associations between of our continuous dietary exposures and rates of change in cognitive function. Using PROC MIXED in SAS 9.4 (Cary, North Carolina), we modeled the residual covariance structure to account for the correlation of each participant's cognitive measurements over time. Our dietary exposures were modeled continuously and evaluated in separate models. Associations between diet and rates of cognitive change were evaluated by examining the parameter estimate for the interaction between diet and time. To adjust for potential confounding, covariates were incrementally added to two models: Model 1 included adjustments for age, race, sex, region, income, education, and total energy intake. Model 2 added adjustments for exercise frequency, smoking status, body mass index, history of heart disease, hypertensive status, diabetes status, and depressive symptoms. Differences in the association by race were tested by including a three way interaction between race, diet, and time.

Results

Incident Cognitive Impairment

Of the 30,239 original REGARDS participants, this study excluded participants who did not return an FFQ, returned an incomplete FFQ, or returned an FFQ that yielded implausible energy intakes (n=8,603). We additionally excluded participants possessing any of the following criteria: less than two SIS assessments, cognitive impairment at

baseline, incident stroke during follow up or self-reported history of stroke at baseline, or lacking an in-home medical assessment. These exclusions resulted in a final analytic sample of 17,654 participants. Excluded participants were more likely than included participants to be older, male, black, less educated, and have lower income.

Descriptive statistics of participants included in the study are provided in Table 1. Compared to those in the lowest quintile of GI (Q1), participants in the highest quintile of GI (Q5) were more likely to be black, male, reside in stroke-belt, and have a lower income and education. Participants in the highest quintile of GL were slightly younger, more likely to be black, male, reside in stroke-belt, and have a lower income and education than participants in the lowest quintile of GL. Lastly, compared to participants in the lowest quintile of CHO intake, participants in the highest quintile of CHO intake were slightly younger, more likely to be male, reside in stroke-belt, and have a lower income.

Over a median follow up of 8.1 years, 1,564 of the 17,654 participants (~8.9%) developed incident cognitive impairment. Odds of incident cognitive impairment by quintile of GI, GL, and CHO are displayed in Table 2. After adjustments for demographic variables and total energy intake (Model 1), GI was not associated with incident cognitive impairment in our analyses (Q5 vs Q1: OR 1.10; 95% CI 0.92, 1.31; p for trend = 0.058). However, the highest quintiles of GL and CHO were associated with increased odds of incident cognitive impairment (GL - Q5 vs Q1: OR 1.48; 95% CI 1.12, 1.95; p for trend = 0.0025; CHO - Q5 vs Q1: OR 1.61; 95% CI 1.21, 2.14; p for trend = 0.0018). Additional adjustments for socioeconomic status, health behaviors, and comorbidities did not substantially alter the odds ratios for the associations between GI and incident cognitive

impairment (Q5 vs Q1: OR 1.08; 95% CI 0.90, 1.29; p for trend = 0.11). Similarly, the additional adjustments shown in models 2, 3, and 4 resulted in little change in odds ratios for GL and CHO, with higher quintiles of both variables remaining significantly associated with increased odds of incident cognitive impairment (GL - Q5 vs Q1: OR 1.53; 95% CI 1.15, 2.05; p for trend = 0.0030; CHO - Q5 vs Q1: OR 1.66; 95% CI 1.23, 2.24; p for trend = 0.0026).

The test for a racial interaction did not reach significance for any dietary exposure and incident cognitive impairment (p for interactions: GI = 0.33; GL = 0.41; CHO = 0.35). However, due to the *a priori* hypothesis, results stratified by race are presented in Table 3. Stratified analyses show that although no statistically significant racial differences were detected, there are statistically significant associations between GL, CHO, and incident cognitive impairment in white participants and weaker, non-significant but still positive associations in black participants.

Verbal learning, verbal memory, and executive function

Participants possessing at least two assessments of the domain-specific cognitive measures who were also cognitively intact at baseline and free of stroke were included in the analysis of the rates of change in the WLL, WLDR, and AFT assessments over a median follow up of 5.5 years. When examining the associations between GI, GL, and CHO with rates of cognitive change on the domain-specific assessments, no significant associations were observed (data not shown). However, a statistically significant three-way interaction between diet, race, and time was observed for both GL and CHO on verbal learning, as assessed by WLL. The results for the domain-specific assessments are

presented stratified by race in Table 3. The relationship between GL and change in verbal learning was significantly different between black and white participants (p for interaction: 0.012). For black participants, GL was associated with an increase in verbal learning over time in the fully adjusted model ($\beta = 0.0080$; $p = 0.021$). However, for white participants, GL was associated with a non-significant decline in verbal learning in the fully adjusted model ($\beta = -0.0025$; $p = 0.28$). Similarly, significant racial differences were detected in the relationships between CHO and change in verbal learning (p for interaction: 0.0028) and memory (p for interaction: 0.049). For black participants, CHO was associated with an increase in verbal learning ($\beta = 0.0055$; $p = 0.0045$) and memory ($\beta = 0.0018$; $p = 0.030$) in the fully adjusted model, while in white participants, CHO was associated with a non-significant decline in verbal learning ($\beta = -0.0015$; $p = 0.23$) and memory ($\beta = -0.00035$; $p = 0.55$).

Discussion

In a longitudinal analysis of 17,654 black and white participants aged 45 years or older, we found that GL and CHO were associated with higher odds of incident cognitive impairment, and that these associations were independent of socioeconomic status, health behaviors, and comorbidities that may also influence the risk of cognitive impairment. Additionally, our results suggest a potential racial difference where higher GL and CHO may be more detrimental to cognitive outcomes in white populations than black populations, but these results must be cautiously interpreted and further investigated in future studies.

Our results add to the remarkably low number of previous cohort studies that have examined the relationship between GL and cognitive function. In a cross-sectional study of 298 elderly Irish participants, Power et al. found that GL was associated with lower cognitive performance on the Mini-Mental State Examination (MMSE)[10]. A prospective study of 838 Swedish adults ≥ 50 years of age reported an association between GL and poorer overall perceptual speed and spatial ability but did not find an association with cognitive decline for those measures[11]. However, it is worth noting that this study was significantly limited by a poor estimation of GL using only five or six food items. Perhaps the best available literature to date took place in 1,514 women ≥ 65 years of age enrolled the Naples EPIC cohort. Using the Telephone Interview to evaluate Cognitive Status (TICS), Simeon et al. reported a negative association between GL at baseline and cognitive performance 14 years later[9]. Yet, this particular study did not collect cognitive data at baseline, precluding them from assessing incident cognitive impairment or a decline in cognitive function. To the best of our knowledge, our study represents the largest prospective investigation of GL and cognitive function and the first to include both white and black American participants.

It remains unclear through which specific mechanism diets high in GL and CHO may be influencing risk of cognitive impairment, although several hypotheses have been suggested previously in the literature. Chronic consumption of meals high in GL or CHO could lead to frequent elevated postprandial blood glucose levels, which have been associated with increased production of inflammatory cytokines and reactive oxygen species (ROS) in subjects with and without diabetes[30-32]. Accordingly, diets high in GL or CHO could contribute to cognitive impairment through both inflammatory and oxidative

stress mechanisms that have previously been implicated in neurodegeneration and alterations in Aβ and tau protein metabolism typically associated with Alzheimer's disease[33-35]. It is also conceivable that a dietary pattern high in GL or CHO may eventually result in the development of insulin resistance and hyperinsulinemia, which have been associated with cognitive decline in a number of populations[36-39]. Studies have suggested that chronic hyperinsulinemia and peripheral insulin resistance may decrease the transport of insulin across the blood-brain-barrier, reducing brain insulin levels and contributing to increased Aβ deposition, decreased energy and neurotransmitter availability, and reduced synaptic plasticity - all of which could negatively affect cognitive function and increase risk of cognitive impairment[40,41].

In this study, we detected small but significant differences in the associations between GL and CHO and rates of change in cognitive function between white and black participants. Further, although the tests for racial interactions between our measures of carbohydrate consumption and incident cognitive impairment were non-significant, stratified results in Table 3 show that higher GL and CHO were associated with increased incident cognitive impairment in white but not black participants. While the effect sizes are small, especially for the domain-specific analyses, it is plausible that carbohydrate intake could differentially affect the cognitive function of black and white individuals through disparate effects of insulin resistance. Several cohort studies have found racial differences in the associations between insulin resistance and blood pressure, carotid atherosclerosis, and incident stroke, collectively suggesting that insulin resistance may play a larger role in the development of cardiovascular disease in white individuals than black individuals[12-17]. Given the vascular contribution to cognitive decline[17] and the

relationship between dietary carbohydrate and insulin resistance, it is reasonable to suggest a racial difference may also exist in the role of carbohydrate intake, insulin resistance, and cognitive decline. Clearly, these results must be interpreted with caution, and future observational studies and clinical trials with diverse samples should further investigate potential racial differences in the associations between carbohydrate intake, insulin resistance, and cognitive decline.

The results of this study must be understood in light of its limitations. We found positive associations between GL, CHO, and incident cognitive impairment, but found only small, inconsistent associations with cognitive decline in the domain-specific measures assessing verbal learning, memory, and executive function. It is possible that REGARDS participants had already started to decline in cognitive function prior to enrollment in the study (median age at baseline: 64 years; range: 45-94 years), or that the median follow up of 5.5 years for the domain-specific measures is too short to detect meaningful changes. Another limitation is the potential inaccuracies resulting from our use of self-report diet data to estimate GL, GI, and CHO. Particularly in cognitive studies, there is some concern for recall bias when using the FFQ method, with the possibility that participants with poorer cognitive function may provide less accurate self-report diet data. However, we attempted to minimize this bias by excluding cognitively impaired participants at baseline.

In conclusion, in a large prospective study of black and white adults scattered throughout the United States, we found higher GL and CHO were associated with increased odds of incident cognitive impairment, and that the associations between carbohydrate consumption and cognitive function may differ in white and black

populations. Our results provide further evidence that dietary patterns lower in GL or CHO may be beneficial to cognitive health. However, further observational and clinical studies are needed to confirm findings and elucidate causal mechanisms.

References

1. U.S. Department of Health and Human Services. Aging Statistics: Administration on Aging (AoA). 2012.

2. Ott A, Stolk R, Van Harskamp F, Pols H, Hofman A, Breteler M. Diabetes mellitus and the risk of dementia The Rotterdam Study. *Neurology.* 1999;53(9):1937-1937.

3. Wolever T, Bolognesi C. Source and amount of carbohydrate affect postprandial glucose and insulin in normal subjects. *The Journal of Nutrition.* 1996;126(11):2798-2806.

4. Wolever T, Bolognesi C. Prediction of glucose and insulin responses of normal subjects after consuming mixed meals varying in energy, protein, fat, carbohydrate and glycemic index. *The Journal of Nutrition.* 1996;126(11):2807-2812.

5. Biessels G, Kappelle L. Increased risk of Alzheimer's disease in Type II diabetes: insulin resistance of the brain or insulin-induced amyloid pathology? *Biochemical Society Transactions.* 2005;33(5):1041-1044.

6. Kanoski SE, Davidson TL. Western diet consumption and cognitive impairment: links to hippocampal dysfunction and obesity. *Physiology & Behavior.* 2011;103(1):59-68.

7. Philippou E, Constantinou M. The influence of glycemic index on cognitive functioning: a systematic review of the evidence. *Advances in Nutrition.* 2014;5(2):119-130.

8. Gilsenan MB, de Bruin EA, Dye L. The influence of carbohydrate on cognitive performance: a critical evaluation from the perspective of glycaemic load. *British Journal of Nutrition.* 2009;101(07):941-949.

9. Simeon V, Chiodini P, Mattiello A, et al. Dietary glycemic load and risk of cognitive impairment in women: findings from the EPIC-Naples cohort. *European Journal of Epidemiology.* 2015;30(5):425-433.

10. Power SE, O'Connor EM, Ross RP, et al. Dietary glycaemic load associated with cognitive performance in elderly subjects. *European Journal of Nutrition.* 2015;54(4):557-568.

11. Seetharaman S, Andel R, McEvoy C, Aslan AKD, Finkel D, Pedersen NL. Blood glucose, diet-based glycemic load and cognitive aging among dementia-free older adults. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences.* 2015;70(4):471-479.

12. Saad MF, Lillioja S, Nyomba BL, et al. Racial differences in the relation between blood pressure and insulin resistance. *New England Journal of Medicine.* 1991;324(11):733-739.

13. Howard G, O'Leary DH, Zaccaro D, et al. Insulin sensitivity and atherosclerosis. The Insulin Resistance Atherosclerosis Study (IRAS) Investigators. *Circulation.* 1996;93(10):1809-1817.

14. Bertoni AG, Wong ND, Shea S, et al. Insulin Resistance, Metabolic Syndrome, and Subclinical Atherosclerosis The Multi-Ethnic Study of Atherosclerosis (MESA). *Diabetes Care.* 2007;30(11):2951-2956.

15. Howard G, Wagenknecht LE, Kernan WN, et al. Racial differences in the association of insulin resistance with stroke risk The REasons for Geographic And Racial Differences in Stroke (REGARDS) study. *Stroke.* 2014;45(8):2257-2262.

16. Rasmussen-Torvik LJ, Yatsuya H, Selvin E, Alonso A, Folsom AR. Demographic and cardiovascular risk factors modify association of fasting insulin with incident coronary heart disease and ischemic stroke (from the Atherosclerosis Risk In Communities Study). *The American Journal of Cardiology.* 2010;105(10):1420-1425.

17. Gorelick PB, Scuteri A, Black SE, et al. Vascular contributions to cognitive impairment and dementia a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2011;42(9):2672-2713.

18. Howard VJ, Cushman M, Pulley L, et al. The reasons for geographic and racial differences in stroke study: objectives and design. *Neuroepidemiology.* 2005;25(3):135-143.

19. Callahan CM, Unverzagt FW, Hui SL, Perkins AJ, Hendrie HC. Six-item screener to identify cognitive impairment among potential subjects for clinical research. *Medical Care.* 2002;40(9):771-781.

20. Welsh KA, Butters N, Mohs RC, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part V. A normative study of the neuropsychological battery. *Neurology.* 1994;44(4):609-614.

21. Boucher B, Cotterchio M, Kreiger N, Nadalin V, Block T, Block G. Validity and reliability of the Block98 food-frequency questionnaire in a sample of Canadian women. *Public Health Nutrition.* 2006;9(1):84-93.

22. Block G, Woods M, Potosky A, Clifford C. Validation of a self-administered diet history questionnaire using multiple diet records. *Journal of Clinical Epidemiology.* 1990;43(12):1327-1335.

23. Caan BJ, Slattery ML, Potter J, Quesenberry CP, Jr., Coates AO, Schaffer DM. Comparison of the Block and the Willett self-administered semiquantitative food frequency questionnaires with an interviewer-administered dietary history. *American Journal of Epidemiology.* 1998;148(12):1137-1147.

24. Jenkins D, Wolever T, Taylor RH, et al. Glycemic index of foods: a physiological basis for carbohydrate exchange. *American Journal of Clinical Nutrition.* 1981;34(3):362-366.

25. Ludwig DS. The glycemic index: physiological mechanisms relating to obesity, diabetes, and cardiovascular disease. *Journal of the American Medical Association.* 2002;287(18):2414-2423.

26. Foster-Powell K, Holt SH, Brand-Miller JC. International table of glycemic index and glycemic load values: 2002. *American Journal of Clinical Nutrition.* 2002;76(1):5-56.

27. Barclay AW, Petocz P, McMillan-Price J, et al. Glycemic index, glycemic load, and chronic disease risk—a meta-analysis of observational studies. *The American Journal of Clinical Nutrition.* 2008;87(3):627-637.

28. Liu S, Willett WC, Stampfer MJ, et al. A prospective study of dietary glycemic load, carbohydrate intake, and risk of coronary heart disease in US women. *American Journal of Clinical Nutrition.* 2000;71(6):1455-1461.

29. Kohout FJ, Berkman LF, Evans DA, Cornoni-Huntley J. Two shorter forms of the CES-D (Center for Epidemiological Studies Depression) depression symptoms index. *Journal of Aging and Health.* 1993;5(2):179-193.

30. Ceriello A, Bortolotti N, Crescentini A, et al. Antioxidant defences are reduced during the oral glucose tolerance test in normal and non-insulin-dependent diabetic subjects. *European Journal of Clinical Investigation.* 1998;28(4):329-333.

31. Esposito K, Nappo F, Marfella R, et al. Inflammatory cytokine concentrations are acutely increased by hyperglycemia in humans role of oxidative stress. *Circulation.* 2002;106(16):2067-2072.

32. Monnier L, Mas E, Ginet C, et al. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. *Journal of American Medical Association.* 2006;295(14):1681-1687.

33. Jankowsky JL, Patterson PH. Cytokine and growth factor involvement in long-term potentiation. *Molecular and Cellular Neuroscience.* 1999;14(4):273-286.

34. Lin MT, Beal MF. Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. *Nature.* 2006;443(7113):787-795.

35. Butterfield DA, Di Domenico F, Barone E. Elevated risk of type 2 diabetes for development of Alzheimer disease: a key role for oxidative stress in brain. *Biochimica et Biophysica Acta -Molecular Basis of Disease.* 2014;1842(9):1693-1706.

36. Geroldi C, Frisoni GB, Paolisso G, et al. Insulin resistance in cognitive impairment: the InCHIANTI study. *Archives of Neurology.* 2005;62(7):1067-1072.

37. Okereke OI, Kurth T, Pollak MN, Gaziano JM, Grodstein F. Fasting plasma insulin, C-peptide and cognitive change in older men without diabetes: results from the Physicians' Health Study II. *Neuroepidemiology.* 2010;34(4):200-207.

38. Van Oijen M, Okereke OI, Kang JH, et al. Fasting insulin levels and cognitive decline in older women without diabetes. *Neuroepidemiology.* 2008;30(3):174-179.

39. Young SE, Mainous AG, Carnemolla M. Hyperinsulinemia and cognitive decline in a middle-aged cohort. *Diabetes Care.* 2006;29(12):2688-2693.

40. Craft S. Insulin resistance syndrome and Alzheimer's disease: age-and obesity-related effects on memory, amyloid, and inflammation. *Neurobiology of Aging.* 2005;26(1):65-69.

41. Li L, Hölscher C. Common pathological processes in Alzheimer disease and type 2 diabetes: a review. *Brain Research Reviews.* 2007;56(2):384-402.

Table 1. Baseline characteristics by quintile of glycemic index, glycemic load, and available carbohydrate intake in the REasons for Geographic And Racial Differences in Stroke (REGARDS) cohort 2003-2015

	Glycemic Index		Glycemic Load		Available Carbohydrate	
	Q1	Q5	Q1	Q5	Q1	Q5
Age	64.3 (8.8)	63.8 (9.3)	64.1 (8.8)	63.1 (9.1)	64.1 (8.8)	63.1 (9.1)
Race						
Black	834 (23.6)	1378 (39.0)	1121 (31.8)	1277 (36.2)	1186 (33.6)	1258 (35.6)
White	2698 (76.4)	2153 (61.0)	2409 (68.2)	2253 (63.8)	2235 (66.4)	2273 (64.4)
Sex						
Male	1373 (38.9)	1622 (45.9)	981 (27.8)	1929 (54.7)	974 (27.6)	1912 (54.2)
Female	2159 (61.1)	1909 (54.1)	2549 (72.2)	1601 (45.4)	2557 (72.4)	1619 (45.9)
Region						
Stroke Belt	1074 (30.4)	1370 (38.8)	1136 (32.2)	1323 (37.5)	1156 (32.7)	1300 (36.8)
Stroke Buckle	727 (20.6)	930 (26.3)	836 (23.7)	779 (22.1)	864 (24.5)	752 (21.3)
Non-belt	1731 (49.0)	1231 (34.9)	1558 (44.1)	1428 (40.5)	1511 (42.8)	1479 (41.9)
Total energy intake (kcal)	1565 (625)	1768 (758)	1027 (327)	2661 (639)	1002 (295)	2674 (636)
Income						
< $20,000/yr	402 (11.4)	628 (17.8)	467 (13.2)	592 (16.8)	499 (14.1)	589 (16.7)
$20,000 - $34,999	703 (19.9)	938 (26.6)	798 (22.6)	864 (24.5)	817 (23.1)	849 (24.0)
$35,000 - $74,999	1137 (32.2)	1120 (31.7)	1083 (30.7)	1161 (32.9)	1066 (30.2)	1151 (32.6)
>$75,000	865 (24.5)	464 (13.1)	730 (20.7)	554 (15.7)	688 (19.5)	583 (16.5)
Refused	425 (12.0)	381 (10.8)	452 (12.8)	359 (10.2)	461 (13.1)	359 (10.2)
Education						
Less than high school	188 (5.3)	432 (12.2)	302 (8.6)	357 (10.1)	324 (9.2)	337 (9.6)
High school graduate	708 (20.1)	1066 (30.2)	876 (24.8)	929 (26.3)	926 (26.2)	913 (25.9)
Some college	984 (27.9)	966 (27.4)	1003 (28.4)	1006 (28.5)	1006 (28.5)	980 (27.8)
College graduate	1650 (46.7)	1066 (30.2)	1348 (38.2)	1237 (35.1)	1274 (36.1)	1300 (36.8)
Glycemic Index	47.0 (2.9)	58.5 (2.0)	50.6 (5.1)	54.9 (3.4)	51.6 (5.3)	54.2 (3.5)

Glycemic Load	74.6 (36.0)	116.4 (50.1)	47.6 (11.0)	170.4 (35.7)	48.2 (11.7)	169.4 (36.7)
Available carbohydrate (g)	157.6 (73.4)	199.0 (85.2)	94.1 (20.9)	311.0 (65.3)	92.9 (19.3)	312.6 (63.7)

Means and standard deviations are shown for continuous variables. Number of participants and row percentages are shown for categorical variables

Table 2. Odds of incident cognitive impairment by quintile of glycemic index, glycemic load, and available carbohydrate in the REasons for Geographic And Racial Differences in Stroke (REGARDS) cohort 2003-2015

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P_{Trend}
Glycemic Index						
events/total	284/3532	281/3532	316/3535	334/3524	349/3531	
Model 1	1	0.91 (0.76, 1.09)	0.99 (0.83, 1.18)	1.09 (0.92, 1.30)	1.10 (0.92, 1.31)	0.058
Model 2	1	0.89 (0.75, 1.07)	0.95 (0.80, 1.13)	1.04 (0.87, 1.24)	0.99 (0.84, 1.18)	0.46
Model 3	1	0.91 (0.76, 1.09)	1.00 (0.84, 1.19)	1.10 (0.92, 1.31)	1.06 (0.89, 1.27)	0.14
Model 4	1	0.92 (0.76, 1.11)	0.97 (0.81, 1.17)	1.10 (0.92, 1.32)	1.08 (0.90, 1.29)	0.11
Glycemic Load						
events/total	293/3530	300/3532	310/3531	333/3531	328/3530	
Model 1	1	0.97 (0.81, 1.16)	1.07 (0.88, 1.29)	1.26 (1.03, 1.56)	1.48 (1.12, 1.95)	0.0025
Model 2	1	0.97 (0.81, 1.16)	1.05 (0.87, 1.27)	1.22 (0.99, 1.51)	1.35 (1.02, 1.79)	0.014
Model 3	1	0.97 (0.81, 1.17)	1.05 (0.87, 1.28)	1.23 (1.00, 1.53)	1.42 (1.07, 1.88)	0.0086
Model 4	1	1.00 (0.83, 1.20)	1.05 (0.86, 1.28)	1.28 (1.03, 1.60)	1.53 (1.15, 2.05)	0.0030
Available Carbohydrate						
events/total	300/3531	303/3533	303/3531	325/3528	333/3531	
Model 1	1	0.99 (0.83, 1.18)	1.08 (0.89, 1.31)	1.26 (1.02, 1.57)	1.61 (1.21, 2.14)	0.0018
Model 2	1	1.00 (0.83, 1.19)	1.09 (0.90, 1.32)	1.26 (1.01, 1.56)	1.53 (1.15, 2.04)	0.0039
Model 3	1	1.00 (0.89, 1.31)	1.08 (0.89, 1.31)	1.24 (1.00, 1.55)	1.59 (1.19, 2.13)	0.0038
Model 4	1	1.01 (0.84, 1.22)	1.09 (0.89, 1.33)	1.26 (1.00, 1.57)	1.66 (1.23, 2.24)	0.0026

Model 1 is adjusted for age, race, sex, region, total energy intake, and interval between most recent cognitive assessment and baseline telephone interview. Model 2 adds adjustment for income and education. Model 3 adds adjustment for physical activity, body mass index, and smoking status. Model 4 adds adjustment for history of heart disease, hypertensive status, diabetes status, and depressive symptoms.

Table 3. Odds of incident cognitive impairment by quintile of glycemic index, glycemic load, and available carbohydrate stratified by race in the REasons for Geographic And Racial Differences in Stroke (REGARDS) cohort 2003-2015

		Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P_{trend}	P_{int}
Glycemic Index	Black	1	0.85 (0.61, 1.17)	0.91 (0.66, 1.24)	1.02 (0.75, 1.39)	0.92 (0.68, 1.25)	0.90	0.33
	White	1	0.98 (0.78, 1.23)	1.03 (0.82, 1.29)	1.18 (0.94, 1.48)	1.23 (0.98, 1.56)	0.024	
Glycemic Load	Black	1	0.81 (0.59, 1.10)	1.00 (0.72, 1.38)	1.11 (0.78, 1.57)	1.21 (0.76, 1.92)	0.24	0.41
	White	1	1.14 (0.90, 1.45)	1.12 (0.87, 1.45)	1.48 (1.11, 1.97)	1.87 (1.27, 2.73)	0.0017	
Available Carbohydrate	Black	1	0.90 (0.66, 1.22)	1.06 (0.77, 1.47)	1.12 (0.77, 1.59)	1.33 (0.83, 2.12)	0.22	0.35
	White	1	1.09 (0.86, 1.38)	1.13 (0.87, 1.47)	1.40 (1.04, 1.88)	1.98 (1.34, 2.93)	0.0021	

All models adjusted for age, sex, region, total energy intake, interval between most recent cognitive assessment and baseline telephone interview, income, education, physical activity, body mass index, smoking status, history of heart disease, hypertensive status, diabetes status, and depressive symptoms.

Table 4. Rates of change in domain-specific cognitive assessments and associations with glycemic index, glycemic load, and carbohydrate intake by race in the REasons for Geographic And Racial Differences in Stroke cohort 2003-2015

		Glycemic Index (per 10 units)			Glycemic Load (per 10 units)			Available Carbohydrate (per 10 grams)		
	Cognitive Assessment	**β**	**Std. Error**	**p value**	**β**	**Std. Error**	**p value**	**β**	**Std. Error**	**p value**
	Word List Learning									
Black	Model 1	-0.075	0.039	0.058	0.0078	0.0034	0.022	0.0052	0.0019	0.0057
	Model 2	-0.091	0.041	0.028	0.0080	0.0035	0.021	0.0055	0.0019	0.0045
White	Model 1	0.0028	0.023	0.90	-0.0022	0.0022	0.32	-0.0014	0.0013	0.25
	Model 2	0.0012	0.023	0.96	-0.0024	0.0023	0.29	-0.0015	0.0013	0.23
	Delayed Recall									
Black	Model 1	-0.020	0.017	0.25	0.0025	0.0015	0.085	0.0017	0.00081	0.034
	Model 2	-0.022	0.018	0.23	0.0027	0.0015	0.080	0.0018	0.00084	0.030
White	Model 1	-0.011	0.010	0.28	-0.00034	0.00097	0.73	-0.00016	0.00055	0.77
	Model 2	-0.011	0.010	0.27	-0.00054	0.0010	0.59	-0.00035	0.00057	0.55
	Animal Fluency									
Black	Model 1	-0.030	0.035	0.39	-0.0018	0.0030	0.54	-0.00085	0.0016	0.60
	Model 2	-0.036	0.036	0.32	-0.0018	0.0031	0.57	-0.00074	0.0017	0.66
White	Model 1	0.041	0.023	0.074	0.00087	0.0023	0.71	-0.000049	0.0013	0.97
	Model 2	0.029	0.024	0.22	0.00086	0.0024	0.72	0.00013	0.0014	0.92

Model 1 is adjusted for age, sex, region, income, education, and total energy intake. Model 2 includes additional adjustment for smoking status, exercise frequency, body mass index, history of heart disease, hypertensive status, diabetes status, and depressive symptoms.

Interactions by race for glycemic load and word list learning (p=0.012) and available carbohydrate intake and word list learning (p=0.0028) were statistically significant. The interaction by race for available carbohydrate and delayed recall was also statistically significant (p=0.049).

INSULIN RESISTANCE, COGNITIVE IMPAIRMENT, AND COGNITIVE DECLINE IN THE REASONS FOR GEOGRAPHIC AND DIFFERENCES IN STROKE (REGARDS) COHORT

by

KEITH E. PEARSON II, BARBARA A. GOWER, VIRGINIA G. WADLEY, GEORGE HOWARD, PAULA CHANDLER-LANEY, LESLIE A. MCCLURE, JAMES M. SHIKANY, FRED W.UNVERZAGT, SUZANNE E. JUDD

Prepared for submission to Neurology

Format adapted for dissertation

Abstract

Insulin resistance has been previously associated with cognitive decline, but potential racial differences in this relationship have not been adequately investigated. The objective of this study was to evaluate the associations between insulin resistance, cognitive impairment, and cognitive decline and test whether racial differences are present in a cohort of black and white Americans aged 45 years and older. Insulin resistance was assessed using the homeostasis model assessment of insulin resistance (HOMA-IR). Incident cognitive impairment was defined using the Six Item Screener, and changes in verbal learning, memory, and executive function performance were measured using the word list learning, delayed recall, and animal fluency test, respectively. Logistic regression and repeated measures analysis were used to analyze the data. This analysis included 16,046 participants free of stroke and cognitive impairment at baseline. A total of 1,402 cases of incident cognitive impairment were observed over a median follow up of 8.1 years. In the fully adjusted model, participants in the highest quintile of insulin resistance had lower odds of incident cognitive impairment than those in the lowest quintile (OR: 0.75; 95% CI: 0.61, 0.93; p for trend: 0.022). These relationships also did not significantly differ by race, but it appeared that the inverse association between insulin resistance and incident cognitive impairment was predominantly present in black participants. Further investigations are warranted to continue to elucidate the relationship between race, insulin resistance, and cognitive impairment.

Introduction

It is estimated that 5.4 million Americans are currently living with Alzheimer's disease[1], with many more elderly Americans possessing other dementias and cognitive impairments. As this number is expected to rapidly grow in the coming decades, discovering modifiable risk factors to aid in the preservation of cognitive function has become a major public health concern[2]. Over the past two decades, a number of studies have demonstrated that insulin resistance may be an important modifiable risk factor in the pathophysiology of cognitive decline[3,4]. Chronic peripheral insulin resistance and hyperinsulinemia may contribute to cognitive decline through a number of mechanisms, including reduced insulin transport into the brain and increased brain levels of Aβ, tau phosphorylation, inflammation, oxidative stress, and mitochondrial dysfunction[5,6]. Insulin resistance has been previously associated with cognitive decline in several cohorts, but many of these studies took place in relatively small samples or in samples only representing one race[7-10].

The fact that prospective studies are lacking in large, racially diverse cohorts is especially concerning given the growing body of evidence proposing that insulin resistance may play a larger role in the development of chronic disease in white populations than in black populations. Previous studies have reported black-white differences in the associations between insulin resistance and blood pressure[11], carotid atherosclerosis[12,13], and incident stroke[14,15], collectively suggesting that insulin resistance may contribute more to cardiovascular disease pathology in white individuals than black individuals. Given the vascular pathway in cognitive decline[16], it is reasonable to

hypothesize that there may also be racial differences in the association between insulin resistance and cognitive decline.

The objective of this study was two-fold: 1) to evaluate the associations between insulin resistance, incident cognitive impairment, and cognitive decline in a large, prospective cohort of black and white American adults aged 45 or older, and 2) to determine if black-white differences exist in the associations between insulin resistance, incident cognitive impairment, and cognitive decline. Our hypotheses were that higher levels of insulin resistance would be associated with higher odds of incident cognitive impairment and larger declines in cognitive function and that the strength of these associations would be larger in white participants compared to black participants.

Methods

Study Design

The REasons for Geographic And Racial Differences in Stroke (REGARDS) study consists of 30,239 black and white participants aged 45 and older living throughout the continental United States. The recruitment of study participants took place from 2003-2007 and was designed to oversample black Americans and residents of the stroke belt to help elucidate disparities in stroke incidence and stroke mortality. Study exclusion criteria included: belonging to a race other than white or black, currently undergoing active treatment for cancer or another medical condition that could affect long-term study participation, nursing home residence, or the inability to communicate in English.

Computer-assisted telephone interviewing and an in-home medical examination were the primary methods of data collection in the REGARDS study. An initial telephone

call with the participants collected information about demographics, socioeconomic status, cognitive function, and medical history. An in-home medical examination conducted by a trained medical professional followed and collected anthropometric data, blood and urine samples, and blood pressure and ECG measurements. At the conclusion of the in-home assessment, several self-administer questionnaires were left with the participant to complete and return by mail to the REGARDS coordinating center. Participant follow up has occurred primarily through telephone interviews in six month intervals to obtain further cognitive assessments and additional medical information. Further details of the REGARDS study design have been published previously[17]. All participants provided written informed consent and the study was approved by the institutional review boards of all participating universities.

Assessment of Insulin Resistance

Fasting blood samples were obtained during the in-home examination by trained medical personnel. Samples were shipped on ice overnight to the University of Vermont for analysis. Fasting insulin was measured using the Roche Elecsys 2010 system (Roche Diagnostics, Indianapolis, IN), which utilizes an electrochemiluminescence immunoassay method. Insulin resistance was then calculated using the homeostatic model assessment of insulin resistance (HOMA-IR) = (insulin [µU/mL] x glucose [mg/dL])/405).[18]

Assessment of Cognitive Function

Beginning in December 2003, the Six-Item Screener (SIS) was administered to participants during the baseline telephone calls and subsequently on an annual basis. The

SIS is a brief screening assessment that consists of three questions related to temporal orientation and a three item word recall, aiming to identify participants with cognitive impairment[19]. With scores ranging from zero to six, the following definition of incident cognitive impairment was utilized in these analyses: a participant with intact cognitive function at first SIS assessment (score of 5 or 6) shifting to impaired cognitive function on the most recent SIS assessment (score of 4 or less). This definition of cognitive impairment via the SIS has been validated in both black and white samples and found to have a sensitivity of 74% and a specificity of 80% when compared to a combined endpoint of clinically diagnosed dementia and mild cognitive impairment[19].

In January 2006, a three-test battery of domain-specific assessments was administered by telephone to participants and has subsequently been administered in two year intervals. Verbal learning and memory were assessed using the word list learning (WLL) and word list delayed recall (WLDR) tests[20]. Three learning trials of a 10-word list were administered followed by a five minute delay that preceded a recall trial of the 10 words. The WLL reflects participant verbal learning and is the sum of the scores from the three learning trials with scores ranging from 0 to 30. The WLDR represents participant verbal memory, with scores ranging from 0 to 10 depending on the number of words a participant could recall after the delay. The Animal Fluency Test[20], measuring participant executive function, asked participants to name as many animals as they could in one minute and yielded a score that reflects the number of valid responses.

Assessment of Covariates

Age, race, region, sex, income, and education were collected by self-report at the beginning of the study. Height and weight were measured during the in-home examination and used to calculate body mass index (BMI). Physical activity, defined by exercise frequency, and smoking status were self-reported at baseline. History of heart disease was defined as self-reported myocardial infarction, coronary artery bypass graft, angioplasty, stenting, or evidence of myocardial infarction from an ECG performed during the in-home examination. Participants were defined as hypertensive if systolic blood pressure was at or above 140 mmHg or diastolic blood pressure was at or above 90 mmHg or if they self-reported current medication use to control blood pressure. Depressive symptoms were evaluated at baseline over the telephone using the Center for Epidemiological Studies – Depression (CESD) – 4 item version[21].

Statistical analysis

Likelihood-ratio chi-squared tests and t-tests were used to calculate unadjusted means of sociodemographic characteristics and other cognitive risk factors by quintile of insulin resistance. We utilized logistic regression to evaluate the associations between quintiles of insulin resistance and odds of incident cognitive impairment. Four models incrementally adding covariates were modeled in this analysis. Model 1 included adjustment for age, race, sex, region, and interval between most recent cognitive assessment and baseline telephone interview. Model 2 included additional adjustment for income and education. Model 3 added adjustment for exercise frequency, body mass index, and smoking status. Finally, Model 4 included adjustments for history of heart

disease, hypertensive status, and depressive symptoms. Tests for linear trend across quintiles of insulin resistance were evaluated by including insulin resistance in quintiles as a continuous, ordinal variable in each model, and racial interactions were also included in separate models to examine potential racial differences in these associations.

For REGARDS participants possessing at least two cognitive assessments on one of the domain-specific tests, repeated measures analysis was used to evaluate associations between insulin resistance and rates of cognitive change. Using PROC MIXED in SAS 9.4 (Cary, North Carolina), we modeled the residual covariance structure to account for the correlation of each participant's cognitive measurements over time. Insulin resistance had a right-skewed distribution in our cohort and was natural log transformed for these analyses. All further references to insulin resistance as a continuous variable refer to this natural log transformed variable unless otherwise specified. Associations between insulin resistance and rates of cognitive change were evaluated by examining the interaction between insulin resistance and time. To adjust for potential confounding, covariates were incrementally added to two models: Model 1 included adjustments for age, race, sex, region, income, and education. Model 2 added adjustments for exercise frequency, smoking status, body mass index, history of heart disease, hypertensive status, and depressive symptoms. Differences in the association by race were tested by including a three way interaction between race, insulin resistance, and time.

Results

Analytic Cohort

The prospective analysis of insulin resistance and incident cognitive impairment included 16,046 participants. Of the 30,239 participants in the full REGARDS cohort, 56

participants were excluded due to anomalous data, 6,716 had did not have insulin measured (insulin was not measured on participants self-reporting diabetes), 1,542 had fewer than 2 cognitive assessments, 1,682 had cognitive impairment at baseline, 1,346 had history of stroke or incident stroke during follow up, 950 had fasting glucose >125 mg/dL or reported taking diabetic medication or insulin, 86 were missing blood glucose data, 1,804 participants were not fasting for blood draw, and 11 participants did not have an in-home medical examination. Participants with at least two assessments of the word list learning (n=9,931), word list delayed recall (n=9,771), or animal fluency test (n=10,977) were included in the longitudinal analyses of the domain-specific measures.

Demographic characteristics

Descriptive statistics of participants who were included in this analysis are provided in Table 1. Compared to participants in the lowest quintile (Q1) of insulin resistance, participants in the highest quintile (Q5) of insulin resistance tended to be younger, black, male, reside in the stroke-belt, and have a lower income and education level.

Incident cognitive impairment

Over a median follow up of 8.1 years, 1,402 of the 16,046 participants (approximately 8.7%) developed incident cognitive impairment. Comparing participants in the highest quintile to the lowest, higher levels of insulin resistance were associated with lower odds of incident cognitive impairment on the SIS (Model 1 of Table 2: OR 0.81; 95% CI 0.67, 0.97; p for trend = 0.051). This association remained significant after

further adjustment for socioeconomic status, health behaviors, and other comorbidities (Models 2, 3 and 4 of Table 2). Tests for an interaction by race were not statistically significant (p=0.15 in Model 1 and p=0.21 in Model 4) but did reveal a significant association between insulin resistance and lower odds of incident cognitive impairment in blacks but not whites (Black, Q5 vs Q1: OR 0.66; 95% CI 0.48, 0.91; p for trend = 0.038; White, Q5 vs Q1: OR 0.82; 95% CI 0.61, 1.11; p for trend = 0.15). Odds of incident cognitive impairment by quintile of insulin resistance stratified by race are presented in Table 3.

Rates of change in domain-specific cognitive measures

Associations between insulin resistance and changes in cognitive performance on the domain-specific tests are presented in Table 4. No associations were observed between insulin resistance and change in performance on the WLL ($\beta = 0.014$; $p = 0.25$) or the WLDR ($\beta = -0.0022$; $p = 0.68$) assessments. However, we did observe a positive association between insulin resistance and change in performance on the AFT ($\beta = 0.027$; $p = 0.024$). These associations did not differ by race, however, we are presenting stratified results as our a priori hypothesis included examining racial differences (Table 5).

Discussion

Utilizing a large prospective cohort of 16,046 black and white participants, this analysis investigated the relationships between insulin resistance, cognitive impairment, and cognitive function, and observed several associations that did not support our original

hypotheses. Higher levels of insulin resistance were associated with lower odds of incident cognitive impairment and a small increase in executive function over time. Although these relationships also did not significantly differ by race, it appeared that the inverse association between insulin resistance and incident cognitive impairment was primarily present in black participants.

Our original hypothesis was that insulin resistance would be associated with poorer cognitive outcomes. The results of this analysis do not provide evidence to support this hypothesis and differ from the findings reported by a number of other cohort studies. The Atherosclerosis Risk in Communities study reported that insulin resistance (HOMA-IR) was associated with a greater decline in measures of verbal learning and executive function in 7,148 participants over 6 years of follow up[10]. Additionally, the Nurse's Health Study and the Physician's Health Study II reported that higher fasting insulin was associated with greater cognitive decline[8,9]. However, other cohort studies have likewise reported a null association between insulin resistance and poorer cognitive outcomes. In a cross-sectional analysis of the Rotterdam Study, Stolk et al. discovered an association between postload insulin and cognitive performance on the MMSE but failed to find an association with insulin resistance. Additionally, the Uppsala Longitudinal Study of Adult Men found no association with insulin sensitivity, measured by hyperinsulinemic clamp, and risk of dementia or cognitive impairment in 2,322 Swedish men over 50 years old[22].

In our analyses of the SIS assessments, we found that higher levels of insulin resistance were associated with lower odds of incident cognitive impairment in the fully adjusted model (Model 4 of Table 2). We do not have a plausible biological mechanism

for the observed association in our analyses, and instead hypothesize that our findings may be due to a number of factors. Selective attrition is particularly a concern in longitudinal studies of cognitive decline because of the strong associations between cognitive impairment and attrition after study enrollment[23]. Participants who develop cognitive impairment or dementia are more likely to refuse continued study participation, move residence, and be lost to follow up, all of which could preclude these individuals from participating in our cognitive assessment[24]. Still, for selective attrition to bias the results from this analysis, the reason behind the attrition must be influenced by both insulin resistance and cognitive function[23], a statement that lacks supportive data. It is possible, however, that competing risks may at least partially explain the observed associations[25]. Individuals with higher levels of insulin resistance are at a higher risk of mortality from a number of chronic diseases, including cardiovascular disease and cancer, reducing the opportunity for these individuals to develop cognitive impairment.

In addition to the results in the full sample, we also did not find a statistically significant racial difference between insulin resistance and our cognitive outcomes, although the inverse association did appear to be predominantly present in black participants. In a previous cross-sectional study including both black and white older adults, Arvanitakis et al. reported an association between diabetes and semantic memory that also did not differ between black and white individuals[26]. Thus, it is possible that no white-black differences exist in the association between insulin resistance and cognitive function. However, the lack of a racial difference in our study may also be influenced by the use of HOMA-IR to measure insulin resistance in our participants. Previous studies have reported racial differences in the ability of HOMA-IR to predict insulin sensitivity

as measured by the hyperinsulinemic clamp method[27], typically recognized as the gold-standard method of assessing insulin sensitivity. Utilizing the clamp technique is expensive and not plausible for use in large epidemiological studies, underscoring the importance of the development and validation of additional methods of estimating insulin resistance appropriate for use in large samples with more than one race. Many of the previous investigations of insulin resistance and cognitive decline have utilized samples containing primarily white participants. To our knowledge, this study is the first to directly examine racial differences between insulin resistance and cognitive decline, and future investigations are warranted to continue to elucidate the relationship between race, insulin resistance, and cognitive decline.

Although the results of this study must be interpreted in light of the aforementioned limitations, this study is strengthened by a very large sample size and vast number of black participants in the REGARDS study that enables an adequately powered evaluation of racial differences. In a sample of 16,046 black and white participants scattered throughout the continental United States, we found an inverse association between insulin resistance and incident cognitive impairment that did not significantly differ by race, but did appear to be present predominantly in black participants. Additionally, we observed a significant positive association between insulin resistance and change in executive function over time that did not appear to differ by race. Future studies are particularly necessary to further characterize the importance of race in the relationship between insulin resistance and cognitive function.

References

1. Alzheimer's Association. 2016 Alzheimer's disease facts and figures. *Alzheimer's & Dementia.* 2016;12(4):459-509.

2. World Health Organization. *Dementia: A Public Health Priority.* World Health Organization; 2012.

3. de la Monte SM, Wands JR. Review of insulin and insulin-like growth factor expression, signaling, and malfunction in the central nervous system: relevance to Alzheimer's disease. *Journal of Alzheimer's Disease.* 2005;7(1):45-61.

4. Watson GS, Craft S. The role of insulin resistance in the pathogenesis of Alzheimer's disease. *CNS Drugs.* 2003;17(1):27-45.

5. Talbot K, Wang H-Y, Kazi H, et al. Demonstrated brain insulin resistance in Alzheimer's disease patients is associated with IGF-1 resistance, IRS-1 dysregulation, and cognitive decline. *Journal of Clinical Investigation.* 2012;122(4):1316-1338.

6. Craft S. Insulin resistance and Alzheimer's disease pathogenesis: potential mechanisms and implications for treatment. *Current Alzheimer Research.* 2007;4(2):147-152.

7. Geroldi C, Frisoni GB, Paolisso G, et al. Insulin resistance in cognitive impairment: the InCHIANTI study. *Archives of Neurology.* 2005;62(7):1067-1072.

8. Okereke OI, Kurth T, Pollak MN, Gaziano JM, Grodstein F. Fasting plasma insulin, C-peptide and cognitive change in older men without diabetes: results from the Physicians' Health Study II. *Neuroepidemiology.* 2010;34(4):200-207.

9. Van Oijen M, Okereke OI, Kang JH, et al. Fasting insulin levels and cognitive decline in older women without diabetes. *Neuroepidemiology.* 2008;30(3):174-179.

10. Young SE, Mainous AG, Carnemolla M. Hyperinsulinemia and cognitive decline in a middle-aged cohort. *Diabetes Care.* 2006;29(12):2688-2693.

11. Saad MF, Lillioja S, Nyomba BL, et al. Racial differences in the relation between blood pressure and insulin resistance. *New England Journal of Medicine.* 1991;324(11):733-739.

12. Howard G, O'Leary DH, Zaccaro D, et al. Insulin sensitivity and atherosclerosis. The Insulin Resistance Atherosclerosis Study (IRAS) Investigators. *Circulation.* 1996;93(10):1809-1817.

13. Bertoni AG, Wong ND, Shea S, et al. Insulin Resistance, Metabolic Syndrome, and Subclinical Atherosclerosis The Multi-Ethnic Study of Atherosclerosis (MESA). *Diabetes Care.* 2007;30(11):2951-2956.

14. Howard G, Wagenknecht LE, Kernan WN, et al. Racial Differences in the Association of Insulin Resistance With Stroke Risk The REasons for Geographic And Racial Differences in Stroke (REGARDS) Study. *Stroke.* 2014;45(8):2257-2262.

15. Rasmussen-Torvik LJ, Yatsuya H, Selvin E, Alonso A, Folsom AR. Demographic and cardiovascular risk factors modify association of fasting insulin with incident coronary heart disease and ischemic stroke (from the Atherosclerosis Risk In Communities Study). *American Journal of Cardiology.* 2010;105(10):1420-1425.

16. Gorelick PB, Scuteri A, Black SE, et al. Vascular contributions to cognitive impairment and dementia a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2011;42(9):2672-2713.

17. Howard VJ, Cushman M, Pulley L, et al. The reasons for geographic and racial differences in stroke study: objectives and design. *Neuroepidemiology.* 2005;25(3):135-143.

18. Matthews D, Hosker J, Rudenski A, Naylor B, Treacher D, Turner R. Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia.* 1985;28(7):412-419.

19. Callahan CM, Unverzagt FW, Hui SL, Perkins AJ, Hendrie HC. Six-item screener to identify cognitive impairment among potential subjects for clinical research. *Medical Care.* 2002;40(9):771-781.

20. Welsh KA, Butters N, Mohs RC, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part V. A normative study of the neuropsychological battery. *Neurology.* 1994;44(4):609-614.

21. Kohout FJ, Berkman LF, Evans DA, Cornoni-Huntley J. Two shorter forms of the CES-D depression symptoms index. *Journal of Aging and Health.* 1993;5(2):179-193.

22. Rönnemaa E, Zethelius B, Sundelöf J, et al. Impaired insulin secretion increases the risk of Alzheimer disease. *Neurology.* 2008;71(14):1065-1071.

23. Weuve J, Tchetgen EJT, Glymour MM, et al. Accounting for bias due to selective attrition: the example of smoking and cognitive decline. *Epidemiology.* 2012;23(1):119.

24. Matthews FE, Chatfield M, Brayne C. An investigation of whether factors associated with short-term attrition change or persist over ten years: data from the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS). *BMC Public Health.* 2006;6(1):1.

25. Schrijvers EM, Witteman J, Sijbrands E, Hofman A, Koudstaal P, Breteler M. Insulin metabolism and the risk of Alzheimer disease The Rotterdam Study. *Neurology.* 2010;75(22):1982-1987.

26. Arvanitakis Z, Bennett DA, Wilson RS, Barnes LL. Diabetes and cognitive systems in older black and white persons. *Alzheimer Disease and Associated Disorders.* 2010;24(1):37.

27. Pisprasert V, Ingram KH, Lopez-Davila MF, Munoz AJ, Garvey WT. Limitations in the Use of Indices Using Glucose and Insulin Levels to Predict Insulin Sensitivity Impact of race and sex and superiority of the indices derived from oral glucose tolerance test in African Americans. *Diabetes Care.* 2013;36(4):845-853.

Table 1. Baseline characteristics by quintile of homeostatic model assessment of insulin resistance in the REasons for Geographic And Racial Differences in Stroke (REGARDS) cohort 2003-2015

	Insulin Resistance					
	Q1	Q2	Q3	Q4	Q5	p value
Age	64.0 (9.9)	64.5 (9.5)	64.1 (9.3)	63.6 (9.0)	62.3 (8.5)	<0.0001
Race						<0.0001
Black	788 (24.6)	884 (27.8)	1029 (32.1)	1192 (37.2)	1412 (44.0)	
White	2421 (75.4)	2325 (72.5)	2181 (67.9)	2017 (62.9)	1797 (56.0)	
Sex						0.0030
Male	1293 (40.3)	1361 (42.4)	1330 (41.4)	1406 (43.8)	1430 (44.6)	
Female	1916 (59.7)	1848 (57.6)	1880 (58.6)	1803 (56.2)	1779 (55.4)	
Region						<0.0001
Stroke Belt	1007 (31.4)	1049 (32.7)	1094 (34.1)	1107 (34.5)	1181 (36.8)	
Stroke Buckle	652 (20.3)	661 (20.6)	707 (22.0)	762 (23.8)	710 (22.1)	
Non-belt	1550 (48.3)	1499 (43.9)	1409 (43.9)	1340 (41.8)	1318 (41.1)	
Income						<0.0001
< $20,000/yr	339 (10.6)	392 (12.2)	422 (13.2)	430 (13.4)	506 (15.8)	
$20,000 - $34,999	671 (20.9)	696 (21.7)	744 (23.2)	749 (23.3)	730 (20.3)	
$35,000 - $74,999	1025 (31.94)	1046 (32.6)	1066 (33.2)	1106 (34.5)	1024 (31.9)	
>$75,000	753 (23.5)	667 (20.8)	611 (19.0)	567 (17.7)	606 (18.9)	
Refused	421 (13.1)	408 (12.7)	367 (11.4)	357 (11.1)	343 (10.7)	
Education						<0.0001
Less than high school	216 (6.7)	223 (7.0)	252 (7.9)	300 (9.4)	314 (9.8)	
High school graduate	685 (21.4)	761 (23.7)	789 (24.6)	811 (25.3)	860 (26.8)	
Some college	793 (24.7)	841 (26.2)	896 (27.9)	885 (27.6)	943 (29.4)	
College graduate	1514 (47.2)	1382 (43.1)	1272 (39.6)	1212 (37.8)	1092 (34.0)	
HOMA-IR	0.81 (0.22)	1.44 (0.17)	2.09 (0.22)	3.09 (0.39)	6.63 (4.1)	<0.0001

Fasting insulin (μU/mL)	3.9 (1.1)	6.6 (1.0)	9.3 (1.3)	13.2 (2.0)	26.3 (15.0)	<0.0001
Fasting glucose (mg/dL)	85.0 (8.71)	89.5 (8.6)	92.2 (9.0)	95.4 (9.5)	101.6 (10.6)	<0.0001

Means and standard deviations are shown for continuous variables. Number of participants and row percentages are shown for categorical variables. HOMA-IR = homeostatic model assessment of insulin resistance. HOMA-IR represents the original non-transformed continuous variable in this table.

Table 2. Odds of incident cognitive impairment by quintile of homeostatic model assessment of insulin resistance in the REasons for Geographic And Racial Differences in Stroke (REGARDS) cohort 2003-2015

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	p trend
HOMA-IR						
events/total	306/3209	287/3209	295/3210	280/3209	234/3209	
Model 1	1	0.92 (0.77, 1.09)	0.95 (0.80, 1.14)	0.92 (0.77, 1.10)	0.81 (0.67, 0.97)	0.051
Model 2	1	0.91 (0.76, 1.09)	0.94 (0.79, 1.12)	0.89 (0.75, 1.07)	0.77 (0.64, 0.93)	0.012
Model 3	1	0.90 (0.75, 1.09)	0.92 (0.77, 1.11)	0.88 (0.73, 1.07)	0.77 (0.62, 0.95)	0.025
Model 4	1	0.89 (0.74, 1.06)	0.93 (0.77, 1.12)	0.87 (0.72, 1.06)	0.75 (0.61, 0.93)	0.022

Model 1 is adjusted for age, race, sex, region, and interval between most recent cognitive assessment and baseline telephone interview. Model 2 adds adjustment for income and education. Model 3 adds adjustment for physical activity, body mass index, and smoking status. Model 4 adds adjustment for history of heart disease, hypertensive status, and depressive symptoms.

Table 3. Odds of incident cognitive impairment by quintile of homeostatic model assessment of insulin resistance stratified by race in the REasons for Geographic and Racial Differences in Stroke (REGARDS) cohort 2003-2015

			Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	p trend
HOMA-IR	Blacks	events/total	124/788	106/884	131/1029	132/1192	114/1412	
		Model 1	1	0.79 (0.59, 1.06)	0.93 (0.70, 1.23)	0.84 (0.64, 1.12)	0.65 (0.49, 0.87)	0.012
		Model 2	1	0.81 (0.60, 1.09)	0.94 (0.71, 1.25)	0.86 (0.65, 1.14)	0.64 (0.48, 0.85)	0.0083
		Model 3	1	0.81 (0.60, 1.09)	0.94 (0.70, 1.27)	0.88 (0.66, 1.19)	0.67 (0.49,0.92)	0.043
		Model 4	1	0.80 (0.59, 1.08)	0.96 (0.71, 1.29)	0.87 (0.65, 1.18)	0.66 (0.48, 0.91)	0.038
	Whites	events/total	182/2421	181/2325	164/2181	148/2017	120/1797	
		Model 1	1	0.99 (0.79, 1.24)	0.96 (0.77, 1.21)	0.97 (0.77, 1.22)	0.95 (0.74, 1.23)	0.67
		Model 2	1	0.97 (0.77, 1.21)	0.93 (0.74, 1.17)	0.91 (0.72, 1.15)	0.90 (0.70, 1.15)	0.31
		Model 3	1	0.95 (0.76, 1.20)	0.90 (0.71, 1.14)	0.85 (0.65, 1.10)	0.84 (0.63, 1.12)	0.15
		Model 4	1	0.93 (0.74, 1.17)	0.90 (0.71, 1.15)	0.84 (0.65, 1.10)	0.82 (0.61, 1.11)	0.15

Model 1 is adjusted for age, sex, region, and interval between most recent cognitive assessment and baseline telephone interview. Model 2 adds adjustment for income and education. Model 3 adds adjustment for physical activity, body mass index, and smoking status. Model 4 adds adjustment for history of heart disease, hypertensive status, and depressive symptoms.

No statistically significant racial interactions were observed (p=0.15 for Model 1 and p=0.21 for Model 4).

Table 4. The associations between homeostatic model assessment of insulin resistance and rates of change in domain-specific cognitive assessments in the REasons for Geographic And Racial Differences in Stroke (REGARDS) cohort 2003-2015

		Word List Learning			Word List Delayed Recall			Animal Fluency		
		β	**Std. Error**	**p value**	**β**	**Std. Error**	**p value**	**β**	**Std. Error**	**p value**
Ln (IR)	Model 1	0.014	0.012	0.24	-0.0017	0.0054	0.75	0.022	0.012	0.057
	Model 2	0.014	0.012	0.25	-0.0022	0.0054	0.68	0.027	0.012	0.024

Model 1 is adjusted for age, race, sex, region, income, and education. Model 2 includes additional adjustment for smoking status, exercise frequency, body mass index, history of heart disease, hypertensive status, and depressive symptoms.

Table 5. The associations between homeostatic model assessment of insulin resistance and rates of change in domain-specific cognitive assessments by race in the REasons for Geographic And Racial Differences in Stroke (REGARDS) cohort 2003-2015

			Word List Learning			Word List Delayed Recall			Animal Fluency		
			β	Std. Error	p value	β	Std. Error	p value	β	Std. Error	p value
Ln (IR)	Black	Model 1	0.013	0.023	0.56	-0.0029	0.010	0.78	0.029	0.020	0.14
		Model 2	0.013	0.023	0.58	-0.0036	0.011	0.73	0.033	0.020	0.10
	White	Model 1	0.014	0.015	0.33	-0.00042	0.0064	0.95	0.0082	0.015	0.57
		Model 2	0.015	0.015	0.31	-0.00031	0.0064	0.96	0.013	0.015	0.39

Model 1 is adjusted for age, sex, region, income, and education. Model 2 includes additional adjustment for smoking status, exercise frequency, body mass index, history of heart disease, hypertensive status, and depressive symptoms.

No statistically significant racial interactions were detected for the Word List Learning (p=0.97), Word List Delayed Recall (p=0.83), or the Animal Fluency Test (p=0.33).

GENERAL DISCUSSION

Using a large cohort of black and white American adults aged 45 and order, we conducted three studies to investigate the impact of dietary patterns, carbohydrate consumption, and insulin resistance on cognitive outcomes. Results from the studies showed that a plant-based dietary pattern and a dietary pattern high in green leafy vegetables and alcohol intake were associated with more favorable cognitive outcomes, while a dietary pattern containing foods typical of a Southern diet was associated with lower cognitive performance. Additionally, diets higher in GL and CHO were associated with poorer cognitive outcomes, with some evidence that this relationship may differ by race. Finally, the associations between insulin resistance and cognitive outcomes were less clear, with results suggesting that higher levels of insulin resistance may be associated with lower odds of cognitive impairment, particularly in black participants.

The objective of Aim 1 of this dissertation sought to evaluate the role of dietary patterns on cognitive impairment and cognitive performance. Using dietary patterns derived by PCA, we were able to identify three dietary patterns that were associated with our cognitive outcomes: the plant-based, alcohol/salads, and Southern dietary patterns. Both the plant-based dietary pattern and the alcohol/salads dietary pattern appeared to be fairly consistent in their associations with favorable cognitive outcomes. The plant-based dietary pattern was associated with higher cognitive performance on the assessments of verbal learning and memory, and greater consumption of the alcohol/salads dietary pattern was associated with lower odds of incident cognitive impairment and higher performance on assessments of verbal learning, memory, and executive function. These

two dietary patterns both loaded highly on multiple types of vegetables. The plant-based pattern consisted of high intakes of cruciferous, dark yellow, green leafy, and other types of vegetables, and the alcohol/salads pattern consisted of high intakes of green leafy vegetables and tomatoes. Greater consumption of these two dietary patterns likely results in a high intake of several antioxidants that are commonly found in these vegetables. Oxidative stress has been implicated in the pathology of cognitive decline[60], and it is possible that the plant-based and alcohol/salads patterns could improve antioxidant status and protect against oxidative damage in the brain[16].

The plant-based pattern also loaded highly in fish consumption, which has been associated with favorable cognitive outcomes in many observational studies[6-10]. The ω-3 fatty acids found in fatty fish such as salmon, trout, and tuna may possess anti-inflammatory and cardiovascular benefits that could partially contribute to the associations observed in our study[9,10]. Unique to the alcohol/salads pattern was the high factor loadings for alcohol-containing beverages: wine, beer, and liquor. Several cohort studies have indicated that moderate alcohol consumption is associated with lower risk of Alzheimer's disease and other dementias as well as higher cognitive function[61-65]. Notably, most versions of the Mediterranean diet – the dietary pattern with the most evidence for protection against cognitive decline and dementia[21-23] – gives higher scores for moderate alcohol consumption and lower scores for abstinence from alcohol[66]. The cardiovascular benefits of moderate alcohol consumption, such as increased HDL, have been hypothesized to play a role in the observed cognitive benefits[61,65], but the antioxidant effects of the flavonoids found in red wine may also be contributing to the associations[67]. Further, moderate alcohol consumption may also be a marker for higher

socioeconomic status, which itself has a strong positive influence on cognitive status[68]. This is particularly relevant to the alcohol/salads pattern from Aim 1 considering the results of a previously published study in the REGARDS cohort, where we found that participants with higher income and education were between 1.5 and 2 times as likely as participants with lower income and education to be high consumers of this dietary pattern[69]. Although all of the associations between the alcohol/salads pattern and cognitive outcomes in Aim 1 remained significant after adjustment for both income and education, we cannot dismiss the potential for residual confounding involving unmeasured socioeconomic constructs.

A Southern dietary pattern consisting of high factor loadings for fried foods, processed meats, and sugar sweetened beverages was associated with lower performance on assessments of verbal learning, memory, and executive function. This dietary pattern was associated with higher odds of incident cognitive impairment in the model adjusted for demographics only, but the point estimates were attenuated after further adjustment for socioeconomic status. Another study by Akbaraly et al. similarly found an attenuation of associations between dietary patterns and cognitive function after adjusting for education[26], further emphasizing the strong influence of socioeconomic status in dietary patterns. This Southern dietary pattern has additionally been associated with incident stroke[70] and coronary heart disease[71] in the REGARDS study, and other cohorts have derived similar "processed foods" or "Western" dietary patterns that have been associated with decreased cognitive function[72].

Aim 2 of this dissertation similarly sought to evaluate the associations between several measures of dietary carbohydrate consumption (GI, GL, and CHO) and incident

cognitive impairment and cognitive decline. We found that GL and CHO were associated with increased odds of incident cognitive impairment and that these associations may differ by race. The finding that carbohydrate consumption was related to poorer cognitive outcomes is consistent with the associations observed with the Southern dietary pattern in Aim 2. The Southern pattern had high loadings of refined grains, white bread, soda, and other sugar sweetened beverages, likely contributing to a high GL and CHO intake for participants who were high consumers of this pattern. Initially we hypothesized that insulin resistance may be mediating the negative associations between GL, CHO and cognitive outcomes. However, aim 3 of this dissertation did not provide evidence to support this hypothesis. If not by insulin resistance, it is possible that the elevated postprandial blood glucose following meals high in GL or CHO could be contributing to cognitive impairment through inflammatory and oxidative stress mechanisms[73-75].

The public health implications of the dietary findings in Aims 1 and 2 are significant. With the population of elderly Americans growing at a rapid pace, the interest in dietary interventions to prevent or delay cognitive decline continues to increase as well. The results from Aims 1 and 2 from this dissertation, in conjunction with other observational and randomized trials, collectively suggest that an individual's dietary pattern can impact their cognitive health as he or she ages. The dietary patterns associated with higher cognitive performance and lower cognitive impairment in our study consisted of high consumption of vegetables, fruits, fish, beans, nuts, and alcoholic beverages – all food items that are commonly associated with the Mediterranean diet [20]. The Mediterranean diet has been attributed cognitive benefits for decades, and recent clinical trials have demonstrated that Mediterranean diets supplemented with nuts or extra virgin

olive oil may improve cognitive function[76]. Based on our results from Aim 2, we hypothesize that a lower carbohydrate Mediterranean diet may provide even more benefits to cognitive health than the traditional Mediterranean diet. In a randomized study of 259 overweight diabetic adults, a lower carbohydrate Mediterranean diet improved cardiovascular risk factors and glycemic control more than the traditional Mediterranean diet and the American Diabetic Association diet[77]. Given the relationship between cardiovascular disease risk factors, glycemic control, and cognition, future randomized trials evaluating the effects of lower carbohydrate Mediterranean diets on cognitive function could be informative for dietary interventions seeking to preserve cognitive health in older ages.

The need for randomized, controlled dietary intervention studies is underscored by the discordance in the results of observational studies compared to clinical studies examining diet and cognitive function. Similar to the findings in this dissertation, the large majority of studies reporting the beneficial effects of fruits and vegetables, fish/fish oil, and moderate alcohol consumption have been observational in design and thus cannot determine causality or easily elucidate mechanisms. Clinical studies have mainly focused on providing participants with dietary antioxidant or ω-3 fatty acid supplementation and have not shown consistent results[78]. The state of the dietary pattern literature is similar, with the majority of evidence coming from large epidemiologic cohorts. Conducting large interventions targeting dietary change with any amount of follow up is time-consuming, labor-intensive, and very expensive but will be necessary to truly gain valuable insight into the effects of dietary patterns on cognitive health.

There are a number of clinical studies that have evaluated the effects of GL and CHO of cognitive function[39,40]. However, nearly all of these studies examined the acute effects of consuming carbohydrate or a carbohydrate-containing meal, which provides little information on the chronic effects of carbohydrate intake on cognitive function over time. Brinkworth et al. evaluated the effects of both low carbohydrate and low fat dietary interventions on cognitive function after one year of intervention and found no differences in cognitive performance between the two diets[79]. However, this study was done in a relatively young group of participants (mean age = 50 years). Further, it is reasonable to propose that the detrimental effects of diets high in GL and CHO on cognitive function accumulate over decades and may require longer follow up to observe significant changes in cognition. Although the Block98 FFQ used in our study was designed to assess dietary intake only over the previous year, we believe that the dietary patterns observed in Aims 1 and 2 likely reflect dietary habits that participants have practiced for the majority of their adult lives.

In Aim 2 of this dissertation, we hypothesized that diets higher in GL and CHO may contribute to poorer cognitive health through insulin resistance. In Aim 3, we hypothesized that insulin resistance would be associated with increased cognitive impairment and faster cognitive declines. However, we were not able to provide evidence supporting this hypothesis, and instead found that higher insulin resistance was associated with lower odds of cognitive impairment and increases in executive function over time. Other mechanisms may explain the observed associations between carbohydrate and cognitive impairment. As mentioned previously in this discussion, it is possible that GL and CHO may contribute to poorer cognitive outcomes through oxidative stress and

inflammation generated from frequent post-prandial hyperglycemia following meals high in GL or CHO[73-75]. However, despite the lack of association in our study, it is still possible that insulin resistance may be associated with poorer cognitive outcomes. With a follow up of over 8 years, it is reasonable to suggest that competing risks may at least partially explain the observed inverse association in this analysis[80]. Individuals with higher levels of insulin resistance are at a higher risk of mortality from a number of chronic diseases, including cardiovascular disease[81] and cancer[82,83], reducing the opportunity for these individuals to develop cognitive impairment. It is also possible that participants in our study in the highest quintile of HOMA-IR were more likely to develop type 2 diabetes during follow up and receive treatment that could result in improved glycemic control and preserved cognitive function[84]. Both of these scenarios would bias our point estimates towards the null, and in profound cases, could result in an inverse association.

One of our original hypotheses was that the associations between carbohydrate intake, insulin resistance, and cognitive outcomes would be stronger in white participants than in black participants. Although not statistically significant, the associations in Aim 2 between GL, CHO, and incident cognitive impairment appeared to be stronger in white participants. Additionally, GL and CHO was associated with an increase in verbal learning over time in blacks but was non-significantly associated with a decline in verbal learning in whites. In total, the results from Aim 2 provided evidence in support of our original hypothesis. In Aim 3, we did not observe a significant racial interaction, but the inverse association between insulin resistance and incident cognitive impairment appeared to be predominantly present in black participants. We do not have a plausible

biological mechanism through which insulin resistance may be protective of cognitive impairment in black but not white individuals. Therefore, it is important to interpret the results of this analysis with caution. Previous studies have noted racial differences in the ability of HOMA-IR to predict insulin sensitivity as measured by the hyperinsulinemic clamp[85], emphasizing the necessity to develop additional tools to assess insulin resistance in large, racially diverse cohorts to further elucidate this relationship.

Despite these limitations, our study represents a novel insight into the relationship between carbohydrate consumption, insulin resistance, and cognitive outcomes – topics that have been extensively studied in predominantly white samples[86]. Further investigations to help better understand potential racial differences are needed. If causal mechanisms are confirmed between carbohydrate consumption, insulin resistance, and cognitive decline, a proper understanding of racial differences in these risk factors could help target the sub-populations that may benefit most from interventions[58]. In conclusion, this dissertation demonstrated that dietary patterns consisting of vegetables and alcohol intake were associated with more favorable cognitive outcomes, while dietary patterns high in GL, CHO, and fried and processed foods typical of a Southern dietary pattern were associated with less favorable cognitive outcomes. Insulin resistance appeared to be inversely associated with cognitive impairment, especially in black participants. Further studies are necessary to confirm associations and determine causal mechanisms in the relationships between diet, race, insulin resistance, and cognitive health.

LIST OF REFERENCES

1. Nelson PT. Graying of America. *Journal of Extension.* 1987;25(4).

2. Ortman JM, Velkoff VA, Hogan H. An aging nation: the older population in the United States. *Washington, DC: US Census Bureau.* 2014:25-1140.

3. World Health Organization. *Dementia: A Public Health Priority.* World Health Organization; 2012.

4. Alzheimer's Association. 2016 Alzheimer's disease facts and figures. *Alzheimer's & Dementia.* 2016;12(4):459-509.

5. Hurd MD, Martorell P, Delavande A, Mullen KJ, Langa KM. Monetary costs of dementia in the United States. *New England Journal of Medicine.* 2013;368(14):1326-1334.

6. Morris MC, Evans DA, Tangney CC, Bienias JL, Wilson RS. Fish consumption and cognitive decline with age in a large community study. *Archives of Neurology.* 2005;62(12):1849-1853.

7. Kalmijn Sv, Van Boxtel M, Ocke M, Verschuren W, Kromhout D, Launer L. Dietary intake of fatty acids and fish in relation to cognitive performance at middle age. *Neurology.* 2004;62(2):275-280.

8. Dangour A, Allen E, Elbourne D, Fletcher A, Richards M, Uauy R. Fish consumption and cognitive function among older people in the UK: baseline data from the OPAL study. *Journal of Nutrition, Health and Aging.* 2009;13(3):198-202.

9. Barberger-Gateau P, Letenneur L, Deschamps V, Pérès K, Dartigues J-F, Renaud S. Fish, meat, and risk of dementia: cohort study. *British Medical Journal.* 2002;325(7370):932-933.

10. van Gelder BM, Tijhuis M, Kalmijn S, Kromhout D. Fish consumption, n− 3 fatty acids, and subsequent 5-y cognitive decline in elderly men: the Zutphen Elderly Study. *American Journal of Clinical Nutrition.* 2007;85(4):1142-1147.

11. Innis SM. Dietary (n-3) fatty acids and brain development. *Journal of Nutrition.* 2007;137(4):855-859.

12. Simopoulos AP. Omega-3 fatty acids in health and disease and in growth and development. *American Journal of Clinical Nutrition.* 1991;54(3):438-463.

13. Kang JH, Ascherio A, Grodstein F. Fruit and vegetable consumption and cognitive decline in aging women. *Annals of Neurology.* 2005;57(5):713-720.

14. Roberts RO, Geda YE, Cerhan JR, et al. Vegetables, unsaturated fats, moderate alcohol intake, and mild cognitive impairment. *Dementia and Geriatric Cognitive Disorders.* 2010;29(5):413-423.

15. Loef M, Walach H. Fruit, vegetables and prevention of cognitive decline or dementia: a systematic review of cohort studies. *Journal of Nutrition, Health & Aging.* 2012;16(7):626-630.

16. Polidori MC, Pratico D, Mangialasche F, et al. High fruit and vegetable intake is positively correlated with antioxidant status and cognitive performance in healthy subjects. *Journal of Alzheimer's Disease.* 2009;17(4):921-927.

17. Crichton GE, Bryan J, Murphy KJ. Dietary antioxidants, cognitive function and dementia-a systematic review. *Plant Foods for Human Nutrition.* 2013;68(3):279-292.

18. Hu FB. Dietary pattern analysis: a new direction in nutritional epidemiology. *Current Opinion in Lipidology.* 2002;13(1):3-9.

19. Newby P, Tucker KL. Empirically derived eating patterns using factor or cluster analysis: a review. *Nutrition Reviews.* 2004;62(5):177-203.

20. Trichopoulou A, Kouris-Blazos A, Wahlqvist ML, et al. Diet and overall survival in elderly people. *British Medical Journal.* 1995;311(7018):1457-1460.

21. Psaltopoulou T, Sergentanis TN, Panagiotakos DB, Sergentanis IN, Kosti R, Scarmeas N. Mediterranean diet, stroke, cognitive impairment, and depression: A meta-analysis. *Annals of Neurology.* 2013;74(4):580-591.

22. Lourida I, Soni M, Thompson-Coon J, et al. Mediterranean diet, cognitive function, and dementia: a systematic review. *Epidemiology.* 2013;24(4):479-489.

23. Panza F, Solfrizzi V, Colacicco A, et al. Mediterranean diet and cognitive decline. *Public Health Nutrition.* 2004;7(07):959-963.

24. Morris MC, Tangney CC, Wang Y, et al. MIND diet slows cognitive decline with aging. *Alzheimer's & Dementia.* 2015.

25. Morris MC, Tangney CC, Wang Y, Sacks FM, Bennett DA, Aggarwal NT. MIND diet associated with reduced incidence of Alzheimer's disease. *Alzheimer's & Dementia.* 2015.

26. Akbaraly TN, Singh-Manoux A, Marmot MG, Brunner EJ. Education attenuates the association between dietary patterns and cognition. *Dementia and Geriatric Cognitive Disorders.* 2009;27(2):147-154.

27. Kesse-Guyot E, Andreeva VA, Jeandel C, Ferry M, Hercberg S, Galan P. A healthy dietary pattern at midlife is associated with subsequent cognitive performance. *Journal of Nutrition.* 2012;142(5):909-915.

28. Ashby-Mitchell K, Peeters A, Anstey KJ. Role of dietary pattern analysis in determining cognitive status in elderly Australian adults. *Nutrients.* 2015;7(2):1052-1067.

29. Kim J, Yu A, Choi BY, et al. Dietary patterns and cognitive function in Korean older adults. *European Journal of Nutrition.* 2015;54(2):309-318.

30. Sugawara N, Yasui-Furukori N, Umeda T, et al. Relationship between dietary patterns and cognitive function in a community-dwelling population in Japan. *Asia-Pacific Journal of Public Health.* 2015;27(2):NP2651-NP2660.

31. Shakersain B, Santoni G, Larsson SC, et al. Prudent diet may attenuate the adverse effects of Western diet on cognitive decline. *Alzheimer's & Dementia.* 2015.

32. Qin B, Adair LS, Plassman BL, et al. Dietary Patterns and Cognitive Decline Among Chinese Older Adults. *Epidemiology.* 2015;26(5):758-768.

33. Ott A, Stolk R, Van Harskamp F, Pols H, Hofman A, Breteler M. Diabetes mellitus and the risk of dementia The Rotterdam Study. *Neurology.* 1999;53(9):1937-1937.

34. Wolever T, Bolognesi C. Source and amount of carbohydrate affect postprandial glucose and insulin in normal subjects. *Journal of Nutrition.* 1996;126(11):2798-2806.

35. Wolever T, Bolognesi C. Prediction of glucose and insulin responses of normal subjects after consuming mixed meals varying in energy, protein, fat, carbohydrate and glycemic index. *Journal of Nutrition.* 1996;126(11):2807-2812.

36. Ludwig DS. The glycemic index: physiological mechanisms relating to obesity, diabetes, and cardiovascular disease. *Journal of the American Medical Association.* 2002;287(18):2414-2423.

37. Sheard NF, Clark NG, Brand-Miller JC, et al. Dietary carbohydrate (Amount and Type) in the prevention and management of diabetes a statement by the American diabetes association. *Diabetes Care.* 2004;27(9):2266-2271.

38. Salmerón J, Ascherio A, Rimm EB, et al. Dietary fiber, glycemic load, and risk of NIDDM in men. *Diabetes Care.* 1997;20(4):545-550.

39. Philippou E, Constantinou M. The influence of glycemic index on cognitive functioning: a systematic review of the evidence. *Advances in Nutrition.* 2014;5(2):119-130.

40. Gilsenan MB, de Bruin EA, Dye L. The influence of carbohydrate on cognitive performance: a critical evaluation from the perspective of glycaemic load. *British Journal of Nutrition.* 2009;101(07):941-949.

41. Kanoski SE, Davidson TL. Western diet consumption and cognitive impairment: links to hippocampal dysfunction and obesity. *Physiology & Behavior.* 2011;103(1):59-68.

42. Simeon V, Chiodini P, Mattiello A, et al. Dietary glycemic load and risk of cognitive impairment in women: findings from the EPIC-Naples cohort. *European Journal of Epidemiology.* 2015;30(5):425-433.

43. Seetharaman S, Andel R, McEvoy C, Aslan AKD, Finkel D, Pedersen NL. Blood glucose, diet-based glycemic load and cognitive aging among dementia-free older adults. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences.* 2015;70(4):471-479.

44. Power SE, O'Connor EM, Ross RP, et al. Dietary glycaemic load associated with cognitive performance in elderly subjects. *European Journal of Nutrition.* 2015;54(4):557-568.

45. Craft S. Insulin resistance syndrome and Alzheimer's disease: age-and obesity-related effects on memory, amyloid, and inflammation. *Neurobiology of Aging.* 2005;26(1):65-69.

46. Neumann KF, Rojo L, Navarrete LP, Farías G, Reyes P, Maccioni RB. Insulin resistance and Alzheimer's disease: molecular links & clinical implications. *Current Alzheimer Research.* 2008;5(5):438-447.

47. Cholerton B, Baker LD, Craft S. Insulin resistance and pathological brain ageing. *Diabetic Medicine.* 2011;28(12):1463-1475.

48. Talbot K, Wang H-Y, Kazi H, et al. Demonstrated brain insulin resistance in Alzheimer's disease patients is associated with IGF-1 resistance, IRS-1 dysregulation, and cognitive decline. *Journal of Clinical Investigation.* 2012;122(4):1316-1338.

49. Craft S. Insulin resistance and Alzheimer's disease pathogenesis: potential mechanisms and implications for treatment. *Current Alzheimer Research.* 2007;4(2):147-152.

50. Geroldi C, Frisoni GB, Paolisso G, et al. Insulin resistance in cognitive impairment: the InCHIANTI study. *Archives of Neurology.* 2005;62(7):1067-1072.

51. Okereke OI, Kurth T, Pollak MN, Gaziano JM, Grodstein F. Fasting plasma insulin, C-peptide and cognitive change in older men without diabetes: results from the Physicians' Health Study II. *Neuroepidemiology.* 2010;34(4):200-207.

52. Van Oijen M, Okereke OI, Kang JH, et al. Fasting insulin levels and cognitive decline in older women without diabetes. *Neuroepidemiology.* 2008;30(3):174-179.

53. Young SE, Mainous AG, Carnemolla M. Hyperinsulinemia and cognitive decline in a middle-aged cohort. *Diabetes Care.* 2006;29(12):2688-2693.

54. Saad MF, Lillioja S, Nyomba BL, et al. Racial differences in the relation between blood pressure and insulin resistance. *New England Journal of Medicine.* 1991;324(11):733-739.

55. Howard G, O'Leary DH, Zaccaro D, et al. Insulin sensitivity and atherosclerosis. The Insulin Resistance Atherosclerosis Study (IRAS) Investigators. *Circulation.* 1996;93(10):1809-1817.

56. Bertoni AG, Wong ND, Shea S, et al. Insulin Resistance, Metabolic Syndrome, and Subclinical Atherosclerosis The Multi-Ethnic Study of Atherosclerosis (MESA). *Diabetes Care.* 2007;30(11):2951-2956.

57. Howard G, Wagenknecht LE, Kernan WN, et al. Racial Differences in the Association of Insulin Resistance With Stroke Risk The REasons for Geographic And Racial Differences in Stroke (REGARDS) Study. *Stroke.* 2014;45(8):2257-2262.

58. Rasmussen-Torvik LJ, Yatsuya H, Selvin E, Alonso A, Folsom AR. Demographic and cardiovascular risk factors modify association of fasting insulin with incident coronary heart disease and ischemic stroke (from the Atherosclerosis Risk In Communities Study). *American Journal of Cardiology.* 2010;105(10):1420-1425.

59. Gorelick PB, Scuteri A, Black SE, et al. Vascular contributions to cognitive impairment and dementia a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2011;42(9):2672-2713.

60. Lin MT, Beal MF. Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. *Nature.* 2006;443(7113):787-795.

61. Stampfer MJ, Kang JH, Chen J, Cherry R, Grodstein F. Effects of moderate alcohol consumption on cognitive function in women. *New England Journal of Medicine.* 2005;352(3):245-253.

62. Lang I, Wallace RB, Huppert FA, Melzer D. Moderate alcohol consumption in older adults is associated with better cognition and well-being than abstinence. *Age and Ageing.* 2007;36(3):256-261.

63. Hendrie HC, Gao S, Hall KS, Hui SL, Unverzagt FW. The relationship between alcohol consumption, cognitive performance, and daily functioning in an urban sample of older black Americans. *Journal of the American Geriatrics Society.* 1996;44(10):1158-1165.

64. McGuire LC, Ajani UA, Ford ES. Cognitive functioning in late life: the impact of moderate alcohol consumption. *Annals of epidemiology.* 2007;17(2):93-99.

65. Peters R, Peters J, Warner J, Beckett N, Bulpitt C. Alcohol, dementia and cognitive decline in the elderly: a systematic review. *Age and Ageing.* 2008;37(5):505-512.

66. Scarmeas N, Stern Y, Tang MX, Mayeux R, Luchsinger JA. Mediterranean diet and risk for Alzheimer's disease. *Annals of Neurology.* 2006;59(6):912-921.

67. Commenges D, Scotet V, Renaud S, Jacqmin-Gadda H, Barberger-Gateau P, Dartigues JF. Intake of flavonoids and risk of dementia. *European Journal of Epidemiology.* 2000;16(4):357-363.

68. Nurk E, Refsum H, Drevon CA, et al. Intake of flavonoid-rich wine, tea, and chocolate by elderly men and women is associated with better cognitive test performance. *Journal of Nutrition.* 2009;139(1):120-127.

69. Kell K, Judd S, Pearson K, Shikany J, Fernández J. Associations between socio-economic status and dietary patterns in US black and white adults. *British Journal of Nutrition.* 2015;113(11):1792-1799.

70. Judd SE, Gutierrez OM, Newby PK, et al. Dietary patterns are associated with incident stroke and contribute to excess risk of stroke in black Americans. *Stroke.* 2013;44(12):3305-3311.

71. Shikany JM, Safford MM, Newby P, Durant RW, Brown TM, Judd SE. Southern dietary pattern is associated with hazard of acute coronary heart disease in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study. *Circulation.* 2015:CIRCULATIONAHA. 114.014421.

72. Torres SJ, Lautenschlager NT, Wattanapenpaiboon N, et al. Dietary patterns are associated with cognition among older people with mild cognitive impairment. *Nutrients.* 2012;4(11):1542-1551.

73. Ceriello A, Bortolotti N, Crescentini A, et al. Antioxidant defences are reduced during the oral glucose tolerance test in normal and non-insulin-dependent diabetic subjects. *European Journal of Clinical Investigation.* 1998;28(4):329-333.

74. Esposito K, Nappo F, Marfella R, et al. Inflammatory cytokine concentrations are acutely increased by hyperglycemia in humans role of oxidative stress. *Circulation.* 2002;106(16):2067-2072.

75. Monnier L, Mas E, Ginet C, et al. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. *Journal of the American Medical Association.* 2006;295(14):1681-1687.

76. Martínez-Lapiscina EH, Clavero P, Toledo E, et al. Mediterranean diet improves cognition: the PREDIMED-NAVARRA randomised trial. *Journal of Neurology, Neurosurgery & Psychiatry.* 2013;84(12):1318-1325.

77. Elhayany A, Lustman A, Abel R, Attal-Singer J, Vinker S. A low carbohydrate Mediterranean diet improves cardiovascular risk factors and diabetes control among overweight patients with type 2 diabetes mellitus: a 1-year prospective randomized intervention study. *Diabetes, Obesity and Metabolism.* 2010;12(3):204-209.

78. Otaegui-Arrazola A, Amiano P, Elbusto A, Urdaneta E, Martínez-Lage P. Diet, cognition, and Alzheimer's disease: food for thought. *European Journal of Nutrition.* 2014;53(1):1-23.

79. Brinkworth GD, Buckley JD, Noakes M, Clifton PM, Wilson CJ. Long-term effects of a very low-carbohydrate diet and a low-fat diet on mood and cognitive function. *Archives of Internal Medicine.* 2009;169(20):1873-1880.

80. Schrijvers EM, Witteman J, Sijbrands E, Hofman A, Koudstaal P, Breteler M. Insulin metabolism and the risk of Alzheimer disease The Rotterdam Study. *Neurology.* 2010;75(22):1982-1987.

81. Isomaa B, Almgren P, Tuomi T, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care.* 2001;24(4):683-689.

82. Colangelo LA, Gapstur SM, Gann PH, Dyer AR, Liu K. Colorectal cancer mortality and factors related to the insulin resistance syndrome. *Cancer Epidemiology Biomarkers & Prevention.* 2002;11(4):385-391.

83. Gapstur SM, Gann PH, Lowe W, Liu K, Colangelo L, Dyer A. Abnormal glucose metabolism and pancreatic cancer mortality. *Journal of the American Medical Association.* 2000;283(19):2552-2558.

84. Ryan CM, Freed MI, Rood JA, Cobitz AR, Waterhouse BR, Strachan MW. Improving metabolic control leads to better working memory in adults with type 2 diabetes. *Diabetes Care.* 2006;29(2):345-351.

85. Pisprasert V, Ingram KH, Lopez-Davila MF, Munoz AJ, Garvey WT. Limitations in the Use of Indices Using Glucose and Insulin Levels to Predict Insulin Sensitivity Impact of race and sex and superiority of the indices derived from oral glucose tolerance test in African Americans. *Diabetes Care.* 2013;36(4):845-853.

86. Arvanitakis Z, Bennett DA, Wilson RS, Barnes LL. Diabetes and cognitive systems in older black and white persons. *Alzheimer Disease and Associated Disorders.* 2010;24(1):37.

APPENDIX A

INSTITUTIONAL REVIEW BOARD APPROVAL

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Institutional Review Board for Human Use

DATE: September 23, 2015

MEMORANDUM

TO: Keith Pearson
Principal Investigator

FROM: Nancy Stansfield, CIP
Assistant Director
Institutional Review Board for Human Use (IRB)

RE: Request for Determination—Human Subjects Research
IRB Protocol N150918003 – Dietary Patterns, Insulin Resistance, and Cognitive Outcomes in Cohort of Black and White Americans

A member of the Office of the IRB has reviewed your Application for Not Human Subjects Research Designation for above referenced proposal.

The reviewer has determined that this proposal is **not** subject to FDA regulations and is **not** Human Subjects Research. Note that any changes to the project should be resubmitted to the Office of the IRB for determination.

470 Administration Building
701 20th Street South
205.934.3789
Fax 205.934.1301
irb@uab.edu

The University of
Alabama at Birmingham
Mailing Address:
AB 470
1720 2ND AVE S
BIRMINGHAM AL 35294-0104