A PROSPECTIVE STUDY OF MEDITERRANEAN DIET AND COGNITIVE DECLINE

A Thesis
by
ASHLEY CHILDERS

Submitted to the Graduate School
at Appalachian State University
in partial fulfillment of the requirements for the degree of
MASTER OF SCIENCE

May 2018
Department of Nutrition and Health Care Management

A PROSPECTIVE STUDY OF MEDITERRANEAN DIET AND COGNITIVE DECLINE

A Thesis
by
ASHLEY CHILDERS
May 2018

APPROVED BY:

Martin Root, PhD
Chairperson, Thesis Committee

Kimberly Fasczewski, PhD
Member, Thesis Committee

Melissa Davis Gutschall, PhD, RD, LDN
Member, Thesis Committee

Margaret Barth, PhD, MPH
Chairperson, Department of Nutrition and Health Care Management

Max C. Poole, Ph.D.
Dean, Cratis D. Williams School of Graduate Studies

Abstract

A PROSPECTIVE STUDY OF MEDITERRANEAN DIET AND COGNITIVE DECLINE

Ashley Childers
B.S., Appalachian State University

Chairperson: Martin Root, PhD

Cognitive impairment, which affects 16-25% of older adults in the US and Canada, can have profound effects on health and quality of life. Adherence to a Mediterranean Diet has been associated with better cognitive function and lower incidence of cognitive impairment in some studies, but results have been inconsistent. The present study aims to analyze the relationship between Mediterranean Diet adherence and rates of cognitive decline.

Data for this research were taken from the Atherosclerosis Risk in Communities (ARIC) study and includes 10,104 adults age 45-64 at baseline from 4 counties in the United States. Food frequency questionnaire data were used to assess Mediterranean Diet adherence according to the Mediterranean-Style Dietary Pattern Score. Cognitive function was assessed by combining the Delayed Word Recall, the Digit Symbol Substitution, and the Word Fluency tests administered at baseline and six-year follow-up. Linear regression analysis, controlling for important covariates, was used to assess the association between Mediterranean Diet score and change in cognitive function over six years.

The average Mediterranean Diet score at baseline was 20.0 ± 6.5 with average sub-scores for whole grain and wine consumption at 1.2 ± 1.1 and 0.4 ± 1.1, respectively, out of a possible score of 10. There was no significant relationship between Mediterranean Diet Score and cognitive change in univariate, demographic, or fully adjusted models.

ARIC participants had low Mediterranean Diet adherence, particularly in whole grain and wine consumption. Mediterranean Diet adherence had no significant relation with rates of cognitive change among ARIC participants.

Acknowledgments

I would like to thank my committee chair, Dr. Martin Root, for his guidance and patient editing of this work. I would also like to thank Dr. Melissa Gutschall and Dr. Kimberly Fasczewski for serving on my committee and for providing support throughout this process. Finally, I would like to thank the faculty of the Department of Nutrition and Healthcare Management for their commitment to facilitating learning and supporting student research.

Table of Contents

List of Tables

List of Figures

Foreword

Chapter 2 of this thesis will be submitted to *Nutrition and Healthy Aging*, a peer-reviewed journal published by IOS Press; it has been formatted according to the style guide for that journal.

Chapter One

Declines in cognition, defined as the ability to think, reason, and remember and encompassing language, attention, judgement and the ability to learn new things, are associated with increasing age and can have profound effects on health and quality of life.[1, 2] As of 2007, an estimated 16-25% of people aged 65 and over in the United States and Canada were affected by cognitive impairment.[1] Additionally, cognitive impairment increases the risk for more severe dementia, with an average of 32-38% of those diagnosed with mild cognitive impairment progressing to a diagnosis of Alzheimer's disease (AD) – the sixth leading cause of death in the US and the fifth leading cause of death among people aged 65 and over.[3] As this segment of the population grows, the impact of cognitive impairment and AD is also expected to increase – it is projected that the number of older adults with AD will reach 7.1 million by 2025, a 35% increase over the current 5.3 million.[3]

The relationship between diet and cognitive impairment is complex, with dietary factors affecting both disease risk and progression and being affected by loss of function during the late stages of the disease.[4] In their meta-analysis of plasma markers of nutrient status among people with AD, Lopes da Silva *et al*. found that those with AD had significantly lower plasma levels of folate and vitamins A, B_{12}, C, and E ($p < 0.001$) than those without AD and that these lowered levels occurred independently of the protein-energy malnutrition common during the advanced stages of the disease.[5] Dietary factors may also play a role in preventing the occurrence and slowing the progression of cognitive decline. Shakersain *et al*. used factor analysis to derive two dietary patterns among participants of the longitudinal Swedish National Study on Aging and Care – Kungsholmen (SNAC-K). They found that high adherence to a Western dietary pattern, characterized by higher intakes of red

and processed meats, saturated and trans fats, refined grains, sugar, beer, and spirits, was associated with higher cognitive declines as measured by the Mini-Mental State Examination (MMSE) ($\beta = -0.156$, $p < 0.001$), while higher adherence to a "prudent" dietary pattern, characterized by higher intakes of fruits, vegetables, cooking oil, cereals, legumes, whole grains, rice, pasta, fish, low-fat dairy products, poultry, and water, was associated with less cognitive decline ($\beta = 0.106$, $p = 0.011$).[6] In a randomized controlled trial of 233 older adults with mild cognitive impairment, de Jager *et al*. found that participants who received supplemental folate, vitamin B_{12} and vitamin B_6, performed significantly better on the CLOX test of executive function at the 24-month follow-up than participants receiving placebo ($p = 0.015$) when controlling for age, sex, education level and CLOX scores at baseline.[7] In contrast, Haring *et al.* found no association between dietary patterns and risk of mild cognitive impairment (MCI) or probable dementia (PD) among participants in the Women's Health Initiative Memory Study. A sample of 6,425 postmenopausal women were assessed for incidence of MCI and PD over a median follow-up period of 9.11 years. No significant relationship was found between relative risk of MCI and PD across quintiles of alternate Mediterranean Diet, Healthy Eating Index-2010, Alternate Healthy Eating Index-2010, and Dietary Approaches to Stop Hypertension scores (*P* values for trend = 0.30, 0.44, 0.23, and 0.45, respectively)[8].

The Mediterranean diet (MedDiet) is a dietary pattern consistent with the traditional foods of people living in countries bordering the Mediterranean Sea. It is characterized by high intakes of fruits, vegetables, legumes, and whole grains, moderate intakes of fish and red wine, and use of olive oil as the primary source of fat.[9] The protective effects of the MedDiet on cardiovascular disease risk and endpoints has been well-established and

adherence has also been associated with reduced all-cause mortality, incidence of and mortality due to cancer, and incidence of neurodegenerative diseases.[9, 10]

There has been conflicting evidence of the effect of the MedDiet on cognitive decline. Ye *et al*. found that better adherence to the MedDiet was associated with better global cognitive function as measured by the MMSE among middle-aged and older adults in a cross-sectional analysis of participants in the Boston Puerto Rican Health Study. Each one-point increase in adherence to the MedDiet (scores ranged from 0 to 9) was associated with a 0.14-point increase in MMSE score ($\beta = 0.14$, $p = 0.012$). Furthermore, participants in the highest quintile of MedDiet adherence were 50% less likely to have cognitive impairment, which was defined as MMSE scores < 21 for those with less than a high school education, < 23 for those who had completed high school, and < 24 for those with some college education or higher (OR = 0.51; 95% CI 0.33 to 0.79).[11] Similarly, Bhushan *et al.* examined the relationship between MedDiet adherence and subjective cognitive function (SCF), self-assessed change in cognition measured by questions such as "Do you have more trouble than usual remembering recent events?" and "Do you have more trouble than usual following a group conversation or a plot in a TV program due to your memory?"[12] SCF has been found to correlate with the presence of biomarkers of AD and is a strong predictor of future dementia[13, 14]. Results showed that men in the highest quintile of MedDiet adherence were 36% less likely to have a poor SCF score (defined as affirmative answers on 3 or more items of the 6-item SCF questionnaire) (OR = 0.64; 95% CI 0.55 to 0.75, $p < 0.001$) and 24% less likely to have a moderate SCF score (defined as affirmative answers on 1-2 items of the 6-item SCF questionnaire) (OR = 0.76; 95% CI 0.70 to 0.83; $p < 0.001$) than those in the lowest quintile of MedDiet adherence.[12] In their analysis of 1,410 participants from the

Three-City prospective cohort study of older adults in France, Feárt *et al.* found that higher adherence to the MedDiet was associated with slower cognitive decline as measured by the MMSE over a seven year follow-up period (β = -0.006; 95% CI -0.01 to -0.0003; *p* = .04).[15] In a subset of the PREDIMED randomized controlled trial of the MedDiet among people at high risk for cardiovascular disease, Martínez-Lapiscina *et al.* found that participants following the MedDiet supplemented with extra-virgin olive oil had significantly higher scores on the MMSE and the Clock Drawing Test (CDT) than those following the low-fat control diet (adjusted differences: 0.62; 95% CI 0.18 to 1.05, *p* = 0.005 and 0.51; 95% CI 0.20 to 0.82, p = 0.001 for MMSE and CDT, respectively).[16] A follow-up sub-study of the PREDIMED trial measured the rates of cognitive decline over a median follow-up period of 4.1 years among a group of 447 older adults at high cardiovascular risk. Participants were randomized to intervention with MedDiet supplemented with extra-virgin olive oil, MedDiet supplemented with nuts, or a low-fat control diet. Valls-Pedret *et al.* found that participants in the MedDiet plus nuts group had significantly less decline in memory, as measured by a composite score consisting of the mean standardized individual change scores of the Rey Auditory Verbal Learning Test (RAVLT) and the Verbal Paired Associates test from the Wechsler Memory Scale with a mean change of 0.09 (95% CI -0.05 to 0.23) compared with a mean change of -0.17 (95% CI -0.32 to -0.01) in the control group (*p* = 0.04). Additionally, the MedDiet plus extra-virgin olive oil group had significantly less decline in global cognition, determined using the mean standardized changes for all neuropsychological tests (including the above mentioned as well as the Digit Scale subtest of the Wechsler Adult Intelligence Scale, parts one and two of the Color Trail Test, and the

MMSE) with a mean change of 0.05 (95% CI -0.11 to 0.21) compared with -0.38 (95% CI -0.57 to -0.18) in the control group ($p = 0.005$).[17]

One possible reason for the association between MedDiet and better cognitive outcomes is the effect of MedDiet on brain volumes and cortical thickness, measures that have been associated with cognitive decline.[18] In their cross-sectional study of 674 older adults (aged 65 or greater) from the Washington Heights/Hamilton Heights Inwood Columbia Aging Project (WHICAP), Gu *et al.* found that higher MedDiet adherence was associated with larger total brain volumes, total gray matter volumes, and total white matter volumes, as measured by MRI. Compared to those with high MedDiet adherence, participants with low MedDiet adherence had brain atrophy similar to that found after five years of aging. Secondary analysis found that higher fish intake and lower meat intake were the two MedDiet components significantly associated with larger brain volumes.[19] These findings support the hypothesis that the increased polyunsaturated fatty acid (PUFA) content of the MedDiet may play a role in preserving cognitive function by slowing the degeneration of cholinergic basal forebrain neurons which has been shown to play a role in age-related cognitive decline and AD.[20] The high antioxidant content of the MedDiet may also play a role in its potential neuroprotective effect through several mechanisms including preventing oxidative damage to existing neurons and the neurogenerative process, inhibiting cytokine production in microglia cells, and improving cerebral blood flow.[20]

While many studies have shown an association between MedDiet and cognitive outcomes, results have been inconsistent. Vercambre *et al.* found no significant differences in the rate of cognitive decline, as measured by a battery of five validated tests administered at baseline and an average of 5.4 years later, across tertiles of MedDiet adherence among a

subsample of participants in the Women's Antioxidant Cardiovascular Study. These results held true in secondary analyses using an alternate MedDiet scoring method.[21] Similarly, in their analysis of middle-aged participants (60 to 64 years old at baseline) in the PATH Through Life Study in Canberra, Australia, Cherbuin and Anstey found that higher adherence to the MedDiet did not have a protective effect against the development of cognitive impairment over a four-year follow-up period.[22] In their analysis of a subset of participants aged 65 and older from the Women's Health Study, Samieri *et al.* also found no significant relationship between MedDiet adherence and mean global cognition and verbal memory scores over a four-year follow-up period. The fact that no association was found despite a large sample size of 6,174 participants, a test battery with high validity and reliability (including the Telephone Interview for Cognitive Status, immediate and delayed recalls of the East Boston Memory Test, and delayed recall of the Telephone Interview for Cognitive Status 10-word list), and a low loss to follow-up (82% of participants completed all three cognitive assessments over time), raises important questions about MedDiet and cognitive outcomes.[23]

These conflicting results, coupled with the current lack of effective treatments for cognitive impairment and AD, indicate a need for further research into possible preventative measures.[4] The aim of the present study is to analyze the association between adherence to the MedDiet and cognitive outcomes among participants of the Atherosclerosis Risk in Communities (ARIC) study. Based on the above mentioned results from similar studies, it is hypothesized that better adherence to the MedDiet will be associated with decreased rates of cognitive decline over time.

Chapter Two

Abstract

BACKGROUND: Cognitive impairment affects 16-25% of older adults in the US and Canada and has profound effects on quality of life. Adherence to a Mediterranean Diet (MedDiet) has been associated with better cognitive function in some studies, but results have been inconsistent.

OBJECTIVE: To analyze the relationship between MedDiet adherence and rates of cognitive decline.

METHODS: Data were taken from the ARIC study, which included 10,104 adults age 45-64 from 4 counties in the US. Food frequency questionnaire data was used to assess MedDiet adherence according to the Mediterranean-Style Dietary Pattern Score. Cognitive function was assessed by combining Delayed Word Recall, Digit Symbol Substitution, and Word Fluency tests administered at baseline and six-year follow-up. Linear regression was used to assess the association between MedDiet score and change in cognitive function.

RESULTS: The average MedDiet score was 20.0 ± 6.5 with sub-scores for whole grain and wine consumption at 1.2 ± 1.1 and 0.4 ± 1.1, respectively. There was no significant relationship between MedDiet Score and cognitive change in univariate, demographic, or fully adjusted models.

CONCLUSIONS: ARIC participants had low MedDiet adherence, particularly in whole grain and wine consumption. MedDiet adherence was not significantly associated with cognitive change among ARIC participants.

Keywords: diet; diet, Mediterranean; cognition; cognitive dysfunction

Introduction

Declines in cognition, defined as the ability to think, reason, and remember and encompassing language, attention, judgement and the ability to learn new things, are associated with increasing age and can have profound effects on health and quality of life.[1, 2] As of 2007, an estimated 16-25% of people aged 65 and over in the United States and Canada were affected by cognitive impairment.[1] Additionally, cognitive impairment increases the risk for more severe dementia, with an average of 32-38% of those diagnosed with mild cognitive impairment progressing to a diagnosis of Alzheimer's disease – the sixth leading cause of death in the US and the fifth leading cause of death among people aged 65 and over.[3] As this segment of the population grows, the impact of cognitive impairment and AD is also expected to increase – it is projected that the number of older adults with AD will reach 7.1 million by 2025, a 35% increase over the current 5.3 million.[3]

The relationship between diet and cognitive impairment is complex, with dietary factors affecting both disease risk and progression and being affected by loss of function during the late stages of the disease.[4, 5] Dietary factors may also play a role in preventing the occurrence and slowing the progression of cognitive decline. Shakersain *et al*. found that high adherence to a Western dietary pattern, characterized by higher intakes of red and processed meats, saturated and trans fats, refined grains, sugar, beer, and spirits, was associated with higher cognitive declines as measured by the Mini-Mental State Examination (MMSE) ($\beta = -0.156$, $p < 0.001$). In contrast, higher adherence to a "prudent" dietary pattern, characterized by higher intakes of fruits, vegetables, cooking oil, cereals, legumes, whole grains, rice, pasta, fish, low-fat dairy products, poultry, and water, was associated with less cognitive decline ($\beta = 0.106$, $p = 0.011$).[6]

The Mediterranean diet (MedDiet) is a dietary pattern consistent with the traditional foods of people living in countries bordering the Mediterranean Sea. It is characterized by high intakes of fruits, vegetables, legumes, and whole grains, moderate intakes of fish and red wine, and use of olive oil as the primary source of fat.[9] The protective effects of the MedDiet on cardiovascular disease risk and endpoints has been well-established and adherence has also been associated with reduced all-cause mortality, incidence of and mortality due to cancer, and incidence of neurodegenerative diseases.[9, 10]

Previous studies of the relationship between the MedDiet and cognitive decline have yielded mixed results. In their analysis of middle-aged participants in the PATH Through Life Study in Canberra, Australia, Cherbuin and Anstey found that higher adherence to the MedDiet did not have a protective effect against the development of cognitive impairment over a four-year follow-up period.[22] Similarly, Vercambre *et al.* found no significant differences in the rate of cognitive decline, as measured by a battery of five validated tests administered at baseline and an average of 5.4 years later, across tertiles of MedDiet adherence among a subsample of participants in the Women's Antioxidant Cardiovascular Study. These results held true in secondary analyses using an alternate MedDiet scoring method.[21]

In contrast, Ye *et al*. found that better adherence to the MedDiet was associated with better global cognitive function as measured by the MMSE among middle-aged and older adults in the Boston Puerto Rican Health Study. Each one-point increase in adherence to the MedDiet was associated with a 0.14-point increase in MMSE score ($\beta = 0.14$, $p = 0.012$). Furthermore, participants in the highest quintile of MedDiet adherence were 50% less likely to have cognitive impairment than those in the lowest quintile (OR = 0.51; 95% CI 0.33 to

0.79).[11] In a subset of the PREDIMED randomized controlled trial of the MedDiet among people at high risk for cardiovascular disease, Martínez-Lapiscina *et al.* found that participants following the MedDiet supplemented with extra-virgin olive oil had significantly higher scores on the MMSE and the Clock Drawing Test (CDT) than those following the low-fat control diet (adjusted differences: 0.62; 95% CI 0.18 to 1.05, $p = 0.005$ and 0.51; 95% CI 0.20 to 0.82, $p = 0.001$ for MMSE and CDT, respectively).[16] A follow-up sub-study by Valls-Pedret *et al.* found that participants following the MedDiet supplemented with nuts had significantly less decline in memory over a median follow-up period of 4.1 years than those in the control group ($p = 0.04$) while participants following the MedDiet supplemented with olive oil had significantly less decline in global cognition than those in the control group ($p = 0.005$).[17]

These conflicting results, coupled with the current lack of effective treatments for cognitive impairment and AD, indicate a need for further research into possible preventative measures.[4] The aim of the present study is to analyze the association between adherence to the MedDiet and cognitive outcomes among participants of the Atherosclerosis Risk in Communities (ARIC) study. It is hypothesized that better adherence to the MedDiet will be associated with decreased rates of cognitive decline over time.

Materials and Methods

Study Population

The ARIC study, sponsored by the National Heart, Lung, and Blood Institute, is a large prospective cohort study designed to examine the risk factors for and clinical outcomes of atherosclerosis. Participants were recruited from four communities in the US: Forsyth County, NC, the city of Jackson, MS, the northwestern suburbs of Minneapolis, MN, and

Washington County, MD. The cohort recruited from Jackson, MS includes only African Americans, while cohorts from the other three communities include both African American and White participants. Probability sampling was used to recruit approximately 4,000 participants between the ages of 35 and 74 from each community for a total of 14,590 participants. Baseline examinations were performed between 1987 and 1989 and follow-up examinations occurred at three-year intervals (between 1990 and 1992 for visit 2, 1993 to 1995 for visit 3, and 1996 to 1998 for visit 4)[24, 25]

Dietary Intake and Mediterranean Diet Score

Dietary intake was measured using a 66-item food frequency questionnaire (FFQ), modified from the validated Willett FFQ, administered by trained interviewers at baseline and visit 3.[26, 27] Caloric intake was derived from FFQ data using the Willett nutrient database.[28] Dietary data were evaluated for adherence to the MedDiet using the Mediterranean-Style Dietary Pattern Score (MSDPS) developed by Rumawas *et al*. for use in a non-Mediterranean population. Participants' consumption of whole grains, fruits, vegetables, dairy, wine, fish, poultry, olives, legumes, nuts, potatoes and other starchy root vegetables, eggs, sweets, and meat were evaluated against the recommended intakes from the Mediterranean diet pyramid. Participants consuming the recommended number of servings received the highest score, with scores incrementally lowered for under- and overconsumption. The MSDPS also factors in the proportion of total energy intake from MedDiet foods to account for the high consumption of foods outside of the Mediterranean diet pyramid expected in cohorts from the United States (see Figure 1). While there is no gold standard by which MedDiet scores can be validated, the MSDPS was tested for validity in the Framingham Offspring Cohort and found to correlate well with intakes of nutrients

associated with the MedDiet.[29] The average MSDPS score from baseline and visit 3 was used in analysis. One significant limitation of the application of the MSDPS to the ARIC cohort involved the assessment of participants' use of olive oil. Use of olive oil as the primary cooking oil is one component of the MSDPS, with those using only olive oil receiving the maximum score of 10, those using olive oil and other oils receiving a score of 5, and those using no olive oil receiving a score of zero. The FFQ used in the ARIC study did not assess the use of olive oil, so all participants were assigned a score of zero for this component.

Cognition

Cognitive function was assessed using the Delayed Word Recall (DWR) test, the Digit Symbol Substitution (DSS) test from the Wechsler Adult Intelligence Scale, and the Word Fluency (WF) test from the Multilingual Aphasia Examination. The DWR evaluates short term memory by requiring participants to recall a series of 10 words after a five minute interval during which another test is administered. After the five minute interval, participants are asked to compose sentences using the 10 words and are given a score from 0 to 10 based on the number of words recalled. The DSS is a timed test of psychomotor ability during which participants are asked to translate a series of numbers into symbols using a key. Scores are assigned based on the number of translations made during a 90 second interval, with a maximum possible score of 93. The WF is used as an indicator of linguistic impairment and early cognitive decline. Participants are given a letter of the alphabet and asked to list as many words beginning with that letter as possible during a 60 second time frame. ARIC participants were asked to perform the test three times, using the letters F, A, and S. Scores were assigned based on the total number of words over the three tests. The

test battery was administered by trained interviewers during the second and fourth examinations.[30, 31] For the present study, scores for each test were standardized by taking the difference of baseline scores from 6-year follow-up scores and dividing by the standard deviation of the difference. A total score for change in cognitive function was obtained by summing the three standardized test change scores for each participant.

Demographic and Other Confounding Variables

Demographic information, including age, race/ethnicity, sex, and education level, was collected by trained interviewers at baseline. Self-reported smoking status was classified as current smoker or non-smoker.[26] Blood pressure was measured three times while participants were seated and after five minutes of rest. The average of the second and third measurements was recorded. Hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, or use of antihypertensive medication.[32] Diabetes was defined as fasting plasma glucose ≥ 126 mg/dL, self-reported physician diagnosis, or use of glucose-lowering medications. Body mass index was calculated as kg/m^2. Physical activity level was assessed using the sum of work, leisure, and sports activity scores.[26]

Statistics

Statistical analysis was performed using IBM SPSS Statistics, version 24 (IBM Corp., Armonk, NY). Linear regression models of change in cognitive function versus MedDiet score were created, controlling for age, race/ethnicity, sex, education level, smoking status, physical activity, BMI, and presence of hypertension and diabetes.

Results

A total of 14,950 participants were assessed for inclusion in the present study. Of those, 5,036 participants were excluded due to missing FFQ, cognitive function, or covariant data. A further 48 participants were excluded due to very high or very low cognitive difference scores for a total sample size of 10,104 (see Figure 1). The majority of study participants were white (n = 823,476) and female (n = 559,762). Ages at baseline ranged from 44 to 66 years with a mean age of 54.0 ± 5.7. Participants were overweight on average, with MedDiet scores that ranged from 1.2 to 47.0. Total cognitive change scores from baseline to visit four ranged from -12.3 to 12.9, with participants declining by 0.6 points, on average. Characteristics of the study sample are presented in Table 1.

MedDiet adherence was low overall, with particularly low adherence in the wine and whole grain categories, with average scores of 0.4 ± 1.1 and 1.2 ± 1.1 respectively. Highest adherence was seen in the fruit category, with an average score of 5.3 ± 2.4 (see Table 2). Participants in the ARIC cohort consumed, on average, only 1.0± 0.9 servings per day of whole grains out of the 8 servings per day recommended on the traditional MedDiet pyramid. The ARIC cohort had similar low intakes of wine (0.08 ± 0.27 servings per day out of the recommended 3 servings for men and 1.5 servings for women), vegetables (1.5 ± 1.0 servings per day out of the recommended 6), and fish (2.1 ± 2.1 servings per week out of the recommended 6). ARIC participants also consumed greater than three times the recommended amounts of sweets (9.6 ± 8.6 servings per week of the recommended 3) and meats (3.2 ± 2.5 servings per week of the recommended 1).[33]

Linear regression comparing MedDiet scores and change in cognitive scores revealed no significant association. This was maintained when controlling for demographic variables

(age, sex, and ethnicity) and important covariates (education level, smoking status, physical activity level, BMI, presence of hypertension, and presence of diabetes) (see Table 3). Subsequent analyses of subgroups revealed no significant differences in MedDiet score between males and females or between participants from the four examination centers. No significant association between MedDiet scores and cognitive change was found in any of these subgroups.

Discussion

In this large sample of middle aged adults, there was no significant association between adherence to a Mediterranean Style diet pattern and preserved cognitive function.

These results are inconsistent with much of the literature on Mediterranean Diet and cognitive decline. It is possible that the low MedDiet adherence in this sample contributed to the null results. Out of a possible score of 100, the average MSDPS in this cohort was 20.0 ± 6.5. In contrast, the average MedDiet score among participants in the Boston Puerto Rican Health Study, in which Ye *et al.* found that better adherence to the MedDiet was associated with better global cognitive function as measured by the MMSE among middle-aged and older adults, was 4.37 ± 1.61 out of a maximum possible score of 9.[11] Similarly, Féart *et al*. reported a mean MedDiet score of 4.36 ± 1.66 out of a maximum possible score of 9 in their study of 1,410 participants from the Three-City prospective cohort study of older adults in France, in which they found that higher adherence to the MedDiet was associated with slower cognitive decline as measured by the MMSE over a seven year follow-up period.[15]

Compared with the recommended intakes from the MedDiet pyramid, the ARIC cohort had very low intake of whole grains, wine, vegetables and fish. While Samieri *et al.* found a similar lack of association between MedDiet and mean global cognition scores in

their analysis of women aged 65 and over from the Women's Health Study, they also noted a modest association between higher intakes of whole grains and better cognitive scores.[23] Whole grains are rich in B-vitamins, higher intakes of which have been associated with less cognitive decline, possibly through their role in lowering plasma levels of homocysteine.[34, 35] Antioxidant compounds found in vegetables and wine may also play a protective role against cognitive decline, as oxidative damage may contribute to the development of AD and mild cognitive impairment.[36-38] As an important source of omega-3 fatty acids, a component of neural membrane phospholipids, higher intake of fish may also be protective against cognitive decline.[39-41] In their cross-sectional analysis of participants from the Washington Heights/Hamilton Heights Inwood Columbia Aging Project, Gu *et al.* found that, compared with those with high MedDiet adherence, participants with low MedDiet adherence had brain atrophy similar to that found after five years of aging, with higher fish intake and lower meat intake both being significantly associated with larger brain volumes.[19]

Additionally, ARIC participants also consumed sweets and meats in quantities much greater than those recommended on the MedDiet pyramid. In their analysis of dietary patterns among participants of the longitudinal Swedish National Study on Aging and Care – Kungsholmen (SNAC-K), Shakersain *et al.* found that a Western-style dietary pattern high in red and processed meats, refined grains, and sugars was associated with greater cognitive decline as measured by the MMSE.[6] A case-control study of people with and without AD in Poland, in which researchers used factor analysis to derive the dietary patterns of people with AD and those without, found that the diets of people with AD were higher in meat and refined sugar while the diets of people without AD were higher in grains and vegetables.[42]

The low overall adherence to the MedDiet, with very low intakes of components that have been associated with less cognitive decline and high intakes of foods that have been associated with greater cognitive decline and incidence of AD found in the ARIC cohort may have contributed to the null results – this cohort may not have been consuming great enough amounts of MedDiet foods to show significant results.

This study has some significant limitations. Though the 66-item semi-quantitative FFQ used in the ARIC study was validated, it was not designed to measure adherence to the Mediterranean Diet. Specifically, the FFQ did not evaluate the use of olive oil, a major component of the MedDiet. Sales of olive oil tripled between 1990 and 2012 in response to increasing public awareness of the possible health benefits associated with its use.[43] It is likely that olive oil was not widely used among ARIC participants at the time of baseline examinations. The FFQ also failed to distinguish between whole and refined grains on several food items, leaving the researchers to determine which food items were likely to be whole grains and which were likely to be refined based on knowledge of food products available at the time of data collection ("cooked cereals" and "dark or whole grain breads" were classified as whole grains, while "biscuits or cornbread," "cold cereals," and "white bread" were not). Despite these limitations, this study is strengthened by the large sample size and the use of a MedDiet scoring system developed for non-Mediterranean populations. While many MedDiet scoring systems assign scores based the mean intake of each component found in the study population, meaning that participants with intakes higher than the population mean receive higher scores and those with intakes lower than the population mean receive lower scores, the MSDPS assigns scores based on the recommended intakes of each component from the Mediterranean Diet pyramid. This allows for better evaluation of

true MedDiet adherence in populations where intakes of MedDiet components may be low. The MSDPS also accounts for overconsumption of each MedDiet component and the proportion of total calories from MedDiet components. This attenuates the possibility of participants receiving a higher MedDiet score by simply consuming more food.[29] In a US population with traditionally low intake of MedDiet foods and higher intake of total energy, use of the MSDPS may be a better reflection of true MedDiet adherence than traditional scoring systems. To our knowledge, this is the first study to use the MSDPS to analyze MedDiet adherence and cognitive decline. The present study also uses a MedDiet score calculated from two food frequency questionnaires administered at baseline and visit 3 (approximately six years after baseline). Using the mean MedDiet score from baseline and visit 3 accounts for changes in the participants' dietary patterns over time.

In conclusion, this observational study of a large diverse cohort of middle-aged adults found no significant associations between MedDiet adherence as measured by the MSDPS and rates of cognitive decline. While these findings are inconsistent with many previous studies, this discrepancy may be explained by the novel approach to MedDiet scoring, which was designed for use in non-Mediterranean populations and bases scores on adherence to the traditional MedDiet pyramid rather than population means. The very low MedDiet scores found using this scoring system may have contributed to the null results.

References

1. Day KL, McGuire LC, Anderson LA. The CDC Healthy Brain Initiative: Public health and cognitive impairment. Generations. 2009;33(1):11-7.
2. Tucker-Drob EM. Neurocognitive functions and everyday functions change together in old age. Neuropsychology. 2011;25(3):368-77.
3. Alzheimer's Association. 2017 Alzheimer's disease facts and figures. Alzheimers Dement. 2017;13(4):325-73.
4. Vandewoude M, Barberger-Gateau P, Cederholm T, Mecocci P, Salvà A, Sergi G, et al. Healthy brain ageing and cognition: Nutritional factors. Eur Geriatr Med. 2016;7(1):77.
5. Lopes da Silva S, Vellas B, Elemans S, Luchsinger J, Kamphuis P, Yaffe K, et al. Review Article: Plasma nutrient status of patients with Alzheimer's disease: Systematic review and meta-analysis. Alzheimers Dement. 2014;10(4):485-502.
6. Shakersain B, Santoni G, Larsson SC, Faxén-Irving G, Fastbom J, Fratiglioni L, et al. Prudent diet may attenuate the adverse effects of Western diet on cognitive decline. Alzheimers Dement. 2016;12(2):100-9.
7. de Jager CA, Oulhaj A, Jacoby R, Refsum H, Smith AD. Cognitive and clinical outcomes of homocysteine-lowering B-vitamin treatment in mild cognitive impairment: a randomized controlled trial. Int J Geriatr Psychiatry. 2012;27(6):592-600.
8. Haring B, Wu C, Mossavar-Rahmani Y, Snetselaar L, Brunner R, Wallace RB, et al. Research: No association between dietary patterns and risk for cognitive decline in

older women with 9-year follow-up: data from the Women's Health Initiative Memory Study. J Acad Nutr Diet. 2016;116:921-30.e1.

9. Sofi F, Abbate R, Gensini GF, Casini A. Accruing evidence on benefits of adherence to the Mediterranean diet on health: an updated systematic review and meta-analysis. Am J Clin Nutr. 2010;92(5):1189-96.

10. Widmer RJ, Flammer AJ, Lerman LO, Lerman A. The Mediterranean diet, its components, and cardiovascular disease. Am J Med. 2015;128(3):229-38.

11. Ye X, Scott T, Gao X, Maras JE, Bakun PJ, Tucker KL. Research: Mediterranean diet, Healthy Eating Index 2005, and cognitive function in middle-aged and older Puerto Rican adults. J Acad Nutr Diet. 2013;113(2):276-81.e3.

12. Bhushan A, Fondell E, Ascherio A, Yuan C, Grodstein F, Willett W. Adherence to Mediterranean diet and subjective cognitive function in men. Eur J Epidemiol. 2017;33(2):223-34.

13. Perrotin A, Mormino EC, Madison CM, Hayenga AO, Jagust WJ. Subjective cognition and amyloid deposition imaging: A Pittsburgh Compound B positron emission tomography study in normal elderly individuals. Arch Neurol. 2012;69(2):223-9.

14. Jonker C, Geerlings MI, Schmand B. Are memory complaints predictive for dementia? A review of clinical and population-based studies. Int J Geriatr Psychiatry. 2000;15(11):983-91.

15. Féart C, Samieri C, Rondeau V, Amieva H, Portet F, Dartigues J-F, et al. Adherence to a Mediterranean diet, cognitive decline, and risk of dementia. J Am Med Assoc. 2009;302(6):638-48.

16. Martínez-Lapiscina EH, Clavero P, Toledo E, Estruch R, Salas-Salvadó J, Julián BS, et al. Mediterranean diet improves cognition: The PREDIMED-NAVARRA randomised trial. J Neurol Neurosurg Psychiatry. 2013;84(12):1318-25.

17. Valls-Pedret C, Sala-Vila A, Serra-Mir M, Corella D, de la Torre R, Martínez-González MÁ, et al. Mediterranean diet and age-related cognitive decline: a randomized clinical trial. JAMA Intern Med. 2015;175(7):1094-103.

18. Pacheco J, Goh JO, Kraut MA, Ferrucci L, Resnick SM. Greater cortical thinning in normal older adults predicts later cognitive impairment. Neurobiol Aging. 2015;36(2):903-8.

19. Gu Y, Brickman AM, Stern Y, Habeck CG, Razlighi QR, Luchsinger JA, et al. Mediterranean diet and brain structure in a multiethnic elderly cohort. Neurology. 2015;85(20):1744-51.

20. Knight A, Bryan J, Murphy K. Review: Is the Mediterranean diet a feasible approach to preserving cognitive function and reducing risk of dementia for older adults in Western countries? New insights and future directions. Ageing Res Rev. 2016;25:85-101.

21. Vercambre M-N, Grodstein F, Berr C, Kang JH. Research: Mediterranean diet and cognitive decline in women with cardiovascular disease or risk factors. J Acad Nutr Diet. 2012;112(6):816-23.

22. Cherbuin N, Anstey KJ. Brief Report: The Mediterranean diet is not related to cognitive change in a large prospective investigation: The PATH Through Life Study. Am J Geriatr Psychiatry. 2012;20(7):635-9.

23. Samieri C, Grodstein F, Rosner BA, Kang JH, Cook NR, Manson JE, et al. Mediterranean diet and cognitive function in older age. Epidemiology. 2013;24(4):490-9.

24. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. Am J Epidemiol. 1989;129(4):687-702.

25. Kwon Y, Norby FL, Jensen PN, Agarwal SK, Soliman EZ, Lip GYH, et al. Association of smoking, alcohol, and obesity with cardiovascular death and ischemic stroke in atrial fibrillation: The Atherosclerosis Risk in Communities (ARIC) Study and Cardiovascular Health Study (CHS). Plos One. 2016;11(1):e0147065-e.

26. ARIC. Atherosclerosis Risk in Communities Study Protocol: cohort component procedures. 1988.

27. ARIC. ARIC Dietary Intake Form. 1986.

28. ARIC. ARIC Data Book - Cohort, Exam 1, Nutrition Derived Variables in ANUT2.

29. Rumawas ME, Dwyer JT, McKeown NM, Meigs JB, Rogers G, Jacques PF. The development of the Mediterranean-Style Dietary Pattern Score and its application to the American diet in the Framingham Offspring Cohort. Journal of Nutrition. 2009;139:1150-6.

30. Szklo M, Cerhan J, Diez-Roux AV, Chambless L, Cooper L, Folsom AR, et al. Estrogen replacement therapy and cognitive functioning in the Atherosclerosis Risk in Communities (ARIC) Study. Am J Epidemiol. 1996;144(11):1048-57.

31. ARIC. Atherosclerosis Risk in Communities Study Protocol, manual 2 - cohort component procedures for the second examination. 1990.

32. ARIC. Atherosclerosis Risk in Communities Study protocol manual 11 - sitting blood pressure and postural changes in blood pressure and heart rate. 1987.

33. Ministry of Health and Welfare Supreme Scientific Council of Greece. Dietary guidelines for adults in Greece. Archives of Hellenic Medicine. 1999;16(5):516-24.

34. Tucker KL, Qiao N, Scott T, Rosenberg I, Spiro III A. High homocysteine and low B vitamins predict cognitive decline in ageing men: the Veterans Affairs Normative Ageing Study. Am J Clin Nutr. 2005;82(3):627-35.

35. Hughes CF, Ward M, Tracey F, Hoey L, Molloy AM, Pentieva K, et al. B-vitamin intake and biomarker status in relation to cognitive decline in healthy older adults in a 4-year follow-up study. Nutrients. 2017;9(1).

36. Praticò D. Alzheimer's disease and oxygen radicals: new insights. Biochem Pharmacol. 2002;63(4):563-7.

37. Galasko D, Montine, TJ. Biomarkers of oxidative damage and inflammation in Alzheimer's disease. Biomark Med. 2010;4(1):27.

38. Rafnsson S, Dilis V, Trichopoulou A. Antioxidant nutrients and age-related cognitive decline: a systematic review of population-based cohort studies. Eur J Nutr. 2013;52(6):1553-67.

39. Horrocks LA, Farooqui AA. Docosahexaenoic acid in the diet: its importance in maintenance and restoration of neural membrane function. Prostaglandins Leukot Essent Fatty Acids. 2004;70:361-72.

40. Del Brutto O, Mera R, Gillman J, Zambrano M, Ha J-e. Oily fish intake and cognitive performance in community-dwelling older adults: The Atahualpa Project. J Community Health. 2016;41(1):82-6.

41. Qin B, Plassman BL, Edwards LJ, Popkin BM, Adair LS, Mendez MA. Fish intake is associated with slower cognitive decline in Chinese older adults. J Nutr. 2014;144(10):1579-85.

42. Gustaw KA, Włodarek D, Leszczyńska B, Petot G. Dietary patterns associated with Alzheimer's disease - a population based study (BERCAL). Alzheimers Dement. 2009;5(Supplement):P296-P7.

43. Xiong B, Sumner D, Matthews W. A new market for an old food: The U.S. demand for olive oil. Agric Econ. 2014;45:107-18.

Tables

Table 1. Descriptive Statistics of ARIC Study Participants

Variable	Percent of Study Population
Female	55.4%
Black	18.5%
Current Smoker	20.3%
College Educated	39.3%
Hypertensive	30.4%
Diabetic	8.9%
	Mean ± SD
Age (years)	54.0 ± 5.7
BMI (kg/m^2)	27.4 ± 5.1
Physical Activity Score	7.1 ± 1.4
Average Mediterranean Diet Score	20.0 ± 6.5
Baseline Delayed Word Recall Score	6.7 ± 1.5
Baseline Digit Symbol Substitution Score	46.5 ± 13.3
Baseline Word Fluency Score	34.2 ± 12.1
Total Cognitive Change Score	-0.6 ± 1.9

- DWR scores are out of maximum possible score of 10
- DSS scores are out of a maximum possible score of 93
- WF scores ranged from 0-99

Table 2. Descriptive Statistics of Mediterranean Diet Sub-scores

Variable	Mean ± SD
Whole Grains	1.2 ± 1.1
Fruits	5.3 ± 2.4
Vegetables	2.5 ± 1.4
Dairy	4.7 ± 2.3
Wine	0.4 ± 1.1
Fish and other seafood	3.0 ± 2.1
Poultry	4.9 ± 2.3
Olives, legumes, and nuts	4.3 ± 2.5
Potatoes and other starchy roots	5.1 ± 2.7
Eggs	3.7 ± 3.1
Sweets	2.2 ± 2.5
Meat	2.4 ± 2.8

- Sub-scores are out of a maximum possible score of 10

Table 3. Association of Mediterranean Diet Score and Cognitive Change

Change in Cognition Scores	Beta	95% Confidence Interval	*p* Value
Univariate Model	-0.03	-0.09; 0.02	0.266
Demographic Model	-0.02	-0.08; 0.03	0.424
Fully Adjusted Model	0.02	-0.04; 0.08	0.603

- Univariate model compares average MedDiet score and change in cognitive scores
- Demographic model includes sex, age, and ethnicity
- Fully adjusted model includes education level, smoking status, physical activity level, BMI, hypertension, and diabetes
- Beta represents the change in the difference between cognitive scores from visit 4 and visit 2 per 10 point increase in MedDiet score

Figures

Figure 1. Exclusion Flow Diagram

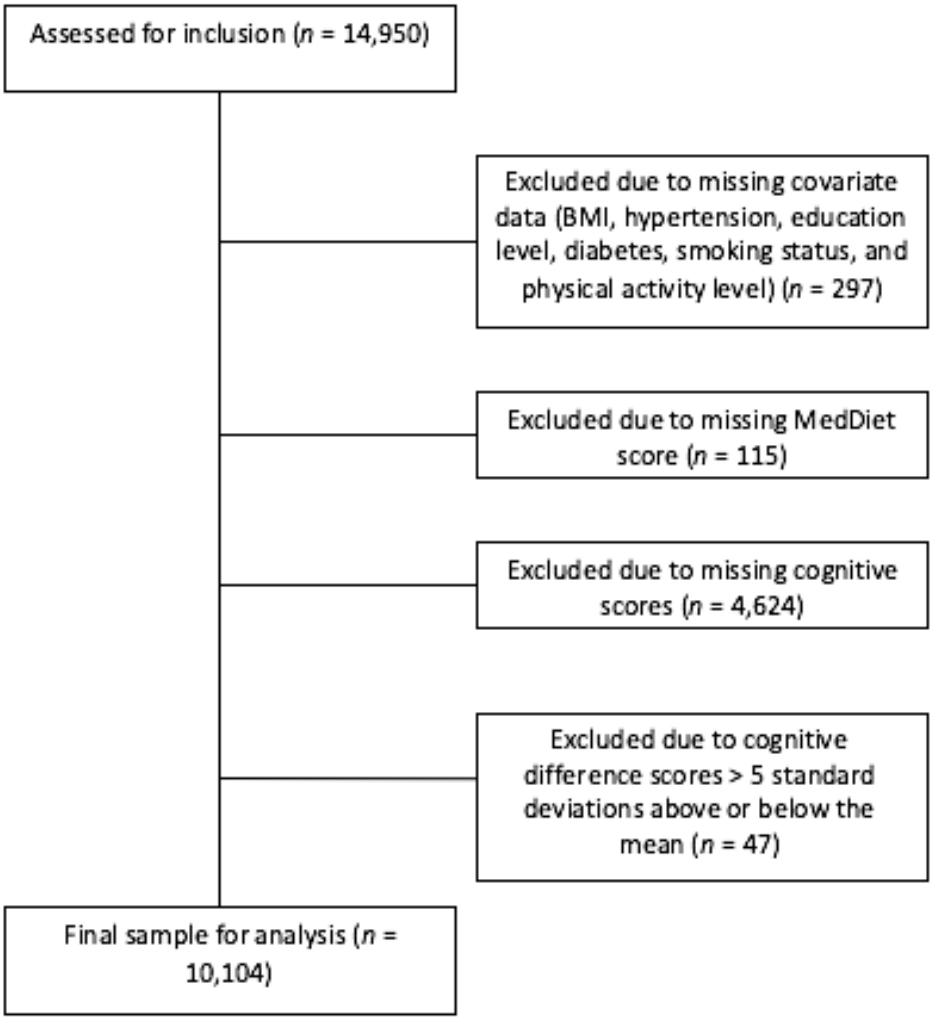

Figure 2. MSDPS Equation

$$MSDPS = \left[\left(\frac{\sum_{i=1}^{13} Si}{130}\right) \times 100\right] \times P*$$

*Where *Si* is the individual item score for each MedDiet component and *P* is the proportion of total energy intake from MedDiet foods

Vita

Ashley Elizabeth Childers was born in Charlotte, NC to Robert and Raphonza Childers. She graduated from North Gaston High School in Dallas, NC in 2006. She earned a Bachelor of Science degree in Theatre Arts Education from Appalachian State University in May 2010. In August 2014, she returned to Appalachian State to complete a didactic program in dietetics. She was accepted into and began the combined Master of Science in Nutrition and Dietetic Internship at Appalachian in 2016. Ms. Childers resides in Dallas, NC.