ARIC Manuscript Proposal #2145

PC Reviewed: 5/_14/13	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:
Nutrition, Healthy Diet and 21-year Cognitive Decline

b. Abbreviated Title (Length 26 characters):
Nutrition and Cognition

2. Writing Group:

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _JD_ **[please confirm with your initials electronically or in writing]**

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3. Timeline: Analyses to begin as soon as manuscript proposal is approved.
Goal for completion with calendar year.

4. Rationale:

Cognitive outcomes in later life are a complex interplay of genetic and environmental factors. Alzheimer (AD) and Parkinson's diseases are on a spectrum of cognitive and functional impairment that are mediated by environment. Nutritional status, and dietary patterns over a lifetime certainly impact health outcome measures, and there is an emerging body of literature suggesting that cognitive outcomes are related to diet history. This proposal seeks to explore the relationship between various nutritional parameters and change in cognitive status in the ARIC

population. We will also evaluate whether MRI brain volumetrics is a potential mechanism for the proposed interrelationships.

Adherence to a healthful dietary pattern is one aspect of nutrition that has been hypothesized to be associated with cognitive health. The Mediterranean diet (Med Diet) is consumed by populations bordering the Mediterranean Sea and has been associated with positive health outcomes. The Med Diet is rich in vegetables (legumes and greens), fish and olive oil, with a moderate amount of alcohol, while low in red meat and chicken. Results from a meta-analysis and a recent intervention trial showed that this dietary pattern reduced overall mortality, mortality from cardiovascular diseases, incidence of or mortality from cancers, and incidence of Parkinson's disease and AD [1, 2]. One mechanism by which this occurs is thought to be through anti-inflammatory mediators, and through reduced antioxidant stress.

The interaction with dietary patterns and cognition, both with mild cognitive impairment (MCI) and AD being secondary outcomes, is only beginning to be understood. For example, in a biracial population of Midwestern adults, aged greater than or equal to 65 years, the Med Diet was associated with a slower rate of cognitive decline, as measured by a Med Diet index[3]. Adherence with the Med Diet was associated with a slower decline in the mini mental status exam (MMSE), but not incident dementia in a cohort in Bordeaux, France[4] . Physical activity and adherence to a Med Diet were associated with decreased incidence of AD in two community dwelling cohorts of elderly individuals without dementia[5]. In another cohort of older adults, intake of a Med diet pattern was also associated with a lower risk of prevalent AD, incident AD, and incident MCI. In this analysis, however, the Med Diet was not associated with biomarkers of inflammation such as high sensitivity C-reactive protein (hsCRP) or metabolic markers such as insulin and adiponectin[6] .

Another aspect of nutrition that has been associated with cognitive health is consumption of polyunsaturated fatty acids (PUFA), [7, 8] PUFA is a large component of the fatty acid profile of the Med Diet and contain more than one double bond in their chemical structure, as opposed to saturated fats which have no double bonds.). Omega 3 fatty acids (n3 PUFA) eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) are found in many plant and fish oils, and are unable to be synthesized by the human body. Omega 6 fatty acids (n6 PUFA) are also essential, and compete for the same metabolic enzymes as n3 PUFA. High intake of fish (a prominent source of PUFA) is associated with less cognitive decline[7]. DHA and EPA levels have been associated with better cognitive function in a cross sectional study[8] .

A food frequency questionnaire was administered in ARIC to determine dietary intake was assessed over the previous year. It was an interviewer administered, 66-item questionnaire, during visits 1 and 3. Despite inherent weakness in food recall, there have been several interesting studies using ARIC FFQ data. An increase in the consumption of n3 to n6 PUFA was associated with a smaller decline in the word fluency test (WFT), one subset of neurocognitive testing[9] .An interesting paper looked at adipokine angiopoietin-like-4 (ANGPTL4) which is a protein that is thought to regulate fatty acid transport across tissues through inhibition of lipoprotein lipase (LPL). In the ARIC cohort, a loss of function mutation in the ANGPTL4 gene resulted in lower triglyceride and higher HDL levels.[10]

This proposal seeks to further explore core relationships of nutrition with cognitive outcome and MRI brain volumetrics, to better define the interaction of these components on brain structure and function. The significance of this work is that it allows us to examine potentially modifiable risk factors, such as diet supplementation, that might mitigate the effects of cognitive decline in midlife.

5. Main Hypothesis/Study Questions:

Hypothesis 1. A healthy dietary pattern modeled after the Med Diet (high in fish, essential fatty acids, moderate alcohol, and high intake of vegetables, which we will call Healthy Diet) will be inversely associated with cognitive dysfunction, as measured by neuropsychological testing. It will also be associated with a change in cognitive performance, as determined by examining change in neuropsychological testing at two time points (visit 2 (1990-92) and visit 4 (1996-99) in the whole cohort). For the subset of individuals who have cognitive assessment as part of the ARIC BRAIN MRI ancillary study, we will evaluate change in cognitive performance across these three visits, from visit 2 (1990-2) through the BRAIN 2004-6 and Carotid MRI visit in the same time period. We will add an analysis to include 21-year change in cognition incorporating visit 5 data. We expect the relationship between diet and cognition to be strongest for this group, since the likelihood of decline in cognitive performance is greatest in this group. Using techniques previously used in ARIC in which cognitive data from either the Brain or Carotid MRI visit is used (whichever is done earlier in individuals with testing at both time points), we will be able to include more individuals who were in either of these two ancillary studies.

Hypothesis 2: Certain aspects of Healthy Diet (fish, essential fatty acids, moderate alcohol, and high intake of vegetables) will be inversely associated with cognitive performance, but each component alone will be less associated than the composite Healthy Diet. Similar analysis will be performed as per above.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodological limitations or challenges if present).

Study Design: Prospective data collection on risk factors with cross-sectional definition of the outcome based on the neuropsychological assessment performed 1990-92 and 1996-99, and 2004 to 2006 and the ARIC Brain MRI in 1993 to 1995 and 2004-2006. We will also incorporate data from the ongoing neurocognitive study in the current analysis, and rerun the analysis when the dataset is complete.

Inclusion Criteria: All individuals in the ARIC cohort with at least one cognitive assessment

Exclusion Criteria: Missing Missing nutrition data, Missing neuropsychological testing, pre-existing neurologic condition that might impact cognition, use of medications felt to impact cognition at the time of testing (exclude only those testing dates when these medications are in use).

Data Analysis:

Hypothesis 1:

The Healthy Diet like pattern will be defined according to a definition established by Trichoupoulu et al. created for the Med Diet[11] which creates a score based on 9 components, giving a 0 or 1 score to those with high adherence. The component used will be: (1) high ratio of MUFAs to saturated fatty acids (SFAs), (2) moderate alcohol intake, (3) high intake of legumes, (4) high intake of cereal (such as bread), (5) high intake of fruit and nuts, (6) high intake of vegetables, (7) low intake of meat and meat products, and (8) moderate intake of milk and dairy products and (9) a high intake of fish. The population in ARIC, as a whole, does not eat a Med Diet like pattern, and therefore it is expected that the relative consumption of the above components will be low. Therefore, the sex-specific sample medians will be used as the cut-off point, and those above the median consumption will be given a score of 1. Our diet pattern will be renamed the Healthy Diet because of the relatively low intake of the above components in our sample, so relative to the population, it may not represent a true Med Diet.

Linear regression with adherence to a dietary pattern similar to the Healthy Diet at visit 1 (composite variable, divided into quintiles), or its individual components, as independent variables, predicting cognitive outcome, as measured by either change in neuropsychological testing scores between visit 2 and visit 4, or scores at visit 4. Depending on the available sample size, for individuals in the Brain MRI or Carotid MRI study, we will use random-effects linear regression models to account for the intra-individual correlation of cognitive scores.

The primary exposure of interest will be the diet adherence X time term in these random-effects models, or just diet adherence in the linear regression looking at change for people with scores at 2 time points. The measures for the independent variables will be taken from visit 1.

The delayed word recall, digit symbol substitution task and word fluency tests will each be analyzed independently. We will also consider a "global" z-score from the 3 neuropsychological tests as a composite variable.

Covariates will include age, gender, prevalent CHD, ApoE status, hypertension, education, physical activity, lipid profile and diabetes.

Independently, we will estimate cognitive decline incorporating visit 5 data. Random-effects models will be used that are similar to methods used during the Education and Cognitive Change manuscript currently under preparation, and incorporating methods used in ARIC (Schneider 2012).

Hypothesis 2:
Linear regression with the independent variables divided into the highest quintile of consumption versus quintile 1-4 at visit 1. The primary exposure will be either: alcohol intake, fish intake, n3 fatty acids, n6 fatty acids, vegetable intake, fruit intake, olive oil intake, coffee intake which are expected to be inversely associated with cognitive function.), Cognitive outcome, is the dependent variable, as measured by either change in neuropsychological testing scores between visit 2 and visit 4, or with cross-sectional scores at visit 4. Depending on the available sample size, for individuals in the Brain MRI or Carotid MRI study, we will use random-effects linear regression models to account for the intra-individual correlation of cognitive scores.

The delayed word recall, digit symbol substitution task and word fluency tests will each be analyzed independently. We will also consider a "global" z-score from the 3 neuropsychological tests as a composite variable.

Covariates will include age, gender, prevalent CHD, ApoE status, hypertension, education, physical activity, lipid profile and diabetes.

Independently, we will estimate cognitive decline incorporating visit 5 data. Random-effects models will be used that are similar to methods used during the Education and Cognitive Change manuscript currently under preparation, and incorporating methods used in ARIC (Schneider 2012).

Limitations:
Nutritional patterns throughout life can affect cognitive outcomes. The FFQ is only a rudimentary assumption of dietary patterns that is prone to over and underreporting. Persons may change their dietary patterns through life. The Med Diet has received much focus. We will create a composite variable, Healthy Diet, but it will be related only to items of interest, and it will be difficult to say

of what weight each item should have in the composite. Therefore, the analysis of each individual component (e.g. fish consumption, olive oil use), may be more accurate. Also, the Med diet type pattern is likely low in the ARIC cohort, therefore we will look at consumption above the median in the sample, which still may be low in comparison to those eating a "true" Med diet. The time window of 5 to 6 years between cognitive testing may be too small to appreciate a change in brain structure or function that is occurring with a lifetime exposure such as nutrition. Also, in this subset, neuropsychological testing was performed fairly early, perhaps before the subjects exhibited cognitive decline. Therefore the absence of an association in this study will not negate the presence of an association in later life. Because of this, we will incorporate data on 21-year cognitive decline, using visit 5 data. Analysis will be rerun when complete data is available.

The paper currently under publication, on Education and Cognitive Change, will address period effects and drop out effects on cognitive decline, and knowledge gained from this analysis will be used to assess the limitations of these effects on our outcome measure.

7. a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes __X_ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? ____ Yes ____ No
(This file ICTDER03 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8. a. Will the DNA data be used in this manuscript? _X__ Yes __ No (We will use ApoE genotype data)

8. b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"? __X_ Yes ____ No

8. c. If yes, is the author aware that the participants with RES_DNA = 'not for profit' restriction must be excluded if the data are used by a for profit group? ____Yes ____No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php

__X__ Yes _____ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

Houston DK, Stevens J, Cai J, Haines PS. Dairy, fruit, and vegetable intakes and functional limitations and disability in a biracial cohort: the Atherosclerosis Risk in Communities Study. Am J Clin Nutr. 2005 Feb;81(2):515-22.

Beydoun MA, Kaufman JS, Sloane PD, Heiss G, Ibrahim J. n-3 Fatty acids, hypertension and risk of cognitive decline among older adults in the Atherosclerosis Risk in Communities (ARIC) study. Public Health Nutr. 2008 Jan;11(1):17-29.

Nettleton JA, Volcik KA, Hoogeveen RC, Boerwinkle E. Carbohydrate intake modifies associations between ANGPTL4[E40K] genotype and HDL-cholesterol concentrations in White men from the Atherosclerosis Risk in Communities (ARIC) study. Atherosclerosis. 2009 Mar;203(1):214-20. Epub 2008 Jul 2.

Beydoun MA, Kaufman JS, Ibrahim J, Satia JA, Heiss G. Measurement error adjustment in essential fatty acid intake from a food frequency questionnaire: alternative approaches and methods. BMC Med Res Methodol. 2007 Sep 14;7:41.
Stevens J, Ahn K, Juhaeri, Houston D, Steffan L, Couper D. Dietary fiber intake and glycemic index and incidence of diabetes in African-American and white adults: the ARIC study. Diabetes Care. 2002 Oct;25(10):1715-21.

Hart Sailors ML, Folsom AR, Ballantyne CM, Hoelscher DM, Jackson AS, Linda Kao WH, Pankow JS, Bray MS. Genetic variation and decreased risk for obesity in the Atherosclerosis Risk in Communities Study. Diabetes Obes Metab. 2007 Jul;9(4):548-57.

Shimakawa T, Nieto FJ, Malinow MR, Chambless LE, Schreiner PJ, Szklo M. Vitamin intake: a possible determinant of plasma homocyst(e)ine among middle-aged adults. Ann Epidemiol. 1997 May;7(4):285-93.

Shimakawa T, Sorlie P, Carpenter MA, Dennis B, Tell GS, Watson R, Williams OD. Dietary intake patterns and sociodemographic factors in the atherosclerosis risk in communities study. ARIC Study Investigators. Prev Med. 1994 Nov;23(6):769-80.

Bidulescu A, Chambless LE, Siega-Riz AM, Zeisel SH, Heiss G. Usual choline and betaine dietary intake and incident coronary heart disease: the Atherosclerosis Risk in Communities (ARIC) study. BMC Cardiovasc Disord. 2007 Jul 13;7:20.

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? _X_ Yes ____ No

11.b. If yes, is the proposal

_X_ A. primarily the result of an ancillary study (list number* ARIC Brain MRI:__1999.01_____)

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

References:

1. Estruch R, Ros E, Salas-Salvadó J, et al. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet. New England Journal of Medicine 2013;368:1279-1290.
2. Sofi F, Cesari F, Abbate R, Gensini GF, Casini A. Adherence to Mediterranean diet and health status: meta-analysis. BMJ 2008;337:a1344.
3. Tangney CC, Kwasny MJ, Li H, Wilson RS, Evans DA, Morris MC. Adherence to a Mediterranean-type dietary pattern and cognitive decline in a community population. Am J Clin Nutr 2011;93:601-607.
4. Feart C, Samieri C, Rondeau V, et al. Adherence to a Mediterranean diet, cognitive decline, and risk of dementia. JAMA 2009;302:638-648.
5. Scarmeas N, Luchsinger JA, Schupf N, et al. Physical activity, diet, and risk of Alzheimer disease. JAMA 2009;302:627-637.
6. Gu Y, Luchsinger JA, Stern Y, Scarmeas N. Mediterranean diet, inflammatory and metabolic biomarkers, and risk of Alzheimer's disease. J Alzheimers Dis 2010;22:483-492.
7. 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;62:1849-1853.
8. Whalley LJ, Deary IJ, Starr JM, et al. n-3 Fatty acid erythrocyte membrane content, APOE varepsilon4, and cognitive variation: an observational follow-up study in late adulthood. Am J Clin Nutr 2008;87:449-454.
9. Valls-Pedret C, Lamuela-Raventos RM, Medina-Remon A, et al. Polyphenol-rich foods in the Mediterranean diet are associated with better cognitive function in elderly subjects at high cardiovascular risk. J Alzheimers Dis 2012;29:773-782.
10. Nettleton JA, Volcik KA, Hoogeveen RC, Boerwinkle E. Carbohydrate intake modifies associations between ANGPTL4[E40K] genotype and HDL-cholesterol concentrations in White men from the Atherosclerosis Risk in Communities (ARIC) study. Atherosclerosis 2009;203:214-220.
11. Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean diet and survival in a Greek population. N Engl J Med 2003;348:2599-2608.