ARIC Manuscript Proposal # 3239

PC Reviewed: 9/11/2018 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Dietary patterns and risk of incident dementia and cognitive decline: Results from the ARIC study.

b. Abbreviated Title (Length 26 characters): Dietary patterns and dementia

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

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3. Timeline: Analyses will begin immediately after manuscript proposal is approved. We plan to have a manuscript ready for co-authors to review within one calendar year.

4. Rationale:

It has been estimated that 47 million people worldwide lived with dementia in 2016. With an aging population, this number is projected to increase to at least 131 million people by the year 2050 [1]. The economic burden of dementia is also growing and the total estimated cost of dementia worldwide is $818 billion and is expected to increase.

Prevention of cognitive decline and dementia is critical due to the current lack of effective treatments for dementia. Modifiable lifestyle factors such as diet are a low-cost and potentially effective way to reduce the risk and burden of cognitive decline and dementia. Increasing evidence suggests that the Mediterranean diet may be associated with a reduced risk of cognitive decline and dementia. The Mediterranean diet is known for a combination of foods that have high amounts of omega-3 fatty acids and polyphenols, which have been found to be associated with better cognitive function [2, 3]. For example, olive oil and nuts contain high amounts of phenolic compounds that may counteract the oxidative processed in the brain that lead to neurodegeneration [4]. Further, polyphenols may improve cerebrovascular blood flow and stimulate neurogenesis [5]. Omega-3 fatty acids (EPA, DHA, and ALA) are known for reducing inflammation and oxidative stress, which are associated with cognitive function [6, 7]. Another reason may involve the cardioprotective role of the Mediterranean diet, which has been found to reduce cardiovascular disease and potentially reduce obesity, hypertension and dyslipidemia [8, 9]. Since obesity and hypertension are risk factors of Alzheimer's disease, they may be mediators in the diet and cognitive decline/dementia association. One study found that participants who had lower adherence to the Mediterranean diet had reduced rates of glucose metabolism and increased beta-amyloid deposition in Alzheimer Disease-affected areas compared to the group that had high adherence to the Mediterranean diet [10].

Fewer studies have focused on other dietary patterns such as the Dietary Approaches to Stop Hypertension (DASH) diet or dietary scores based on national guidelines such as the Healthy Eating Index (HEI) or Alternate Healthy Eating Index (AHEI). However, these dietary patterns have been found to also reduce the risk of cardiovascular disease and its comorbidities and therefore may also reduce the risk of cognitive decline and dementia as vascular risk factors have been found to be associated with risk of dementia [11]. If these dietary patterns indeed do have similar effects on reducing cognitive decline, they may serve as alternate recommendations to the Mediterranean diet for primary prevention since the Mediterranean diet may not fit everyone's lifestyle and sociocultural preferences.

We aim to determine whether healthy dietary patterns (Mediterranean, DASH, HEI, AHEI) are associated with cognitive decline and incident dementia in the ARIC Study. If these dietary patterns are associated with slower cognitive decline and lower risk of dementia, it will confirm previous findings that the Mediterranean diet is useful as a preventive measure and may suggest that the other dietary patterns may be alternative options of healthy dietary patterns to reduce cognitive decline and dementia.

5. Main Hypothesis/Study Questions: We hypothesize that higher scores, indicating greater adherence, for the alternate Mediterranean (aMed) diet score, DASH diet score, HEI-2015, and AHEI-2010 are associated with a lower risk of incident dementia and cognitive decline in the ARIC study.

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 methodologic limitations or challenges if present).

Study Design:
We will conduct a prospective analysis using a definition of cognitive dysfunction based on neuropsychological assessments performed in visit 2 (1990-92), visit 4 (1996-98), and visit 5 (2011-2013). We will also use measures of dementia from the ARIC-NCS study (visit 5, 2011-2013).

Inclusion/Exclusion:
We will exclude participants who are missing food frequency questionnaire (FFQ) data, participants with extreme total caloric intake (females: <500 kcal/d or >3,500 kcal/d; males: <700 kcal/d or >4,500 kcal/d), participants who did not undergo neuropsychological testing at visit 2, participants with stroke at baseline, and participants with missing covariates.

Exposure:
The 4 primary exposures are the alternate Mediterranean diet score, DASH diet score, HEI-2015 score, and the AHEI-2010 score. Diet scores will be coded using the average FFQ responses from visits 1 and 3. The scores will be divided into quantiles for analyses.

Alternate Mediterranean diet score (aMed) [8]:

- Ranges from 0 (lowest) to 9 (highest)
- 9 components (vegetables excluding potatoes, fruits, nuts, whole grains, legumes, fish, fatty acids, red and processed meats, alcohol)
- Each of the first 7 components will be scored 1 if they are above the median intake; otherwise 0; red and processed meats will be scored 1 if they are below the median intake; otherwise 0; alcohol will be scored 0 or 1 based on sex-specific cutoffs

DASH diet score [12]:

- Ranges from 8 to 40
- 8 components (fruits, vegetables, whole grains, nuts and legumes, low-fat dairy, red and processed meat, sweetened beverages, sodium)
- Each component is scored from 1 to 5 based on rank distribution in quintiles with higher scores for lower intake of red and processed meat, sweetened beverages, and sodium, and with higher scores for higher intake of fruits, vegetables, whole grains, nuts and legumes, and low-fat dairy
- We will conduct a sensitivity analysis for the DASH diet score using a DASH score based on 9 nutrients (saturated fat, total fat, cholesterol, sodium, protein, fiber, magnesium, calcium, potassium) [13]

HEI-2015 score[a]:

- Ranges from 0 to 100
- 13 components: adequacy (total fruits, whole fruits, total vegetables, greens and beans, whole grains, dairy, total protein, seafood and plant protein, fatty acids) and moderation (refined grains, sodium, added sugars, and saturated fats)
- Each component is scored based on whether the participant meets the energy-adjusted cutoffs for achieving the minimum or maximum scores

AHEI-2010 score [14]:

- Ranges from 0 to 110
- 11 components (fruits, vegetables, sugar-sweetened beverages and juices, nuts and legumes, whole grains, alcohol, omega-3 fatty acids, trans fats, polyunsaturated fatty acids, sodium, and red meat)
- Similar to the HEI-2015 index, each component receives a score based on a cutoff (servings/day) for minimum or maximum scores

Outcomes:

Incident dementia from visit 1 to visit 5: There were 3 levels of dementia ascertainment. For our definition of dementia we will use Level 3, which includes Levels 1 and 2 [11].

- Level 1: Adjudicated dementia defined as >1 cognitive domain worse than -1.5 z, functional activities questionnaire<=5, clinical dementia rating between 0.5 and 3, decline below 10^{th} percentile on 1 test or 20^{th} percentile on 2 tests, or MMSE score <21 for whites, <19 for blacks from visit 5 (ARIC-NCS) neuropsychological battery interview
- Level 2: Level 1 + Participants who were classified as having dementia based on Telephone Interview for Cognitive Status-Modified (TICSm), living or deceased persons classified as having dementia using Clinical Dementia Rating and Functional Activities Questionnaire among a subset that were suspected of having dementia
- **Level 3**: Level 2 + Dementia identified by surveillance based on a prior discharge hospitalization ICD-9 or death certificate code

Cognitive decline from visit 2 to visit 5

- Scores based on the Delayed Word Recall Test (DWRT), Digit Symbol Substitution Test (DSST), and Word Fluency Test (WFT)
- Test scores will be converted to z-scores standardized to the visit 2 mean and SD for each test
- Global cognition z-scores standardized to visit 2 global z mean and SD will be generated for each visit

Covariates: We will use the following variables as covariates: sex, race-center, age, physical activity, smoking, education, total energy intake, total cholesterol, prevalent CHD, ApoE status, BMI, hypertension, and diabetes.

[a] https://epi.grants.cancer.gov/hei/developing.html#2015

Main Analyses: Incident Dementia

1) We will assess differences in baseline (visit 2) characteristics by dietary pattern quantiles.
2) We will use Cox proportional hazards regression models to study the association between dietary patterns and incident dementia using the following models.
    a. Model 1: Age, sex, race-center, total energy intake
    b. Model 2 (primary model): Model 1 + adjusted for education, ApoE status, smoking, physical activity
    c. Model 3 (mediation analysis): Model 2 + adjusted diabetes, hypertension, BMI, prevalent CHD, HDL cholesterol
3) We will use the cumulative average of FFQ responses from visits 1 and 3 for a more precise measurement of food intake.
4) We will stratify analyses by age, race, smoking, diabetes, hypertension, ApoE status and test for interactions.
5) We will examine the association between individual components of each diet pattern and incident dementia.

Main Analyses: Cognitive Decline

1) We will assess differences in baseline (visit 2) characteristics by dietary pattern quantiles.
2) We will use mixed effects models to study the association between dietary pattern quantiles and cognitive change from visit 2 to visit 5, with a spline term at visit 4, using the following models.
    a. Model 1: Age, sex, race-center, total energy intake
    b. Model 2 (primary model): Model 1 + adjusted for education, ApoE status, smoking, physical activity
    c. Model 3 (mediation analysis): Model 2 + adjusted diabetes, hypertension, BMI, prevalent CHD, HDL cholesterol
3) We will stratify analyses by age, race, smoking, diabetes, hypertension, ApoE status and test for interactions.
4) We will assess whether attrition differs by quantile of diet scores. If attrition needs to be addressed, we will use the MICE method to impute missing values for visits 4 and 5, which has been described previously [15]. Missing values for global z-score will be imputed based on observed values for individuals.
5) We will examine the association between individual components of each diet pattern and cognitive decline.

Limitations:

A limitation of measuring dietary exposures through FFQ is self-reporting bias, as there may be over- or underreporting. Additionally, diet may change over time; however, previous analyses in ARIC have shown that there is minimal change in dietary pattern scores from visit 1 to visit 3. We will use the average of FFQ responses from visits 1 and 3 for a more precise estimate of food intake. Another limitation is that cognitive function was only measured several times throughout a long time period, with no measures between visits 4 and 5 (15 year gap). However, we have early measures of cognitive function from the beginning of the study, allowing for long follow-up. The number of participants who attended visit 5 was only 6,471, despite a larger number of

participants being alive at that time. Therefore, we will use multiple imputation method to calculate cognitive function of participants who were alive but did not attend visit 5.

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 ICTDER 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? ____ Yes __x__ No

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"? ____ 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)?

Manuscript proposals:
MS #2145: Nutrition, Healthy Diet and 21-year Cognitive Decline (first author: Dearborn)
Our proposal does not overlap with this paper as the first author has notified us that her paper will only include principal components analysis and not the Mediterranean diet.

MS #2200: Lipids, statins, and dementia: The ARIC-Neurocognitive Study
Does not examine dietary patterns.

MS #1916: Dietary predictors of structural brain MRI abnormalities (first author: Steffen)
This proposal examines exposures that are nutrients (omega-3 fatty acids, vitamin B) and food groups (fish, red and processed meat) and a Western dietary pattern derived from principal components analysis. The exposures do not overlap with the dietary patterns we plan to use.

MS #3155: Diet quality scores and incident kidney disease in the ARIC study (first author: Hu, last author: Rebholz)
Uses a different outcome.

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

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* _____)

___ 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/

12a. 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.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PubMed Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes _x___ No

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