1.a. Full Title: Dietary predictors of structural brain MRI abnormalities

b. Abbreviated Title (Length 26 characters): Diet and brain MRI measures

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

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3. Timeline: 1 year
   (lit review; data analysis, manuscript prep, coauthor review, ARIC review)

4. Rationale:
   There is increasing evidence that greater intake of long-chain omega-3 PUFAs, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), may confer benefits in a variety of neurological disorders, including ischemic stroke (1), cognitive dysfunction (2), and Alzheimer’s disease (3). Brain MRI measures, such as brain volume, white matter hyperintensity, and sulcal width, that have been linked with these conditions (4,5) have recently been related to plasma and dietary intake of B vitamins and omega3 fatty acids as well as foods rich in these nutrients.
Fish and omega3 fatty acid intake, stroke, and cognitive function. Regular intake of fish has been inversely related to the risk of developing ischemic stroke and Alzheimer’s disease but also atherosclerotic dementia (1,6,7). Further, elderly men and women with dementia but also minor cognitive impairment have lower red blood cell phospholipid DHA compared to controls (8).

Fish and brain MRI measures. In the Cardiovascular Health Study brain MRI study of 2313 older adults, tuna and other fish intake was associated with lower incidence of subclinical infarcts and better white matter grade, but not with markers of brain atrophy, sulcal and ventricular grades (9). No significant association was found between fried fish consumption and any brain MRI measure. These results add to the growing body of evidence that omega3 fatty acids are beneficial to health.

Vitamin B intake, cognitive function, and brain MRI measures. Low vitamin B12 status was related to faster rate of cognitive decline among a subsample of participants enrolled in the Chicago Health and Aging Project (CHAP) (10) and among Mexican American seniors (11). In another analysis of CHAP data using brain MRI measures, homocysteine and other vitamin B12 markers were related to lower total brain volume and higher white matter hyperintensity volume (12).

Most studies of brain MRI have been small and cross-sectional or short follow-up in design. Further, few studies have reported the relations of dietary intake with brain MRI measures. Therefore, we propose to examine the relations of dietary intake, including selected nutrients (vitamin Bs and omega3 and saturated fatty acids), foods rich in these nutrients (fruit, vegetables, meat, and fish) and measures of brain MRI. Because the Western diet pattern is characterized by low intake of fruit, vegetables, and fish but high intake of red and processed meat, we will also examine the relations of the Western diet pattern with the brain MRI measures ventricular size, white matter hyperintensities, sulcal width, and burden of infarcts in over 1000 adults enrolled in the ARIC ancillary study #1999.01 ‘MRI and Neurocognitive Longitudinal Study (BrainMRI)’.

5. Main Hypothesis/Study Questions:

We hypothesize that dietary antioxidant, vitamin B, and omega3 fatty acid intake will be beneficially related and that saturated fat intake is adversely related to structural brain MRI abnormalities. Further, foods rich in these nutrients will follow a similar pattern and that a Western diet pattern (a diet characterized by lower intake of fruit, vegetables, and fish and higher in meat) will be related to brain MRI abnormalities.

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: Cross-sectional and prospective study
We will examine cross-sectional relations between dietary intake (exams 1+3) and MRI measures at exam 3; we further, will examine the relations of dietary intake (exams 1+3) and change in brain MRI measures between year 6 (exam 3: 1994-95) and year 14 (2004-06).

**Study population:** African American and white ARIC participants enrolled in the BrainMRI ancillary study (n=1812) at exam 3 (1994-95) and year 14 (2004-06) (n=1112). These participants were recruited from the Forsythe County, NC and Jackson, MS field centers.

**Inclusion criteria:**
Cross-sectional study: Participants with exam 1 and 3 food frequency questionnaires and had complete brain MRI data (of sufficient quality) at exam 3.
Prospective study: Participants with baseline and exam 3 food frequency questionnaires and complete brain MRI data (of sufficient quality) at both an initial and follow-up brain MRI scans.

**Exclusion criteria:** Outlying dietary intake 500 and 700 kcal for women and men, respectively and > 3500 and 4500 for women and men respectively. Brain MRI scans which were not of sufficient quality.

**Cross-sectional study**

**Exposure variables – the average of dietary intake at exams 1+3 FFQ:**
1) Dietary EPA, DHA, n3 fatty acids (EPA+DHA=n3), saturated fat
2) Vitamin B intakes include vitamin B6, B12, and folate
3) Food intake: fish; red and processed meat; fruit, vegetables, refined and whole grains
4) Western dietary pattern derived from principal components analysis (PCA)

**Outcome variables include brain MRI measures in 1994-95:**
Prevalent MRI infarcts, white matter hyperintensities (grade) and cerebral atrophy (sulcal size, ventricular size). The methods described in previous ARIC studies (13, 14) will be used to estimate the extent of white matter hyperintensities, sulcal size and ventricular size. Prevalent infarcts will be defined according to previous methods (13).

**Prospective study**

**Exposure variables - the average of dietary intake at exams 1+3 FFQ:**
1) Dietary EPA, DHA, n3 fatty acids (EPA+DHA=n3), saturated fat
2) Vitamin B intakes include vitamin B6, B12, and folate
3) Food intake: fish; red and processed meat; fruit, vegetables, refined and whole grains
4) Western dietary pattern derived from principal components analysis (PCA)

**Outcome variables include brain MRI measures in 1994-95 and 2004-06:**
Incident MRI infarcts, white matter hyperintensities (progression of grade) and cerebral atrophy (progression of sulcal size and ventricular size). The methods described in
previous ARIC studies (13, 14, 15) will be used to estimate the extent of and progression of white matter hyperintensities, sulcal size and ventricular size. Prevalent and incident infarcts will be defined according to previous methods (13).

**Confounding factors at exam 3:**
Age, race, sex, field center, education, smoking, alcohol use, BMI, blood pressure, hypertension status, diabetes status, lipids, glucose, depression (vital exhaustion at V2 as proxy), prevalent CHD, stroke, and HF at V3, and HRT and menopausal status (women).

**Analysis plan:**

1. **Descriptive characteristics at exam 3.**
2. **Cross-sectional study:** The average of exams 1+3 dietary data will be categorized into tertiles. Linear regression analysis will evaluate the relations of exam 3 brain MRI measures across tertiles of dietary intake, adjusting for confounding factors. Logistic regression analysis will evaluate the relations between tertiles of dietary intake (the average of exams 1+3 dietary intake variables) and prevalent MRI infarcts adjusting for confounding factors.
3. **Prospective study:** The average of exam 1+3 dietary data will be categorized into tertiles. Linear regression analysis will be used to evaluate the relations of the progression of brain MRI measures across tertiles of dietary intake, adjusting for confounding factors. Logistic regression analysis will be used to evaluate the relations between average of exams 1+3 dietary intake and incident brain MRI infarcts adjusting for confounding factors.

**We expect** that omega3 fatty acids (EPA+DHA) and fish intake will be greater among individuals with lower grade and less progression of brain MRI measures and fewer infarcts, while the opposite will be true for greater intakes of saturated fat, red and processed meat, and higher scores for the Western diet pattern. Greater vitamin B intake will likely be related to lower grade and less progression of brain MRI measures; however, significant relations have only been observed with plasma data in previous studies.

**References**


7.a. Will the data be used for non-CVD analysis in this manuscript?  ____ Yes  ___ 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?  ____ Yes  ___ 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.csc.unc.edu/ARIC/search.php
   ___X___ Yes    _______ No overlap

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)?

Brain MRI papers published in Neurology 2011, 2005

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 (#___1999.01_____
MIR and Neurocognitive Longitudinal Study (BrainMRI)
   ____ 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.csc.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.csc.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.