ARIC Manuscript Proposal #2558

PC Reviewed: 5/12/15	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Plasma fatty acids and cognitive decline: the ARIC Neurocognitive Study

b. Abbreviated Title (Length 26 characters):
Plasma fatty acids and cognition

2. Writing Group:
Danni Li, Alvaro Alonso, Jeff Misialek, Lyn Steffen, David Knopman, Lisa Wruck, Rebecca Gottesman, Thomas Mosley, A. Richey Sharrett

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

First author: **Danni Li**
Address: 420 Delaware Street, MMC609, Minneapolis, MN 55455
University of Minnesota
Phone: 612 626 8597
E-mail: alonso@umn.edu

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).
Name: **Alvaro Alonso**
Address: 1300 S 2nd St, Suite 300
Epidemiology and Community Health
University of Minnesota

Phone: 612 626 8597 Fax:
E-mail: alonso@umn.edu

3. Timeline:
Analysis to be done over the next 6 months. A final draft will be completed in 2 months afterwards.

4. Rationale:
Concentrations of plasma fatty acids are biomarkers of dietary fat intake and also provide information on lipid-related metabolic pathways. Thus, studying the association of plasma fatty acids with cognitive decline can yield evidence for the development of preventive interventions (through dietary recommendations and supplementation) and inform our understanding of the role of lipid metabolism in cognitive function. A previous analysis in the participants from the ARIC Minneapolis field center, considering plasma fatty acids measured at baseline and cognitive data from visits 2 and 4, found that higher levels of palmitic acid (a saturated fatty acid), lower levels of linoleic acid (an essential ω-6 PUFA), and lower levels of ω-3 polyunsaturated fatty acids (PUFA) were associated with faster cognitive decline.[1] These observations, particularly those regarding ω-3 PUFAs, are consistent with results from separate cohorts.[2-4] Results from other studies, however, have been inconsistent, which may be due to study design and differences in population characteristics. For example, a recent publication from the Women Health Initiative Study of Cognitive Aging (WHISCA), which included women 65 and older, did not find an association between red blood cell levels of fish-derived ω-3 fatty acids and cognitive impairment.[5]

In the present proposal, we will assess the association of plasma fatty acids, measured in ARIC participants from the Minnesota field center at baseline, with cognitive decline over a 20 year period. This analysis will extend the published ARIC analysis taking into account the additional cognitive information collected during ARIC visit 5/NCS.

5. Main Hypothesis/Study Questions:
The main aim of this study is to assess the association of plasma concentrations of cholesteryl ester and phospholipid fatty acids in ARIC participants from the Minnesota field center.

We hypothesize that higher concentrations of total saturated fatty acids (SFA) and lower of polyunsaturated fatty acids (PUFA), including total ω-3 PUFA, fish-derived ω-3 PUFA, and α-linolenic acid, will be associated with more pronounced cognitive decline over a 20 year follow-up.

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 population
Participants from the Minnesota field center with plasma fatty acids measurement at visit 1 and cognitive assessment at visit 2.

Participants will be excluded if they were not white, had missing education information, missing APOE genotype or missing other covariates, were missing one or more cognitive function tests at baseline, did not consent for non-CVD research or for the use of their

genetic data. We will also exclude participants using fish supplements or lipid lowering medications at visit 1 (in a sensitivity analysis, we will include fish supplement users).

Exposure of interest

At baseline, fatty acid analysis was done in plasma phospholipid and cholesteryl ester fractions from visit 1 samples. In total, 29 different fatty acids were measured. To facilitate comparison across fatty acids, mean-centered standardized values will be used in all analyses.

Outcome

Cognitive testing using the Delayed Word Recall test (DWR), Digit Symbol Substitution test (DSS), and Word Fluency test (WF) was done at visits 2 (1990-92), 4 (1996-98) and 5 (2011-13). Cognitive testing will be standardized using the mean and standard deviation at visit 2. We will also calculate a global cognitive score as the standardized mean of the 3 cognitive tests at each visit.

Other variables

Covariates to be considered in our analysis include: age, sex, education level, occupation, APO ε4 status (number of APOE ε4 alleles), cigarette smoking, alcohol consumption, physical activity, body mass index, systolic blood pressure, use of antihypertensive medication, diabetes, total cholesterol, HDL-cholesterol, triglycerides, prevalent CHD, prevalent HF, and prevalent stroke. In our analysis, we will use covariates assessed at visit 1, when plasma fatty acids were measured. We will assume that exposure that affect fatty-acid levels and covariates remain consistent from Visit 1 to Visit 2.

Statistical analysis

Analyses will follow the recommendations from the ARIC-NCS Analysis Committee.

Based on the associations found in the previously published ARIC analysis, we will conduct separate analysis for the following fatty acids:

- Total SFA
- Total ω-3 PUFA, and separately:
    - α-linolenic acid
    - Fish-derived ω-3 PUFA (DHA, EPA, DPA)
- Palmitic acid
- Linoleic acid

In a hypothesis-generating analysis, we will assess individually the remaining 24 fatty acids measured as part of the lipid profiling done at baseline. The threshold to consider an association statistically significant will be adjusted using a Bonferroni correction (0.05 / 24 = 0.002).

We will run GEE models with an unstructured correlation matrix and robust variance estimates, including the fatty acid and an interaction of the fatty acid with time as the main independent variables, adjusting for the previously mentioned covariates and interaction of those covariates with time. Age will be centered at baseline, and included

as both a linear and quadratic term. Time from visit 2 will be considered as the time variable. We will use a spline for time, consistent with the analysis committee's recommendations.

We will conduct sensitivity analyses using inverse probability weighting and multiple imputation chained equations (MICE) to adjust for attrition, using extended models that use TICS data, and modeling expected scores among individuals who did not participate in visit 5/NCS and had a dementia hospitalization between visits 4 and 5, as previously described.[6]

We will test effect modification by age, sex, APOE ε4 status, and obesity.

7.a. Will the data be used for non-CVD analysis in this manuscript? __X__ 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? _X__ 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?
__X__ 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"?
__X__ 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)?

MS 1010: Omega-3 fatty acids, hypertension and risk of cognitive decline among older adults (Beydoun). This published manuscript used cognitive data from visits 2 and 4.

MS 2145: Nutrition, healthy diet and 21-year cognitive decline (Dearborn). This manuscript uses information obtained from the food-frequency questionnaires, not from plasma fatty acid measurements.

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*)

___ 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.

REFERENCES

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2. Heude B, Ducimetière P, Berr C. Cognitive decline and fatty acid composition of erythrocyte membranes—The EVA Study. *Am J Clin Nutr.* 2003;77:803-808.
3. Dullemeijer C, Durga J, Brouwer IA, et al. n−3 Fatty acid proportions in plasma and cognitive performance in older adults. *Am J Clin Nutr.* 2007;86:1479-1485.
4. Samieri C, Féart C, Proust-Lima C, et al. Omega-3 fatty acids and cognitive decline: modulation by ApoEε4 allele and depression. *Neurobiology of Aging.* 2011;32:2317.e2313-2317.e2322.
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6. Gottesman RF, Rawlings AM, Sharrett AR, et al. Impact of differential attrition on the association of education with cognitive change over 20 years of follow-up: the ARIC Neurocognitive Study. *Am J Epidemiol.* 2014;179:956-966.