ARIC Manuscript Proposal # 1836

PC Reviewed: 8/9/11	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:

Plasma Fatty Acid Composition and Incidence of Ischemic Stroke in Middle Aged Adults: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters):

Plasma FA and stroke

2. Writing Group:

Writing group members: Kazumasa Yamagishi, Aaron R. Folsom, Lyn Steffen, and others.

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

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3. Timeline: 3 months

Approval of proposal	
Outline paper	- 1 week
Data analysis	- 3 weeks
Manuscript writing	- 4 weeks
Review and edit	- 4 weeks

4. Rationale:

Previous epidemiological studies have examined the association of dietary intake of several fatty acids with stroke (1-3), but evidence of an association between plasma fatty acids composition, common biomarkers of fatty acid, and stroke is limited. The results have not been consistent and conclusive, for example, dietary saturated fatty acids was inversely associated with ischemic stroke in Framingham Heart Study (4) and not associated in Health Professionals Follow-up Study (5), but a serum study reported it was positively associated (6).

In the ARIC Minneapolis field center, fractions of cholesterol ester (CE) and phospholipids (PL) plasma fatty acids at baseline were measured by gas-liquid chromatography. The associations with carotid artery intima-media thickness (7), hypertension (8), diabetes (9), coronary heart disease (10), cognitive decline (11) and heart failure (12) have been already examined. We propose to examine the association of CE and PL fractions of plasma fatty acids composition and ischemic stroke in the ARIC Minneapolis cohort.

5. Main Hypothesis/Study Questions:

(1) Plasma long-chain omega-3 PUFAs are associated inversely with ischemic stroke. These associations persist for EPA and DHA separately.
(2) Plasma saturated fatty acids are associated positively with stroke.
(3) Plasma monounsaturated fatty acids and omega-6 PUFAs are associated inversely and modestly with stroke. MUFA in plasma often is correlated positively with SFA, so the opposite association could.
(4) We will further analyze association of stroke with specific fatty acids, including linoleic acid, oleic acid etc, enzyme activities and P/S ratio.

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).

Sample: Minnesota participants (n=4,009) with fatty acid data

Exclusions: missing fatty acid compositions, prevalent prevalent stroke, non-white

Dependent variable: incident ischemic stroke (n=170).

Independent variable: PL and CE fatty acids

Covariates: age, sex, smoking, cigarette-year, alcohol intake, education levels and other factors. Food frequency data will be used to help interpret our findings.

Analysis plan: Hazard ratios and 95% confidence intervals of stroke for quartiles of fatty acids composition will be calculated adjusted for age and other covariates using

Cox proportional hazard model. Factors potentially on the causal pathway, such as high blood pressure or diabetes, will be added to examine whether they attenuate the associations. If there are significant sex interactions, data will be analyzed sex-specifically. Interactions will be tested using cross product terms.

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 ICTDER02 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 ICTDER02 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 ICTDER02 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)?

#890 Plasma fatty acid composition and incidence of coronary heart disease in middle aged adults: The Atherosclerosis Risk in Communities (ARIC) Study
First author: Lu Wang

#890B Plasma fatty acid composition and incidence of heart failure in middle aged adults: The Atherosclerosis Risk in Communities (ARIC) Study
First author: Kazumasa Yamagishi

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/

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.

Reference

(1) Psota TL, Gebauer SK, Kris-Etherton P. Dietary omega-3 fatty acid intake and cardiovascular risk. *Am J Cardiol* 2006;98(suppl):3i-18i.

(2) Siri-Tarino PW, Sun Q, Hu FB, Krauss RM. Meta-analysis of prospective cohort studies evaluating the association of saturated fat with catdiovascular disease. Am J Clin Nutr 2010;91:535-46.

(3) Wang C, Harris WS, Chung M, Lichtenstein AH, Balk EM, Kupelnick B, Jordan HS, Lau J. n-3 Fatty acids from fish or fish-oil supplements, but not alpha-linolenic acid, benefit cardiovascular disease outcomes in primary- and secondary-prevention studies: a systematic review. Am J Clin Nutr 2006;84:5-17.

(4) Gillman MW, Cupples LA, Millen BE, Ellison RC, Wolf PA. Inverse association of dietary fat with development of ischemic stroke in men. JAMA 1997;278:2145-50.

(5) He K, Merchant A, Rimm EB, et al. Dietary fat intake and risk of stroke in male US healthcare professionals: 14 year prospective cohort study. BMJ 2003;327:777-82.

(6) Iso H, Sato S, Umemura U, Kudo M, Koike K, Kitamura A, Imano H, Okamura T, Naito Y, Shimamoto T. Linoleic acid, other fatty acids, and the risk of stroke. Stroke 2002;33:2086-93.

(7) Ma J, Folsom AR, Lewis L, Eckfeldt JH. Relation of plasma phospholipid and cholesterol ester fatty acid composition to carotid artery intima-media thickness: the Athersoclerosis Risk In Communities (ARIC) Study. *Am J Clin Nutr* 1997;65:551-559.

(8) Zheng ZJ, Folsom AR, Ma J, Arnett DK, McGovern PG, Eckfeldt JH. Plasma fatty acid composition and 6-year incidence of hypertension in middle-aged adults: the Athersoclerosis Risk In Communities (ARIC) Study. *Am J Epidmiol* 1999;150:492-500.

(9) Wang L, Folsom AR, Zheng ZJ, Pankow JS, Eckfeldt JH; ARIC Study Investigators. Plasma fatty acid composition and incidence of diabetes in middle-aged adults: the Athersoclerosis Risk In Communities (ARIC) Study. *Am J Clin Nutr* 2003;78:91-98.

(10) Wang L, Folsom AR, Eckfeldt JH. Plasma fatty acid composition and incidence of coronary heart disease in middle-aged adults: the Athersoclerosis

Risk In Communities (ARIC) Study. *Nutr Metab Cardiovasc Dis* 2003;13:256-266.

(11) Beydoun MA, Kaufman JS, Satia JA, Rosamond W, Folsom AR. Plasma n-3 fatty acids and the risk of cognitive decline in older adults: the Athersoclerosis Risk In Communities (ARIC) Study. *Am J Clin Nutr* 2007;85:1103-1111.

(12) Yamagishi K, Nettleton JA, Folsom AR. Plasma fatty acid composition and incident heart failure in middle-aged adults: the Athersoclerosis Risk in Communities (ARIC) Study. *Am Heart J* 2008;156:965-974.