ARIC Manuscript Proposal # 802 (Revised)

1. a. Full Title: Dietary fat and risk of CHD and stroke incidence and mortality in the ARIC study.
   b. Abbreviated Title (Length 26 characters): Dietary fat and CVD

2. Writing Group (list individual with lead responsibility first):

   Lead:

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   As requested by the Publications Committee, we are also contacting Dr. Chambless and Dr. Goff to assess their interest in this proposal.

3. Timeline: 6 months
   - Approval of proposal
   - Literature review – 4 weeks
   - Outline paper – 2 weeks
   - Data analysis – 10 weeks
   - Write manuscript – 4 weeks
   - Review and edit paper – 4 weeks

4. Rationale:

   International comparisons and metabolic studies suggest that diets high in saturated fats and
cholesterol and low in polyunsaturated fats increase the risk of cardiovascular incidence and mortality. Unfortunately, the results of prospective epidemiological investigations of nutrient intake and of biomarkers have been inconsistent. We propose to explore the relationships between fat intake and CVD incidence and mortality in the ARIC study.

Dietary fat and CHD mortality

Previous data are compatible with the hypothesis that saturated fat and cholesterol intakes affect the risk of coronary heart disease as predicted by their effects on blood cholesterol concentration. They also support a specific preventive effect of polyunsaturated fatty acid intake. The effects of fatty acids, however, may affect CVD risk beyond their effects on serum cholesterol. In particular, \textit{trans} fatty acids may promote and \textit{ω}-3 fatty acids may prevent CHD. In addition, experimental studies in animals have raised concerns about atherogenic effect of monounsaturated fatty acids. The proposed study will investigate these relationships among men and women, including African Americans.

Dietary fat and stroke mortality

Saturated fatty acids have been found positively correlated with stroke, and low intake of unsaturated fatty acids has been found in patients with stroke. Nevertheless data from prospective studies are scant. The proposed study will assess these associations.

5. Main Hypothesis/Study Questions:

We will explore cardiovascular risk as a function of fatty acid intake. We propose to test the following hypotheses:

Hypothesis 1: The risk of all-cause, CHD and stroke mortality and the risk of CHD and stroke incidence will increase monotonically with increasing intake of saturated fat.

Hypothesis 2: The risk of all-cause, CHD and stroke mortality and the risk of CHD and stroke incidence will increase monotonically with increasing intake of \textit{trans} fatty acids.

Hypothesis 3: The risk of all-cause, CHD and stroke mortality and the risk of CHD and stroke incidence will decrease monotonically with increasing polyunsaturated fatty acids, including \textit{ω}6 and \textit{ω}3 fatty acids.

Hypothesis 4: The risk of all-cause, CHD and stroke mortality and the risk of CHD and stroke incidence will increase monotonically with increasing monounsaturated fatty acid intake.

Proportional hazards regression will be used to examine the relationship between food intake and all-cause, CHD and stroke mortality and the incidence of CHD and stroke in participants enrolled in the ARIC cohort. These hypothesis may result in more than one manuscript.
6. Data (variables, time window, source, inclusions/exclusions):
Variables - Baseline data; and diet at visit 3

Independent variables: Total fat intake, saturated fat intake, polyunsaturated fat intake, monounsaturated fat intake, cholesterol intake, \textit{trans} fatty-acids, and intake of specific fatty acids.

Covariates: age, sex, ethnicity, education, fiber, center, protein intake, BMI, waist/hip ratio, blood pressure, serum cholesterol, serum glucose, HDL-cholesterol, smoking status, physical activity (Sport index 0-5), diabetes status, vitamin intake, blood pressure treatment, alcohol, and total energy intake (kcal).

Dependent variables: time to first event (separate analysis for CHD and stroke mortality and CDH and stroke incidence).

Three models will be fitted:

**Model 1:** This model will include age, race, center, sex and total energy intake, protein intake and intake of the different fatty acids.

**Model 2:** This model will include variables in model 1 and the rest of the covariates at baseline.

**Model 3:** This model will include the same variables as model 2, but will correct for measurement error in nutrient intake data. Measurement error models will be based on the available additional data on intake in visit 2 (about 800 subjects) and visit 3 (full cohort). Using this information, two approaches to correct for measurement error will be explored. The first approach will be to correct the regression coefficients using a calibration method similar to Rosner’s calibration method. The second method will be to develop a Bayesian model to estimate the true intake at baseline based on the diet available at any of the visits collecting diet and other participant characteristics.

Inclusions/exclusions: Exclusions are individuals with: CHD or angina at baseline; missing data for nutritional variables; poor quality in intake data (as defined in the ARIC dataset)...

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 ICTDER01 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 ICTDER01 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

   b. If yes, is the author aware that either DNA data distributed by the Coordinating
      Center must be used, or the file ICTDER01 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://bios.unc.edu/units/csc/ARIC/stdy/studymem.html](http://bios.unc.edu/units/csc/ARIC/stdy/studymem.html)

   _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)?

The present proposal overtakes ms. proposal #44, that was withdrawn. A related ms. was #750,
on food intake patterns and mortality, but their interest in on food patterns (not on nutrients).
Also, the publications committee indicated that we should invite Dr. Goff to participate in this
ms. to ensure that there are no overlaps with ms #591.