1.a. **Full title:** Dietary fat intake modulates the association between the Apolipoprotein E polymorphism and cardiovascular-related disease risk factors and outcomes

1.b. **Abbreviated title:** Apolipoprotein E and dietary fat

2. **Writing group:**
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3. **Time line:**
   Measurement of the apolipoprotein E polymorphism in all African American samples is complete and statistical analyses are expected to be complete by March/April 2001. A draft manuscript is projected to be distributed for internal circulation by June/July 2001.

4. **Rationale:**
   Hypercholesterolemia, hypertriglyceridemia, and decreased serum high-density cholesterol are well-established risk factors for cardiovascular disease (CVD). The apolipoprotein E gene plays a critical role in lipid metabolism and its protein product is an element of very-low-density lipoproteins, chylomicrons, and HDL lipoproteins (Mahley, 1988). The apo E gene is highly variable, with the variant (ε2, ε3, ε4) varying at codons 112 and 158. The ε2 allele (Cys112, Cys158) is associated with lower total cholesterol serum levels, whereas the ε4 allele (Arg112, Arg158) is associated with increased cholesterol serum levels, relative to the ε3 allele (Cys112, Arg158), the most common allele in all populations (Guo et al., 1993; Hallman et al., 1991). African Americans have an increased risk for cardiovascular disease than Caucasians and a higher ε4 allele frequency (Eichner et al., 1989). Although an individual’s genotype may predict his/her disease risk, environmental factors, such as diet, may modulate the effect of an individual’s genotype on disease outcomes. Few studies have examined the influence of dietary fat intake on the relationship between the apolipoprotein E polymorphism and CVD risk factors in a large population-based sample size. Therefore, the purpose of this investigation will be to determine if intake of dietary fat modulates the relationship between the apolipoprotein E polymorphism and cardiovascular-related disease risk factors.

5. **Main Issues/Hypotheses to be addressed:**
a. Influence of dietary intakes of total fat, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, trans fatty acids, the Keys score, and animal fat on the relationship between the apolipoprotein E polymorphism and CVD risk factors (e.g., plasma cholesterol, LDL, HDL, triglycerides).

b. Influence of total fat, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, trans fatty acids, the Keys score, and animal fat consumption on the relationship between the apolipoprotein E polymorphism and incident coronary heart disease (CHD). Analyses will be done univariately and after controlling for a vector of traditional cardiovascular disease risk factors.

c. For all analyses, gender-specific effects will be explored. Analyses of dietary fat will initially be performed using multivariate regression analysis (for quantitative outcome measures) and multivariate survival analysis (for incident CHD). As a follow-up to multivariate analyses, stratified analyses will be performed using centiles of total dietary fat, specific fatty acids, and fat derived from animal sources.

6. Data:
The apolipoprotein E variant will be analyzed using all African Americans residing in Jackson, MS (n = 3,506) and Forsyth County, NC (n = 479) from the ARIC cohort. Exclusion criteria will include diabetes mellitus status and use of cholesterol lowering medications (for analyses of plasma lipids) and prevalent or missing CHD and prevalent or missing transient ischemic attack (for analyses of CHD). Incident CHD will be defined as CHD cases occurring subsequent to visit 1 through 1998. ARIC baseline nutrition and plasma lipid level data will be used in these analyses. Multivariate ANCOVA analyses will be conducted for plasma total cholesterol, high-density cholesterol, low-density cholesterol, and log-transformed total triglycerides, as outcome measures. Cox proportional hazard survival analyses will be conducted for the incident CHD cases. Interactions between ApoE genotyping and total fat, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, trans fatty acids, fat derived from animal sources, and the Keys score will be tested and post hoc stratified analyses for variables exhibiting significant interaction will be performed. Covariates will include age, gender, BMI, and menopausal status/hormone use (for women only).

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 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?  X 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?  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 ICTDER01 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://bios.unc.edu/units/csc
c
_____ X  Yes   _____ No