1.a. Full Title: Retinal Microvascular Abnormalities and the Multiple Metabolic Syndrome

b. Abbreviated Title (Length 26 characters): Retinal Narrowing and MMS

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

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3. Timeline:
   The intent of this analysis is to investigate the cross-sectional association of retinal microvascular disease (as reflected by retinal arteriolar narrowing, retinopathy and other abnormalities) and components of the multiple metabolic syndrome at Visit 3. Initial analyses and writing will take place between October and Jan 2003, final analysis between Feb 2003 and May 2003, and final writing and manuscript submission between June 2003 and October 2003.

4. Rationale:
   The multiple metabolic syndrome (MMS), which consists of a clustering of diseases, including diabetes, hypertension, central obesity and dyslipidemia, is increasingly recognized as being a distinct entity affecting a large proportion of the adult population. The etiology of MMS remains unclear. Microvascular processes have been hypothesized to contribute to the development of the syndrome. In support of such a hypothesis, several characteristics of microvascular disease, including inflammation, endothelial dysfunction and microalbuminuria, have been linked to its occurrence.

   Recent data from the ARIC study indicate that the retina provides a non-invasive window to study correlates of microvascular disease in vivo. Retinal microvascular changes, as assessed via photography, are associated with blood pressure, and independent of blood pressure, with various systemic markers of inflammation and endothelial dysfunction. We have previously shown that baseline retinal arteriolar narrowing was related to incident diabetes and hypertension, suggesting that common microvascular processes (i.e., increased arteriolar resistance and reduced flow) may underlie the pathogenesis of both conditions.

   In the proposed study, we will investigate the cross-sectional relationship of retinal abnormalities with the MMS and its components in the ARIC Study.
5. Main Hypothesis/Study Questions:

1. Retinal microvascular changes are associated with presence of the MMS, as defined according to National Cholesterol Education Program\(^{21,22}\). These include 3 or more of the following signs:
   - Waist circumference greater than 102 cm in men and 88 cm in women
   - Serum triglycerides level of at least 150 mg/dL (1.69 mmol/L);
   - High-density lipoprotein cholesterol level of less than 40 mg/dL (1.04 mmol/L) in men and 50 mg/dL (1.29 mmol/L) in women;
   - Blood pressure of at least 130/85 mm Hg;
   - Serum glucose level of at least 110 mg/dL (6.1 mmol/L).

2. The association of retinal microvascular changes and the MMS complex is significantly stronger than the association of retinal microvascular changes and individual components of the MMS (e.g., hypertension, diabetes).

6. Data (variables, time window, source, inclusions/exclusions):

   (1) MMS component variables at Visit 3: fasting glucose, diabetes, hypertension, hypertensive medications, BP, HDL-C, triglyceride and waist-hip ratio.
   (2) Summary MMS variables: MMS (present is defined as 3 or more components), Number of MMS abnormalities (0, 1, 2, 3, 4, 5).
   (3) Retinal variables at Visit 3: Focal retinal microvascular changes include arteriovenous nicking, focal arteriolar narrowing, retinal hemorrhage and type of hemorrhage (flame-shaped and blot hemorrhage), microaneurysms and soft exudates. Generalized arteriolar narrowing quantified as retinal arteriole-to-venule ratio (AVR), central retinal arteriolar equivalent, central retinal venular equivalent.
   (4) Covariates: age, sex, race, center, prevalent CHD and MI, hemostatic and inflammatory markers (von Willebrand factor, factor VIIIc, fibrinogen, WBC), cigarette smoking, alcohol consumption, body mass index (variables from ARIC visit 1-3, except for von Willebrand factor, factor VIIIc, WBC, fibrinogen available ARIC visit 1 only).
   (5) Exclusion criteria: From participants at ARIC visit 3 (n=12,887), exclude persons who whose race is not black/white, with no or ungradeable retinal photographs and missing information for MS abnormalities at visit 3. Medication use for hypertension, diabetes or dyslipidemia will be used as exclusion criteria for some of the analyses.

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

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”?  ____ 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/cscct/ARIC/study/studymem.html](http://bios.unc.edu/units/cscct/ARIC/study/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)?


References