

ARIC Manuscript Proposal # 1440C

PC Reviewed: 11/11/08
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Longitudinal predictors of retinal microvascular dysfunction: The Atherosclerosis Risk in Communities (ARIC) Carotid MRI Study

b. Abbreviated Title (Length 26 characters): Cumulative exposure and retinopathy

2. Writing Group:

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

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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).

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3. Timeline: Analyses will begin immediately upon approval. We expect data analysis to be complete by spring 2009 with resulting manuscripts complete by summer 2009.

4. Rationale:

Research has consistently implicated microvascular dysfunction in the pathogenesis of several cardiac diseases including incident carotid artery plaque, stroke, and congestive heart failure (Marcus, Chilian et al. 1990; Strauer and Schwartzkopff 1997; Klein, Sharrett et al. 2000; Wong, Klein et al. 2001; Wong, Rosamond et al. 2005). Indicators of retinal microvascular disease (e.g. retinopathy, narrowed retinal arterioles, and wider retinal venules) are potential markers of systemic arteriolar disease and have been associated with impaired glucose metabolism in individuals without diabetes (Rajala, Laakso et al. 1998; Singleton, Smith et al. 2003), and diabetes in those with a family history of the disease (Wong, Mohamed et al. 2006). However, predictors of microvascular disease are not well understood. As markers of retinal microvascular disease presumably reflect a decades-long process, understanding how time integrated exposure to traditional cardiovascular disease risk factors influences these characteristics would offer insight into these etiologic processes and eventually suggest opportunities for prevention and early intervention.

The Carotid MRI (CarMRI) study, an ancillary study of the Atherosclerosis Risk in Communities (ARIC) Study, was conducted in 2004-2005, at study calendar year 18 (also referred to as Visit 5). CarMRI investigators obtained contrast enhanced MRI image data of the carotid artery and performed retinal exams on approximately 2000 ARIC cohort participants (1200 with high values of carotid artery wall thickness and a random sample of 800 with normal thickness). These unique data, combined with data collected over the previous four visits, is exceptionally well-suited to examine associations of cumulative exposure to traditional cardiovascular disease risk factors with retinal microvascular changes.

5. Main Hypothesis/Study Questions:

Cumulative exposure to traditional risk factors (see table below) measured over five ARIC exams since 1987 predicts microvascular dysfunction as measured by focal arteriolar narrowing, presence of A/V nicking, and decrease in the arteriolar and venular diameter.

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).

Outcome variables:

The primary outcomes will include retinopathy, defined as the presence of specific retinal lesions (e.g. retinal microaneurysms, blot hemorrhages) by the Early Treatment Diabetic Retinopathy Study (ETDRS) severity scale, presence of focal retinal arteriolar narrowing, presence of retinal arterio/venous (A/V) nicking, retinal arteriolar narrowing as quantified by central retinal artery equivalent (CRAE), and retinal venular widening as quantified by central retinal venular equivalent (CRVE). These latter two measures represent average calibers of retinal arterioles and venules, respectively.

Exposure variables:

Traditional cardiovascular disease risk factors we propose to examine as cumulative exposure measures are as follows:

Anthropometrics	BMI, waist circumference, waist-hip ratio
Blood lipids/lipoproteins	Total, LDL, and HDL cholesterol, triglycerides
Diabetic indicators	Glucose, insulin, HOMA
Blood pressure	Systolic and diastolic

Statistical methods:

Using etiologic modeling strategies, we propose to examine the association between cumulative exposure to traditional risk factors and microvascular dysfunction as measured by retinal photography. Cumulative exposures will be estimated using a method developed by Cook et al (Cook, Rosner et al. 2004). Briefly, their method uses the multiple exposure measurements of various traditional cardiovascular risk factors calculated over 18 years of follow-up and longitudinal growth curve models to estimate each participant's area under the curve (AUC), interpreted as the average value of exposure over a specified age range. Random intercepts account for the fact that some individuals consistently have higher values than others, and specifying slopes as random allows individuals to differ in their overall rate of growth. We will use these AUC estimates to fit linear predictive models for microvascular dysfunction measures (measured at Visit 5). We will evaluate creating the predictive models using just those individuals in the CarMRI study as well as with the entire ARIC cohort. The advantage to the latter being in the greater numbers allowing us to explain more variability. We will of course be sensitive to exclusion criteria.

It is important to note that alternative cumulative exposure variables (CEV) have been developed by Dr. Chambless, defined as the cumulative area of the exposure variable for the five ARIC visits divided by the total time of follow-up. These trapezoidal measures are interpreted as the average value of the exposure variable over the period of time from Visit 1 to Visit 5. As an initial step, we will contrast several previously estimated CEV measures with those estimated using the methodology of Cook et al. While previous analyses using the CEV measures to predict plaque characteristics resulted in null findings, to our knowledge they have not been used to examine microvascular characteristics. Further, there are a number of differences between the methodologies that we feel would warrant reevaluating cumulative exposure metrics. For instance, the model-based method developed by Cook et al is independent of the ages at measurement and is able to extrapolate over the entire age range. Further, we can specify the AUC to be a function of not only age, but of sex, race, and other characteristics deemed important. Similarly, it is possible to allow growth trajectories to be nonlinear by including a quadratic term for age in the model. Finally, these models can accommodate short-term fluctuations (within-person variability) around an individual's growth pattern. Other strengths of Cook et al's method are reflected by the application of mixed models: accommodating unbalanced repeated measurements, and using all of the available data for an individual, and borrowing information from the entire cohort experience when measurements are missing.

7.a. Will the data be used for non-CVD analysis in this manuscript? 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? Yes
 No

(This file ICTDER03 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 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"?
 Yes No

8.c. If yes, is the author aware that the participants with RES_DNA = 'not for profit' restriction must be excluded if the data are used by a for profit group?
 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.csc.unc.edu/ARIC/search.php>

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)?

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? Yes 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.csc.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.

References:

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- Marcus, M. L., W. M. Chilian, et al. (1990). "Understanding the coronary circulation through studies at the microvascular level." Circulation **82**(1): 1-7.
- Rajala, U., M. Laakso, et al. (1998). "Prevalence of retinopathy in people with diabetes, impaired glucose tolerance, and normal glucose tolerance." Diabetes Care **21**(10): 1664-9.
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