ARIC Manuscript Proposal # 1440C

PC Reviewed: 11/11/08	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

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

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

2. Writing Group:

Christy L. Avery
Keri L. Monda
Anna Kucharska-Newton
Ronald Klein
Lloyd Chambless
Richey Sharrett
Tien Wong
Kari E. North
Tom Mosley
Barbara Klein
Mary Frances Cotch
Other investigators welcome

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]**

F**irst author**: Christy L. Avery
Address: 137 E. Franklin St., Ste. 32
CB #8050
Chapel Hill, NC 27514
Phone: 919.966.8491 Fax: 919.966.9800
E-mail: christy_avery@unc.edu

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).
Name: Kari North
Address: 137 E. Franklin St., Ste. 32
CB #8050
Chapel Hill, NC 27514
Phone: 919.966.2148 Fax: 919.966.9800
E-mail: kari_north@unc.edu

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 and cerebral diseases including incident carotid artery plaque, congestive heart failure, stroke, cerebral atrophy, cognitive function, among others (Marcus, Chilian et al. 1990; Strauer and Schwartzkopff 1997; Klein, Sharrett et al. 2000; Wong, Klein et al. 2001; Wong, Mosley et al. 2003; Wong and McIntosh 2005; Wong, Rosamond et al. 2005; Cooper, Wong et al. 2006; Baker, Marino Larsen et al. 2007). Indicators of retinal microvascular disease (e.g. retinopathy, narrowed retinal arterioles, and wider retinal venules) are potential markers of systemic arteriolar disease (Marcus, Chilian et al. 1990) 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). In the ARIC study, we have reported that over a 3-year period, the incidence of retinopathy was 3.8%, and was related to higher baseline blood pressure, serum glucose, total cholesterol and plasma fibrinogen levels (Wong, Klein et al. 2007). However, outside of blood pressure (Sharrett, Hubbard et al. 1999; Wong, Hubbard et al. 2002; Leung, Wang et al. 2004), long-term predictors of microvascular disease in people without diabetes are not well understood. As markers of retinal microvascular disease presumably reflect a decades-long process, understanding how cumulative exposure to traditional and novel cardiovascular disease risk factors influences these characteristics would offer insight into these etiologic processes in microvascular disease, and thus 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 retinopathy, focal arteriolar narrowing, presence of A/V nicking, decrease in arteriolar diameter and increase in 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 at Visit 5 of specific retinal lesions (e.g. retinal microaneurysms, blot hemorrhages) by the Early Treatment Diabetic Retinopathy Study (ETDRS) severity scale (level 14 and above), 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. However, we note that CRAE and CRVE are only indices of these variables, and are much larger than the vessels that they index.

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, HbA1c
Blood pressure	Systolic and diastolic

We will also consider smoking and inflammatory factors (e.g. WBC, CRP, IL-6, PAI-1, ICAM-1 if available) as predictors and /or covariates.

Statistical methods:
Using etiologic modeling strategies, we propose to examine the association between cumulative exposure to traditional and novel risk factors and retinal microvascular signs 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 __X__ 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 __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 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.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)?

MS1234 (Wong et al): 10-year incidence, Progression, and Regression of retinal vascular abnormalities and their relationship with vascular and inflammatory risk markers.

- Our proposal is complementary to the above MS1234 in that while Wong and colleagues are investigating the effect of baseline (as measured at visit 3) risk factors on changes in retinal vascular abnormalities between visits 3 and 5, we propose to look at the *cumulative effect* of these risk factors measured at all five visits on prevalence of retinal characteristics at visit 5. Please note that a number of individuals are members of both writing groups. We have thoroughly discussed how these two proposals are both different and complementary and we plan to work together to resolve differences and put forth a consistent message.

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.

References:

Baker, M. L., E. K. Marino Larsen, et al. (2007). "Retinal microvascular signs, cognitive function, and dementia in older persons: the Cardiovascular Health Study." Stroke **38**(7): 2041-7.

Cook, N. R., B. A. Rosner, et al. (2004). "Using the area under the curve to reduce measurement error in predicting young adult blood pressure from childhood measures." Stat Med **23**(22): 3421-35.

Cooper, L. S., T. Y. Wong, et al. (2006). "Retinal microvascular abnormalities and MRI-defined subclinical cerebral infarction: the Atherosclerosis Risk in Communities Study." Stroke **37**(1): 82-6.

Klein, R., A. R. Sharrett, et al. (2000). "Are retinal arteriolar abnormalities related to atherosclerosis?: The Atherosclerosis Risk in Communities Study." Arterioscler Thromb Vasc Biol **20**(6): 1644-50.

Leung, H., J. J. Wang, et al. (2004). "Impact of current and past blood pressure on retinal arteriolar diameter in an older population." J Hypertens **22**(8): 1543-9.

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.

Sharrett, A. R., L. D. Hubbard, et al. (1999). "Retinal arteriolar diameters and elevated blood pressure: the Atherosclerosis Risk in Communities Study." Am J Epidemiol **150**(3): 263-70.

Singleton, J. R., A. G. Smith, et al. (2003). "Microvascular complications of impaired glucose tolerance." Diabetes **52**(12): 2867-73.

Strauer, B. E. and B. Schwartzkopff (1997). "Left ventricular hypertrophy and coronary microcirculation in hypertensive heart disease." Blood Press Suppl **2**: 6-12.

Wong, T. Y., L. D. Hubbard, et al. (2002). "Retinal microvascular abnormalities and blood pressure in older people: the Cardiovascular Health Study." Br J Ophthalmol **86**(9): 1007-13.

Wong, T. Y., R. Klein, et al. (2007). "Three-year incidence and cumulative prevalence of retinopathy: the atherosclerosis risk in communities study." Am J Ophthalmol **143**(6): 970-6.

Wong, T. Y., R. Klein, et al. (2001). "Retinal microvascular abnormalities and incident stroke: the Atherosclerosis Risk in Communities Study." Lancet **358**(9288): 1134-40.

Wong, T. Y. and R. McIntosh (2005). "Systemic associations of retinal microvascular signs: a review of recent population-based studies." Ophthalmic Physiol Opt **25**(3): 195-204.

Wong, T. Y., Q. Mohamed, et al. (2006). "Do retinopathy signs in non-diabetic individuals predict the subsequent risk of diabetes?" Br J Ophthalmol **90**(3): 301-3.

Wong, T. Y., T. H. Mosley, Jr., et al. (2003). "Retinal microvascular changes and MRI signs of cerebral atrophy in healthy, middle-aged people." Neurology **61**(6): 806-11.

Wong, T. Y., W. Rosamond, et al. (2005). "Retinopathy and risk of congestive heart failure." Jama **293**(1): 63-9.