ARIC Manuscript Proposal # 1442C

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

1.a. Full Title: Longitudinal predictors of carotid plaque characteristics: The Atherosclerosis Risk in Communities (ARIC) Carotid MRI Study

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

2. Writing Group:

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _KM_ **[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:

The composition of atherosclerotic plaque, including volume and thickness of the arterial wall, as well as the presence of a fibrous cap and a lipid core, plays a critical role in the progression and manifestation of cardiovascular disease and subsequent coronary events (Falk 1991; Zhou, Chew et al. 1999). Although understanding the etiology of plaque composition is important, predictors are not well defined. As plaque composition characteristics 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 in approximately 2000 ARIC cohort participants (1200 with high values of carotid artery wall thickness measurements and a random sample of 800 with normal thickness measurements). 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 plaque characteristics.

The majority of previous studies examining plaque characteristics examined symptomatic populations of small sample size. Very few studies were population-based. Exceptions include Wasserman et al, who, using MRI data from the Multi-Ethnic Study of Atherosclerosis (MESA), reported increased odds of the presence of a lipid core for those in the middle and highest tertiles of total cholesterol measured concurrently (Wasserman, Sharrett et al. 2008), and research by Wagenknecht et al who used ARIC MRI data to investigate the ability of traditional cardiovascular risk factors (e.g. total, LDL, and HDL cholesterol, glucose, blood pressure, and body mass index [BMI]) measured at study baseline to predict MRI-detectable carotid wall and plaque characteristics (Wagenknecht, Wasserman et al. submitted). The authors reported that while a number of risk factors measured at baseline predicted increased wall volume and maximum wall thickness 18 years later, risk factors measured concurrently were rarely predictive. Fewer risk factors, measured either at baseline or concurrently, predicted lipid core or fibrous cap phenotypes.

5. Main Hypothesis/Study Questions:

Cumulative exposure to traditional risk factors (see table below) measured over five ARIC exams since 1987 predict carotid wall and plaque characteristics such as wall thickness, presence of a lipid core, fibrous cap thickness, and lipid core volume.

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 wall thickness, plaque (presence/absence and/or volume), lipid core volume, and fibrous cap thickness.

Exposure variables

The 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 build on the work undertaken by Wagenknecht et al by examining the association between cumulative exposure to traditional risk factors and plaque characteristics as measured by MRI. 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 plaque characteristics (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 resulted in null findings, 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)?
MS #1211 (Wagneknecht et al.): Determinants of carotid plaque presence and pathology as measured by magnetic resonance imaging: The ARIC Study.

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:

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.

Falk, E. (1991). "Coronary thrombosis: pathogenesis and clinical manifestations." Am J Cardiol **68**(7): 28B-35B.

Wagenknecht, L., B. A. Wasserman, et al. (submitted). "Correlates of carotid plaque presence and composition as measured by magnetic resonance imaging: The Atherosclerosis Risk in Communities (ARIC) Study."

Wasserman, B. A., A. R. Sharrett, et al. (2008). "Risk factor associations with the presence of a lipid core in carotid plaque of asymptomatic individuals using high-resolution MRI: the multi-ethnic study of atherosclerosis (MESA)." Stroke **39**(2): 329-35.

Zhou, J., M. Chew, et al. (1999). "Plaque pathology and coronary thrombosis in the pathogenesis of acute coronary syndromes." Scand J Clin Lab Invest Suppl **230**: 3-11.