1.a. Full Title: Determinants of carotid plaque presence and pathology as measured by magnetic resonance imaging: The ARIC Study

b. Abbreviated Title (Length 26 characters): Risk factors & MRI plaque

2. Writing Group:
   Writing group members: Wagenknecht, Chambless, Coresh, Folsom, Heiss, Mosley, Ballantyne, Wasserman, Boerwinkle, and others as appropriate

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. LW

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Corresponding/senior author (if different from first author correspondence will be sent to both the first author & the corresponding author):
   Address:
   Phone:          Fax:          E-mail:  

3. Timeline:
   First draft by March 31, 2007 (this draft will only include a portion of the MRI data);
   Final draft within 2 months of receipt of final MRI variables and corresponding analyses.

4. Rationale: Recent evidence indicates that atherosclerotic plaque composition plays a role in the progression and clinical manifestations of cardiovascular disease. MRI data
now available from the ARIC Carotid MRI substudy allow an analysis of the determinants of plaque presence and composition. This is one of the first studies to analyze plaque characteristics and its determinants in a population-based sample.

5. Main Hypothesis/Study Questions: (Specific Aim #1 from the grant). Evaluate the ability of traditional CVD risk factors (e.g., cholesterol and blood pressure) measured over five ARIC exams since 1987 to predict MRI-detectable carotid wall and plaque characteristics. Hypothesis 1: Levels and longitudinal change of traditional risk factors for CVD are predictors of wall and plaque characteristics.

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).

This is an analysis of traditional atherosclerosis risk factors and MRI-measured variables obtained from the nearly 2000 ARIC cohort members who participated in the ARIC Carotid MRI examination. The analysis includes both cross-sectional and longitudinal elements. All participants with acceptable quality MRI scans will be included in the analysis (quality criteria to be determined).

MRI variables of interest:
1. stenosis
2. wall thickness
3. plaque (presence/absence and/or volume)
4. lipid core volume
5. fibrous cap thickness (lowest priority due to complicated nature of variable)

Risk factors of interest: (both concurrent measures of these risk factors as well as cumulative exposure and/or slope over the five previous ARIC exams, when available)

1. Lipids and lipoproteins (TC, LDL, HDL, TG)
2. Glucose homeostasis (fasting glucose, fasting insulin, HOMA, diabetes status)
3. Hypertension (resting blood pressures and med use, and/or hypertension)
4. Body size (BMI, waist)
5. Smoking
6. Other (ACR, prevalent CVD)
7. Framingham or ARIC predicted risk score
Covariates:

1. Age, sex, race, field center, statins

Proposed Tables/Analyses:

1. Descriptive statistics by high/not high IMT status for all risk factors and MRI-variables.

2. Analyses using MRI measures as continuous variables: Multivariate linear regression analyses with continuous MRI variables (wall thickness, plaque volume, other) as a function of risk factors, adjusting for covariates above, and accounting for stratified sampling design (e.g., SURVEYREG).

   2.a. Multivariate linear regression analyses with continuous MRI variables (lipid core volume, fibrous plaque thickness) restricted to the subset of persons with plaque present.

3. Analyses using MRI measures as categorical variables: MRI variables will be categorized by plaque presence, and then further subdivided into lipid core (yes or no), and with lipid core present further categorized into fibrous cap (thin/ruptured or thick). Cutpoints for categories will be refined at the Coordinating Center using reproducibility data.

<table>
<thead>
<tr>
<th>Plaque</th>
<th>Lipid core</th>
<th>Present</th>
<th>Present</th>
<th>Present</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present</td>
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<tr>
<td></td>
<td>Thin/ruptured</td>
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<tr>
<td></td>
<td>Absent</td>
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<tr>
<td>Fibrous cap</td>
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</tbody>
</table>

3a. Descriptive statistics will be presented for the 3 dichotomous variables (and/or for the 4 exclusive categories currently being used by the Coordinating Center, see table [or the 3 groups if the fibrous cap variable is collapsed]).

3b. Statistical testing via logistic regression adjusting for covariates listed above and accounting for sampling design.

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 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?  ____ Yes  
     ____ No
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 ICTDER02 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://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)?  None

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.  
Agree