1.a. Full Title:
Characterization of Asymptomatic Intracranial Atherosclerosis using 3D High Resolution Contrast-enhanced MRI

1.b. Abbreviated Title (Length 26 characters):
Contrast-enhanced MRI characterization of asymptomatic ICAD

2. Writing Group:
Writing group members: Huan Yang, Xuefeng Zhang, Mona Shahriari, Li Liu, Qing Hao, Victor Urrutia, Qin Qin, Bruce A. Wasserman, Ye Qiao

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

First author: Huan Yang
Address: Johns Hopkins School of Medicine
Park 367D, 600 N. Wolfe St., Park 367F
Baltimore, MD 21287

Phone: (443) 743-4159 Fax: (410) 502-5955
E-mail: hyang59@jhmi.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: Ye Qiao
Address: Johns Hopkins School of Medicine
Park 367D, 600 N. Wolfe St., Park 367F
Baltimore, MD 21287

Phone: (410) 614-3309 Fax: (410) 502-5955
E-mail: yqiao4@jhmi.edu
3. **Timeline:**
MRI image Data will be collected and analyzed after interpreting the MRI scans. Manuscript preparation is expected to be accomplished by the end of December, 2016.

4. **Rationale:**

Intracranial atherosclerotic disease (ICAD) is a common cause of stroke and affects 34% old adults in the general population in the US [1]. It is a chronic disease and prone to progress over years without symptoms [2, 3]. Approximately 77% of strokes occur abruptly in asymptomatic individuals [4], emphasizing the necessity of effective diagnosis before cerebrovascular events occur. However, most studies have been conducted after the onset of symptoms or in those who referred for a family history of stroke [1]. Therefore, the detection and characterization of ICAD in its asymptomatic stage may provide insight into stroke risk and its prevention.

It has become apparent that lumen narrowing is a poor indicator of plaque burden when vessels accommodate plaque formation by compensatory dilatation (remodeling) [5]. Recent development of 3D high-resolution black-blood MRI imaging (BBMRI) allows for screening ICAD [6-8] and provides reliable plaque measurements. The plaque enhancement on 3D BBMRI entailed after gadolinium contrast is associated with culprit plaques (i.e., responsible for downstream ischemic events)[9], while its role in stroke-free individuals remains unknown. Therefore, we aim to characterize intracranial atherosclerosis in an asymptomatic population (ARIC participants) using 3D high-resolution contrast-enhanced BBMRI and compare with those plaques from stroke patients (JHH).

5. **Main Hypothesis/Study Questions:**

- To identify intracranial plaque components and wall features that are associated with ischemic stroke by comparing ARIC exams (i.e., asymptomatic group) with MR exams from individuals with completed ischemic strokes (i.e., JHH)

Hypothesis: Specific plaque features (i.e., plaque eccentricity, surface irregularity and enhancement) will be associated with ischemic stroke.

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).**

*Study design:*
Asymptomatic participants (n=50) with ICAD identified in ARIC-NCS brain MRI (from 2011 to 2013) are enrolled. Symptomatic stroke patients (n=50) will be recruited from Johns Hopkins Hospital with ICAD based on prior MRA/CTA or DSA examination.

Inclusion/Exclusion criteria:

**Inclusion criteria:**
1) ICAD located at major arteries (ICA, MCA, ACA, PCA, VA or BA) confirmed by MRA/BBMRI for ARIC participants or by CTA, DSA, or MRA for stroke patients.
2) Symptomatic group has had a recent (<6 months) TIA or nondisabling ischemic stroke within the territory of the stenosis.

**Exclusion criteria:**
Contraindication to MRI scans or contrast administration, including renal failure.

**Data Analysis:**
All images are interpreted by 3 certified trained readers. MRI Images with adequate or excellent qualities are included in this study.

Each analyst uses picture archiving and communication system (PACS) software for the qualitative analysis of the MRA and BBMRI scans. Using the PACS software, the BBMRI and MRA images are co-registered and reconstructed in both short and long axes relative to the flow direction for each vascular territory (RMCA, LMCA, RPCA, LPCA, ACA, Basilar, Vertebral, RICA, and LICA).

Qualitative analysis of the MRI images included plaque presence by vessel territory (RMCA, LMCA, RPCA, LPCA, ACA, BA, VA, RICA, and LICA), number of plaques, and the ordinal degree of narrowing (i.e., no detectable stenosis, <50%, 51%-70%, 71-99%, and occlusion), contrast enhancement, presence of intraplaque hemorrhage (IPH) and calcification for the most stenotic plaque per territory. An atherosclerotic plaque was defined as eccentric wall thickening, with or without luminal stenosis seen on BBMRI.

Quantitative measurements were obtained for each plaque identified for each vascular territory in the qualitative assessment using vesselMass software. For each plaque, we recorded lumen size and stenosis, wall/plaque thickness, area, volume, normalized wall index (wall area/outer wall area) and plaque contrast enhancement.

**Primary endpoints:**
Downstream stroke within the vascular territories with intracranial atherosclerosis.

**Outcome and other variables of interest with specific reference to the time of their collection:**

Variables of interest (include but are not limited to):

Qualitative variables:
- Presence of plaque (plaque)
- Total number of plaques (n_plaq)
- Presence of plaque by vessel segment (e.g., n_rmca_plaq, n_lmca_plaq, n_raca_plaq, etc)
- Degree of stenosis (i.e., zero to minimal luminal indentation, <50%, 50 to 70%, >70% and occlusion) (rmca_plaq_stenosis, lmca_plaq_stenosis, raca_plaq_stenosis, etc...)
- Presence of intraplaque hemorrhage
- Presence of calcification
- Luminal irregularity

Quantitative variables:
- Area Degree of Stenosis (%)
- Area Length of Stenosis (mm)
- Diameter Degree of Stenosis (%)
- Diameter Length of Stenosis (mm)
- Diameter Obstruction (mm)
- VesselWall Segment Average (mm2)
- VesselWall Segment Maximum (mm2)
- Segment Length (mm)
- Vessel Segment Wall Volume (mm3)
- Normalized Wall Index (%)
- Wallthickness Segment Average (mm)
- Wallthickness Segment Maximum (mm)

Statistical Analysis:

Categorical data were presented as frequencies, and continuous data were presented as means ± standard deviations. Robust variance estimates were used to account for repeated measurements within patients. Quantitative analysis of plaque contrast enhancement were compared by using the Kruskal-Wallis test and posthoc pairwise comparison (Wilcoxon rank sum tests). To evaluate the association between plaque features and the likelihood having the downstream stroke, logistic and multinomial logistic regression will be used for categorical outcome (downstream stroke).

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 ICTDER 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

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)?

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  ___X___ Yes    ____ No

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* 2009.28 MRI imaging of intracranial atherosclerosis

___ 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/

12a. 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.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is your responsibility to upload manuscripts to PUBMED Central whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms.

http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.
References: