ARIC Manuscript Proposal # 3081

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SC Reviewed: _____ **Status: _____** **Priority: ____**

1. a. Full Title:
Association of high sensitivity C-reactive protein levels with asymptomatic intracranial arterial stenosis

  b. Abbreviated Title (Length 26 characters):
Association of Inflammation with Intracranial Atherosclerotic Stenosis

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

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3.   Timeline: 11/15/2017 (proposal submission)
            01/15/2018 (data acquisition)
             03/30/2018 (manuscript submission)

4.   Rationale:

Intracranial Atherosclerotic Stenosis (ICAS) is associated with 8-10% of all strokes in the U.S. Stroke patients with ICAS tend to have higher National Institutes of Health Stroke Score at admission than those without and a higher risk of recurrent ischemic events caused by ICAS, reaching nearly 15% per year.

High sensitivity C-reactive protein (hs-CRP), an indicator of inflammation, is closely related to cardiovascular events, coronary artery stenosis and carotid stenosis. A community-based study conducted in China, showed hs-CRP is an independent predictor of asymptomatic ICAS and intracranial atherosclerotic burden. In this study, after adjusting for possible risk factors, high level of hs-CRP (≥ 3 mg/l) remained significantly associated with asymptomatic ICAS (OR 1.28, 95% CI 1.02–1.61).

Although there is evidence in the Asian population that inflammation plays a role in ICAS, it has not been shown in the U.S. population. The reproducibility of such findings consistently in different studies and among different populations would be fundamental for i) accumulation and strengthening of scientific evidence; ii) identifying population at high risk.

A mounting body of evidence from observational studies has shown associations between diet and regulation of inflammation (hs-CRP and other pro-inflammatory cytokines) (1-5). The western diet, rich in red meat, processed and artificially sweetened food products, refined grains, high fat-dairy products and sugar-sweetened beverages, has been linked with increased levels of inflammatory biomarkers and increased risk for CVD (6). On the contrary, a Mediterranean dietary pattern, rich in nuts, olive oil, legumes and fish, fruits and vegetables, moderate intake of wine, has been associated with lower levels of inflammation and a reduced risk of CVD (7-10).

The dietary inflammatory index (DII) is a new, validated tool to quantify the inflammatory potential of a diet (11-12). The DII was developed based upon a meta-analysis incorporating multiple basic science and population based epidemiologic studies on the effect of diet on inflammation. Using DII individual diets can be assessed on a continuum from maximally anti-inflammatory to maximally pro-inflammatory. The overall inflammatory score calculated using this method is dependent on the whole diet, not just certain nutrients or foods. Previously, in both cross sectional and prospective studies, the DII has been shown to predict hs-CRP levels (11-12).

In light of the important role of inflammation in intermediate stroke risk factors including atherosclerotic disease, and potential modulation of inflammation by diet, classifying individuals' diets according to their inflammatory properties could yield important information about the links between diet, inflammation, and ischemic stroke.

For this study, our objectives are twofold: i) To study the association between hs-CRP levels and ICAS, specifically in the US population; ii) To assess whether pro-inflammatory diets, as measured by the DII, are associated with increased risk of ICAS.

5.   Main Hypothesis/Study Questions:

We hypothesized:

    i)   Midlife hs-CRP, a marker of systemic inflammation, is associated with late-life ICAS in the U.S. population.

    ii)   Consumption of a pro-inflammatory diet increases risk of moderate to severe ICAS.

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).

    1. Study design:

Inclusion/Exclusion:

Participants in the ARIC study who completed an interviewer-administered 66-item semi quantitative food frequency questionnaire (FFQ), at the baseline (1987–1989) and Exam 3 (1993–1995), will be included.

Of this analytic group, we will ascertain participants who had blood samples obtained to measure the serum inflammatory marker (hs-CRP) measured on visit 4, and subsequently in visit-5 underwent 3T magnetic resonance angiogram (2011-2013) for ICAS grading (all images were analyzed in a centralized lab and ICAS was graded as lab - no stenosis, <50% stenosis, >50% stenosis/complete occlusion). Participants who did not complete the baseline FFQ and those with missing hs-CRP or ICAS will be excluded. Those with race other than whites or black will be excluded due to limited sample size.

Main exposures of interest:

i): High sensitivity C-reactive protein (stratified as <1, 1-3 and >3 mg/l).

ii): Dietary inflammatory index (stratified by quartiles ranging from maximally anti-inflammatory to maximally pro-inflammatory score)

The design and development of the DII has been described elsewhere [13]. DII was developed based on an extensive review of the literature from 1950 to 2010, including articles that had assessed the effect of dietary constituents on six inflammatory biomarkers, namely IL-1β, IL-4, IL-6, IL-10, TNF-α and C-reactive protein. A total of 45 food derived parameters were included in the DII including various macronutrients, micronutrients and individual food items. Overall DII scores for each participant represent the sum of each of the DII components in relation to the comparison global diet database. The inflammatory potential for each of the 45 food parameter was scored according to whether it increased, decreased or had no effect on these biomarkers (IL-1β, IL-4, IL-6, IL-10, TNF-α and C-reactive protein). Using the DII score an individual's diet can be characterized on a continuum from maximally anti-inflammatory to maximally anti-inflammatory. The DII score can range from -8.87 (maximally anti-inflammatory) to +7.98 (maximally pro-inflammatory).

Usual dietary habits, defined as the average intake over the last year, were estimated in ARIC by a semi-quantitative 66-item food-frequency questionnaire, a modified version of a 61-item instrument developed and validated by Willett et al (14). The information dietary information gathered from FFQ has been used to derive multiple food parameters in the ARIC study. Among the derived food parameters, 28 of the 45 original DII components are available in ARIC for inclusion in the overall DII score (see (11) for list of 45 DII components). These include energy, carbohydrate, protein, total fat, alcohol, fiber, cholesterol, saturated fat, mono-unsaturated fat, poly-unsaturated fat, omega-3 fatty acids, omega-6 fatty acids, niacin, thiamin, riboflavin, vitamin B12, vitamin B6, iron, magnesium, selenium, zinc, vitamin A, vitamin C, vitamin D, vitamin E, folic acid, carotene, and caffeine. Components such as ginger, turmeric, garlic, oregano, hot pepper, rosemary, eugenol, saffron, flavan-3-ol, flavones, flavonols, flavonones, and anthocyanidins that are included in the original DII calculation [13] will not be included in the current study because they are not available from the ARIC FFQ derived dietary variables. The absence of these components is likely to have a minimal impact on overall DII scores because most of the missing food items are likely consumed in small quantities in this population.

All of the food parameter-specific DII scores will be summed to create the overall DII score for each participant in the ARIC study. Exposure status based on DII score will be stratified by quartiles ranging from maximally anti-inflammatory to maximally pro-inflammatory score.

Construct validation of the DII was performed using data derived from two different sources of dietary intake information and serum high-sensitivity C-reactive protein (CRP) as the construct validator [12]. Thus far, the DII has been found to be associated with inflammatory cytokines including CRP and IL-6 [11,12], body mass index [15], and various inflammation-related diseases [16–21].

Main Outcome: Intracranial Atherosclerotic Stenosis (no stenosis, <50% stenosis, >50% stenosis/complete occlusion)

Co-variates: Age, gender, education, race (categorized as white, black, or other), smoking status, alcohol use, coronary artery disease (CAD), congestive heart failure (CHF) assessed by self-report. Body mass index (BMI) calculated as weight in kilograms divided by height in meters squared. Hypertension defined as a systolic blood pressures of 140mmHg or higher, a diastolic blood pressure higher than 90mmHg, or use of medications to treat hypertension. Diabetes as determined by self-report of a physician diagnosis of diabetes, non-fasting blood glucose level of 200 mg/dL or higher, fasting blood glucose level of 126mg/dL or higher, or use of insulin or other oral hypoglycemic medications. Physical activity is considered significant if performed for 4hrs/week for at least a month. Prevalent CAD ass defined by electrocardiographic evidence of previous myocardial infarction (MI), history of physician diagnosed MI, or previous coronary revascularization procedure (bypass, angioplasty). Medications including use of statins, fibrates and antiplatelet drugs.

Statistical analysis:

For the descriptive analysis, patient's sociodemographic, medical history variables, and baseline clinical characteristics will be compared across hs-CRP categories. Chi square testing and Wilcoxson rank testing will be used for comparison of categorical and continuous variables, respectively.

Logistic regression models will be used to calculate odds ratios (ORs) of the effects of variables on the relationship between hs-CRP levels and ICAS. Separate logistic regression models will be used to calculate ORs, and 95% CIs for risk of the ICAS, by DII quartiles and with adjustment for multiple covariates. Several models may be run including covariates --demographic (i.e. age, race, sex, education, socioeconomic status, vascular risk factors (i.e. BMI, physical activity, hypertension, hyperlipidemia, DM, smoking, alcohol, CAD, and CHF) and medications (example statins, fibrates and antiplatelet drugs). These covariates will initially be assessed for evidence of significant confounding between the exposure and each outcome variable, before being included in a final model.

All statistical analyses will be two-tailed, and a P value of 0.05 will be considered for statistically significance.

Exposure Variable	1) hs-CRP (stratified as <1, 1-3 and >3 mg/l) measured at V4 2) Dietary inflammatory index (stratified by quartiles ranging from maximally anti-inflammatory to maximally pro-inflammatory score) measured between V1 and V3
Outcome Variable	ICAS (no stenosis, <50% stenosis, >50% stenosis/complete occlusion) measured V5
Covariates	Sex Age Race Socioeconomic Status Education BMI Physical activity Hypertension Diabetes Smoking Status Alcohol use LDL CAD CHF Medications
Analysis	Logistic regression

1. Limitation:

1. Although, the ascertainment of exposure (hs-CRP) and of the outcome was done at two different time points separated by years, given these were not measured longitudinally (multiple repeated measurements), temporality can't be established. And of course, we can only infer association, stroke risk, not causality.

2. Traditionally digital subtraction angiography (DSA) is regarded as the gold standard for the diagnosis of ICAS; however, it is expensive and risky. Although MRA has been regarded as a minimally-invasive and convenient screening method to diagnose ICAS, it is not as accurate as digital subtraction angiogram for determining ICAS. Having said that, doing DSA in asymptomatic study participants would not practical.

3. Components such as ginger, turmeric, garlic, oregano, hot pepper, rosemary, eugenol, saffron, flavan-3-ol, flavones, flavonols, flavonones, and anthocyanidins that are included in the original DII calculation [13] will not be included in the current study because they are not available from the ARIC FFQ derived dietary variables. The absence of these components is likely to have a minimal impact on overall DII scores because most of the missing food items are likely consumed in small quantities in this population.

    This proposal has important clinical implications and may help point the way to future research to identify and target populations with ICAS and high stroke risk. Hence the results may help clinicians regarding stroke prevention strategy for high risk populations.

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

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)?

- Qiao Y, Guallar E, Suri FK, Liu L, Zhang Y, Anwar Z, Mirbagheri S, Xie YYJoyce, Nezami N, Intrapiromkul J et al.. 2016. MR Imaging Measures of Intracranial Atherosclerosis in a Population-based Study.. Radiology. 280(3):860-8.

- Suri M, Fareed K, Qiao Y, Ma X, Guallar E, Zhou J, Zhang Y, Liu L, Chu H, Qureshi AI, Alonso A et al.. 2016. Prevalence of Intracranial Atherosclerotic Stenosis Using High-Resolution Magnetic Resonance Angiography in the General Population: The Atherosclerosis Risk in Communities Study.. Stroke. 47(5):1187-93.

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
_X_   A. primarily the result of an ancillary study (list number*1996.01, 2009.27)
___   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.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes __X__ No.

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14. The ARIC Investigators. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives

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