

ARIC Manuscript Proposal #2372

PC Reviewed: 5/13/14
SC Reviewed: _____

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Priority: 2
Priority: _____

1.a. Full Title:

Dietary Intake, and Carotid MRI plaque characteristics

b. Abbreviated Title (Length 26 characters):

Dietary Intake and Carotid MRI plaque characteristics

2. Writing Group:

Writing group members: Jennifer Dearborn, Bruce Wasserman, Ye Quiao, Yuan Yuan Xie, Lyn Steffen, Eliseo Guallar; Rebecca Gottesman

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

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3. Timeline: Analyses to begin as soon as manuscript proposal is approved.
Goal for completion with calendar year.

4. Rationale:

As the population ages, recent attention is being given to the burden of atherosclerosis and its contribution to morbidity and mortality in the form of coronary artery disease, stroke and peripheral vascular disease. Carotid artery atherosclerosis is a direct cause of stroke, is associated

with multiple stroke subtypes¹ and is a marker of systemic vascular disease, including coronary artery and peripheral vascular disease.² High-resolution “black blood” MRI (BBMRI) is a powerful technique to quantify carotid plaque characteristics, allowing them to serve as biomarkers of disease severity or progression.

Recent work in ARIC has identified that the internal carotid arteries have remodeling characteristics that may be distinct from the common carotid arteries and coronary arteries.³ Carotid artery geometry has been carefully quantified and is a weak predictor of carotid wall thickening.⁴ Contrast-enhanced and non-contrast techniques have been used to identify and characterize the morphology of plaque ulceration.⁵ Lipid core quantification, fibrous cap thickness and carotid wall thickness have been carefully characterized.⁶ These distinct plaque characteristics may demonstrate disease associations not previously identified using carotid IMT or other measures of systemic atherosclerosis.

For example, in ARIC, serum lipoprotein measurements have been examined in relation to plaque characteristics and the authors found that the ratio of atherogenic to non-atherogenic lipids was associated with the presence of a lipid core.⁷ Blood cellular markers such as monocyte toll-like receptor (TLR-2) and myeloperoxidase were also associated with larger plaque size.⁸ Blood lactate was demonstrated to be an independent marker for carotid wall thickness.⁹ These specific plaque characteristics (such as lipid core, geometry, plaque size, etc.) offer an approach to study more complex exposures such as dietary intake, as they influence burden of atherosclerosis and might be associated with relatively subtle changes in plaque that would otherwise not be identified in more crude evaluations of carotid disease.

The Mediterranean (Med Diet), which is high in vegetables (legumes and greens), fish and olive oil, with a moderate amount of alcohol, while low in red meat and chicken, has been shown to improve health. One meta-analysis showed that this dietary pattern reduced overall mortality, mortality from cardiovascular diseases, incidence of or mortality from cancers, and incidence of Parkinson’s disease and Alzheimer’s Disease.¹⁰ Not much about the mechanism of these interesting findings is known. Recently, the PREDIMED study showed that a Med Diet supplemented with tree nuts was associated with delayed progression of carotid artery intima media thickness and plaque height, as measured by ultrasound, which provides insight into one biological effect.¹¹ A Med Diet has also been shown to reduce lipid levels and LDL oxidation.¹² This is in contradiction to another cohort study which showed no relationship with Med Diet type pattern and carotid atherosclerosis.¹³

Other dietary patterns, such as a Healthy Diet Pattern, as described in the MESA study,

have shown an inverse association with carotid intima media thickness.^{14,15} Another cohort, the British IRAS study, found a positive correlation with an unhealthy diet pattern (high in low-fiber breads and cereals, red and processed meat, cottage cheese, tomato foods, regular soft drinks and sweetened beverages and low in wine, rice and pasta, meal replacements and poultry) and common carotid but not internal carotid intima media thickness.¹⁶ An unhealthy diet pattern, labeled the “traditional” pattern in a Finnish cohort, yielded similar results.¹⁷ Although it is clear that associations between dietary intake and carotid atherosclerosis are present, there is no consensus on which particular dietary pattern is most important and no data on which aspects of carotid plaque are affected.

The ARIC data used a food frequency questionnaire (FFQ) to determine dietary preferences. Dietary intake was assessed over the previous year using an interviewer administered, 66-item food frequency questionnaire, during visit 1 and 3, and the Carotid MRI visit. The frequency of intake of certain items was ranked from 0 to 9 (almost never to > 6 times per day). This is different from other methods such as 24-hour food recall, or food recall records, which also have their strengths and weaknesses in terms of accuracy. Biomarkers such as the percent of fatty acids in either cholesterol ester or phospholipids fraction of plasma can be used to standardize the accuracy of the FFQ in reliably determining FFA consumption.¹⁸

Despite inherent weakness in the FFQ, there have been several interesting studies produced from this ARIC data using dietary patterns. Using principal components analysis, a “Healthy” and “Western” dietary pattern were identified.^{19,20} Diet patterns and alcohol intake were shown to have specific associations with markers of cellular activation and inflammation, such as platelet glycoprotein IIb and other flow cytometry markers.¹⁹ In the carotid intima media thickness subset (case controlled to those that had carotid intima thickening and those that did not), intake of the vitamins folate, vitamin B6 and vitamin B12 and cold breakfast cereals (presumed fortified with vitamins) had lower levels of plasma homocysteine.²¹ Homocysteine has been identified a risk factor for atherosclerotic and thromboembolic disease. A study also addressed the angiotensin-like 4 gene (*ANGPTL4*[E40K]), which has a common allele that mediates HDL levels, and found that diet, specifically carbohydrate intake, modified HDL and triglyceride levels.²² Together, these data suggest that diet patterns modify gene expression, and inflammatory biomarker levels. Carotid plaque morphology may be a biomarker of these associations.

This proposal seeks to further explore core relationships of dietary intake with carotid plaque characteristics using the cutting edge BBMRI, as utilized in the Carotid MRI ARIC ancillary study, which has the capacity to elucidate imaging biomarkers of disease status.

5. Main Hypothesis/Study Questions:

1. A Healthy Diet pattern, as defined by principal components analysis, will be inversely associated with carotid plaque characteristics, as measured by lipid core presence and volume, mean fibrous cap thickness and maximum wall thickness in the internal carotid artery. A Mediterranean-Diet-Like Pattern (MED-Like), as determined by a score defined below, will also be inversely associated with carotid plaque characteristics.
2. A diet high in processed sweets and fructose consumption, “Sweet Diet” as measured by the glycemic index and glycemic load, AND an Unhealthy Diet Pattern defined by principal components analysis will be associated with increased burden of carotid plaque, as measured by similar characteristics.
3. The Unhealthy Diet and the Sweet Diet (elevated glycemic load and index) will each be associated with plaque inflammation, as measured by contrast-enhanced BBMRI.

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 methodological limitations or challenges if present).

Study Design: Prospective data collection on risk factors with cross-sectional definition of the outcome based on the nutrition assessment performed at the Carotid MRI visit (2004 to 2005 years).

Inclusion: All individuals in the ARIC cohort with a completed Carotid MRI and a complete food frequency questionnaire (FFQ) at the Carotid MRI visit.

Exclusion: Missing Carotid MRI data; Missing dietary data, outlying energy intake

Data Analysis:

Hypothesis 1: Linear regression; the Healthy Diet, as described by PCA and MED-like diet (composite variable, divided into quintiles) will be used in separate models. The independent variables, predicting carotid plaque characteristics, as measured by lipid core volume, mean fibrous cap thickness and maximum wall thickness in the internal carotid artery. The measures for the independent variables will be taken from the Carotid MRI visit. We will also consider a “global” z-score from all variables of plaque characteristics that represents total “plaque burden”.

Hypothesis 2: Linear regression; Sweet diet and Unhealthy diet as defined by PCA (composite variable, divided into quintiles), will be used in separate models. Predictors will be the same as in Hypothesis 1.

Hypothesis 3: A novel method for detecting plaque “inflammation” will be assessed using the contrast-enhanced BBMRI results, based on an analysis that is currently underway in ARIC.²³ A secondary analysis, assessing plaque “inflammation” will be assessed. In this method, the thickness of the non-contrast enhanced segment at the level of the common carotid artery will be subtracted from the diameter of the contrast-enhanced segment at this level. This measurement will represent “adventitial thickness, an established measure of vascular inflammation due to neovascularization”. Inflammation will be categorized as a categorical variable (0,1,2). Logistic regression will be used with inflammation (yes/no) and inflammation score (ordinal logistic regression) as the outcome. The Sweet Diet and Unhealthy Diet will be predictors. Linear regression will be used with the continuous outcome of “neovascularization” with the same predictors.

Diet Pattern Definition:

Healthy and Unhealthy Diet patterns will be determined by principal components analysis (PCA). Daily intakes of food categories, as listed on the FFQ, will be calculated, and then summed into relevant food groups, with a target of 30 to 40 “food categories”. These categories will be used in pca, and an eigenvalue >2 will be used to select the diet patterns. Diet Patterns will be described by food categories achieving a factor loading score of ≥ 0.2 .

The MED-Like Diet pattern will be defined based on a modification by the criteria put forth by Trichenopoulou et al. in the EPIC cohort.²⁴ Briefly, the sex-specific medians of foods such as fruits, vegetables and fish, will be calculated, and a score will be created based on 9 to 10 food group items selected for similarity to a MED-Like Diet.

The Sweet Diet will be defined with the glycemic load and the glycemic index. As has been done previously in ARIC, the average dietary glycemic load for each participant will be calculated by summing the products of the carbohydrate content per serving for each food times the average number of servings of that food per day times the glycemic index for that food. Glycemic index will be determined by dividing the glycemic load by the total carbohydrate intake per day.²⁵

Covariates of interest: Other variables that may influence carotid artery plaque characteristics will be included in the models and will include: age, race/center (combined variable), sex, education, composite physical activity variable, hypertension, diabetes, history of coronary artery disease, history of smoking, total caloric intake, and body-mass index. Statin medications is another important covariate. There may also be an interaction by FTO genotype, which has a known link with BMI and obesity.

Outcome: Carotid plaque artery characteristics (total wall volume ICA; maximum wall thickness ICA; maximum lipid core area; mean cap thickness) as outline by Wasserman et al⁶ will be the major outcome. Inflammation will be dichotomized using the contrast-enhanced BBMI (yes/no) and an ordinal score, as well as a continuous measure using “neovascularization”.

Variables of interest: Diet similar to Med Diet (composite variable), Sweet Diet (glycemic index), pca using FFQ data, alcohol intake, nutrition data from Carotid MRI, physical activity index.

Other potential confounders: Hypertension, diabetes, age, APOE E genotype, FTO genotype and education.

Limitations:

Dietary patterns throughout life can affect carotid plaque characteristics. The FFQ is only a rudimentary assumption of dietary patterns that is prone to over and underreporting. Persons may change their dietary patterns through life. The Med Diet has received much focus. We will create two composite variables (Med-Like and Sweet Diet), but it will be related only to items of interest, and it will be difficult to say of what weight each item should have in the composite. Therefore, the construct will limit the conclusions. The use of contrast-enhanced BBMRI as a marker of “inflammation” has not been well studied, and is only hypothesis driven. The burden of high-risk plaques is only about 20%, and there may not be enough subjects to demonstrate an association with high-risk plaques. The covariates of interest, such as smoking and hypertension, may have a much greater effect size on plaque characteristics that negates the association with diet patterns.

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 No
(We will use ApoE genotype data and FTO genotype data)

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.cscce.unc.edu/ARIC/search.php>

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)?

Astor BC, Sharrett AR, Coresh J, Chambless LE, Wasserman BA. Remodeling of Carotid Arteries Detected with MR Imaging: Atherosclerosis Risk in Communities Carotid MRI Study. Radiology 2010;256:879-886.

Bijari PB, Wasserman BA, Steinman DA. Carotid Bifurcation Geometry Is an Independent Predictor of Early Wall Thickening at the Carotid Bulb. Stroke 2014;45:473-478.

Etesami M, Hoi Y, Steinman DA, et al. Comparison of Carotid Plaque Ulcer Detection Using Contrast-Enhanced and Time-of-Flight MRA Techniques. American Journal of Neuroradiology 2013;34:177-184.

Wasserman BA, Astor BC, Sharrett AR, Swingen C, Catellier D. MRI measurements of carotid plaque in the atherosclerosis risk in communities (ARIC) study: Methods, reliability and descriptive statistics. Journal of Magnetic Resonance Imaging 2010;31:406-415.

Houston DK, Stevens J, Cai J, Haines PS. Dairy, fruit, and vegetable intakes and functional limitations and disability in a biracial cohort: the Atherosclerosis Risk in Communities Study. Am J Clin Nutr. 2005 Feb;81(2):515-22.

Beydoun MA, Kaufman JS, Sloane PD, Heiss G, Ibrahim J. n-3 Fatty acids, hypertension and risk of cognitive decline among older adults in the Atherosclerosis Risk in Communities (ARIC) study. Public Health Nutr. 2008 Jan;11(1):17-29.

Nettleton JA, Volcik KA, Hoogeveen RC, Boerwinkle E. Carbohydrate intake modifies associations between ANGPTL4[E40K] genotype and HDL-cholesterol concentrations in White men from the Atherosclerosis Risk in Communities (ARIC) study. Atherosclerosis. 2009 Mar;203(1):214-20. Epub 2008 Jul 2.

Stevens J, Ahn K, Juhaeri, Houston D, Steffan L, Couper D. Dietary fiber intake and glycemic index and incidence of diabetes in African-American and white adults: the ARIC study. Diabetes Care. 2002 Oct;25(10):1715-21.

Shimakawa T, Nieto FJ, Malinow MR, Chambless LE, Schreiner PJ, Szklo M. Vitamin intake: a possible determinant of plasma homocyst(e)ine among middle-aged adults. Ann Epidemiol. 1997 May;7(4):285-93.

Shimakawa T, Sorlie P, Carpenter MA, Dennis B, Tell GS, Watson R, Williams OD. Dietary intake patterns and sociodemographic factors in the atherosclerosis risk in communities study. ARIC Study Investigators. Prev Med. 1994 Nov;23(6):769-80.

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

11.b. If yes, is the proposal

A. primarily the result of an ancillary study (list number* ARIC Carotid MRI _____)

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.csc.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.

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2. Held C, Hjerdahl P, Eriksson SV, Björkander I, Forslund L, Rehnqvist N. Prognostic implications of intima-media thickness and plaques in the carotid and femoral arteries in patients with stable angina pectoris. European Heart Journal 2001;22:62-72.

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3. Astor BC, Sharrett AR, Coresh J, Chambless LE, Wasserman BA. Remodeling of Carotid Arteries Detected with MR Imaging: Atherosclerosis Risk in Communities Carotid MRI Study. *Radiology* 2010;256:879-886.
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