ARIC Manuscript Proposal # 1027

1.a. Full Title: Common Carotid Artery Diameter: What is Normal and Do Risk Factor Profiles Vary with Level of Disease?

b. Abbreviated Title (Length 26 characters): Variation in CCA Diameter

2. Writing Group (list individual with lead responsibility first):

Lead: Marsha L. Eigenbrodt
Address: Department of Epidemiology
UAMS College of Public Health
4301 West Markham, #820
Little Rock, AR 72205

Phone: (501) 526-6610 Fax: (501) 526-6750 E-mail: eigenbrodtmarshal@uams.edu

Writing group members: Zoran Bursac, David Couper, Jawhar Mehta, Kathy Rose, Richard Tracy, Fred Brancati, Greg Evans? From Wake Forest

3. Timeline:
Analyses have begun using the limited access data and a draft is being composed. Reanalysis using the full ARIC data will be completed: 1 month from receiving full data Draft to co-authors: 2 months from receiving full data Manuscript proposal to ARIC publications committee: 4 months from receiving data Manuscript to journal: 6 months from receiving data

4. Rationale:
Determining optimal common carotid artery diameter and risk factors associated with diameter in a normal and diseased population. Association between common carotid artery diameter with atherosclerosis and atherosclerotic risk factors is well recognized,1-5 with thicker IMT being associated with greater artery diameter. While age- and height-adjusted means for carotid diameters have been reported for men and women in a population-based sample including persons with risk factors for atherosclerosis,1 information for persons without atherosclerotic disease and risk factors is limited.6 Prevalence and age of onset of atherosclerosis is highly variable across populations. Since prevalence of the risk factors within the population will impact the mean of the covariates, variation of atherosclerotic disease and risk factors in the population will contribute to a difference in what diameter is considered normal.

To better understand the role of diameter enlargement in atherosclerosis and the impact of normal aging and atherosclerosis on the arterial wall, normal values for CCA diameters need to be estimated in an optimal population (eg. persons without evidence of atherosclerosis)6 or adjusted to an optimal level. Diameter enlargement may occur as the result of diffuse changes...
in response to hemodynamic factors or general degeneration from aging and have concurrent diffuse intimal thickening prior to the development of clinically recognized atherosclerosis; or diameter enlargement could occur as a focal response to atherosclerosis. The risk factor profiles associated with diameter enlargement may therefore vary in persons with and without atherosclerosis.

Because gender, age, height, and possibly race affect arterial diameter, the contribution of these factors to arterial diameter must be separated from the effect of atherosclerosis. While weight may impact the size of arteries, obesity is a risk factor for atherosclerosis and so anthropomorphic features of obesity should be considered in defining the “normal” population.

5. Main Hypothesis/Study Questions:

Primary Questions:

Aim 1: We hypothesize that age-specific diameters will be larger in a population sample than in a population containing persons without atherosclerosis or atherosclerosis risk factors even after adjusting for race, gender, and height.

Aim 2. We hypothesize that, in the normal population, age, birth weight, and hemodynamic factors or factors associated with hemodynamic changes such as blood pressure, obesity, and alcohol consumption (adjusting for cigarette years of smoking) will be positively associated with diameter even after adjusting for race, height, and gender. We hypothesize that diameter will explain much of the variation in intima-medial thickness associated with these risk factors in this normal population.

Aim 3. We hypothesize that the risk factor profiles for diameter enlargement will be different among persons with and without evidence of atherosclerosis. Specifically we hypothesize that age (as a marker of wear and tear) will be associated with diameter in both populations with and without evidence of atherosclerosis. We propose that hemodynamic factors and factors associated with hemodynamic change, but not markers of inflammation or acute phase reactants (fibrinogen, vonWillebrand factor) will be positively associated with diameter in persons without plaque or shadowing. Among persons with plaques or shadowing, we propose that acute phase reactants (fibrinogen, vonWillebrand factor) as indicators of vulnerable plaques will be positively associated with diameter. We hypothesize that the diameter will explain much of the variation in intima-medial thickness that is associated with these risk factors.

Factors to be considered for aims 2 and 3 include age, race, sex, height, measures of obesity (BMI), diabetes, grams of alcohol consumption, white blood count (WBC), cigarette years smoked, blood glucose, systolic, diastolic, or mean blood pressure, fibrinogen, vonWillebrand factor, Cornell voltage criteria, HDL cholesterol, LDL cholesterol, medications, and glucose.

Secondary question:

We will evaluate the following question that may not provide information for a manuscript but will provide better understanding of the CCA diameter measures in the ARIC Study.

While the carotid bifurcation is known to be elliptical in shape, there is little published on the change in common carotid artery (CCA) diameter determined by B-mode ultrasound over the segment from proximal (near its origin) to distal (adjacent to the bifurcation) in a middle aged population. The difference in diameters in the ARIC study in optimal, anterior, and posterior view could be because of true differences or because of differences in measurement errors introduced in the different views. True differences could be because of incorporation of the dilatation of the carotid sinus in some distal CCA diameter measurements or because of increase of plaques as the bifurcation is approached.

To investigate whether the differences in anterior, posterior and optimal view diameter differences may be due to anatomy, we propose to describe the diameters from the most
proximal measurements to the distal measurements in the "normal" population for each view. If the variation is due to differences because of anatomy, there should be an increase in the differences between anterior, posterior and optimal view diameters from proximal to distal CCA segment in the normal sample.

Data (variables, time window, source, inclusions/exclusions):

**Baseline variables needed:** age, race, sex, center, standing height at baseline, prevalent coronary heart disease, stroke, diabetes, blood glucose, fasting information, hypertension, anti-hypertensive medication use, systolic and diastolic blood pressure, body mass index, smoking status, years of cigarette smoking, drinking status, ethanol consumption, LDL and HDL cholesterol, cholesterol medication use, plaques or shadowing in any carotid, WBC, fibrinogen, vonWillebrand factor, Cornell voltage criteria, plaques/shadowing in right or left common carotid artery, mean and ten individual CCA diameter and far wall measurements for each view: optimal, anterior, and posterior views.

**Methods:**

From baseline data, a random sample of two thirds of participants who have B-mode ultrasound measurements of the right common carotid artery (CCA) or left common carotid artery will be used as the developmental sample and the remaining sample will be used for model testing/validation. We will determine mean diameters using mean optimal view measurements.

Defining normal population:

Determine the age-specific diameters among a “normal” subset of the population (defined by absence of CVD disease and absence of plaques and absence of detrimental atherosclerosis risk factor levels-see below) adjusting for gender, height, center, and race. From those excluded from the “normal” population, there will be two subsets: 1) those with clinical cardiovascular disease disease (CVD) (ischemic heart disease or stroke), and 2) those without clinical CVD but with atherosclerosis risk factors. We will determine the diameters in these two subgroups also adjusting for gender, height, and race.

For determining the “normal” diameters two approaches will be taken. First, the “normal” age-specific diameters will be determined within a subset of the population without disease and excluding persons with detrimental levels of the risk factors (specified below) adjusting for race, sex, center and height. A second approach will be to exclude persons with CVD or plaques and other related diseases (specified below), but instead of excluding persons with unfavorable levels of continuous variables, the diameters would be adjusted to the optimal level of the covariates as defined below.

To define the “normal” subset of the population we will use the following exclusions: prevalent coronary heart disease (electrocardiographic evidence of a myocardial infarction (MI), self-reported physician diagnosis of a MI, or a cardiac procedure), prevalent stroke (baseline self reported history of stroke and/or algorithm), persons with prevalent diabetes (physician diagnosis, medication, or fasting blood glucose≥126mg/dL), hypertension (anti-hypertensive medication within 2 wks or BP≥140/90), body mass index (BMI) ≥ 30 (computed as weight in kg divided by height in meters squared), current or previous cigarette smoking, high LDL cholesterol (≥160) or use of cholesterol lowering medication. (While these exclusions remove a large proportion of the population, we believe it is necessary to do so to find what the optimal diameters should be. From the limited access data the numbers after exclusions would be 840 if we exclude ever smokers, and 1,429 if we exclude only current smokers. The smallest sample is for black women with only 32-59 persons available depending upon the smoker status exclusion.) Adjustment will be made for gender, height, race, and center.

For the alternate method of determining the normal diameter, we will exclude persons with disease (heart disease, stroke, plaque, diabetes, hypertension, and cholesterol medication use) but adjustments rather than exclusions will be made for continuous covariates. Persons with
极值数据将被排除，因为它们可能影响线性关系，并且数据在极值附近稀疏，难以确定适当的关系。此外，除性别、身高、种族和中心外，我们将调整主要连续变量（葡萄糖、LDL、HDL、BMI、平均血压）的最优值，以确定理想的CCA直径。使用常规线性模型和百分位图。血糖（110 mg/dL）、LDL（100 mg/dL）、HDL（60 mg/dL）、收缩压（115 mm Hg）、舒张压（75 mm Hg）的阈值用于分离受损/边缘风险组和低风险组（根据ATPIII和JNCVII指南、MMWR 2003/52(35);833-837），BMI为21.5可用于正常范围的中间值。

年龄、性别、身高、种族和中心调整的直径将在人群中确定，并在不同疾病水平的人群中确定（临床疾病或仅风险因素）。

非参数检验将用于比较调整后的直径分布之间的几个子群体：正常人群、全数据集、临床疾病的 subset、仅风险因素组（无临床疾病）、无和有斑块的 subset。比较子样本与全人口样本将使用单样本检验，将人口均值作为标准。

在正常人群中，包含脂质沉积（基于用于排除正常人群的因子定义），以及定义为存在或不存在脂质斑块和阴影的子集，直径增大的风险因素组合及多变量模型将用于分析CCA直径与LDL胆固醇、HDL胆固醇、BMI、血糖、收缩压、舒张压、纤维蛋白原、Von Willebrand因子、白细胞计数、吸烟状态、吸烟年数、饮酒和酒精消耗、Cornell电压指标用于LVH、以及对年龄、种族、性别、身高和中心的调整。

II. 使用三个动脉视图在所有正常子集的十根直径测量数据：确定是否直径在更远的端点更大，并且是否存在三个直径测量值从最远端CCA到最近端CCA的最大值到最小值的差值更小。使用重复测量方法。

7.a. 将数据用于非-CVD分析吗？是 ____，否 ___

b. 如果是，作者是否知道必须使用文件ICTDER02来排除RES_OTH = “CVD Research”用于非-DNA分析，而DNA分析RES_DNA = “CVD Research”将使用？是 ____，否 ___

(此文件ICTDER02已分发给ARIC PIs，包含与存储样本使用的更新相关的同意书回应。)

8.a. DNA数据将用于此分析吗？是 ____，否 ___

8.b. 如果是，作者是否知道要么使用Coordinating中心分发的DNA数据，要么使用文件ICTDER02来排除RES_DNA = “No use/storage DNA”？是 ____，否 ___
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.csee.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)?

11. 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: