ARIC Manuscript Proposal # 1820

PC Reviewed: 7/12/11	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: A comparison of the impact of major risk factors for stroke in African-Americans and whites: The Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters):

2. Writing Group:
Rachel R. Huxley, Liz Bell, Pamela L. Lutsey, Wayne Rosamond, Eyal Shahar, Rebecca Gottesman, Aaron R. Folsom others welcome

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

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3. Timeline:
Data analysis – 3 months
First draft of the manuscript – 3 months

4. Rationale:

Stroke is the third leading cause of mortality in the United States behind coronary heart disease and cancer, and accounts for over 137,000 deaths each year.[1] African Americans are twice as likely to die from stroke compared with Whites. [2] Most of this

mortality differential is known to be due to higher levels of traditional risk factors for stroke among African Americans including high blood pressure, diabetes and obesity.[2] In addition, more than 700,000 non-fatal strokes occur annually in the US often causing severe and chronic morbidity especially among African-American stroke survivors who are more likely to become disabled and experience difficulties with daily living and activities.[2]

Although there have been several dozen papers published on the etiology of stroke from the Atherosclerosis Risk in Communities Study (ARIC) no single publication has examined whether stroke risk factors are comparable in Whites and African-Americans. Studies suggest that a significant proportion of the US population are unable to identify a single stroke risk factor, and worryingly, that high-risk groups, such as the elderly, African-Americans and men, were the least knowledgeable about stroke warning signs and risk factors. [3,4] Hence, distilling such information into a single and comprehensive publication may contribute to raising awareness about the most important modifiable risk factors for stroke.

In a previous publication from ARIC, Chambless and colleagues showed that the optimal risk prediction model for ischemic stroke included, in addition to age and sex, a combination of the following risk factors [5]: current smoking, diabetes mellitus, systolic blood pressure, antihypertensive therapy, prior CHD and left ventricular hypertrophy, body mass index, waist:hip ratio, high density lipoprotein cholesterol, alcohol consumption, peripheral arterial disease, and carotid artery wall thickness. However, this paper did not examine whether there were racial differences in the associations between these risk factors with stroke nor in their contributions to stroke burden.

In this paper, we propose to provide a comprehensive summary of the impact that these risk factors have on stroke risk as well as the burden of stroke due, in turn, to each of these risk factors separately in African-Americans and whites in ARIC. A novel aspect of this proposal is that we will estimate the impact of these risk factors on the burden of stroke using the generalized impact fraction (GIF) as well as the more commonly used method of population attributable fractions [6]. GIF is a measure that measures the effect of a reduction in the distribution of a risk factor (e.g. obesity, smoking) rather than the elimination of a risk factor in a population and as such may be more relevant to public health.

5. Main Hypothesis/Study Questions:

The objectives of the proposal are as follows:

i. To compare the associations of modifiable risk factors with stroke between African-Americans and whites
ii. To calculate the population attributable fraction (PAF) for stroke due to each of these risk factors separately in African-Americans and whites

We hypothesize that racial differences in the PAFs of stroke risk factors will exist due largely to differences in the prevalence of established risk factors.

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).

We will formally evaluate whether interactions are present by race in the relations of the exposures to risk of ischemic stroke. Regardless of whether race interactions are present, given inherent interest, race-stratified results will be reported showing the association between risk factors and stroke risk and their contribution to the burden of stroke in ARIC using a longitudinal data analysis approach.

Exposure

Based on a previous publication from ARIC that developed a risk prediction tool for ischemic stroke, we will examine the relationships between risk factors for ischemic stroke separately in whites and African-Americans, which include:

- current smoking
- diabetes mellitus
- systolic blood pressure and blood pressure medication
- prior CHD
- left ventricular hypertrophy
- body mass index
- waist:hip ratio
- high density lipoprotein cholesterol
- alcohol consumption
- peripheral arterial disease
- carotid artery wall thickness

Outcome

Incident cases from ischemic stroke identified in the follow-up through the end of 2008 will be included (individuals who had a hemorrhagic stroke will be censored from the analysis due to differences in the pathophysiology of this stroke type). Stroke events will be defined as a validated definite or probable hospitalized ischemic (or hemorrhagic) stroke confirmed by imaging.

Exclusions

Study participants will be excluded from the analysis if they fulfill at least one of the following criteria:

- ethnicity other than Black or White
- missing data on co-variates at baseline
- prior stroke history at study baseline

Statistical analysis

Means and standard deviations (SD) for the continuous variables and percentages for the categorical variables will be obtained separately for men and women and for White and African American participants. We will determine the age- and gender-standardized prevalence of risk factors separately in whites and African-Americans. Associations between risk factors at baseline and the incidence of stroke will be estimated using Cox proportional hazards models. Race interactions will be evaluated by including cross-product terms in the models. Race-specific analyses will be conducted and models will adjust for sex, age and study site with each of the risk factors in turn. We will explore the assumption of proportional hazards adding to the model an interaction term between follow-up time and exposure of interest, computing Schoenfeld residuals, and by inspection of the log(-log[survival function]) curves.

Population attributable fractions will be computed according to the following formula:

$$PAF = \sum_{i=0}^{k} pd_i \left(\frac{RR_i - 1}{RR_i} \right)$$

where pd_i is the proportion of cases falling into *i*th exposure level and RR_i is the relative risk comparing *i*th exposure level with unexposed group (*i*=0).

The GIF will be computed according to the methods given in a previous ARIC publication [7]:

> The generalized impact fraction (GIF) for a given bootstrap sample and stratum *a*, *b*, *c* is
>
> *a,b,c* is
>
> $$\frac{\sum \left(P_{i,abc} \times \mathrm{HR}_{i,abc}\right) - \sum \left(P^{*}_{i,abc} \times \mathrm{HR}_{i,abc}\right)}{\sum \left(P_{i,abc} \times \mathrm{HR}_{i,abc}\right)},$$
>
> where
>
> GIF = generalized attributable fraction for 1 bootstrap sample, from a given stratum of *a*, *b*, *c*;
>
> P_i = proportion of the population in exposure category *i*;
>
> HR = hazard ratio;
>
> P_i^* = proportion of the population in exposure category *i* after an intervention or other change;
>
> HR_i = crude hazard ratio in exposure category *i* as compared with the reference level;
>
> *i* = normal weight, overweight, or obese status as defined by body mass index (weight (kg)/height $(m)^2$) category; and

Limitations

The main limitation concerns the number of stroke events when the analyses are stratified by race. Additional limitations include residual confounding and misclassification of the exposure at baseline and due to their time-varying nature.

7.a. Will the data be used for non-CVD analysis in this manuscript? x_ Yes __ 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? __x__ 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 _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

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.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)?
1. Lloyd E. Chambless, Gerardo Heiss, Eyal Shahar, Mary Jo Earp, and James Toole. Prediction of Ischemic Stroke Risk in the Atherosclerosis Risk in Communities Study. Am J Epidemiol 2004;160:259–269.

2. Aaron R. Folsom, Kazumasa Yamagishi, Atsushi Hozawa and Lloyd E. Chambless Absolute and Attributable Risks of Heart Failure Incidence in Relation to Optimal Risk Factors. Circ Heart Fail 2009;2;11-17;

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* 2008.09)

___ 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.

References

1. Heron MP, Hoyert DL, Murphy SL, Xu JQ, Kochanek KD, Tejada-Vera B. Deaths: Final data for 2006, Adobe PDF file [PDF–5.3M] National Vital Statistics Reports; 57(14). Hyattsville, MD: National Center for Health Statistics. 2009.
2. Lloyd-Jones D, Adams R, Carnethon M, et al. Heart Disease and Stroke Statistics—2009 Update. A Report From the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2009;119:e21–e181.
3. Kleindorfer D, Khoury J, Broderick JP, Rademacher E, Woo D, Flaherty ML, Alwell K, Moomaw CJ, Schneider A, Pancioli A, Miller R, Kissela BM. Temporal trends in public awareness of stroke: warning signs, risk factors, and treatment. Stroke. 2009 Jul;40(7):2502-6.
4. Schneider AT, Pancioli AM, Khoury JC, Rademacher E, Tuchfarber A, Miller R, Woo D, Kissela B, Broderick JP. Trends in community knowledge of the warning signs and risk factors for stroke. JAMA. 2003 Jan 15;289(3):343-6.
5. Lloyd E. Chambless, Gerardo Heiss, Eyal Shahar, Mary Jo Earp, and James Toole. Prediction of Ischemic Stroke Risk in the Atherosclerosis Risk in Communities Study. Am J Epidemiol 2004;160:259–269.
6. Vander Hoorn S, Ezzati M, Rodgers A, et al. Estimating attributable burden of disease from exposure and hazard data. In: Ezzati M, Lopez AD, Rodgers A, et al, eds. Comparative Quantification of Health Risks: Global and Regional Burden of Disease Attributable to Selected Major Risk Factors. Geneva, Switzerland: World Health Organization; 2004:2129–2140.
7. Loehr LR, Rosamond WD, Poole C, McNeill AM, Chang PP, Deswal A, Folsom AR, Heiss G. The potentially modifiable burden of incident heart failure due to obesity: the atherosclerosis risk in communities study. Am J Epidemiol. 2010 Oct 1;172(7):781-9. Epub 2010 Aug 17.