ARIC Manuscript Proposal #2030

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

1.a. Full Title: Twenty-five years trends in stroke incidence and mortality in the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Trends in stroke incidence and mortality

2. Writing Group:
Writing group members: Silvia Koton, Li Xing, Andreea Rawlings, Wayne Rosamond, Rebecca Gottesman, Josef Coresh.
Additional members are welcome.

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

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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).

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3. Timeline: To be written during anticipated sabbatical (starting August-October 2013).

4. Rationale:
Long-term trends have shown a decrease in stroke incidence rates in several countries in the last decades[1-4]; however, reports on changes in gender- and race-specific incidence and case-fatality rates over time are not consistent. Gender disparities in stroke rates in

adults aged 45-54 years are growing with time[5-7]. Data from the Rochester community study[5] and from the Swedish Hospital Discharge Register[6] show an increasing incidence of stroke among women in their midlife years. Furthermore, women 45-54 years old in the NHANES 1999 to 2004 had twice the odds of having experienced a stroke versus men of the same age[7]. These findings suggest that the observed disparity in stroke prevalence is more likely explained by an increasing incidence of stroke among women than by differential survival.

Studies from the US and the UK on race-specific trends generally show a decline in stroke incidence for the white population[8-10]. No changes in stroke incidence in the black population have been reported in some studies[9-10], while others show a decline in stroke incidence in black women, but not in men[8]. Trends in stroke incidence and 30-day mortality over several decades have been described based on the Framingham Study original and offspring cohorts' data. Fifty-year trends show a decrease in lifetime risk of stroke in men and women, along with a decline in 30-day mortality in men only[11]; however this study does not include analysis of trends in recent years.

The Atherosclerosis Risk in Communities (ARIC) cohort study presents a unique opportunity for evaluating trends in stroke incidence and case fatality, as well as differences by gender and race. A previous ARIC study on middle-aged adults followed up from 1987 to 1995 showed highest age-adjusted incidence rates for black men followed by black women, white men and white women. Age-adjusted case fatality rates tended to be higher among blacks and men, although this finding was not statistically significant[12]. Updated trends in stroke incidence and case fatality, and trends by gender and race based on more than 20 years of follow-up have not been published. The present study, using data collected in ARIC during the last 25 years, will provide the required information for estimating the actual burden of stroke.

5. Main Hypotheses:

1. Age-adjusted stroke incidence and case-fatality are decreasing. The decrease differs by gender, race and time period.
2. In middle-aged (45-54 years old) women stroke incidence rates are increasing with time.

In addition to the main hypotheses, the following question will be studied:
How do risk factors for stroke impact trends in stroke incidence?

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).

Validated data on stroke collected for all participants in the ARIC Cohort will be used.

Main Outcome Variables:

- Rates of first-ever stroke, recurrent stroke, 28-day case fatality and 1-year survival
- Trends in age-and gender-specific incidence rates and in age-adjusted gender, race and time period-specific rates

Study population:
The study population includes ARIC participants who attended Visit 1 and who do not meet the following exclusion criteria:

- Non-black or non-white
- Missing covariates included in statistical models (see below)

Summary of Data Analysis:

1. Age-adjustment will be conducted according to the ARIC Cohort (Visit 1) age-distribution, and secular trends in age-adjusted stroke incidence rates will be presented.
2. Kaplan-Meier survival curves will be used to show the overall survival function of the first-ever stroke as well as the stratified curves based on gender and race separately. Differences between the strata will be studied with the log-rank test.
3. Cox proportional hazard models will be computed entering age, gender and race as covariates, and further adding stroke risk factors included in the ARIC risk score (current smoking, systolic blood pressure, left ventricular hypertrophy, coronary heart disease, hypertension medication and diabetes)[13] to evaluate their effect on stroke trends. Using the first ARIC visit as baseline, we will use Cox analysis to assess the effect of time (plotting log RH vs. time). In addition to the linear trend, we will describe the survival curve using splines.
4. Conditional risk set model will be considered to model ordered recurrent stroke time with adjustment to a set of confounders mentioned above.
5. Mortality and 28-day case fatality after the first-ever stroke will be also analyzed using nonparametric and parametric approaches in survival analysis.
6. A potential healthy volunteers' effect will be assessed analyzing trends in the first 3 years of ARIC in comparison with later periods.

Anticipated challenges/ limitations:

1. There might not be enough power for all the proposed analyses. However, by 2009, 1115 definite and probable incident strokes have occurred in the ARIC Cohort, of them 976 definite and probable incident ischemic strokes. By the end of next summer, more cases will be available for analyses.
2. Although stroke is adjudicated in ARIC, potential differences in the definition of stroke cases during this prolonged period (e.g. due to increasing availability of CT and MRI) will have to be assessed and accounted for as needed.
3. Due to the small number of hemorrhagic strokes (111 incident cases by 2009), secular trends will be presented only for rates of all incident hemorrhagic 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)?

- Rosamond WD, Folsom AR, Chambless LE, Wang CH, McGovern PG, Howard G, Copper LS, Shahar E. Stroke incidence and survival among middle-aged adults: 9-year follow-up of the Atherosclerosis Risk in Communities (ARIC) Cohort. *Stroke*. 1999;30:736-743
- Chambless LE, Heiss G, Shahar E, Earp MJ, Toole J. Prediction of ischemic stroke risk in the Atherosclerosis Risk in Communities Study. *Am J Epidemiol*. 2004;160:259-269

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* _____)
___ 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

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10. May DS, Kittner SJ. Use of medicare claims data to estimate national trends in stroke incidence, 1985-1991. *Stroke*. 1994;25:2343-2347
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