ARIC Manuscript Proposal # 1772

PC Reviewed: 4/8/2011	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:
Birth weight as a risk factor for atrial fibrillation amongst whites and African Americans: the ARIC Study

b. Abbreviated Title (Length 26 characters):
BW and AF in ARIC

2. Writing Group:

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal.

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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:

Data analysis will start upon manuscript approval. We would expect to have a final draft of the manuscript by August 2011.

4. Rationale:

Low birth weight (BW) has been associated with an increased risk of cardiovascular disease, including coronary heart disease (CHD) and stroke (Eriksson, Wallander, Krakau, Wedel, & Svärdsudd, 2004)(Frankel et al., 1996)(Fan et al., 2010). A meta-analysis of observational studies of the association between BW and CHD suggests that a 1kg higher BW is associated with a 10-20% reduction in the risk of subsequent CHD although it is unknown whether residual confounding drives the association (Huxley et al., 2007). The pathophysiology of these associations has been suggested to be explained by the fetal origins hypothesis, which postulates that suboptimal nutrition in utero may lead to intrauterine growth retardation (IUGR) of the fetus. A long-term consequence of such IUGR is an increased propensity towards the development of cardiovascular, metabolic and endocrine abnormalities in later life. Little is known about the possible impact of birth weight on atrial fibrillation (AF). In the one study that has examined the relationship, which only included women, BW was positively associated with subsequent risk of AF rather than inversely as might be predicted by the fetal origins hypothesis, (Conen, Tedrow, Cook, Buring, & Albert, 2010). These findings have yet to be confirmed, or refuted, by other studies.

The incidence of AF is significantly lower in African Americans compared to whites despite the increased prevalence of other predictors of AF, such as hypertension or obesity, among the former (Soliman, Alonso, & Goff, 2009)(Psaty et al., 1997). In the ARIC cohort, incidence of AF in whites (6.7 cases per 1000 person-year) was twice that in African-Americans (3.0 cases per 100,000 person-years)(Alonso et al, 2009). This is in contrast to most cardiovascular diseases, in which both the prevalence and incidence is higher in the African-American population. A possible explanation is the relatively lower BW in African Americans when compared with the white population (David & Collins, 1997). Lower BW has been associated with a lower adult heart size in adult life, which could partly explain the low incidence of AF in African-Americans since heart size, and specifically left atrial size, has been shown to correlate with the incidence of AF (Marcus et al., 2010).

Therefore, we propose to examine the relationship between AF and BW in the ARIC cohort. We will also examine if this relationship differs by race while adjusting for other possible predictors of the association. The ARIC cohort provides an excellent setting to address this association in both men and women, and by race.

5. Main Hypothesis/Study Questions:

We hypothesize that individuals with higher birth weight will have an increased hazard ratio of AF, independent of other risk factors, and that this association partly explains the differences in whites and African-Americans

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).

Study design

We will conduct a follow-up analysis of the ARIC cohort, using visit 1 as baseline. (Visit 4 will also be used as baseline for a secondary analysis)

Inclusion/exclusion criteria

White and African Americans who attended visit 4 follow-up and provided information on BW will be included. Individuals with missing information on any of the variables of interest, reported cases of prematurity, twins, and individuals with prevalent AF at visit 1 will be excluded. We will also exclude all individuals whose race is not listed as white or African American. We expect approximately 9500 ARIC individuals will meet inclusion criteria.

Variables of interest

- Birth weight

This is the main independent variable and it is defined by two methods: (1) as the self reported value giving at visit 4 in pounds or ounces or (2) in those who did not know their exact birth weight, as a categorical variable (low, medium or high birth weight). We will classify quantitative birth weight in 3 categories (<2.5 kg, 2.5-4 kg, >4 kg) and combine both this categorized variable and the self-reported categories to be used as a single variable in the analysis.

- Atrial fibrillation incidence

AF in ARIC is ascertained from three different sources: (1) 12-lead ECGs done in study exams, (2) ICD-9 codes from hospitalization discharges (427.31, 427.32), and (3) death certificates including AF as any cause of death (427.3 or I48).[19] More than 90% of AF cases have been identified from hospital discharges. For the present proposal, we will consider incident AF as any first occurrence of AF between visit 1 and December 31, 2007. We estimate that more than 600 incidence cases of AF will be available for analysis.

- Other variables

We will consider other variables: age, gender, study center, race, income and education, height and body mass index, and cardiovascular risk factors, including diabetes, systolic blood pressure, use of antihypertensive medication, smoking, alcohol intake, and prevalence of myocardial infarction and heart failure.

Statistical Analysis

We will use Cox proportional hazards models to calculate hazard ratios and 95% confidence intervals of AF across the categories of birth weight.

We will run a series of models, with additional adjustment for potential confounders and mediators:

- Model 1: age, race, gender adjusted
- Model 2: model 1 + center, education, income,
- Model 3: M2 + diabetes, SBP, HTN meds, smoking, alcohol, height, BMI
- Model 4: M3 + prevalent MI and HF

We will run separate models by gender and race, and test for interactions including multiplicative terms in the models. In additional models we will explore whether race is a predictor of AF by categories of birth weight

Finally, we will repeat analyses including only those individuals who provided exact birth weight, and also using visit 4 as the baseline.

Strengths and limitations

The major strength of this study is the large sample size, the presence of both whites and African-Americans, extended follow-up and availability of information on confounding variables (socioeconomic status) and mediators (anthropometry, cardiovascular risk factors). The fact that the ARIC study oversampled the African American population makes this study particularly well suited to address this research question.

Major limitations include that about 50% of the birth weights recorded were not numerical, concerns about the validity of information on birth weight, and that AF is mostly ascertained from hospital discharge codes.

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)?
#685: Birth weight and CVD
#686: Birth weight and metabolic syndrome
Kathryn Rose is the contact author for these two manuscripts, and she is a coauthor in this proposal.

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 2008.09, 2008.12)
___ 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.

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