1.a. Full Title:

Temporal Trends in the Population Attributable Risk for Atrial Fibrillation: the Atherosclerosis Risk in Communities Study

b. Abbreviated Title:

Temporal Trends in the Population Attributable Risk for Atrial fibrillation

2. Writing Group:

Writing group members:


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

First author: Wilson Nadruz Junior
Address: Brigham and Women’s Hospital
Cardiovascular Division
75 Francis Street, PBB-1 North
Boston, MA 02115
Phone: 617-971-7867 Fax: 617-582-6027
E-mail: wilsonnadruz@gmail.com or wnadrujunior@partners.org

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).

Name: Susan Cheng
Address: Brigham and Women’s Hospital
Cardiovascular Division
75 Francis Street, PBB-1 North
Boston, MA 02115
Phone: 617-595-7127 Fax: 617-812-0425
E-mail: scheng3@partners.org
3. **Timeline:** Analysis will begin following proposal approval with the aim of completing analysis and a manuscript within 6 months.

4. **Rationale:**

Atrial fibrillation (AF) is one of the most common cardiac arrhythmias in clinical practice, affecting more than 3 million people in the United States \(^1\). Individuals with AF have a 5-fold increased risk of stroke and twice the overall mortality rate compared with those with normal sinus rhythm \(^2\). Epidemiological studies have demonstrated that most of AF risk is attributable to clinical risk factors, such as elevated systolic blood pressure, use of antihypertensive medications, obesity, diabetes, smoking and the presence of cardiac disease (i.e. coronary heart disease or heart failure) \(^2\)\(^3\). Traditional risk factors, including hypertension and smoking have been the focus of concentrated prevention and/or treatment efforts over the last decades \(^4\)\(^5\). Accordingly, decreasing temporal trends in the incidence of coronary artery disease and heart failure have been observed in several populations \(^6\)\(^7\). Nevertheless, particular AF risk factors, such as obesity and diabetes mellitus, have been increasing in prevalence \(^8\)\(^9\). Hence, it is possible that the relative contribution of some risk factors to the development of AF may be varying over time. Furthermore, available evidence has suggested that age-adjusted AF incidence rates may be increasing among men, but not in women \(^5\). The reasons for these discrepancies between subgroups in AF incidence are unknown, but could be potentially related to differences in the relative contribution of certain risk factors to AF risk over time. The population attributable risk method allows estimations of the proportion of disease risk in a population that can be attributed to the assumed effects of one or more risk factors \(^10\)\(^11\)\(^12\). This method offers the ability to assess the relative importance of risk factors, with respect to an outcome, over time.

Applying this type of analysis in the ARIC cohort may shed light on the temporal trends in the proportion of AF risk attributable to major modifiable clinical risk factors in a large biracial community-based sample of women and men.

5. **Main Hypothesis/Study Questions:**

Our main hypothesis is that the population attributable risk of major modifiable risk factors is varying over time with respect to incidence of AF. In particular, we hypothesize that the contribution of hypertension (assessed by high blood pressure levels and use of antihypertensive medications), smoking and cardiac disease (coronary artery disease or heart failure) to AF is decreasing, whereas the contribution of obesity and diabetes is increasing over time.

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).**
Using available participant data from all ARIC visits (Visit 1 through Visit 5) attended while free of AF, we will estimate the prevalence of each major risk factor as well as its associated hazard for incident AF continuously throughout the duration of ARIC follow-up (from 1987 to 2012). Using both prevalence and hazard estimates, we will then calculate the population attributable risk of each major risk factor over the same time period.

**Study sample**

The study sample will include individuals who attended ARIC examination Visit 1. Those who were not black or white, with missing information on studied risk factors (i.e. blood pressure levels, use of antihypertensive medications, obesity, diabetes, smoking status and diagnosis of coronary artery disease or heart failure) at Visit 1, or with prevalent AF at Visit 1, and black participants from Minnesota and Washington County will be excluded.

**Descriptive Analyses**

**Independent variables.** For calculating population attributable risk estimates, we will evaluate major risk factors that have been previously related to AF incidence in the ARIC population. It will be necessary to define presence versus absence of the main risk factors as binary variables. Therefore, for risk factors that are based on continuous measures, the following definitions will be used:

1) *Elevated systolic blood pressure* will be defined as systolic blood pressure $\geq 140$ mmHg;
2) *Anti-hypertensive medication use*;
3) *Obesity* will be defined as body mass index $\geq 30$ kg/m$^2$;
4) *Diabetes* will be defined as a fasting glucose $\geq 126$ mg/dL, non-fasting glucose $\geq 200$ mg/dL or taking glucose lowering medication;
5) *Smoking* will be defined as self-reported active smoking within 1 year prior to the exam visit;
6) *Heart disease* will be defined as the presence of coronary heart disease (defined as a definite or probable hospitalized myocardial infarction, or electrocardiographic evidence of an unrecognized prior myocardial infarction) or heart failure (defined based on adjudicated heart failure hospitalization since 2005 or hospitalization with a heart failure ICD code prior to 2005).

Individuals identified as having diabetes and heart disease at a given visit will be considered to have diabetes and heart disease, respectively, at all subsequent visits. In instances of missing information on risk factors at follow-up visits, information will be carried forward from the most recent observation.

**Dependent variables.** The primary dependent variable of interest will be the incidence of AF (from study ECGs and hospital discharge records), through year 2012.

**Analytical approach.** We will calculate the percentage population attributable risk of each primary risk factor at each time point using a method that is considered internally valid when adjusted relative risks must be used to account for possible confounding:

$$\text{Population attributable risk} \% = \text{pd}_i \times [(\text{HR}_i-1)/\text{HR}_i]$$

where pd$_i$ is the proportion of total cases in the population arising from the $i$th exposure category and HR$_i$ is the adjusted hazard ratio for the $i$th exposure category. We performed all population attributable risk calculations using the HR
estimate derived from a time-updated multivariable Cox proportional hazards models stratified by sex, race, study center and age, while adjusting for all other primary risk factors, and including time-varying coefficients for each of the major risk factors. The prevalence over time of each risk factor will be modeled using logistic regression, accounting for sex, race, study center and age, and will be standardized to represent the prevalence over time in a population of 60-years with demographics mimicking the overall ARIC population. In addition, we will use data collected from baseline (visit 1) through 2012 to estimate AF incidence rates (per 100 person-years) adjusted for age, sex, race, and field center. We will perform all analyses using STATA version 13.1 (College Station, TX) and will consider a 2-tailed P value <0.05 as statistically significant.

**Secondary analyses.** We will repeat the analyses using all available follow-up data, stratified by sex and race.

**Limitations and challenges.** We will use trend tests to assess for change in the prevalence as well as hazards associated with risk factors over time. Both prevalence and hazard ratios are components used to calculate the PAR, and our analyses of difference between the estimated PAR for a given risk factor at the earliest time point compared to the estimated PAR at the latest time point will ignore the potential of correlations between cohort observations made over time, resulting in estimated P values that are likely to be conservative.

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  ____x__ 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  ____x__ 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)?

MS#1713 Absolute and attributable risks of diabetes in relation to optimal risk factors: the ARIC Study

MS#1628 (Huxley) Absolute and attributable risk of atrial fibrillation in relation to optimal and borderline risk factors: the Atherosclerosis Risk in Communities Study

#2006 (Cheng) Age and the Population Attributable Risk for Cardiovascular Disease in the Community

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.cscu.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


