ARIC Manuscript Proposal # 3002

PC Reviewed: 07/11/2017	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Heart rate and atrial fibrillation: a Mendelian randomization analysis in the AFGen consortium

b. Abbreviated Title (Length 26 characters): **MR analysis of heart rate and AF**

2. Writing Group:

Writing group members: ARIC investigators: Alvaro Alonso, Dan E. Arking, Wesley T. O'Neal, Elsayed Soliman, Lin Yee Chen. Other coauthors from cohorts participating in AFGen consortium

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

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3. Timeline: Analysis to be conducted over the next 2 months. Data from ARIC will be combined with results from other cohorts in the AFGen consortium. A manuscript should be completed over the next 6-8 months

4. Rationale:
Heart rate is regulated by complex interactions of biological systems, including the autonomous nervous and hormonal systems. Resting heart rate is associated with many other cardiovascular risk factors, including blood pressure, smoking, glucose metabolism, blood lipid and C-reactive protein levels, metabolic syndrome, body mass index and diabetes mellitus. In some conditions, including heart failure, reduction of heart rate has been shown to lead to event reduction, providing evidence that heart rate may be a modifiable, causal risk factor and not just a risk marker or a reflection of comorbidities.[1] Numerous observational studies have demonstrated that an elevated heart rate is associated with cardiovascular disease, myocardial infarction, heart failure, and mortality.[2] Recently, several community-based cohorts demonstrated that lower heart rate is associated with an increased risk of atrial fibrillation (AF), a common cardiac arrhythmia.[3,4] However, other studies have reported association in the opposite direction, with higher heart rate associated with increased risk of AF,[5] and also an U-shaped association.[6] In the past 10 years, several genome-wide association studies revealed genetic variants associated with heart rate.[7-11] By performing a Mendelian Randomization study with previously found genetic variants of heart rate, we aim to determine a potential causal relation between heart rate and AF.

5. Main Hypothesis/Study Questions:
To use a heart rate genetic risk score as an instrumental variable analysis for comparing the estimated influence of heart rate on AF risk with the observed risk as evidence for a causal relationship.

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).

Participants:
Individuals of European ancestry with successful GWAS genotyping, with heart rate measured at the baseline ECG, without AF.

Exclusions:
Individuals not in sinus rhythm at baseline (prevalent AF, pacemaker, complete heart block, others).

Exposure:

- Genetic risk score (for heart rate): Create a weighted genetic risk score, as was done in previous studies,[12,13] for heart rate. On a study specific basis, the genotype or the maximum likelihood dose for imputed genes will be summed at all SNPs in the heart rate genetic risk score, weighted by the effect size (beta-coefficient). The score will then be analyzed as continuous variable.
- Heart rate: Heart rate (as continuous covariate) measured at baseline.
- Incident atrial fibrillation, identified from study ECGs, hospital discharge diagnosis codes, death certificates.[14]

Statistical analysis (common across all cohorts participating in this project):
Cohort-specific analysis will be meta-analyzed by the leading writing group at University Medical Center Groningen. Two-step approach:

Step one

- Assess the association between baseline heart rate and incident AF using Cox proportional hazards models. Models:
    - Model 1: Heart rate, square of heart rate, age at baseline ECG, sex, eigenvector, and, if appropriate, center.
    - Model 2: Model 1 and additionally adjust for hypertension, diabetes, heart failure, myocardial infarction, body mass index.

Step two

- Based on the results of the Step 1 analysis, the meta-analysis team will decide if the Step 2 analysis needs to be stratified according to instrumental variable-free heart rate (will be separately communicated).
- Irrespective of the results of Step 1, the association between heart rate gene score and baseline heart rate using linear regression models in the population before stratification according to instrumental variable-free heart rate is needed. Models:
    - Model 1: Heart rate genetic risk score, age at baseline ECG, sex, eigenvector, and, if appropriate, center.
    - Model 2: Model 1 and additionally adjust for hypertension, diabetes, heart failure, myocardial infarction, body mass index.
- Assess the association between heart rate gene score and baseline heart rate using linear regression models in the population after stratification according to instrumental variable-free heart rate if needed. Models:
    - Model 1: Heart rate genetic risk score, age at baseline ECG, sex, eigenvector, and, if appropriate, center.
    - Model 2: Model 1 and additionally adjust for hypertension, diabetes, heart failure, myocardial infarction, body mass index.
- Assess the association between heart rate gene score and AF incidence using Cox proportional hazards models. Models:
    - Model 1: Heart rate genetic risk score, age at baseline ECG, sex, eigenvector, and, if appropriate, center.
    - Model 2: Model 1 and additionally adjust for hypertension, diabetes, heart failure, myocardial infarction, body mass index.
    - Model 3: Heart rate genetic risk score, heart rate, age at baseline ECG, sex, eigenvector, and, if appropriate, center. (evaluate horizontal pleiotropy)

Calculation of causal OR/HR of AF per unit increase of heart rate.
Instrumental variable estimates of causal beta coefficients will be derived using the Wald-type estimator, which involves taking the ratio of the beta coefficient of increase in log HR of AF per unit heart rate gene score increase and the beta coefficient of the increase in heart rate per unit increase of heart rate gene score. This beta coefficient is then exponentiated to express the result as a causal OR/HR. We will do this for models M1 and M2 to determine contribution of

confounding. With reasonable assumptions, the significance of any difference between the observed and estimated relationships can derive from a z-statistic test.

Potential follow-up analyses may stratify by age, given the difference in the association between resting heart rate and outcomes in younger vs older individuals, and exclude individuals taking medications that affect heart rate (e.g. beta-blockers, digoxin, anti-arrhythmics).

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? __X_ Yes ____ 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"? __X_ 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)?

MS #1483: Heart rate GWAS

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.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes __X__ No.

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