ARIC Manuscript Proposal #2285

PC Reviewed: 1/14/14 Status: A Priority: 2
SC Reviewed: _________ Status: _____ Priority: ____

1.a. Full Title: Body mass index and atrial fibrillation: a Mendelian randomization analysis in the CHARGE cohort

b. Abbreviated Title (Length 26 characters): Mendelian randomization BMI-AF

2. Writing Group:
   Writing group members: Alvaro Alonso, Dan Arking, Jeff Misialek, Elsayed Soliman, others welcome, investigators from other CHARGE cohorts

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 and manuscript to be completed over the next 6-9 months.

4. Rationale:
Several prospective studies have reported strong associations between obesity and the subsequent development of AF (1-4) even after controlling for other AF risk factors. As
BMI increases, AF risk appears to increase in a linear fashion and dynamic changes in BMI also impact incident AF risk in observational studies (4). If these relationships are causal, then weight reduction has the potential to greatly lower the incidence of AF. The proportion of incident AF explained by short term elevations in BMI is quite substantial (18.3%), even among women without prior cardiovascular disease (4). BMI also appears to be associated with AF progression (5), which has been associated with increased morbidity and mortality (6). Although weight loss may be a promising strategy for the reduction of AF based upon these data, it is not possible to establish causality in observational studies and randomized trial data are not readily available.

In order to obtain further evidence for a causal association between BMI and AF, we propose a Mendelian randomization analysis (7). This approach may be less subject to confounding, particularly confounding by reverse causation, as well as the bias that can influence observational analyses. If BMI is directly involved in the development of AF, then inherited genetic variation influencing BMI should affect AF risk in the direction and magnitude predicted by the observational associations, given the assumption that any additional pleiotropic effects of the genetic variation do not also influence AF risk. A BMI genotype score will be created from 39 single nucleotide polymorphisms (SNP’s) that associate with BMI (8, 9) in GWAS among adults of European Ancestry, and the association of this score with BMI and AF in the CHARGE cohorts will be quantitated. The association of the score with BMI will be utilized to estimate a predicted AF risk associated with the score, or genetically raised BMI, and instrumental variable analysis will be utilized to estimate the causal odds ratio.

We also propose to examine the FTO gene locus separately, which constitutes the strongest association with BMI (10), and is also the only SNP implicated in gene-environment interactions. These later effects likely include suggest interactions with physical inactivity (11) which may need to be taken into account in the analysis.

5. Main Hypothesis/Study Questions:
   1. To determine whether a BMI genotype score based upon published alleles and/or the individual FTO genotype is associated with AF in the CHARGE Consortium.
   2. To use a genotype score as an instrumental variable analysis for comparing the estimated influence of BMI 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).

Sample
Individuals with successful GWAS genotyping and information on BMI available. Exclude individuals with a race/ethnicity other than white, and those with prevalent AF at baseline.

Exposures:
1. BMI Genetic Risk Score: Create a weighted genetic risk score as was done in the Speliotes GWAS meta-analysis (8, 9). On a study specific basis, the genotype or the maximum likelihood dose for imputed genes will be summed at each of the 39 SNPs, weighted by the effect size (beta-coefficient). The score will then be analyzed as a continuous variable.

2. FTO: rs1558902 alone (additive mode with A-allele the affected allele)

3. BMI: Continuous BMI measured at baseline in prospective cohorts

Statistical Analysis:
Aim 1: To determine whether a BMI genotype score based upon published alleles and/or the individual FTO genotype is associated with AF in the CHARGE Consortium

A. Assess the association between BMI gene score and AF incidence using Cox proportional hazards models

Models:
1. BMI Genetic Risk Score, age, sex, eigenvector, and, if appropriate, center.
2. Model 1 + smoking status (current/past/never) and alcohol intake.
3. Model 2 + systolic blood pressure, diastolic blood pressure, antihypertensive medication, diabetes mellitus, prevalent heart failure, and prevalent CHD.
4. Model 3 + height
5. Models 5-8: Add BMI to models 1-4

B. Assess the association between the FTO locus and AF incidence using Cox proportional hazards models.

Models:
1. rs1558902, age, sex, eigenvector, and, if appropriate, center.
2. Model 1 + smoking status (current/past/never) and alcohol intake.
3. Model 2 + systolic blood pressure, diastolic blood pressure, antihypertensive medication, diabetes mellitus, prevalent heart failure, and prevalent CHD.
4. Model 3 + height
5. Models 5-8: Add BMI to models 1-4

Aim 2: To estimate the causal odds ratio between BMI and AF using instrumental variable analysis.

Part I: Association of BMI genetic score with BMI

A. Assess the association between BMI gene score and baseline BMI using linear regression models.

Models:
1. BMI Genetic Risk Score, age, sex, eigenvector, and, if appropriate, center
2. Model 1 + smoking status (current/past/never) and alcohol intake.
3. Model 2 + systolic blood pressure, diastolic blood pressure, antihypertensive medication, diabetes mellitus, prevalent heart failure, and prevalent CHD.
4. Model 3 + height.

B. Assess the association between the FTO and baseline BMI using linear regression models.

Models:
1. rs1558902, age, sex, eigenvector, and, if appropriate, center
2. Model 1 + smoking status (current/past/never) and alcohol intake.
3. Model 2 + systolic blood pressure, diastolic blood pressure, antihypertensive medication, diabetes mellitus, prevalent heart failure, and prevalent CHD.
4. Model 3 + height.

Part II: Association of BMI with AF.
C. Assess the association between baseline BMI and AF incidence using Cox proportional hazards models.

Models:
1. rs1558902, age, sex, eigenvector, and, if appropriate, center
2. Model 1 + smoking status (current/past/never) and alcohol intake.
3. Model 2 + systolic blood pressure, diastolic blood pressure, antihypertensive medication, diabetes mellitus, prevalent heart failure, and prevalent CHD.
4. Model 3 + height.

Part III: Instrumental Variable Analysis:
Instrumental variable estimates of causal hazard ratios will be derived using the Wald-type estimator, which involves taking the ratio of the AF-allele score log HR to the standardized BMI-allele score coefficient and then exponentiating to express as a causal HR. We will do this for each model above to determine contribution of confounding. With reasonable assumptions, the significance of any difference between the observed and estimated relationships can be derived by a z-statistic test.

7.a. Will the data be used for non-CVD analysis in this manuscript?  ____ 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?  ____ 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.csc.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)?

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.


