ARIC Manuscript Proposal #1925

PC Reviewed: 4/17/12                  Status: A            Priority: 2
SC Reviewed: __________              Status: ____        Priority: ____

1a. Full Title: Fasting glucose, insulin and thiazide diuretic: gene interactions

b. Abbreviated Title: Glucose, insulin & thiazide: gene interaction

2. Writing Group: Jorge L. Del-Aguila, Christy L. Avery, Eric A. Whitsel, Til Stürmer, Eric Boerwinkle, (and attempting to maintain symmetry across contributing cohorts), other members of the CHARGE Drug-Gene GWAS Consortium, as well as other interested members of the ARIC CHD, stroke, or blood pressure working groups.

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

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3. Timeline:
Statistical analyses: May 2012 – June 2012
Manuscript preparation: July, 2012 – August, 2012
Manuscript revision: August, 2012 – September, 2012
4. Rationale:

Hydrochlorothiazide (HCTZ) is the most prescribed diuretic in the USA in order to control hypertension. However, its ability to produce a variety of adverse metabolic effects (AMEs) is well-known including hyperglycemia and dyslipidemia. Furthermore, HCTZ use increases the long-term risk for the development of diabetes. For instance, a previous meta-analysis study estimated an odd ratio for diabetes when using HCTZ compared to placebo of 1.30 (95% CI 1.07-1.58).

The precise mechanism by which HCTZ influences glucose and triglyceride levels is not well understood, but multiple competing hypotheses have been proposed. One way to distinguish among these competing hypotheses is to identify genetic variants that are predictive of inter-individual variation in the AME of HCTZ treatment. This manuscript proposal is part of a larger effort examining gene-drug associations in the CHARGE consortium. Briefly, CHARGE was formed to facilitate GWAS meta-analyses and replication opportunities among multiple large population-based prospective cohort studies, including the Age, Gene/Environment Susceptibility (AGES) -- Reykjavik Study, the Atherosclerosis Risk in Communities Study (ARIC), the Cardiovascular Health Study (CHS), the Framingham Heart Study (FHS), Rotterdam Study (RS), HealthABC (HABC), and the Multi-Ethnic Study of Atherosclerosis (MESA). Since the inception of CHARGE, five additional cohorts have joined the effort: the Erasmus Rucphen Family study (ERF), the Health Aging, Body and Composition (Health ABC) study, Health 2000 the Multi-Ethnic Study of Atherosclerosis (MESA), and the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER). The number of participants using thiazide/thiazide-like users at ARIC visits 1-4 is 2,823, 2144, 1864 and 1821 respectively and will likely increase in number as cohort participants age.

5. Main Hypotheses/Study Questions:

Common genetic variants modify the association between diuretic use and measures of fasting glucose and insulin over time. There will be a follow-up study focusing on triglycerides.

6. Design and Analysis:

A within-study analysis of genetics variants modifying the association between diuretic use and measures of fasting glucose and insulin over time for each of the 2.5 imputed autosomal SNPs, then, combined across studies by the method of inverse-variance weighted meta-analysis.

Outcome. The proposed work focuses on fasting glucose and insulin concentration measured over the course of follow-up. Analyses of the two measures will be conducted separately. Participants with diabetes at baseline will be excluded (definition of diabetes: self-reported history, physician-reported diagnosis of diabetes, fasting glucose levels of more than 126mg/dL, non-fasting glucose more than 200mg/dL or use of anti-diabetic medication). We will also exclude all participants treated with only loop diuretics (due to their different mechanism of action in the nephron).

Exposure. Use of a thiazide or thiazide-like diuretic (yes/no) at each visit, in a single or combination preparation with or without concomitant use of a loop diuretic, potassium-sparing diuretic, or potassium supplement, as assessed by medication inventory at each visit in ARIC.
**Model.** We propose using generalized estimation equations (GEE) among all participants with genotype data and at least one fasting glucose measure. The GEE model is given by

\[ Y_{ij} = \beta_0 + \beta_1 I_{ij} + \beta_2 SNP_i + \beta_3 I_{ij} \times SNP_i + \beta_4 C_{ij} \]

where \( Y_{ij} \) is a log-transformed interval-scale outcome (fasting glucose or insulin concentration) for the \( i \)th participant at the \( j \)th visit, \( \beta_0 \) is the intercept, \( I_{ij} \) is an indicator of thiazide diuretic use (as defined above) use, \( SNP_i \) is the genetic variant of interest, and \( C_{ij} \) is a vector of covariables (e.g., age, sex, study site, body mass index, and ancestry principal components). The parameter of interest is \( \beta_3 \), the multiplicative interaction term. A robust variance estimator will be used.

**Potential for confounding by indication.** Confounding by indication is clearly a concern of any study that examines drug use in a non-randomized setting, which includes the majority of studies in the CHARGE consortium. However, simulation studies performed by Whitsel, Sturmer and Avery suggest that the influence of bias and loss of power from confounding by contraindication in this setting is likely small. This observation is based on an extensive series of drug-gene simulations for the QT interval, which demonstrated that confounding by contraindication resulted in a small increase in bias and decrease in power with increasing SNP main effect\(^{11}\). These simulations can be easily extended to examine the hypotheses presented here.

**Genome-Wide Significance Level:** P-value: 0.05 ÷ number of tests

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 ICTDER04 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 ICTDER04 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 ICTDER04 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)?
Manuscript proposal #151 (“Genome-wide association study of blood pressure using genotype-by-smoking and genotype-by-alcohol intake interactions: the ARIC Study”, Franceschini), #1484 (“A Gene-Environment Interaction Approach to Genome-Wide Association Analysis of Blood Pressure in the ARIC Study: Gene-Age Interactions in European Americans”, Shi), and #1406 (Genome-wide Association Study of Coronary Heart Disease in White Adults of European ancestry: the CHARGE Consortium”, Boerwinkle). However, none of the above-referenced manuscripts evaluate interactions with anti-hypertensive agents. Dr. Boerwinkle is also a co-author on this manuscript.

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 (AS #2009.10)
   ____ 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/

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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.

Reference List


