ARIC Manuscript Proposal #1924

PC Reviewed: 4/17/12  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: _____

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

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

2. Writing Group: Mark O. Goodarzi, 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
Manuscript submission: October, 2012

4. Rationale:

Statins are one of the most prescribed medication around the world\(^1\). They are well known for their capacity to decrease low-density lipoproteins concentration and to reduce the incidence of coronary heart disease\(^2\). However, it was reported in a previous meta-analysis study that patients who use intensive-dose statins have increased risk of developing diabetes compared to those using moderate-dose statins (odds ratio 1.09)\(^3\)

The precise mechanism by which statins influence glucose levels is not well understood, but multiple competing hypotheses have been proposed\(^4\), many focusing on the functional alteration of the islet B-cells. One way to distinguish among these competing hypotheses is to identify genetic variations that are predictive of inter-individual variation in glucose concentration changes in response to statin 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).

5. Main Hypotheses/Study Questions:

Common genetic variants modify the association between statin use and measures of fasting glucose and insulin over time.

6. Design and Analysis:

A within-study analysis of genetic variants modifying the association between statin 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 concentrations 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 non-statin cholesterol lowering medications (fibrates, niacin, colesevelam, ezetimibe), due to their different mechanism of action.

**Exposure.** Use of a statin (atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, simvastatin, rosuvastatin, or pitavastatin) (yes/no) at each visit, 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 statin use (as defined above), \( SNP_i \) 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 \( \div \) 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  

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.cscu.unc.edu/ARIC/search.php  
___ 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 #1513 (“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


