ARIC Manuscript Proposal #1532B

PC Reviewed: 6/9/15  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: _____

1.a. Full Title: GWAS of BMI interaction with diabetes-related traits: Meta-Analysis of Glucose- and Insulin-related traits Consortium (MAGIC) – Statistical Methods to Account for Multiple Sources of Heterogeneity

b. Abbreviated Title (Length 26 characters):

2. Writing Group:
Writing group members: Jim Pankow (or TBD) to represent the ARIC diabetes working group. Each cohort is being asked to nominate one cohort representative for this MAGIC consortium paper.

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

First author: Ching-Ti Liu or another external collaborator from the MAGIC Consortium

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).

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3. Timeline: Analysis: Already completed within ARIC
               Writing/review: August 2015
               Submission: September 2015

4. Rationale:

ARIC participated in a GWAS meta-analysis organized by the MAGIC consortium to investigate interactions between BMI and genetic variants on glycemic traits. The corresponding ARIC manuscript number is 1532. The publication that arose from this work is:

Abstract of this publication:

Recent genome-wide association studies have described many loci implicated in type 2 diabetes (T2D) pathophysiology and β-cell dysfunction but have contributed little to the understanding of the genetic basis of insulin resistance. We hypothesized that genes implicated in insulin resistance pathways might be uncovered by accounting for differences in body mass index (BMI) and potential interactions between BMI and genetic variants. We applied a joint meta-analysis approach to test associations with fasting insulin and glucose on a genome-wide scale. We present six previously unknown loci as associated with fasting insulin at $P < 5 \times 10^{-8}$ in combined discovery and follow-up analyses of 52 studies comprising up to 96,496 non-diabetic individuals. Risk variants were associated with higher triglyceride and lower high-density lipoprotein (HDL) cholesterol levels, suggesting a role for these loci in insulin resistance pathways. The discovery of these loci will aid further characterization of the role of insulin resistance in T2D pathophysiology.

We were recently contacted by MAGIC collaborators from this paper (Ching-Ti Liu and James Megis) who indicated that they have developed novel statistical methods to account for multiple sources of heterogeneity which may be quantified by cohort-specific characteristics such as age, ancestry, sex, BMI, etc. and wish to prepare a statistical methods paper describing the approach, and would like to include an example to illustrate their methods using analysis of summary-level results collected for the Manning et al. paper cited above.

5. Main Hypothesis/Study Questions:

Development and application of statistical methods to account for multiple sources of heterogeneity in genome-wide association analysis.

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).

The study is a cross-sectional GWAS meta-analysis. ARIC has already contributed results for the published meta-analysis. All ARIC GWAS analyses were completed by ARIC analysts and the summary results sent to the MAGIC collaborators for inclusion in the meta-analysis. The proposed methodologic paper will not require any new analyses of ARIC data, but rather will utilize summary results already submitted to MAGIC.

The following information describes to the ARIC-specific GWAS analyses that were previously completed:

All phenotypic data were taken from visit 1 data. The traits analyzed included fasting insulin, fasting glucose, HOMA-IR, and HOMA-B. HOMA-IR and HOMA-B derived from equations which include both fasting glucose and fasting insulin. For all traits, individuals fasting less than 8 hours were excluded. For all traits, individuals with prevalent diabetes at visit 1 were excluded. Only participants of European ancestry were included in the analysis.
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 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  _____ 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  _____ 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

   _____ 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)?

   ARIC Manuscript Proposal # 1536 -- GWAS of BMI interaction with diabetes-related traits: 
Meta-Analysis of Glucose- and Insulin-related traits Consortium (MAGIC)

   This proposal is a follow-up to proposal #1536 and its accompanying paper.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any 
ancillary study data? _____ Yes  _____ No

11.b. If yes, is the proposal

   _____ A. primarily the result of an ancillary study (list number* 2006.03) 
   _____ B. primarily based on ARIC data with ancillary data playing a minor role 
   (usually control variables; list number(s)* (Data from LITE)

*ancillary studies are listed by number at http://www.csc.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.