ARIC Manuscript Proposal # 1409

PC Reviewed: 07/30/08	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Genome-wide Association Study of Diabetes-Related Quantitative Traits in ARIC Whites

b. Abbreviated Title (Length 26 characters): GWAS of Diabetes Traits

2. Writing Group:

Diabetes GWAS working group:
Linda Kao (co-lead)
Jim Pankow (co-lead)
David Couper
Sue Bielinski

Other writing group members:
Mandy Li
Anna Kottgen
We wish to add representation from the DNA lab and also welcome additional nominations from other sites.

We are submitting a single, umbrella manuscript proposal for diabetes-related quantitative traits at this time because publication of results for some of these traits may proceed rapidly due to ARIC's participation in the Meta-Analysis of Glucose and Insulin Consortium (MAGIC). MAGIC is an international consortium of over a dozen epidemiologic cohorts that currently includes the following studies: EPIC Norfolk, CoLaus, British Cohort 1958, Twins UK, KORA, Sardinia, Diabetes Genetics Initiative, FUSION, Framingham, Cardiovascular Health Study, NFBC66, deCode, ERGO, NTR, NESDA.

Due to the fluid nature of data analysis and manuscript development within MAGIC, it is unclear how many manuscripts will emerge from this work, but we anticipate more than one. At the time of submission of this manuscript proposal we have committed to full participation in a MAGIC manuscript providing meta-analysis results for 2-hour glucose.

The specific authors for ARIC for the 2 hr glucose paper, including order, have yet to be negotiated with the MAGIC writing group. Each manuscript on diabetes quantitative traits will likely have a different order and number of ARIC authors, and will likely expand beyond the core group above.

Authorship guidelines for MAGIC specify that opportunities will be provided to all members of the consortium to participate and play a leading role on manuscripts. The total number of authors per cohort can range from 2 to 9, proportional to the number of genotypes provided for a given study.

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]**

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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).

3. Timeline: Data analysis to start immediately (July 2008), first manuscript (2 hr glucose) drafted by the end of August 2008.

4. Rationale:

Recent genome-wide association studies (GWAS) and candidate gene studies have identified at least 18 gene variants reproducibly associated with type 2 diabetes (Lango et al., Diabetes 2008). More recently, GWAS have begun to identify variants associated with diabetes-associated quantitative traits, such as fasting glucose (Chen, J Clin Invest 2008; Bouatia-Naji, Science 2008). Investigation of diabetes-associated quantitative traits (intermediate phenotypes) in non-diabetic individuals may uncover further loci predisposing to type 2 diabetes and provide new clues into its pathophysiology.

5. Main Hypothesis/Study Questions:

We propose to study the association of ~ 1 million SNPs from the Affy 6.0 array in ARIC participants and the following diabetes-related quantitative traits:

1. fasting glucose
2. fasting insulin and/or HOMA-IR
3. HOMA-beta cell function
4. 2 hour glucose from the oral glucose tolerance test

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).

Study design and inclusion/exclusion: subjects and sample size

Individuals who did not consent to genetic research, those of self-reported race other than "white" will be excluded.

Publication Strategy

We expect that the publication strategy will largely follow working group specifications of the MAGIC consortium. MAGIC has at least four manuscripts completed or in development: (1) fasting glucose; (2) fasting insulin and HOMA-IR; (3) 2 hour glucose and insulin; (4) hemoglobin A1c. Depending on the timeline for data analysis and manuscript preparation, ARIC will participate as a full contributor to meta-analyses for some of these traits, as a replication cohort for others, and may not contribute to others.

Prevalent and incident type 2 diabetes will be analyzed by the same ARIC diabetes working group but those phenotypes are not within the domain of MAGIC and will be covered in a separate manuscript proposal. In addition, we expect that diabetes and diabetes-related traits in ARIC African Americans will be integrated into the publication strategy for CARe and will require a separate manuscript proposal.

The publications committee will be notified by an addendum to this proposal when the publication strategy becomes better developed and additional papers are produced from the science covered in this proposal. For example, we are in discussions with Elizabeth Selvin about the possibility of including hemoglobin A1c values from her ancillary study in this working group.

Exposure Measurements and Definitions

This manuscript proposal is concentrated on the analyses of the SNP data at ~1 million SNPs.

Quality Control of Genotyping Data

Standard ARIC exclusions for individuals and SNPs will be applied, including those for missing data and HWE deviations.

Outcome Measurements and Definitions

Fasting glucose is available at ARIC visits 1, 2, 3, and 4. To maximize sample size, cross-sectional analyses will prioritize measures obtained at visit 1, although analysis of data from other visits will be conducted to evaluate consistency of findings.

Fasting insulin (and HOMA-IR) is available at visits 1 and 4. Similar to fasting glucose, cross-sectional analyses will prioritize measures obtained at visit 1, although analysis of data from visit 4 will be conducted to evaluate consistency of findings.

2 hour glucose measured after an oral glucose tolerance test is available at visit 4. Analysis will be cross-sectional.

Statistical Analysis

Analyses will follow unified analysis specifications agreed to by MAGIC consortium members. The analysis specifications for analysis of 2-hour glucose are provided below for illustrative purposes:

1) Untransformed trait value, without rank normalization.
2) 2-hour glucose in mmol/L
3) Exclude subjects with diagnosed diabetes, on diabetes treatment, or fasting glucose of 126 mg/dl or higher
4) Additive genetic model, 1 d.f. trend test
5) Genotyped SNPs, when available, and imputed SNPs
6) No imputation of missing traits
7) Study specific adjustments (for ARIC: age, gender, and center)
8) Analysis with and without BMI adjustment

Some exclusions specific to ARIC that will be applied to analysis of 2 hr glucose include:

1) Did not participate in visit 4
2) Fasting less than 10 hours before OGTT (screening exclusion)
3) Surgery to remove stomach, small intestine, or dialysis (screening exclusion)
4) Refused OGTT (screening exclusion)
5) Technical problems with OGTT (e.g.., venipuncture, drank less than half of glucola, vomiting, length of OGTT not between 110 and 130 minutes)

Primary analysis in ARIC will be conducted using the MACH QTL program with allele dosage estimates for imputed SNPs. Meta-analysis will be conducted within MAGIC using p-values for all available genotyped and imputed SNPs across participating cohorts using the METAL program.

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? _x__ 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? _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

8.c. If yes, is the author aware that some DNA data is not allowed to be used by 'for profit' groups. Is this data being used by a 'for profit' organization? _X_No If yes, is the author aware that the participants with RES_DNA = 'not for profit' restriction must be excluded? ____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)?

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 (list number* _____)

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)

2006.03

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