ARIC Manuscript Proposal #2756

PC Reviewed: 5/10/16	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Serum Metabolomic Profile of Diabetes and Glycemic Biomarkers

b. Abbreviated Title: Metabolomics and Diabetes

2. Writing Group:
Writing group members:

- Casey M. Rebholz
- Adrienne Tin
- Bing Yu
- Eric Boerwinkle
- Josef Coresh
- Elizabeth Selvin
- *Others welcome*

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

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3. Timeline: Analyses will be started upon approval of the manuscript proposal. We anticipate that a first draft of the manuscript will be available within approximately one year of manuscript approval.

4. Rationale:

Novel glycemic markers are a major line of current diabetes research, which could complement established glycemic markers, including fasting glucose and hemoglobin A1c.[1-6] Examining

metabolites associated with these novel glycemia markers compared to the established markers could provide new knowledge about the pathophysiology of short-term glucose control and glucose metabolism in general.

Recent advances in metabolomic profiling allows for the comprehensive characterization of metabolism through quantification of low-molecular weight metabolites.[7] An untargeted and unbiased metabolomic approach maximizes the potential for discovery of novel markers and could provide new insights about diabetes pathophysiology.[8] Given the availability of metabolomic data, well-defined diabetes prevelance and incidence, and recently assayed novel glycemia markers, the ARIC study offers a unique opportunity to characterize the metabolomic fingerprint of diabetes.

5. Main Hypothesis/Study Questions: The overall objective of this analysis is to determine whether metabolites identified through an untargeted metabolomics profile are associated with diabetes. We hypothesize that we will be able to identify novel metabolites associated with diabetes prevalence, diabetes incidence, and biomarkers of glycemic status (fasting blood glucose, hemoglobin A1c, fructosamine, glycated albumin, 1,5-anhydroglucitol).

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: cross-sectional and prospective analysis of metabolomics and diabetes measures

Eligibility Criteria: Approximately 4,000 African-American and Caucasian ARIC study participants with metabolomic profiling data from visit 1 serum specimens (ancillary study #2014.20 and 2008.16; two "batches")

Exposure: Metabolites were measured from stored fasting serum samples by Metabolon, Inc. (Durham, North Carolina) using an untargeted, gas chromatography-mass spectrometry and liquid chromatography-mass spectrometry approach (GC-MS/LC-MS). This untargeted approach identified approximately 600-800 named and unnamed metabolites. In the present study, we will primarily focus on the ~200 metabolites with limited missing values, reasonable reliability and presented in both batches.

Outcomes: We will examine the relationship between the metabolites and a variety of glycemia measures. For the cross-sectional analysis, the outcomes will be prevalent diabetes status and biomarkers of glycemic status (fasting glucose, hemoglobin A1c, fructosamine, glycated albumin, and 1,5-anhydroglucitol). For the prospective analysis, the outcome will be incident diabetes among those without diabetes at baseline.

Other Variables of Interest: In multivariable regression models predicting diabetes and glycemic status, we will consider adjusting for the following variables: age, sex, race-center, education level, blood pressure, body mass index, high density lipoprotein cholesterol, low density lipoprotein cholesterol, smoking status, physical activity level, history of cardiovascular disease,

estimated glomerular filtration rate (eGFR), and batch (batch represents when the metabolomic profiling was conducted).

Statistical Analysis: We will use logistic regression to examine the cross-sectional association between metabolites and diabetes prevalence; linear regression for the cross-sectional association between metabolites and biomarkers of glycemia; and Cox proportional hazards regression for the prospective association between metabolites and incident diabetes. Effect estimates will be calculated per one standard deviation increment of each metabolite. We will run several models to account for potential confounding factors. Model 1 will be adjusted for age, sex, race-center, and batch. Model 2 will additionally adjust for education level, blood pressure, body mass index, high density lipoprotein cholesterol, low density lipoprotein cholesterol, smoking status, physical activity level, and history of cardiovascular disease. Model 3 will additionally adjust for eGFR. We will examine potential effect modification using statistical tests for interaction and by stratifying by sex, race, overweight/obese status, and baseline kidney function (eGFR <90 vs. ≥90 mL/min/1.73 m^2). All analyses will be run in Houston using scripts provided by the first author.

Anticipated Methodologic Limitations or Challenges: Given the large number of metabolites, there is a high likelihood of detecting a false positive association. We will adjust the significance threshold by the Bonferroni method (dividing by the number of metabolites) to account for multiple comparisons.

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? ____ 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? ____ Yes __X__ 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.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)?

The below proposals investigate metabolomics in relation to a variety of disease states, reliability, and dietary intake. None have studied metabolomics in association with diabetes.

#2567: Metabolomic compounds and incident peripheral artery disease: the Atherosclerosis Risk in Communities study (lead author: Kunihiro Matsushita)

#2562: Metabolomics profiles and venous thromboembolism (lead author: Aaron Folsom)

#2398: Metabolomics and cognitive function in middle-aged African American adults: the Atherosclerosis Risk in Communities study (lead author: Jan Bressler)

#2380: Association of the serum metabolome and mortality among African Americans in the Atherosclerosis Risk in Communities study (lead author: Bing Yu)

#2354: Metabolomics and incident atrial fibrillation in African Americans: the ARIC Study (lead author: Alvaro Alonso)

#2056: A medium-term reliability study of the human serum metabolome: the Atherosclerosis Risk in Communities study (lead author: Yan Zheng)

#2034: The human metabolome is associated with dietary intake among African Americans in the Atherosclerosis Risk in Communities Study (lead author: Yan Zheng)

#1918: Associations of the human metabolome with blood pressure, prevalent, and incident hypertension among African Americans in the Atherosclerosis Risk in Communities study (lead author: Yan Zheng)

#1882: A longitudinal study of metabolomics and kidney function among African Americans in the Atherosclerosis Risk in Communities study (lead author: Bing Yu)

#1847: Role of the human metabolome in incident heart failure etiology among African Americans in the Atherosclerosis Risk in Communities Study (lead author: Yan Zheng)

#1696: Metabolomic predictors of incident heart failure: a case-control study nested within the Atherosclerosis Risk in Communities study (lead author: Jennifer Nettleton)

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

2014.20: Genomics, Metabolomics, and Cardiovascular Disease (PI: Eric Boerwinkle)

2009.16: Short-term markers of glycemia and long-term outcomes (PI: Elizabeth Selvin)

2008.16: Metabolomics & Heart Failure: A Novel Approach to Biomarker Discovery (PI: Jennifer Nettleton)

2006.15: Hemoglobin A1c, incident diabetes, and major causes of morbidity and mortality in non-diabetic participants (PI: Elizabeth Selvin)

___ 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.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes __X__ No.

References

1. Parrinello CM, Selvin E. Beyond HbA1c and glucose: the role of nontraditional glycemic markers in diabetes diagnosis, prognosis, and management. *Curr Diab Rep*. 2014;14:548.
2. Selvin E, Rawlings AM, Lutsey PL, Maruthur N, Pankow JS, Steffes M, Coresh J. Fructosamine and Glycated Albumin and the Risk of Cardiovascular Outcomes and Death. *Circulation*. 2015;132:269-277.
3. Selvin E, Rawlings A, Lutsey P, Maruthur N, Pankow JS, Steffes M, Coresh J. Association of 1,5-Anhydroglucitol With Cardiovascular Disease and Mortality. *Diabetes*. 2016;65:201-208.
4. Selvin E, Francis LM, Ballantyne CM, Hoogeveen RC, Coresh J, Brancati FL, Steffes MW. Nontraditional markers of glycemia: associations with microvascular conditions. *Diabetes Care*. 2011;34:960-967.
5. Selvin E, Rawlings AM, Grams M, Klein R, Sharrett AR, Steffes M, Coresh J. Fructosamine and glycated albumin for risk stratification and prediction of incident diabetes and microvascular complications: a prospective cohort analysis of the Atherosclerosis Risk in Communities (ARIC) study. *Lancet Diabetes Endocrinol*. 2014;2:279-288.
6. Selvin E, Rawlings AM, Grams M, Klein R, Steffes M, Coresh J. Association of 1,5-anhydroglucitol with diabetes and microvascular conditions. *Clin Chem*. 2014;60:1409-1418.
7. Tzoulaki I, Ebbels TM, Valdes A, Elliott P, Ioannidis JP. Design and analysis of metabolomics studies in epidemiologic research: a primer on -omic technologies. *Am J Epidemiol*. 2014;180:129-139.
8. Pallares-Mendez R, Aguilar-Salinas CA, Cruz-Bautista I, Del Bosque-Plata L. Metabolomics in diabetes, a review. *Ann Med*. 2016;48:89-102.