ARIC Manuscript Proposal #1918

PC Reviewed: 3/20/12 **Status: A** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title:
Associations of the Human Metabolome with Blood Pressure, Prevalent and Incident Hypertension among African Americans in the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Metabolomics, blood pressure, hypertension

2. Writing Group:
Writing group members: Yan Zheng; Bing Yu; Danny Alexander; Thomas Mosley; Gerardo Heiss; Eric Boerwinkle; and Jennifer A. Nettleton

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. YZ **[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:
We expect that the manuscript will be prepared within six months from approval of the analysis plan.

4. Rationale:

Hypertension is a leading risk factor for heart disease, stroke and kidney failure in the developed world.[1-3] African-American adults have the highest rates (44%) of hypertension [4] and are more resistant[5] to pharmacological treatment than other racial groups. In most cases the specific cause of hypertension is unknown ("primary hypertension"),[6] although it is influenced by several risk factors from both genetic and environmental aspects, such as family history, obesity, smoking, little or no exercise, excess dietary salt and alcohol, and stress.[7] The human metabolome is a reflection of the interaction between genes and the environment.[8] Therefore, studies integrating metabolomic profiling with blood pressure and hypertension may enhance our understanding of the physiopathology underlying development of hypertension. In a well-characterized, population-based sample of African Americans from the Atherosclerosis Risk in Communities (ARIC) study, we propose to explore the cross-sectional associations of multiple metabolites quantified by GS/MS/MS with both blood pressure and hypertension status, as well as their longitudinal associations with incident hypertension.

5. Main Hypothesis:

1. Metabolomic factors are associated cross-sectionally with systolic blood pressure (SBP), diastolic blood pressure (DBP), and/or pulse pressure in African Americans at baseline independent of traditional hypertension risk factors and antihypertensive medication use.

2. Metabolomic factors are associated cross-sectionally with prevalent hypertension status in African Americans at baseline independent of hypertension risk factors.

3. Metabolomic factors are associated prospectively with incident hypertension across visit 2-4, independent of traditional hypertension risk factors measured at baseline in baseline normotensive African Americans (defined as SBP <140mmHg, DBP <90mmHg, and not taking antihypertensive medications during past 2 weeks at baseline).

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 sample:
This is a study consisting of ARIC African Americans with serum metabolomic data quantified at baseline (visit 1).
Exclusion:

- Persons with no metabolomic data (metabolomics profiling was completed in a random sample of African Americans from the Jackson, MS, field center);
- Persons missing outcome variables or baseline covariates;
- For hypothesis 3, persons with prevalent hypertension at baseline will be excluded.

Outcome:

- Blood pressure (mmHg, including SBP, DBP, and pulse pressure; hypothesis 1)
- Prevalent hypertension at baseline (defined as SBP ≥140mmHg or DBP ≥90mmHg or taking antihypertensive medication during past 2 weeks at baseline; hypothesis 2)
- Incident hypertension (defined as SBP ≥140mmHg or DBP ≥90mmHg or taking anti-hypertensive medication use during past 2 weeks at any of the 3 follow-up examinations among baseline normotensives; hypothesis 3)

Likely covariates: [9, 10]

- Age (yrs)
- Sex
- Body mass index (kg/m^2)
- Usual Ethanol Intake (g/week)
- Education level
- Physical activity
- Pack years of cigarette smoking (yrs)
- Estimated Glomerular Filtration Rate (eGFR, mL/min/1.73m^2, calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[11])
- Antihypertensive medication use (for hypotheses 1)

Because of potential effect modification by antihypertensive medication use, medication-metabolite interaction term will be examined for hypothesis 1.

Metabolomics data:

Based on both practical and theoretical considerations, we have placed each measured metabolite into three groups by reliability coefficient (RC; from either the medium-term reliability study or the blind duplicate study) AND missing percentage (MS#1847 Zheng Y, et al.).

- Group 1 contains metabolites (n=187) that are reliably measured (RC ≥0.60) AND have missing values in fewer than 50% of the sample. The metabolites are to be treated as continuous variables during data analysis with the missingness of metabolites are replaced by the lowest measured value.
- Group 2 contains metabolites (n=17) that are reliably measured (RC ≥0.60) but have a moderate amount of missing data (values missing in 50- 80% of the sample). For this group, we consider missing values as category 1. For the measured (non-missing) values, we consider values below the median as category 2 and values above the median as category 3. An ordinal variable is to be used during data analysis.
- Group 3 contains metabolites (n=398) that have >80% missing data or RC <0.6; this group is not included in data analysis.

Statistical Methods:

Minimally adjusted models will adjust for demographics (age, sex; race is limited to African-Americans). Furthermore, we will add additional candidate covariates listed above to construct different hierarchical models. In order to illustrate the changes in effect of metabolites influenced by different group of covariates, the potential

combinations of covariates will be investigated by inspecting how beta-coefficient changes for the metabolite as we add individual covariates in the extended model for each metabolite.

For each metabolite,

1. the adjusted means and partial correlation coefficients of metabolite-blood pressure (including SBP, DBP and pulse pressure) associations (adjusting for covariates in hypothesis 1) will be computed stratified by subpopulation strata (normotensive, hypertensive not taking antihypertensive medication, hypertensive taking antihypertensive medication) to compare the relative strength of the metabolite-blood pressure associations;
2. linear regressions will be conducted to estimate its relations with a 10-mm Hg increment in baseline SBP and DBP, and with a 1-mm Hg increment in baseline pulse pressure (hypothesis 1);
3. relative risk regression will be conducted to estimate its relation with baseline prevalent hypertension by using a prevalence ratio (hypothesis 2);
4. COX proportional hazard regression will be conducted to estimate its relation with incident hypertension during visit2-4 (hypothesis 3).

A composite metabolomic score (MetScore) will be created by summing the quartile ranks of identified metabolites that are associated with outcome. And the overall effect on blood pressure and hypertension of these identified metabolites will be measured using MetScore as the exposure variable in the fullest linear regression, relative risk regression, and Cox regression models.

Statistical significance for the metabolomic data will be pre-specified with an experiment-wise α=0.05 (2 tailed) and a modified Bonferroni procedure will be used to consider the correlations among metabolites.[12, 13]

References:

1. P. M. Kearney, M. Whelton, K. Reynolds, P. Muntner, P. K. Whelton, and J. He. Global burden of hypertension: analysis of worldwide data. Lancet. 2005 Jan 15-21; 365(9455):217-23.
2. M. Ezzati, A. D. Lopez, A. Rodgers, H. S. Vander, and C. J. L. Murray. Selected major risk factors and global and regional burden of disease. Lancet. 2002 Nov 2; 360(9343):1347-60.
3. World Health Organization. *The World Health Report 2002*. Geneva: The Organization; 2002.
4. V. L. Roger, A. S. Go, D.M. Lloyd-Jones et al. Heart disease and stroke statistics-2011 update: a report from the American Heart Association. Circulation. 2011 Feb 1;123(4):e18-e209.
5. W. C. Cushman, C. E. Ford, P. T. Einhorn et al. Blood pressure control by drug group in the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). J Clin Hypertens (Greenwich). 2008 Oct; 10(10):751-60.
6. De Meyer T, Sinnaeve D, Van Gasse B et al. NMR-based characterization of metabolic alterations in hypertension using an adaptive, intelligent binning algorithm. Anal Chem. 2008 May 15;80(10):3783-90.
7. Lupton SJ, Chiu CL, Lind JM. A hypertension gene: are we there yet? Twin Res Hum Genet. 2011 Aug; 14(4): 295-304.
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9. Juhaeri, Jones DW, Arnett D. et al. Associations between weight gain and incident hypertension in a bi-ethnic cohort ARIC study. Int J Obes Relat Metab Disord. 2002 Jan;26(1):58-64.

10. Emily B. Schroeder, Gerardo Heiss et al. Hypertension, Blood Pressure, and Heart Rate Variability The Atherosclerosis Risk in Communities (ARIC) Study. Hypertension. 2003;42:1106-1111.
11. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009; 150:604-612.
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13. Blakesley RE, Mazumdar S, Dew MA, et al. Comparisons of methods for multiple hypothesis testing in neuropsychological research. Neuropsychology. 2009 Mar; 23(2):255-64.

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 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 _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

8.c. If yes, is the author aware that the participants with RES_DNA = 'not for profit' restriction must be excluded if the data are used by a for profit group?
___ 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

Yes. There is no overlap between this proposal and current proposals/published manuscripts. This proposal builds off of the metabolomic HF proposal submitted by Zheng and Nettleton (MS #1847), and both of whom are authors in the proposed study.

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)?
Nettleton J, Follis J L, Alonso A, et al. "Metabolomic predictors of incident heart failure: a case-control study nested within the Atherosclerosis Risk in Communities (ARIC)

Study". Poster section presented at American Heart Association(AHA) Epidemiology Council meeting in Atlanta, GA; March 2011.
MS#1847 Zheng Y, et al. Role of the Human Metabolome in Incident Heart Failure Etiology among African Americans in the Atherosclerosis Risk in Communities (ARIC) Study.
MS#1853 Yu B, et al. Genome-Wide Association Study of Heart Failure-related Human Metabolite Profiles among African Americans in the Atherosclerosis Risk in Communities (ARIC) Study.
MS#1882 Yu B, et al. A longitudinal Study of Metabolomics and Kidney Function among African Americans in the Atherosclerosis Risk in Communities (ARIC) Study.

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? Yes

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* 2008.16 **)**

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* 2008.16 "Metabolomics & Heart Failure: A Novel Approach to Biomarker Discovery")

*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.

Yes, the lead author is aware that manuscript preparation is expected to be completed in 1-3 years, and if this expectation is not met, the manuscript proposal will expire.