ARIC Manuscript Proposal #2394

PC Reviewed: 7/8/14	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:
Determinants of blood pressure trajectories from midlife to older age: the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters):
Predictors of BP trajectories

2. Writing Group:
Poojitha Balakrishnan, Kunihiro Matsushita, Elizabeth Colantuoni, J Hunter Young, Terri Beaty, Others welcomed

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

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3. Timeline:
Start of analysis: July, 2014
Draft of manuscript: January, 2015

4. Rationale:

Hypertension is defined by systolic blood pressure greater than 140 mm Hg or diastolic blood pressure greater than 90 mm Hg. [1] Hypertension is one of the most prevalent modifiable risk factors of cardiovascular disease, affecting 27.8-30.7% – approximately 77.9 million adults in the United States. [1,2] The National Health and Nutrition Examination Survey (NHANES) 2007-2010 found that an additional 6% of adults over 20 years have undiagnosed hypertension. [1] Hypertension is associated with a variety of chronic disease processes through target end organ damage including myocardial infarction, congestive heart failure, kidney disease and stroke[3].

Hypertension can be classified into essential and pulmonary hypertension. Essential or primary hypertension, the most common form of hypertension, is high blood pressure as measured in the systemic circulation. [4] Classic physiology studies suggested that higher blood pressure might be due to increased sodium intake and sodium reabsorption in the kidneys. [4-7] This was further supported by work on monogenetic forms of hypertension. [8-10] More recent research suggests that population-level variation in blood pressure is due to other biological mechanisms. [4,11] Pulmonary or secondary hypertension is high blood pressure in the pulmonary arteries and results from identifiable causes among which kidney disease is the most common. [12-14] Extensive research has been done on the hypertension risk factors among various populations. A few of them include age, sex, race, genetic predisposition, geographic location, sodium intake, obesity, sedentary lifestyle and prevalent cardiovascular disease and kidney disease. [1,2,4,7,11,12]

Of note, previous studies exploring risk factors for hypertension investigated hypertension at any time point of life as an outcome variable and do not account for the trajectory of blood pressure. A few recent studies have demonstrated that trajectory of blood pressure from young to middle age differs by gender and ethnicity impacting the development of coronary artery calcium beyond baseline blood pressure. [15-17] Understanding the relative importance of risk factors at different ages could have important clinical implications in prioritizing preventative and treatment strategies. Thus, investigations of predictors for different blood pressure trajectory are warranted.

In addition to the above traditional risk factors, we will also investigate metabolites as predictors of blood pressure trajectory. Metabolomics is the measurement of small molecules in biological fluids. And these molecules tend to be intermediates in metabolic pathways, thereby elucidating the underlying pathophysiology of diseases. [18] Metabolomics in hypertension is its early phases. So far markers of inflammation and ischemia have been identified. [19-22] Of importance, none of these studies have looked at blood pressure trajectory as an outcome variable.

5. Main Hypothesis/Study Questions:

1. Although risk factors of hypertension will be generally associated with blood pressure trajectories, they will demonstrate different patterns (e.g., some with more influence in middle-age and some others in older age).

2. Metabolites hypothesized to influence blood pressure in the citric acid cycle (e.g. lactate, alanine, alpha-ketoglutarate and succinate) and in the sodium handling pathway (e.g. uromodulin) will be associated with blood pressure trajectories. The associated metabolites will also highlight different patterns by age.

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
Longitudinal data analysis

Inclusion criteria
All ARIC participants with blood pressure measured in at least any two of visits 1-5 (N = 14,641; 10,870 Whites and 3,771 Blacks)

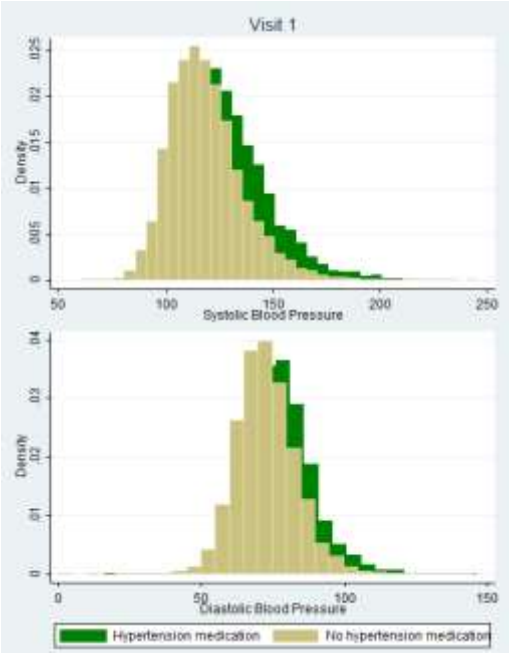
Outcome
Blood pressure trajectory classes

Predictors
1. Indicator variables for determining subclass: systolic and diastolic blood pressure in visits 1-5
2. Conventional risk factors for high blood pressure: age, sex, race, center, socioeconomic status, body mass index, waist circumference, smoking status, alcohol intake, physical activity, prevalent kidney disease, prevalent cardiovascular disease, family history of hypertension
3. Metabolites: lactate, alanine, alpha-ketoglutarate, succinate, uromodulin
4. Additional variables for imputation: antihypertensive medication classes

Statistical analysis
All below statistical analyses will be performed separately for systolic and diastolic blood pressure.

1. Imputation of "untreated" blood pressure values:
Antihypertensive medication is responsible for altering the natural blood pressure trajectory in individuals. So in order to truly assess associations with blood pressure trajectory, the underlying "untreated" blood pressure of individuals on antihypertensive medication needs to be obtained. Based on medication imputation methods literature, the a priori multiple imputation models will incorporate age, sex, race, body mass index, "treated" blood pressure and medication class as predictors. [23-26] The above predictors of "untreated" blood pressure will be assessed for empirical association before inclusion in the final model using the a priori statistical significance threshold of 0.05. Three other methods will also be used to assess the robustness in the estimated "untreated" blood pressure values. One method will be to add a constant of 10mmHg to systolic blood

pressure and 5 mmHg to diastolic blood pressure. [24,25] Another method will be to add a constant based on effects of antihypertensive medication class from existing literature. [23] Finally, a censored normal regression proposed by Tobin et al. will be used which is a non-parametric integrated normal modeling to estimate the "untreated" blood pressure values. [24] This approach assumes that the distribution of blood pressure values among those taking medication is similar and shifted to the right compared to those not taking medication. This seems to be a reasonable assumption among the ARIC participants in visits 1-5 (Visit 1 histogram of observed systolic and diastolic blood pressure presented in the following figure).[24]



2. Blood pressure subclasses:
Latent profile analysis, a subtype of latent variable models, will be used to build blood pressure subclasses. As mentioned previously, the inclusion criterion is the availability of blood pressure measurements for at least any two of visits 1 through 5. Based on previous blood pressure trend research, the number of subclasses to be assessed will be three to five. [15-17] The optimal number of subclasses will be determined empirically using a modified Bayesian information criterion (BIC) due to the high sample size and large number of latent classes. [27] As a sensitivity analysis, other methods of choosing the best model will also be employed including a modified likelihood ratio test and modified Akaike information criterion (AIC). In the latent profile model, posterior probabilities of class membership will be generated using the observed blood pressure for individuals not on antihypertensive medication and the "untreated" blood pressure derived from the imputation for individuals on antihypertensive medication. Each individual will then be assigned a latent class membership by using the largest posterior probability from the latent profile model. In the case of ties in the posterior probability, the latent class membership will be weighted accordingly. These latent class memberships will serve as the outcome for the following analyses.

3. Association of conventional hypertension risk factors:
Using multinomial regression, the latent class memberships will be assessed for association with conventional hypertension risk factors. The risk factors include age, sex, race, center, socioeconomic status, body mass index, waist circumference, smoking status, alcohol intake, physical activity, prevalent kidney disease, prevalent cardiovascular disease and family history of hypertension. The above predictors will be assessed for association with the blood pressure trajectory using the a priori statistical significance threshold of 0.05.

4. Association of metabolites:

Using multinomial regression, the latent class memberships will be assessed for association with candidate metabolic biomarkers (lactate, alanine, alpha ketoglutarate, succinate, uromodulin). Urine dilution will be corrected by adjusting with creatinine concentrations. [28,29] Urinary metabolomics data is available from visit 4 on a subset of 3000 participants (1000 European Americans & 2000 African Americans). Potential confounders to be included in the model include age, sex and race. [19,22] The metabolite predictors will be assessed for association with the blood pressure trajectory using the a priori statistical significance threshold of 0.05.

Strengths and Limitations

This study proposes to investigate risk factors of blood pressure trajectories from midlife to older age, which has not been previously studied. We also aim to explore the role of candidate biomarkers in different patterns of blood pressure over time. Due to the observational nature of the study, residual confounding might be a limitation. Also, only cross-sectional metabolomics data is available from visit 4. In dealing with blood pressure medication, medication adherence and dosage data is unavailable.

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

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)?
No previous proposal in ARIC focus specifically on assessing risk factors of blood pressure trajectory. ARIC Manuscript Proposal #2146 (Systolic blood pressure trajectories and incident cardiovascular disease) includes the association of blood

pressure trajectory with cardiovascular outcomes. Our proposal aims to further understand the risk factors of the trajectory classes themselves in visits 1-5 as well as investigate novel biomarker predictors.

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 2006.04)**

___ **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/

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.

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