ARIC Manuscript Proposal # 1437

1.a. Full Title: The effect of antihypertensive medication use on the relationship between obesity and blood pressure in a bi-ethnic cohort: the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): BMI-BP by Anti-HT Med Status

2. Writing Group: Jill McClain, Eric Whitsel, Linda Adair, Kimberly Truesdale, June Stevens (This research will be performed as part of the lead author’s doctoral dissertation.)

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. ___JM____ [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: Work will begin immediately.

4. Rationale:
Obesity is highly prevalent in the U.S. and contributes to high blood pressure. However, it is not known if the relationship between obesity and blood pressure in persons taking antihypertensive medication is similar to that in persons not taking medication. The reduction in blood pressure
associated with medication use might be expected to attenuate the relationship. On the other hand, blood pressure in obese individuals is known to be more resistant to antihypertensive treatment than in normal weight individuals\textsuperscript{1}, which may reduce the degree of attenuation.

In middle-aged and older populations, such as the ARIC cohort, a substantial portion of the population may receive treatment (medication) for hypertension. In those treated individuals, is excess body weight associated with higher blood pressure?

This question has important methodological implications for cohort data. Traditional analytic approaches for addressing treatment in analyses of blood pressure, such as excluding treated subjects, controlling for treatment as a dichotomous variable in the model, or ignoring the effects, may be inappropriate if the main effect is different in the treated group. Exclusion of treated subjects often results in a substantial loss of power and may significantly bias results\textsuperscript{2}. Controlling for or ignoring treatment may also result in biased coefficients for the main effect if that effect is different in the treated group\textsuperscript{2}. Given that over one quarter of the ARIC cohort was taking antihypertensive medication at baseline, a reduced association between obesity and blood pressure in this group may have significant methodological implications that should be explored.

Our question also has interesting substantive implications. It is not known whether, in a community-based sample, obesity is associated with blood pressure in persons taking antihypertensive medications. A strong association between obesity and blood pressure among treated persons in this cohort may indicate that treatment does not eliminate the impact of obesity on blood pressure.

5. Main Hypothesis/Study Questions:

Determine if antihypertensive medications modify the cross-sectional associations between obesity and blood pressure.

We hypothesize that:

- Blood pressure will be significantly positively associated with obesity both in individuals using antihypertensive medication and in those not using such medication
- The association between obesity and blood pressure will be reduced in those on medication compared to persons not taking antihypertensive medication

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).

Outcomes will be continuous systolic and diastolic blood pressure (separate analyses) at all visits. Exposures will be categorical as well as continuous body mass index (BMI) and waist circumference at all visits. Antihypertensive medication use will be a binary variable (from all visits). We will also explore modeling medication as categorical variables representing number or class of medications. In addition to age, sex, race, and field center, potential covariates include smoking (current, former, never, type of product and dose), alcohol consumption (current, former, never, type of product and dose), education, physical activity, diet, insurance status and history of illness.
Using mixed models (to account for repeated measures within participants), we will first explore how to model the effect of BMI on SBP (e.g.) by modeling BMI as a categorical variable (using indicator variables). We will then model BMI continuously (shown without the possible quadratic term for BMI): 

\[ \text{SBP}_{ij} = \beta_1 + \beta_2 \text{BMI}_{ij} + \beta_3 \text{AntiHTmed}_{ij} + \beta_4 \text{BMI}^* \text{AntiHTmed}_{ij} + \beta_p \text{covariates}_{ijp} + b_i + e_{ij} \]

where \( b_i \) is the random subject effect for the \( i \)th subject and \( e_{ij} \) is the within-subject measurement error for the \( i \)th subject at the \( j \)th visit (\( j=1-4 \)). We will also explore whether time (visits) and/or ARIC field center should be modeled as random effects.

The analysis will be repeated for all combinations of systolic or diastolic blood pressure as the outcome and BMI or waist circumference as the main exposure. We will also test race and gender interactions and, if appropriate, run separate analyses by race and/or gender groups (African American women, White women, African American men and White men).

One limitation to this study is our inability to fully account for medication use. The ARIC data includes information on number and class of medications, but not dosage. Further, it would be ideal if medication use were randomized to avoid confounding by indication. However, since we are interested in stratifying by treatment status rather than considering it as a main effect or confounder, this is less of a problem than it might be.

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)?

MS505 - Associations between weight gain and incident hypertension in a bi-ethnic cohort: the Atherosclerosis Risk in Communities Study
Lead: Juhaeri (June Stevens in writing group)

MS505A - Associations of weight loss and changes in fat distribution with the remission of hypertension in a bi-ethnic cohort: the Atherosclerosis Risk in Communities Study
Lead: Juhaeri (June Stevens in writing group)

MS661 - Impact of new obesity guidelines in the management of hypertensive patients.
Lead: Daniel W. Jones, M.D.

MS683 - Obesity and concomitant risk for cardiovascular disease: implications of obesity Guidelines
Lead: Marion R. Wofford, M.D.

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

11.b. If yes, is the proposal
___ 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)* _________ _________ _________ _________)

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