ARIC Manuscript Proposal #4259

PC Reviewed: 6/13/23	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Sex differences in the risk of uncontrolled hypertension: Variation over the life course

b. Abbreviated Title (Length 26 characters): Sex diff in uncontrolled HTN

2. Writing Group:

Writing group members: Wan-Jin Yeo, Adi Surapaneni, Josef Coresh, Shoshana Ballew, Bige Ozkan, Pascal Schlosser, Morgan Grams *others welcome*

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __WY___ **[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 begin once the manuscript proposal has been approved. We anticipate that the manuscript will be written and submitted to the ARIC Publications Committee within one year of the manuscript proposal being approved.

4. Rationale:

Hypertension is a leading cause of death in the US [1], and is known to be a risk factor for chronic kidney disease (CKD) and end-stage renal diseases (ESRD) [2, 3, 4]. With treatment, hypertension may be controlled to normal blood pressures [5, 6, 7, 8], and its risk for mortality

and CKD can be lowered [9, 10, 11]. Despite this, the prevalence of uncontrolled remains high, with only approximately 24% of adults with hypertension having their condition under control in the United States [12].

Historically, uncontrolled hypertension has been thought to be more prevalent in men. However, recent studies suggest that sex differences in uncontrolled hypertension might vary by age. Below the age of approximately 60, the prevalence of uncontrolled hypertension in men tends to be higher compared to women, but at older ages, uncontrolled hypertension is more prevalent in women as compared to men [13, 14, 15, 16, 17]. It is not known if this pattern of sex difference in uncontrolled hypertension holds in the ARIC population. It is also unknown if sex differences in uncontrolled hypertension can be explained by differences in the prevalence of CKD, coronary heart disease (CHD), or obesity, or if it can be explained by antihypertensive medication prescription patterns or antihypertensive medication adherence.

5. Main Hypothesis/Study Questions:

We aim to assess sex differences in the prevalence of individuals with hypertension and uncontrolled hypertension across different age groups (corresponding to different ARIC visits).

We will assess if sex differences in the prevalence of uncontrolled hypertension are driven by differences in prevalence in CKD, CHD, or obesity, as well as antihypertensive medication prescription patterns (prescription rates, class, number of medications) or antihypertensive medication adherence.

We also aim to assess if uncontrolled hypertension is a risk factor for mortality and kidney function decline.

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).

Prevalence of controlled hypertension or uncontrolled hypertension, and whether sex differences are explained by CKD, CHD, or BMI.

Study population. Participants who attended any of the visits 2 to 7. Any participants missing hypertension status, systolic blood pressure (SBP) or diastolic blood pressure (DBP) data will be excluded. For evaluating if sex differences can be explained by CKD, CHD or BMI, participants missing information about CKD, CHD or BMI respectively will be excluded.

Exposure. Sex.

Covariates/stratifying variables. G-stage, history of CHD, category of BMI.

Outcome. Uncontrolled hypertension (defined as SBP $\geq$ 140 mm Hg or DBP $\geq$ 90), hypertension (defined as having antihypertensive medications prescribed, or having uncontrolled hypertension)

Analysis. A Chi-squared test ($p < 0.05$ for statistical significance) will be performed within each ARIC visit to compare the prevalence of hypertension and uncontrolled hypertension by sex, overall and stratified by covariates.

Investigating whether prescription patterns of antihypertensive medications (prescription rates, classes of antihypertensive medications) explain sex differences in uncontrolled hypertension

Study population. Participants who attended any of visits 2 to 7 with hypertension and were prescribed antihypertensive medications.

Exposure. Sex, antihypertension medication prescription rate, classes of antihypertensive medication

Outcome. Controlled hypertension and uncontrolled hypertension

Analysis. Prescription will be defined as having at least one prescribed antihypertensive medication. Prescribed antihypertensive medications will be categorized into 14 classes: beta-blockers with intrinsic sympathomimetic activity, potassium-sparing diuretics, CCBs-Dihydropyridines, beta-blockers, ACE inhibitors, loop diuretics, angiotensin II antagonists, combined α-blockers and BBs, thiazide diuretics, central α2 agonists and other centrally acting drugs, CCBs-nondihydropyridines, α1 blockers, aldosterone receptor blockers, and direct vasodilators. At each visit, with the population stratified by the exposures, we will evaluate if sex differences persist with Chi-squared tests ($p < 0.05$ for statistical significance).

Investigating whether prescription patterns of antihypertensive medications (number of antihypertensive medications prescribed) explain sex differences in uncontrolled hypertension

Study population. Participants who attended any of visits 2 to 7 with hypertension and were prescribed antihypertensive medications.

Exposure. Sex, number of antihypertensive medications prescribed

Outcome. Controlled hypertension and uncontrolled hypertension

Analysis. The number of antihypertensive medications prescribed will be counted, with combination antihypertensive drugs counting as two antihypertensive medications. At each visit, with the population stratified by the exposures, the median number of prescribed antihypertensive medications will be determined and we will evaluate if sex differences persist with Wilcoxon tests ($p < 0.05$ for statistical significance).

Assessing whether adherence to antihypertensive medications explain sex differences in uncontrolled hypertension

Study population. Participants who attended visit 5 with hypertension and were prescribed antihypertensive medications. Participants with no urine metabolite data will be excluded.

Exposure. Sex, antihypertensive medication adherence

Outcome. Controlled hypertension and uncontrolled hypertension

Analysis. To determine antihypertensive drug adherence, we will first identify drugs that are renally excreted as an unchanged metabolite ("paired metabolites"), if any. For those who are on at least one antihypertensive medication with at least one paired metabolite, adherence will be defined as having at least one non-missing paired metabolite value. Non-adherence be defined as having at least one paired metabolite, and all paired metabolites having missing values. All other cases, i.e., having no paired metabolites, will have unknown adherences. After stratifying the visit 5 population by the exposures and determining adherence rates for each group of individuals, we will evaluate if sex differences persist with Chi-squared tests ($p < 0.05$ for statistical significance).

Associations of hypertension and uncontrolled hypertension with mortality

Study population. We will perform separate analysis corresponding to a middle-aged population and an older population. For the former, the study population will be participants who attended visit 2 (ages 46 to 70) with non-missing hypertension status, SBP, and DBP data. For the latter, the study population will be participants who attended visit 5 (ages 66 to 90) with non-missing hypertension status, SBP, and DBP data.

Exposure. Controlled hypertension and uncontrolled hypertension.

Covariates. Age, sex, race-center, total cholesterol, smoking status, BMI, glucose level, eGFRcr-cys

Outcomes. Mortality

Analysis. Cox proportional-hazards regression models with mortality as the outcome will be performed. Controlled hypertension or uncontrolled hypertension will be the exposures and we will assess the interaction between these exposures and sex using product terms. The model will be adjusted for the listed covariates. The statistical significance will be evaluated using $p < 0.05$ for statistical significance.

Associations of hypertension and uncontrolled hypertension with kidney function decline

Study population. We will perform separate analysis corresponding to a middle-aged population and an older population. For the former, the study population will be participants who attended

visit 2 (ages 46 to 70) with non-missing visit 2 eGFRcr-cys, hypertension status, SBP and DBP data, and at least one non-missing eGFRcr-cys data in visit 4 or 5. For the latter, the study population will be participants who attended visit 5 (ages 66 to 90) with non-missing visit 5 eGFRcr-cys, hypertension status, SBP and DBP data, and at least one non-missing eGFRcr-cys data in visit 6 or 7.

Exposure. Controlled and uncontrolled hypertension.

Covariates. Age, sex, race-center, total cholesterol, smoking status, BMI, glucose level, eGFRcr-cys

Outcomes. 40% decline in eGFRcr-cys

Analysis. Cox proportional-hazards regression models with 40% decline in eGFRcr-cys as the outcome will be performed. Controlled hypertension or uncontrolled hypertension will be the exposures and we will assess the interaction between these exposures and sex using product terms. The model will be adjusted for the listed covariates. The statistical significance will be evaluated using $p < 0.05$ for statistical significance.

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

- **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? ____ 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)* __2011.03_(Selvin for funding on visit 6 labs, Matsushita for funding of visit 3 labs))

*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.

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