

**ARIC Manuscript Proposal # 2580**

**PC Reviewed:** 7/13/15  
**SC Reviewed:** \_\_\_\_\_

**Status:** A  
**Status:** \_\_\_\_\_

**Priority:** 2  
**Priority:** \_\_\_\_\_

**1.a. Full Title:** Impact on the population burden of kidney disease predicted by clinical and public health approaches to the management of blood pressure

**b. Abbreviated Title (Length 26 characters):** Blood pressure changes and CKD

**2. Writing Group:**

Shakia Hardy  
Christy Avery  
Gerardo Heiss  
Ebony Boulware  
Anthony Viera  
Morgan Grams  
Abhijit Kshirsagar  
Donglin Zeng  
Jacqueline Wright

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

**First author:** Shakia Hardy  
**Address:** University of North Carolina Department of Epidemiology  
137 E. Franklin St., Suite 306 CB #8050  
Chapel Hill, NC 27514

Phone: 919/966-1933                      Fax: 919/966-9800  
E-mail: sthardy@live.unc.edu

**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).

**Name:** Gerardo Heiss  
**Address:** University of North Carolina Department of Epidemiology  
137 E. Franklin St., Suite 400 CB #8050  
Chapel Hill, NC 27514

Phone: 919/962-3253                      Fax: 919/966-9800  
E-mail: gerardo\_heiss@unc.edu

### **3. Timeline:**

Analyses will begin once the manuscript proposal is approved and will result in 2 manuscripts by December 2015, as part of doctoral research in the Department of Epidemiology, Gillings School of Global Public Health, UNC at Chapel Hill.

### **4. Rationale:**

Chronic kidney disease (CKD), typically resulting from the gradual loss of kidney function, affects an estimated 26 million or 13% (1999-2004) of US adults and results in approximately 117,000 incident cases of end stage renal disease (ESRD) annually (2009).<sup>1,2</sup> Despite increased screening and emphasis on management of CKD, only 50% to 60% of patients who progress to requiring dialysis are alive 3 years after ESRD diagnosis, and dialysis patients experience adjusted all-cause mortality rates that are 6.5 to 7.9 times greater than those observed in the general population.<sup>3</sup> Considering the rates of hospitalizations, health care costs, disability, and increased risk of all-cause mortality associated with kidney disease<sup>4-8</sup> the potential benefit of modifying risk factors associated with kidney disease presents a valuable opportunity for intervention and prevention.

Modifiable risk factors, such as diabetes and elevated blood pressure, that accelerate declines in renal function reportedly account for over 70% of CKD and ESRD cases.<sup>7</sup> Approximately 37% and 19% of ESRD cases in African Americans and Caucasians, respectively, are attributed to high blood pressure.<sup>9</sup> Even blood pressure levels that are considered “high-normal” (defined as systolic blood pressure between 130 and 139 mm Hg or diastolic 85 to 89 mm Hg) are associated with a 3-fold greater risk of future development of ESRD.<sup>10,11</sup> While lifestyle modifications as well as pharmacological therapies are established as effective methods of decreasing blood pressure;<sup>12-20</sup> the predicted effects of blood pressure reductions on kidney disease have not, to our knowledge, been quantified. The proposed manuscript proposal based on doctoral research will estimate and compare the effects of population wide blood pressure reductions achieved through lifestyle interventions, to the improvement in the management of clinically defined hypertension achieved through lifestyle and/or pharmacological interventions, assessing their impact on the population burden of CKD and ESRD.

### **5. Main Hypothesis/Study Questions:**

#### **Impact of reducing blood pressure on the incidence of CKD and ESRD**

- **Specific Aim #1:** Characterize the potential effectiveness on the population burden of CKD, CKD progression, and ESRD of interventions that reduce blood pressure by contrasting life-style based, population-wide interventions with interventions that implement current clinical guidelines for blood pressure lowering among individuals with hypertension.

**Sub Aim 1.1:** Based on results from published randomized trials and observational studies on the impact of interventions to reduce weight, increase physical activity, and reduce sodium intake on reducing blood pressure, estimate reductions in incident CKD and ESRD associated with decreases in blood pressure by gender, race, and diabetic status,<sup>21, 22</sup> in a population-based, bi-racial sample of middle-aged men and women (n= 15,792) from the Atherosclerosis Risk in Communities (ARIC) study.

**Sub Aim 1.2:** Among the population with clinical hypertension, estimate the benefits of implementing the lifestyle and antihypertensive therapy management guidelines promoted by the 2014 guidelines for the management of high blood pressure ('JNC 8')<sup>23</sup> on incident CKD and ESRD by gender, race, and diabetic status, in the ARIC cohort.

### **Impact of reducing blood pressure on disability attributed to CKD and ESRD**

**- Specific Aim #2:** Characterize the potential benefits on disability attributed to CKD and ESRD, quantified as disability-adjusted life years (DALYS), contrasting interventions that reduce blood pressure by life-style based, population-wide interventions with interventions that implement current clinical guidelines for blood pressure lowering among individuals with hypertension.

**Sub Aim 2.1:** Calculate the burden years of life lost (YLL) due to premature mortality, years of lost due to disability (YLD), and DALYS for CKD and ESRD<sup>24</sup> attributable to blood pressure reductions due to the impact of interventions that reduce weight, increase physical activity, and reduce sodium intake.

**Sub Aim 2.2:** Among the population with clinically defined hypertension, estimate the benefits of initiating antihypertensive therapy and recommendations from the lifestyle management guidelines on DALYS due to CKD and ESRD by gender, race, and diabetic status groups.

### **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).**

Exclusions: Participants with prevalent CKD at baseline will be excluded (i.e. those with an estimated glomerular filtration rate (eGFR) of <60 mL/minute/1.73 m<sup>2</sup> at visit 1 assessed by CKD-EPI equation). We will also exclude participants with self-reported race other than Caucasian or African American.

Outcome definition: Incident CKD will be defined by an eGFR lower than 60 mL/minute/1.73m<sup>2</sup>, death or hospitalization with CKD identified by ICD-9 discharge code 585.X in any position, using samples collected at ARIC visits 1, 2, 4

and 5. Incident kidney failure will be defined by United States Renal Data System (USRDS) registry data linkage indicating ESRD treatment, death or hospitalization with kidney failure identified by discharge or eGFR <15 mL/minute/1.73m<sup>2</sup> at follow up visit. Kidney function decline will be measured by annual eGFR slope. Follow-up time for each event begins on the date of the baseline examination.

Main exposures: Seated blood pressure was measured during each examination. Three measurements were taken after a five-minute rest using a random-zero sphygmomanometer; the mean of the second and third readings will be used for analysis. For participant with age ≥ 60 years, hypertension will be defined as having a systolic blood pressure (SBP) ≥150 mm Hg or a diastolic blood pressure (DBP) ≥ 90 mm Hg. For those participants age <60 or with diabetes, hypertension will be defined as systolic blood pressure ≥140 mm Hg or a diastolic blood pressure (DBP) ≥ 90 mm Hg.<sup>23</sup>

Covariates: Age, gender, race, diabetes mellitus, fasting glucose, medication use, anthropometric measures, baseline eGFR, CHD, and smoking.

## STATISTICAL METHODS

Since our research questions address the impact of well-defined hypothetical interventions on disease risk, in the presence of time varying confounding, we will use the parametric g-formula.<sup>25</sup> The parametric g-formula is more efficient than semi-parametric methods,<sup>26</sup> more flexible than other g-methods and yields stable causal estimates.<sup>25</sup> The parametric g-formula will be used to estimate the race, sex, and diabetic specific 1-year change in risk of CKD and ESRD given that the interventions selected to reduce blood pressure (or participants with unaware, untreated or uncontrolled hypertension) were hypothetically initiated in the entire population at the beginning of follow-up. The g-formula noted below<sup>25</sup> allows us to compare the estimated risk of CKD and ESRD under the selected interventions compared to the estimated risk of CKD and ESRD under no interventions.

$$\sum_{k=1}^{21} \sum_{\bar{Z}_{10}} \sum_{\bar{Z}_{10}^*} \sum_v \left[ \prod_{j=1}^k \left[ \begin{array}{l} \Pr[\bar{D}_{k+1} = 1 | \bar{Z}_k, v, \bar{D}_k = \bar{C}_k = \bar{N}_k = 0] \\ f_d(Z_j | Z_j^*, \bar{Z}_{j-1}, v, \bar{D}_j = \bar{C}_j = \bar{N}_j = 0) \\ f(Z_j^* | \bar{Z}_{j-1}, v, \bar{D}_j = \bar{C}_j = \bar{N}_j = 0) \\ \Pr[\bar{D}_j = \bar{N}_j = 0 | \bar{Z}_j, v, \bar{D}_{j-1} = \bar{C}_{j-1} = \bar{N}_{j-1} = 0] \end{array} \right] \right]$$

Where k=1,.....,21 represents each 1 year interval of follow up starting at baseline

$Z_k$ : is the vector of intervention values of the risk factors  $Z_k$  at time k

$Z_k^*$ : is the vector of values that would be observed without time k intervention

$V$ : the vector of time-independent baseline covariates

$D_{k+1}=1$ : is the event that CKD or ESRD is diagnosed between exams k and k+1

$D_k=0$ : the event that a participant remains CKD or ESRD free through year k

$C_k=0$ : the event that a participant remains uncensored through year k

$N_k=0$ : the event that a subject has not died from other causes through year k

To estimate the change in risk associated with interventions that reduce blood pressure we will first fit logistic regression models for each model component and confounders of the blood pressure/hypertension and CKD and ESRD association using measurements from each relevant ARIC visit. Next, the standardized cumulative risk or weighted average of CKD and ESRD conditional on confounder history and the selected interventions will be approximated from a Monte Carlo simulation. This simulation will assign the sampled baseline and time varying covariates as observed then estimate the distribution of covariates to build follow up data at assigned time points from the regression models fitted from each component after setting values to those achieved by the hypothetical intervention.<sup>27, 28</sup> The predicted probability of CKD and ESRD is then estimated based on the intervened on covariates for the pseudo-participants. Bootstrapping will be used to estimate 95% confidence intervals for the estimates.

Subsequently, we will characterize the potential benefits on disability attributed to CKD and ESRD, quantified as disability-adjusted life years (DALYS), from interventions that reduce blood pressure by contrasting life-style based population-wide interventions with interventions that implement current clinical guidelines for blood pressure lowering among individuals with hypertension. We will calculate population risk difference, risk ratio, and attributable risk comparing the risk of CKD and ESRD under the selected intervention to reduce weight, increase physical activity, and reduce sodium intake (or antihypertensive use among those with hypertension) on the risk of CKD and ESRD under no intervention. Using estimates of the population attributable fraction, DALYs will be calculated as the sum of YLL and YLD and then multiplied by the attributable fraction for blood pressure and blood pressure reductions.<sup>24, 29</sup> This will allow us to compare DALYs for CKD and ESRD due to blood pressure before and after intervention.

**7.a. Will the data be used for non-CVD analysis in this manuscript?** \_\_\_\_ Yes  
\_\_\_\_ 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.csc.unc.edu/ARIC/search.php>

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)?**

MP #	Year	Proposal title and lead author
2183	2013	Progression of CKD focusing on kidney function, Josef Coresh
2031	2012	Interaction of Kidney Disease Measures with Diabetes and Hypertension on Cardiovascular Disease: the Atherosclerosis Risk in Communities (ARIC) Study, Nadine Alexander
2359r	2014	Population impact of adiposity on the chronic disease burden in African Americans and whites: an application of the parametric g-formula, Kapuaola Gellert
1653	2010	The association of glomerular filtration rate and albuminuria with incident hypertension: The Atherosclerosis Risk in Communities (ARIC) Study, Kunihiro Matsushita
223		Risk factors for decreased renal function in the ARIC Study, Josef Coresh

**11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?**  Yes     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.csc.unc.edu/anic/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.csc.unc.edu/anic/index.php>, under Publications, Policies & Forms. [http://publicaccess.nih.gov/submit\\_process\\_journals.htm](http://publicaccess.nih.gov/submit_process_journals.htm) shows you which journals automatically upload articles to Pubmed central.

## References

1. Coresh J, Selvin E, Stevens LA and et al. Prevalence of chronic kidney disease in the United States. *JAMA : the journal of the American Medical Association*. 2007;298:2038-2047.
2. Miller ER, Erlinger TP, Young DR, Jehn M, Charleston J, Rhodes D, Wasan SK and Appel LJ. Results of the Diet, Exercise, and Weight Loss Intervention Trial (DEW-IT). *Hypertension*. 2002;40:612-618.
3. Van Buren PN and Toto R. Hypertension in Diabetic Nephropathy: Epidemiology, Mechanisms, and Management. *Advances in Chronic Kidney Disease*. 2011;18:28-41.
4. Fried LF, Katz R, Sarnak MJ, Shlipak MG, Chaves PHM, Jenny NS, Stehman-Breen C, Gillen D, Bleyer AJ, Hirsch C, Siscovick D and Newman AB. Kidney Function as a Predictor of Noncardiovascular Mortality. *Journal of the American Society of Nephrology*. 2005;16:3728-3735.
5. Hallan S, Astor B, Romundstad S, Aasarød K, Kvenild K and Coresh J. Association of kidney function and albuminuria with cardiovascular mortality in older vs younger individuals: The Hunt II study. *Archives of Internal Medicine*. 2007;167:2490-2496.
6. Schiffrin EL, Lipman ML and Mann JFE. Chronic Kidney Disease: Effects on the Cardiovascular System. *Circulation*. 2007;116:85-97.
7. Szklo M, Barnes R, Folsom A, Heiss G, Hutchinson R, Patsch W, Sharrett AR and Williams OD. The atherosclerosis risk in communities (ARIC) study: Design and objectives. *American Journal of Epidemiology*. 1989;129:687-702.
8. Loehr LR, Rosamond WD, Chang PP, Folsom AR and Chambless LE. Heart Failure Incidence and Survival (from the Atherosclerosis Risk in Communities Study). *The American journal of cardiology*. 2008;101:1016-1022.
9. Appel LJ, Wright JT, Jr, Greene T and et al. Long-term effects of renin-angiotensin system-blocking therapy and a low blood pressure goal on progression of hypertensive chronic kidney disease in African Americans. *Archives of Internal Medicine*. 2008;168:832-839.
10. Klag MJ, Whelton PK, Randall BL, Neaton JD, Brancati FL, Ford CE, Shulman NB and Stamler J. Blood Pressure and End-Stage Renal Disease in Men. *New England Journal of Medicine*. 1996;334:13-18.
11. Crews DC, Plantinga LC, Miller ER, Saran R, Hedgeman E, Saydah SH, Williams DE, Powe NR, Control FCfD and Team PCKDS. Prevalence of Chronic Kidney Disease in Persons With Undiagnosed or Prehypertension in the United States. *Hypertension*. 2010;55:1102-1109.
12. Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, Bray GA, Vogt TM, Cutler JA, Windhauser MM, Lin P-H, Karanja N, Simons-Morton D, McCullough M, Swain J, Steele P, Evans MA, Miller ER and Harsha DW. A Clinical Trial of the Effects of Dietary Patterns on Blood Pressure. *New England Journal of Medicine*. 1997;336:1117-1124.
13. Bibbins-Domingo K, Chertow GM, Coxson PG, Moran A, Lightwood JM, Pletcher MJ and Goldman L. Projected Effect of Dietary Salt Reductions on Future Cardiovascular Disease. *New England Journal of Medicine*. 2010;362:590-599.

14. Eyles H, Webster J, Jebb S, Capelin C, Neal B and Ni Mhurchu C. Impact of the UK voluntary sodium reduction targets on the sodium content of processed foods from 2006 to 2011: Analysis of household consumer panel data. *Preventive Medicine*. 2013;57:555-560.
15. Chobanian AV, Bakris GL, Black HR and et al. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: The jnc 7 report. *JAMA*. 2003;289:2560-2571.
16. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. *The Lancet*. 2000;356:1955-1964.
17. Effects of weight loss and sodium reduction intervention on blood pressure and hypertension incidence in overweight people with high-normal blood pressure: The trials of hypertension prevention, phase ii. *Archives of Internal Medicine*. 1997;157:657-667.
18. Cook NR, Cutler JA, Obarzanek E, Buring JE, Rexrode KM, Kumanyika SK, Appel LJ and Whelton PK. Long term effects of dietary sodium reduction on cardiovascular disease outcomes: observational follow-up of the trials of hypertension prevention (TOHP). *BMJ*. 2007;334:885.
19. Kelley GA and Kelley KS. Progressive Resistance Exercise and Resting Blood Pressure: A Meta-Analysis of Randomized Controlled Trials. *Hypertension*. 2000;35:838-843.
20. Whelton SP, Chin A, Xin X and He J. Effect of Aerobic Exercise on Blood Pressure A Meta-Analysis of Randomized, Controlled Trials. *Annals of Internal Medicine*. 2002;136:493-503.
21. Tarver-Carr ME, Powe NR, Eberhardt MS, LaVeist TA, Kington RS, Coresh J and Brancati FL. Excess Risk of Chronic Kidney Disease among African-American versus White Subjects in the United States: A Population-Based Study of Potential Explanatory Factors. *Journal of the American Society of Nephrology*. 2002;13:2363-2370.
22. Plantinga LC, Johansen K, Crews DC, Shahinian VB, Robinson BM, Saran R, Burrows NR, Williams DE and Powe NR. Association of CKD With Disability in the United States. *American Journal of Kidney Diseases*. 2011;57:212-227.
23. James PA, Oparil S, Carter BL and et al. 2014 evidence-based guideline for the management of high blood pressure in adults: Report from the panel members appointed to the eighth joint national committee (jnc 8). *JAMA*. 2014;311:507-520.
24. Salomon JA, Vos T, Hogan DR, Gagnon M, Naghavi M, Mokdad A, Begum N, Shah R, Karyana M, Kosen S, Farje MR, Moncada G, Dutta A, Sazawal S, Dyer A, Seiler J, Aboyans V, Baker L, Baxter A, Benjamin EJ, Bhalla K, Abdulhak AB, Blyth F, Bourne R, Braithwaite T, Brooks P, Brughha TS, Bryan-Hancock C, Buchbinder R, Burney P, Calabria B, Chen H, Chugh SS, Cooley R, Criqui MH, Cross M, Dabhadkar KC, Dahodwala N, Davis A, Degenhardt L, Díaz-Torné C, Dorsey ER, Driscoll T, Edmond K, Elbaz A, Ezzati M, Feigin V, Ferri CP, Flaxman AD, Flood L, Fransen M, Fuse K, Gabbe BJ, Gillum RF, Haagsma J, Harrison JE, Havmoeller R, Hay RJ, Hel-Baqui A, Hoek HW, Hoffman H, Hogeland E, Hoy D, Jarvis D, Jonas JB, Karthikeyan G, Knowlton LM, Lathlean T, Leasher JL, Lim SS, Lipshultz SE, Lopez AD, Lozano R, Lyons R, Malekzadeh R, Marcenes W, March L, Margolis DJ, McGill N, McGrath J, Mensah GA, Meyer A-C, Michaud C, Moran A, Mori R, Murdoch ME, Naldi L, Newton



CR, Norman R, Omer SB, Osborne R, Pearce N, Perez-Ruiz F, Perico N, Pesudovs K, Phillips D, Pourmalek F, Prince M, Rehm JT, Remuzzi G, Richardson K, Room R, Saha S, Sampson U, Sanchez-Riera L, Segui-Gomez M, Shahrz S, Shibuya K, Singh D, Sliwa K, Smith E, Soerjomataram I, Steiner T, Stolk WA, Stovner LJ, Sudfeld C, Taylor HR, Tleyjeh IM, van der Werf MJ, Watson WL, Weatherall DJ, Weintraub R, Weisskopf MG, Whiteford H, Wilkinson JD, Woolf AD, Zheng Z-J and Murray CJL. Common values in assessing health outcomes from disease and injury: disability weights measurement study for the Global Burden of Disease Study 2010. *The Lancet*. 2012;380:2129-2143.

25. Taubman SL, Robins JM, Mittleman MA and Hernán MA. Intervening on risk factors for coronary heart disease: an application of the parametric g-formula. *International Journal of Epidemiology*. 2009;38:1599-1611.

26. Westreich D, Cole SR, Young JG, Palella F, Tien PC, Kingsley L, Gange SJ and Hernán MA. The parametric g-formula to estimate the effect of highly active antiretroviral therapy on incident AIDS or death. *Statistics in Medicine*. 2012;31:2000-2009.

27. Garcia-Aymerich J, Varraso R, Danaei G, Camargo, Carlos A. and Hernán MA. Incidence of Adult-onset Asthma After Hypothetical Interventions on Body Mass Index and Physical Activity: An Application of the Parametric G-Formula. *American Journal of Epidemiology*. 2014;179:20-26.

28. Danaei G, Pan A, Hu FB and Hernán MA. Hypothetical Midlife Interventions in Women and Risk of Type 2 Diabetes. *Epidemiology*. 2013;24:122-128  
10.1097/EDE.0b013e318276c98a.

29. Steenland K and Armstrong B. An Overview of Methods for Calculating the Burden of Disease Due to Specific Risk Factors. *Epidemiology*. 2006;17:512-519  
10.1097/01.ede.0000229155.05644.43.