BLOOD PRESSURE RELATED APPROACHES TO REDUCE THE BURDEN OF CHRONIC KIDNEY DISEASE AND KIDNEY FAILURE. THE ATHEROSCLEROSIS RISK IN COMMUNITIES (ARIC) STUDY

Shakia T. Hardy

A dissertation submitted to the faculty at the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Epidemiology in the Gillings School of Global Public Health.

Chapel Hill
2017

Approved By:

Christy Avery

Gerardo Heiss

Abhijit Kshirsagar

Anthony Viera

Donglin Zeng

ABSTRACT

Shakia T. Hardy: Blood Pressure-related Approaches to Reduce
the Burden of Chronic Kidney Disease and Kidney Failure.
The Atherosclerosis Risk in Communities (ARIC) study
(Under the direction of Gerardo Heiss)

While much of the chronic kidney disease (CKD) literature examines the role of elevated blood pressure in CKD progression, little is known about the benefits of modest decrements in blood pressure on incident CKD and kidney failure (KF). We estimated the impact of 2 pragmatic interventions hypothesized to reduce the incidence of CKD and KF: (1) a population-wide intervention that reduced systolic blood pressure (SBP) by 2 mmHg and (2) targeted interventions that reduced the prevalence of blood pressure above clinical management goals by 10%. Analyses included 15,744 participants of the Atherosclerosis Risk in Communities Study (45-64 years of age at baseline, 1987-1989). Incident CKD and KF were ascertained from laboratory assays and abstraction of hospital records. Over a mean of 20 years of follow up 3,852 and 954 incident CKD and KF events were ascertained. After adjustment for antihypertensive use, gender, diabetes and age, a population-wide 2 mmHg decrement in SBP was associated 23.5 (95% CI: 12.3-34.6) and 26.8 (95% CI: 20.6-33.1) fewer incident CKD events and 20.1 (95% CI: 12.4-27.8) and 9.3 (95% CI: 6.0-12.5) fewer incident KF events per 100,000 person years (PY) in African Americans (AAs) and white Americans (WAs), respectively. A 10% proportional decrease of participants with blood pressure above JNC 7 goal was associated with 16.1 (95% CI: 10.0-24.3) and 7.8 (95% CI: 5.6-10.2) fewer incident CKD events, and 12.5 (95% CI: 7.8-17.6) and 2.5 (95% CI: 1.3-3.7)

fewer incident KF events per 100,000 PY in AAs and WAs. KF was associated with 12,873 disability adjusted life years (DALYs). A 2 mmHg reduction in SBP was estimated to reduce DALYs associated with KF by 37.5 and 14.0 DALYs in AAs and WAs respectively, while reduction of blood pressure above goal was associated with 23.5 and 3.9 fewer DALYs in AAs and WAs. Modest improvements in the level of SBP and blood-pressure-above-goal are predicted to decrease both the incidence of CKD and KF, and the number of DALYs associated with KF. AAs, who bear a disproportionate burden of KF and its associated disability, could benefit from blood pressure reduction strategies more than WAs.

With affection and gratitude, I dedicate this doctoral research to the memory of grandfather William Clinton Petifer

ACKNOWLEDGEMENTS

I would like to express my sincere appreciation to Dr. Gerardo Heiss, my committee chair and advisor, for his keen insights and enduring patience. This dissertation would not have been possible without his constant support and generosity. I would like to thank Dr. Christy Avery for the practice podium talks and endless hours of manuscript review, those moments allowed for vulnerability and growth. I would also like to acknowledge the other members of my dissertation committee, Drs. Abhijit Kshirsagar, Donglin Zeng, and Anthony Viera for their astute guidance and contributions to this work. I give special thanks to Drs. Susan Hogan, Nora Francshessni, and Laura Loehr who have served as mentors during my time as a predoctoral fellow in the UNC cardiovascular and kidney training programs.

I would like to thank my grandmothers, Hilda Petifer and Essie Hardy, for their tireless demonstration of work ethic, love, and selflessness; their experiences have motivated me to conquer every opportunity that was inaccessible to them. I would like to acknowledge my mother, Trinita Petifer-Hardy, for her constant faith in me and encouragement to press toward the mark; her prayers kept me. I would also like to extend my sincere gratitude to my father, Warren Hardy, sister, Shannon Hardy and my village of brothers, aunts, uncles, cousins and friends for providing a safe haven of support, laughter, and comfort.

Most of all, I want to thank my husband, Kentwan, and my son, Malachi. They have experienced the best and worst of me for the past few years yet love unconditionally. Thank you for your sense of humor, motivation, and endurance. Last but not least, I want to thank every gray hair I've acquired on this journey for reminding me to stand up and live.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ACC	American College of Cardiology
ACE	Angiotensin Converting Enzyme
ADH	Antidiuretic hormone
AHA	American Heart Association
APOL1	Apolipoprotein
ARB	Angiotensin II receptor blockers
ARIC	Atherosclerosis Risk in Communities Study
ATPase	Adenosine triphosphatase
BMI	Body mass index
BUN	Blood urea nitrogen
CD	Collecting duct
CDC	Centers for Disease Control
CHD	Coronary heart disease
CG	Cockcroft-Gault
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic kidney disease epidemiology collaboration
CLR	Confidence limit ratio
CMS	Centers for Medicare and Medicaid
CROWNWeb	Consolidated Renal Operations in a Web-enabled Network
CT	Computed tomography
CVD	Cardiovascular disease

DAG	Directed acyclic graph
DALYs	Disability-adjusted life years
DASH	Dietary approaches to stop hypertension
DBP	Diastolic blood pressure
DCT	Distal Convoluted Tubule
dL	Deciliter
DM	Diabetes mellitus
ECG	Echocardiogram
eGFR	Estimated glomerular filtration rate
ESRD	End stage renal disease
g	gram
GBD	Global Burden of Disease
GFR	Glomerular filtration rate
HF	Heart Failure
HR	Hazard ratio
ICD	International classification of disease
JATOS	Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients
JNC	Joint National Committee
KDIGO	Kidney Disease Improving Global Outcomes
K/DOQI	Kidney Disease Outcomes Quality Initiative
KEEP	Kidney Early Evaluation Program
LDL	Low density lipoprotein

mg	Milligram
MDRD	Modification of diet in renal disease
mGFR	Measured glomerular filtration rate
MI	Myocardial infarction
mL	Milliliter
min	Minute
MmHg	Millimeters mercury
MRI	Magnetic resonance imaging
MSNA	Muscle sympathetic nerve activity
NHBPEP	National High Blood Pressure Education Program
NHANES	National Health and Nutrition Examination Survey
NHES	National Health Examination Survey
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NKDEP	National Kidney Disease Education Program
NKF	National Kidney Foundation
PTH	Parathyroid hormone
PY	Person year
QOL	Quality of life
RAS	Renin-angiotensin system
RBC	Red blood cell
RRT	Renal replacement therapy
RUNT2	Runt related transcription factor 2
SBP	Systolic blood pressure

SLC	Solute carrier
SPRINT	Systolic Blood Pressure Intervention Trial
SR	Self-report
TAL	Thick ascending limb
TONE	Trial of Nonpharmacologic Interventions in Elderly
UMOD	Uromodulin
US	United States
USPSTF	United States Preventative Services Task Force
USRDS	Unites States Renal Data System
VALISH	Valsartan in Elderly Isolated Systolic Hypertension
YLD	Years lived with disability
YLL	Years of life lost

CHAPTER 1. OVERVIEW

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).[1,2] 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 the general population.[3] The rates of hospitalizations, disability, and increased risk of all-cause mortality associated with kidney disease and its severity,[4-8] call for a better understanding of the potential benefits associated with preventative modification of risk factors associated with CKD.

Modifiable risk factors such as diabetes and elevated blood pressure that accelerate declines in renal function reportedly contribute to over 70% of CKD and ESRD cases.[7] Approximately 37% and 19% of ESRD cases in African Americans and white Americans respectively, are attributed to high blood pressure.[9] Even blood pressure levels considered "high-normal" (defined as systolic blood pressure, SBP, between 130 and 139 mmHg or diastolic blood pressure, DBP, between 85 and 89 mmHg) are associated with a 3-fold greater risk of development of ESRD.[10,11] While lifestyle modifications as well as pharmacological therapies are established as effective methods to manage high blood pressure[12-20] the predicted effects of blood pressure reductions on CKD have not, to our knowledge, been quantified. The proposed doctoral research will estimate and compare the

effects of population wide blood pressure reductions achieved through lifestyle interventions, to the management of hypertension through lifestyle and/or pharmacological interventions, to assess their potential impact on the population burden of incident CKD and kidney failure.

CHAPTER 2. SPECIFIC AIMS

Impact of reducing blood pressure on incidence of CKD

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

Sub Aim 1.1: Estimate reductions in incident CKD associated with decreases in blood pressure of a magnitude achievable by lifestyle modifications by gender, race and 10-year age categories.[21,22]

Sub Aim 1.2: Estimate reductions in incident CKD associated with increases in awareness of blood pressure above goal, initiation of antihypertensive therapy, and decreases in uncontrolled blood pressure above goal in the population with hypertension, according to recommended treatment thresholds from the 2014 guidelines for the management of elevated blood pressure[23] and JNC 7, on incident CKD by gender, race, and 10-year age categories.

Impact of reducing blood pressure on disability attributed to CKD

- Specific Aim #2: Characterize the potential benefits from interventions that reduce blood pressure on disability attributed to CKD by contrasting life-style based population-wide interventions with interventions that implement clinical guidelines for blood pressure lowering among individuals with hypertension

Sub Aim 2.1: Estimate the change in burden of disability for incident CKD[24,25] – measured as Years Lived with Disability (YLD) - attributable to population-wide blood pressure reductions of a magnitude consistent with lifestyle interventions, by gender, race, and 10-year age categories.

Sub Aim 2.2: Estimate the change in burden of disability for incident CKD[24,25] – measured as YLD - attributable to increases in awareness of blood pressure above goal, initiating antihypertensive therapy, or decreases in uncontrolled blood pressure above goal in the population with hypertension, according to recommended treatment thresholds from the 2014 guidelines for the management of elevated blood pressure[23] and JNC 7, by gender, race, and 10-year age categories.

Sub Aim 2.3: Estimate the change in years of life lost (YLL) associated with incident CKD attributable to population-wide blood pressure reductions of a magnitude consistent with lifestyle interventions, by gender, race, and 10-year age categories.

Sub Aim 2.4: Estimate the change in YLL attributable to increasing awareness of blood pressure above goal, initiating antihypertensive therapy, or decreasing uncontrolled blood pressure above goal in the population with hypertension, according to recommended treatment thresholds from the 2014 guidelines for the management of elevated blood pressure[23] and JNC 7, by gender, race, and 10-year age categories.

CHAPTER 3. BACKGROUND AND SIGNIFICANCE

3.1 Kidney function overview

The kidneys are a complex pair of retroperitoneal organs, asymmetrically located on each side of the vertebral column, slightly below the rib cage, with the right kidney anatomically lower than the left. The weight of the kidneys varies by gender, ranging from 125 to 170 grams (g) in an adult male to 115 to 155 g in an adult female; the length of each kidney ranges from 4 to 5 inches.[26] The nephron, termed the functional unit of the kidney, contains a glomerulus and renal tubule that regulate the volume and concentration of water and electrolytes in fluid in the body.

Blood and filtrate flow

While both kidneys only constitute approximately 0.5% of total human body mass, approximately 22% of the cardiac output (~350 milliliters (mL)/minute (min) per 100 g tissue) is allocated to the kidneys to meet the demands of both fluid management and the elimination of toxic waste products.[27,28] In this process the kidneys consume about 10% of body oxygen.[29] Blood volume flows into the kidneys' medial surface through the renal hilum, a slit that permits the renal artery to enter the renal sinus; blood continues through the renal artery which bifurcates into anterior and posterior branches forming the segmental arteries, interlobar arteries, arcuate arteries, and then afferent arterioles (Figure 1).[28] Afferent arterioles supply blood to the nephron, which is composed initially of the glomerulus and

Bowman's capsule (which together make the renal corpuscle), followed by the proximal tubule, distal tubule and connecting tubule. The opening portion of the renal corpuscle is the glomerulus, a capillary network lined by a porous thin layer of endothelial cells, where water and solutes from blood flow through the filtering capillaries that are impermeable to large molecules such as proteins and blood particles, yielding a nearly protein free-fluid, ultrafiltrate.[27] Simply, the glomerular filtration rate (GFR) measures kidney function by the volume of ultrafiltrate filtered per minute from plasma through the glomerulus capillaries into the Bowman's capsule, a collecting cavity located between two layers of epithelial cells.[27]

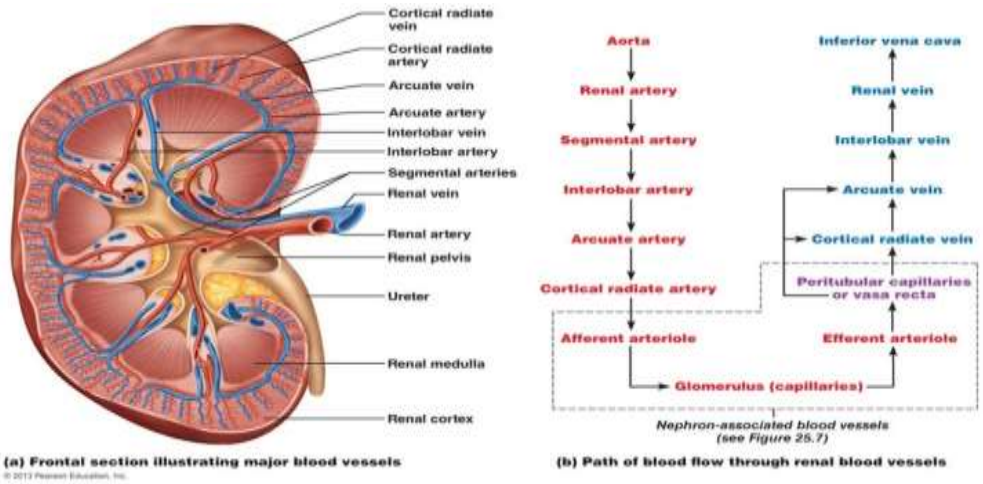


Figure 1. Renal circulation illustrated by the major blood vessels (panel a) and the path of blood flow (Source: Pearson Education Inc.)

From the Bowman's capsule, ultrafiltrate moves through the proximal tubule to the loop of Henle and distal tubule and blood moves through the peritubular capillary walls supplying energy for solute transport.[27] Between the vascular and tubule components, 99% of the glomerular ultrafiltrate is reabsorbed for usable nutrients, and water which is transported back into the blood through the renal vein system.[30] Fluid and metabolic waste

then enter the tubule walls and the merging collecting duct to the renal pelvis for urine excretion through the ureter.[27]

Reabsorption

The large energy supply allocated to the kidneys is largely used to meet the energy demands of solute transport and reabsorption.[27] Reabsorption allows for the transfer of filtered solutes from the renal tubule back to the blood in capillaries and is facilitated by electrochemical gradients, membrane permeability, and active transport. Reabsorption of small solutes ensues predominately within the renal proximal tubule where isosomotic reabsorption accounts for the reabsorption of approximately 60% of filtered salt, and 75% of ultrafiltrate overall (Figure 2).[27,28] The sodium-potassium ATPase pump drives the transport and reabsorption of sodium, chloride and water through primary active transportation.[28] Reabsorption of glucose, amino acids, protein, bicarbonate ions, and many other solutes occur through secondary active transport by crossing the epithelium simultaneously in cotransport with sodium in the proximal tubule.[27] Secretion of waste products of metabolism also occurs in the proximal tubule by secondary active transport.

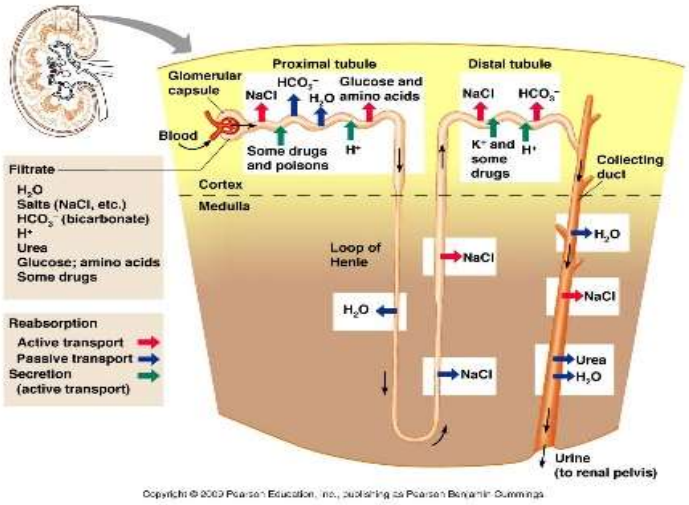


Figure 2. Renal reabsorption by location of permeability (Source: Pearson Education Inc.)

As the remaining filtrate continues to the loops of Henle, the thin descending limb's high permeability to water allows for the passive reabsorption of water whereas the thin ascending limb's permeability to sodium allows for the passive and active transport and reabsorption of sodium. The thick ascending limb (TAL), the initial portion of the distal tube, begins immediately following the thin ascending limb and is composed of thick epithelial cells practically impermeable to water but capable of reabsorbing approximately 30% of filtered sodium, chloride and potassium by a cotransport mechanism.[28] The TAL drains into the distal convoluted tubule (DCT) where the principal cells continue the reabsorption of sodium from the lumen and secretion of potassium into the lumen through sodium-potassium ATPase pumps in the basolateral membranes.[27] Only about 1% of sodium reabsorption happens in the DCT and collecting duct (CD) and is regulated by hormones, principally aldosterone, which increases activity of sodium channels.[28] Secretion of the antidiuretic hormone (ADH), a peptide hormone secreted by neuron in the hypothalamus, alters the impermeability of the DCT and CD to water.[27] This mechanism, in conjunction with the DCT's permeability to urea, allows for late control of the concentration or dilution of solutes in urine.[28]

Water and electrolyte balance

The kidneys' function in maintaining homeostasis of body fluid volumes requires regulation of salt balance and maintenance of the osmotic concentration by regulating water balance.[27] Dietary consumption of water and electrolytes varies daily and can be prompted by the body responses to deficiencies such as thirst or sodium cravings. Intake of water and electrolytes is balanced by the kidneys' adjustment in excretion of water and electrolytes through urine, and also in feces and perspiration.[28] Secretion of ADH allows for fluctuation

in the excretion of water independently of the rate of solute excretion.[27] In response to increased osmotic concentration, ADH secretion increases and enhances the permeability of the membranes of cells lining the distal tubules and the collecting ducts, permitting water reabsorption without altering the rate of solute excretion (Figure 3).[28] In response to decreased osmotic concentration secretion of ADH decreases, diminishing water channels and the amount of water that is reabsorbed in the distal tubule and collecting ducts, and higher volumes of dilute urine is excreted.[28]

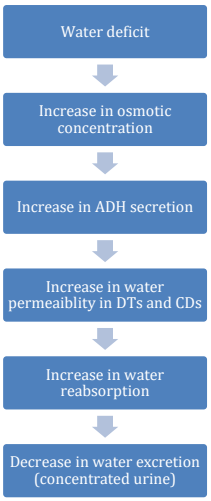


Figure 3. Step-wise mechanism for balancing fluid intake with excretion

Sodium is the primary and most abundant solute in extracellular fluids, and thus effectively determines the osmolarity and volume of extracellular fluids.[27] To maintain osmotic concentration aldosterone, a steroid hormone formed by the adrenal gland, activates the sodium potassium pump increasing sodium and water reabsorption and potassium secretion.[28] Conversely, in response to high sodium levels aldosterone formation is repressed resulting in less tubular sodium reabsorption and increases secretion of sodium.

Autoregulation of blood volume

Constant high levels of renal blood volume are essential to maintain normal levels of glomerulus filtration and renal excretion. The autoregulation of renal blood flow that allows

for changes in vascular resistance to preserve relatively constant blood volume to the kidneys at arterial pressures between 80-170 mmHg has been explained by several mechanisms, including the myogenic mechanism and tubuloglomerular feedback.[27,31,32] The myogenic mechanism posits that increases in blood pressure expand the vessel causing vascular wall tension and smooth muscle fiber contractions, leading to vascular resistance. Changes in resistance to blood flow keeps the blood volume constant despite changes in in pressure.[33] In the tubuloglomerular feedback mechanism, rises in arterial pressure increase renal blood flow, GFR, and solute passage to the DCT.[27] The juxtaglomerular complex, adherent to the glomerulus, comprises of a group of epithelial cells termed the macula densa, where the afferent and efferent arterioles interact with the macula densa in the first portion of the DCT.[27] Macula densa cells are chemoreceptors that detect changes in the concentration of sodium in the fluid inside the tubule as a gauge of GFR levels.[27] When sodium concentration is high and GFR is elevated, the macula densa activates mechanisms that constrict the afferent arterioles thus decreasing renal blood volume, pressure, and GFR.[28] Other metabolic and nerve simulation pathways contribute to autoregulation by the myogenic and tubuloglomerular feedback mechanisms. These mechanisms are not mutually exclusive and interact to regulate blood volume and GFR.

Renin-Angiotensin system

The renin-angiotensin system (RAS) plays a critical role in the regulation of blood pressure, water and sodium balance, in addition to cardiovascular and renal structure and function.[27] As depicted in figure 1, angiotensinogen (a glycoprotein secreted by the liver) is cleaved by renin, a renal hormone secreted from the juxtaglomerular cells, releasing a decapeptide called angiotensin I.[28] Angiotensin converting enzyme (ACE) then converts

angiotensin I to angiotensin II, a biologically active eight-amino acid peptide that increases peripheral vascular resistance, blood pressure, and salt and water retention.[34] Although renin is thought of as the rate limiting step as renin catalyzes the production of angiotensin II, emerging evidence suggests that local synthesis of all components needed for the RAS cascade can happen within the kidney itself and may be a contributing factor in the progression of renal disease.[35]

These RAS cascade also plays a role in sodium balance through production of aldosterone.[27] Contrary to the kidneys' response to increases in blood pressure, when the kidneys baroreceptors detect decreases in blood pressure and thus lower filtrate flow and GFR, signals initiate vasodilation and conservation of fluid volume. Juxtaglomerular cells produce and secrete renin, which through the cascade described above, produces angiotensin II, stimulating the production aldosterone and reabsorption of sodium.[27]

3.2 CKD and Kidney Failure: eGFR Measurement, Classification and Identification

3.2.1 Estimation of Glomerular Filtration Rate

GFR is the best overall measure of kidney function currently available and is critical for determining the staging of kidney disease.[36] The GFR is equivalent to the product of the net ultrafiltration pressure (calculated as the difference between the hydrostatic pressure and osmotic pressure differences on the capillary wall), hydraulic permeability, and the filtration area.[27] These factors are influenced by processes that alter resistance of the afferent and efferent arterioles, increase renal arterial pressure, modify permeability or reduce surface area for filtration.[28] Measuring GFR is ideal for quantifying excretory function as GFR is generally maintained by the compensation of remaining nephrons until structural damage is widespread and kidney function begins to critically suffer.[37]

GFR is measured ideally by quantifying plasma concentration and excretion of a substance that freely penetrates through the glomerulus without being absorbed or excreted by the renal tubules nor metabolized or produced in the kidneys.[28] Inulin, a large polymer of fructose, and radionuclides such as iohexol or iothalamate are consider the gold standard methods of measured GFR (mGFR) as these substances are neither reabsorbed or secreted, but freely cleared from the kidneys by glomerular filtration, making the clearance of inulin equal to the GFR.[38,39] Inulin measurement and nuclear medical techniques are invasive and costly as measuring clearance requires intravenous infusion, multiple repeat blood and/or urine collection and careful timing of blood sampling.[40,41] Although accurate and precise, direct measurement of GFR is burdensome for patients and unfeasible for usual clinical and research settings.

Given the limitations of direct assessments, estimations based on measurements of creatinine are the most practical and commonly used in clinical practice for calculation of GFR. Creatinine is a protein derivative produced by metabolism of creatine, an amino acid produced mainly by the liver but also by the kidneys and pancreas; creatine can also be acquired through dietary intake of milk, nuts, cooked meat and fish.[42] Through phosphorylation, creatine is converted into creatine phosphate or phosphocreatine and subsequently stored as an energy source in skeletal muscle.[43] As creatine phosphate breaks down to produce energy for muscle contraction, creatinine is produced as a byproduct and excreted by the kidneys predominately through glomerular filtration with approximately 10-40% of creatinine cleared through tubular secretion making the clearance of creatinine slighter higher than GFR.[28,44,45] If the filtration of the kidneys is deficient, creatinine blood levels rise allowing for the use of urine or blood to calculate creatinine clearance which is

used to estimate GFR.[45,46] Creatinine is produced at a fairly constant rate in the body and must be stable to estimate eGFR. Levels of creatinine can be variable due to medications interfering with measurement or secretion, variability in muscle mass and protein intake, liver disease, age, sex, race, and body size.[45] Variability in creatinine reduces ideal estimation of GFR, however, many formulas used to calculated eGFR from creatinine incorporate adjustments for these some of these important factors.[47]

3.2.2 Glomerular Filtration Rate Equations

Three main creatinine-based formulas have been extensively used for estimation of GFR: the Cockcroft-Gault (CG) equation, the Modification of Diet in Renal Disease (MDRD) equation, and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation.[47-49] First described in 1976, the CG equation was developed to estimate creatinine clearance from the means of two 24-hour urine creatinine excretions from 249 mostly hospitalized, males patients (4% female) with CKD aged 18-92.[50,51] Given the lack of females included in the study and previous recommendations that creatinine clearance should be reduced by 10 to 20% in females compared to males, an arbitrary correction coefficient of 0.85 was assigned to females to account for their relatively lower muscles mass and thus lower creatinine clearance compared to males.[52]

$$\text{CrCl(mL/min)} = \frac{(140 - age)\ X\ weight\ X\ 1.23\ X\ (0.85\ if\ female)}{Creatinine\ (mircomol/liter)}$$

The CG formula incorporated adjustments for age, weight and gender, however practical implementation of the formula was often restricted due to the limited availability of body weight measurements in laboratories and inconvenient 24-hour urine collections.[27,53] The CG formula's measurement of creatinine clearance as an alternative to GFR tends to

overestimate GFR as measured creatinine representing both filtration by the glomeruli and secretion from the tubules.[52] While ages in the population ranged from 18-92 the patients included were predominately young. Underestimation of GFR using the CG equation often occurs depending on the age of the population and health status of the population, particularly for the elderly and at higher GFRs.[53] Use of the CG equation in diverse populations found that the dependence of eGFR on body weight biased estimates in the obese, and overestimated eGFR when mGFR is low.[53,54] Despite these limitations the CG formula was widely used to assess onset and progression of renal insufficiency and to adjust drug dosing prior to the development of the more precise MDRD formula in 1999.[48]

The MDRD Study equation was also developed in the setting of CKD among 1,628 middle-age nondiabetic patients included in a multicenter trial evaluating the effect of dietary protein restriction and blood pressure control on renal disease progression.[51,55] The MDRD trial measured GFR using renal clearance of an subcutaneous injection of ^{125}I-iothalamate as a goal standard for comparison to the MDRD equation.[56] Creatinine clearance was estimated from both 24-hour urine collection and measurement of serum creatinine (SCr).[55] A formula for estimating GFR was generated using a stepwise multiple logistic regression analysis of variables that best predicted GFR; though more than 15 variables were considered for inclusion, a parsimonious equation comprised of age, gender, plasma creatinine value and race was reached.[55]

$$175\ x\ (SCr)^{-1.154}\ x\ (age)^{-0.203}\ x\ (0.742\ if\ female)\ x\ (1.212\ if\ black)$$

Validation and comparison of the MDRD equation in relation to the CG equation in diverse patient populations including those with diabetes, and African Americans have been

undertaken.[49,52] The MDRD equation's main advantages over the CG equation are the elimination of measures of body weight required for use of the CG equation, the estimation of GFR by the MDRD equation as opposed to merely creatinine clearance estimated by the CG equation, and a higher proportion of eGFR values that correspond with the gold standard.[51] For example, 90% of eGFRs calculated by the MDRD formula were within 30% of the measured GFR compared to approximately 75% of estimates using the CG formula.[53] However, the MDRD equation communally suffers from several limitations restricting use of the CG formula; both the CG and MDRD equations were refined in populations with sub-optimal kidney function and tend to be less accurate at higher GFRs (>60 mL/min/1.73m^2) which can potentially result in under diagnosis of CKD among those with mild kidney impairment.[47,51,53] The MDRD Study equation also tends to underestimate measured GFR particularly in individuals whose normal eGFR is >90 mL/min/1.73m^2. Though the MDRD equation had been commonly used in the United States as the primer formula for calculating eGFR, MDRD is gradually being replaced by the CKD-EPI equation which overcomes some of these limitation, largely by being derived in a population not limited to CKD patients.[27]

In 2009 the CKD-EPI group pooled 10 research and clinical studies (total n=8,254) that measured urinary clearance of iothalamate and included a serum creatinine assay to develop (randomly sampled development subset n=5,504) and internally validate (randomly sampled validation subset n=2,750) a new equation for the estimation of GFR in diverse populations, with and without CKD. The CKD-EPI research group used a least squares linear regression to predict mGFR from serum creatinine with predictor variables including age, race, sex, diabetes, prior organ transplant, and weight.[47] Equations using a combination of the probable predictor variables noted above were ranked according to ease of application

and model performance, measured by goodness-of-fit by means of R^2 and likelihood ratio tests for nested models.[57] The research group selected the leading ranked CKD-EPI model that included clinical measurement widely available to rudimentary laboratories described as:

$$eGFR = 141 \times \min(S_{Cr}/\kappa, 1)^{\alpha} \times \max(S_{Cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018 \text{ [if female]} \times 1.159 \text{ [if African American]}$$

where: eGFR (estimated glomerular filtration rate) =mL/min/1.73m^2, SCr (standardized serum creatinine) = milligrams (mg)/ deciliters (dL), $\kappa = 0.7$ (females) or 0.9 (males), $\alpha = -0.329$ (females) or -0.411 (males), min = indicates the minimum of S_{Cr}/κ or 1, max = indicates the maximum of S_{Cr}/κ or 1, age = years

Both the MDRD and CKD-EPI equations take into account age, gender, and race, however, the use a spline term in the CKD-EPI equation has been shown to be substantially more accurate and less biased in estimating mGFR than the MDRD equation, particularly at GFR levels >60ml/min/1.73m^2.[47,49] The CKD-EPI equation utilizes a 2-slope linear spline with sex-specific knots to model the relationship between estimated GFR and age, sex, and race.[47] The use of these spline terms reflect the weaker association between creatinine and GFR at lower creatinine levels compare to higher creatinine levels.[51] The equation therefore represents four gender and knot-specific equations for each race group (Table 1).[47]

Table 1. Chronic Kidney Disease Epidemiology Collaboration equation for estimating GFR on the natural scale by race, gender, and serum creatinine spline knot level

Race and Sex	Serum Creatinine µmol/L (mg/dL)	Equation
African American		
Female	≤62 (≤0.7)	$GFR = 166 \times (Scr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 166 \times (Scr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 163 \times (Scr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 163 \times (Scr/0.9)^{-1.209} \times (0.993)^{Age}$
White or other		
Female	≤62 (≤0.7)	$GFR = 144 \times (Scr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 144 \times (Scr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 141 \times (Scr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 141 \times (Scr/0.9)^{-1.209} \times (0.993)^{Age}$

After development, the performance of the CKD-EPI equation was compared to the MDRD study equation. The CKD-EPI equation developers aimed to produce an eGFR equation that functioned as accurately as the MDRD equation at measured GFR that were less than 60 mL/min/1.73 m^2 and more accurately than the MDRD equation at GFRs greater than 60 mL/min/1.73 m^2.[47] As shown (Figure 4) by the smoothed regression line (95% CI) with eGFR on the x-axis and mGFR on the y-axis, the CKD-EPI equation accurately predicts mGFR as well as the MRDR equation at GFR at lower eGFR values. When GFR is greater than 60 mL\min\1.73 m^2 a significant deviation is shown between the two equations with the CKD-EPI equation being substantially more accurate than the MDRD equation. [47] Confirming these findings, several external studies have also likened the performance of the CKD-EPI equation to the MDRD study equation.

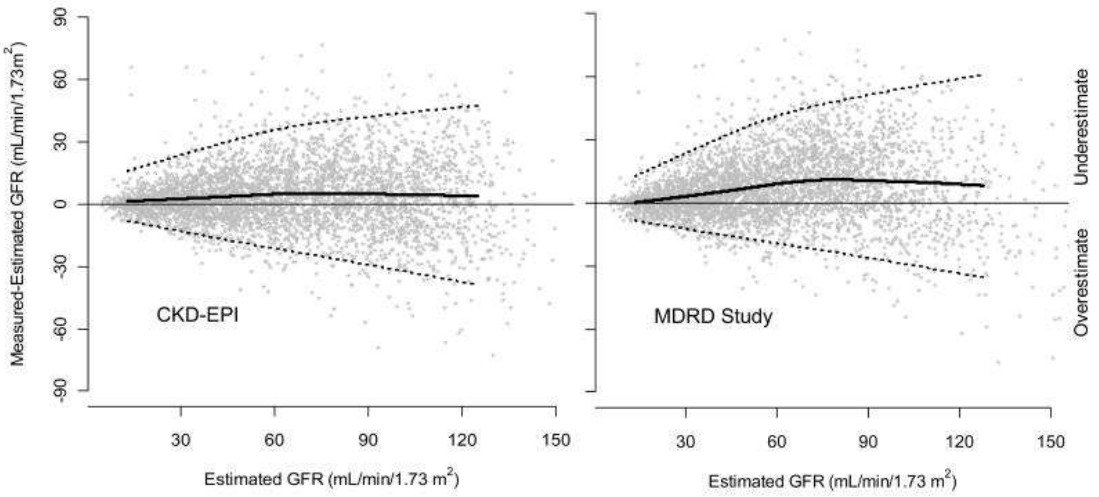


Figure 4. Accuracy of the CKD-EPI and MDRD equations to estimate GFR for the validation data set (N=3896). From Ann Intern Med 2009;150:604-612.

The more accurate GFR estimates produced by the CKD-EPI equation has facilitated a more rigorous characterization of the burden of CKD and distribution of eGFR in the U.S. population.[47] Comparing the distribution of eGFR using creatinine measurements collected by NHANES according to the CKD-EPI and MDRD equations shows a distribution shift to higher levels of eGFR particularly at eGFR values >60 mL/min/1,73 m2 (Figure 5) using the CKD-EPI equation and thus a lower frequency of CKD.[47] A meta-analysis including 1.1 million adults from healthy and diseased cohorts corroborate both the distribution shift and lower prevalence of CKD based on the CKD-EPI equation versus the MDRD equation and innovatively established GFR estimates derived from the CKD-EPI equation as better predictors of mortality and ESRD risk.[58]

All three of the chiefly used eGFR equations rely on creatinine measurements to estimate GFR are thus are inherently vulnerable to the well-characterized physiologic restrictions of creatinine as a filtration marker. As described in section 3.2.1 the levels of endogenous filtration markers such as creatinine can be influenced by dietary intake and body mass

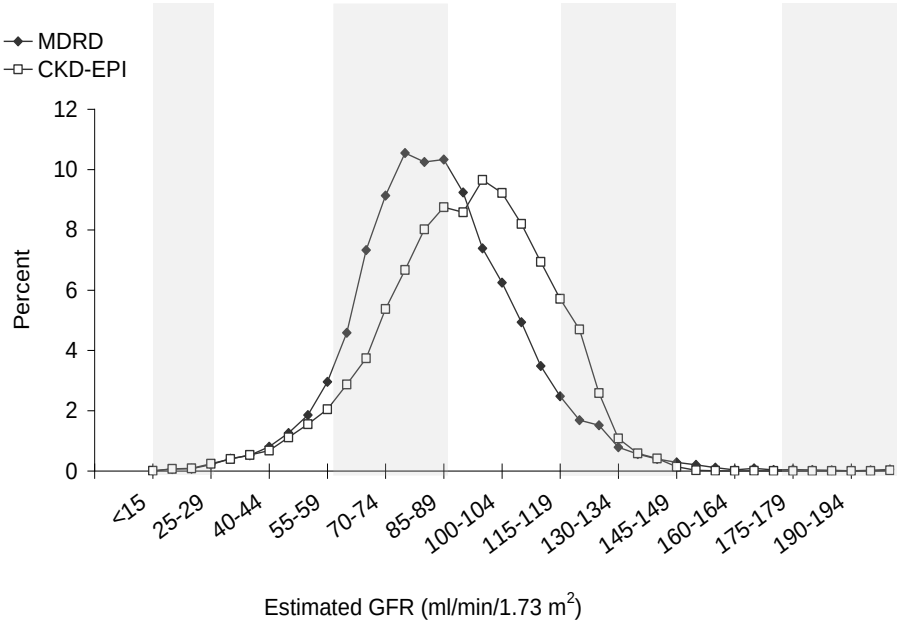


Figure 5. Distribution of estimated GFR in NHANES (1999-2006) as calculated by the CKD-EPI and MDRD equations to estimate GFR for the validation data set (N=3896). From Ann Intern Med 2009;150:604-612.

composition, and thus are suboptimal for application in some population groups. eGFR equations leveraging creatinine measurements are less accurate in individuals with extreme or restricted levels of muscle mass including those who are critically ill, obese, or elderly and should be cautiously used.[59,60] Moreover, creatinine levels can be unstable in ill, hospitalized, or pregnant individuals, limiting the reliability of measurements and their validity when creatinine is dynamic.[61] Dietary preferences, such as protein restriction or supplementation may similarly impact creatinine assessments. In populations with unstable creatinine or comorbid conditions, the gold standard of exogenous mGFR if preferable, as the primary measurement or for validation, to attain exact GFR measurements and classify disease risk. Despite these limitations, creatinine remains the most widely utilized clinical assessment of kidney function and is often the only clinical measurement available in older clinical or epidemiologic studies.

Both the MDRD and CKD-EPI equations only capture a portion of the determinants eGFR, with equations representing the best estimates of associations in certain age, race or gender groups. Additional validation would be beneficial among groups not well represented in the data sources used for equation development, including racial/ethnic minorities other than African Americans or those at the extremes of age. While all three formulas exhibit some imprecision in comparing measured to estimated GFR, this work will use the CKD-EPI equation to calculate eGFR due to its greater accuracy in African American and white American populations, and at higher levels of eGFR.[47]

3.2.3 Categorization of CKD and Kidney Failure

CKD comprises a heterogeneous group of clinical abnormalities that progressively reduce renal volume and function, potentially progressing to kidney failure.[62,63] A healthy kidney contains roughly one million nephrons, with each nephron contributing to balancing solutes, filtering blood and reabsorption, and thus the GFR.[27] Pathophysiologic processes leading to CKD are diverse; in general, structural and functional changes from injury and glomerulosclerosis in diseased kidneys cause nephron loss, subsequently leading to hyperfiltration and hypertrophy among the remaining nephrons.[27,28] The innate compensation by the surviving healthy nephrons initially sustains the maintenance of a high GFR and consistency of extracellular fluid composition. As the functional load burden increases and CKD advances, blood flow to the decreased number of nephrons becomes greater, self-perpetuating the spread of glomerulosclerosis to the remaining nephrons, causing proteinuria and decreased GFR.[64] A detailed discussion of the pathophysiology of elevated blood pressure and CKD is present in section 3.5.

Standardized stages of CKD severity using reductions in GFR were defined by the 2002 Kidney Disease Outcomes Quality Improvement (K/DOQI) guidelines, by which CKD is defined as either kidney damage or GFR <60 mL/min/1.73 m^2 for longer than 3 months, marking loss of kidney function greater than expected due to general aging (Table 2).[65] To classify disease severity of diagnosed CKD, a five-stage system is used with stages 1 and 2 describing mild CKD. Categorization of the continuous assessment of eGFR results in marked variations in severity, risk and progression within categories of CKD and require assessment of other signs and symptoms to verify the appropriate course of management for individual patients.[27] In its early stages CKD is an often undetected form of kidney dysfunction, as the disease can be asymptomatic or only present mild symptoms or decreases in GFR.[66] CKD in stages 1 or 2 is often diagnosed by kidney damage defined as pathologic abnormalities or markers of damage, confirmed by abnormalities in the composition of blood or urine establish by urine testing or structural abnormalities revealed in imaging tests.[65] Kidney damage corresponding to stage 1 is categorized as CKD, despite maintenance of a high GFR since some causes of CKD can result in hyperfiltration that allows for the preservation of high GFR even in the presence of kidney damage and increased risk for kidney complications (Table 1). The rate of glomerular filtration in stage 2 is reduced from the normal range of >90 ml/min per 1.73 m^2 to 89-60 ml/min per 1.73 m^2.[65] As normal GFR decreases with age, a GFR estimate at level indicative of stage 2 CKD is common in older populations, and, in the absence of markers of kidney damage, is generally considered normal.[67]

Stages 3 and 4 of CKD denote moderate to severe loss of renal function and are associated with complications such as hypertension, electrolyte imbalances, anemia, mineral

and bone disorders, and malnutrition.[68] Staging is admittedly arbitrary with <60 ml/min/1.73m^2 for 3 months or more marking the cut point for CKD stage 3 as it represents 50% of the normal adult eGFR value, and leaves time for intervention on kidney function decline before kidney failure.[62,69] A GFR <60 ml/min/1.73 m^2 also confers a higher risk and severity of complications of CKD, such as CVD and all cause morbidity and mortality, than in subjects with CKD and preserved GFR.[37] Kidney damage with high, normal, or mildly decreased GFR denoted by eGFR <60 ml/min/1.73m^2 is used to identify individuals that need periodic estimation of creatinine, urinary protein and risk factors such as elevated blood pressure, cholesterol and diabetes to manage progression of kidney function loss.[70] For patients who progress to an eGFR <30 ml/min/1.73m^2 or stage 4 CKD, severe reductions in eGFR further increase risk of complications, cardiovascular death and progression to kidney failure. Maintaining eGFR through renoprotective lifestyle and pharmacologic methods in these patients is utilized to post-pone dialysis initiation.[71]

Once eGFR is reduced to <20 ml/min/1.73m^2, multidisciplinary preparation for dialysis initiation or transplantation begins to increase survival and quality of life among patients.[27,71] A minority of individuals with CKD progress to GFR levels below 15 ml/min per 1.73 m^2, or CKD Stage 5, which represents progression to kidney failure and likely signifies the need for dialysis, renal transplantation or palliative care to decrease the symptoms of uremia and the risk of mortality and morbidity.[65,67] As shown in Table 1, ESRD is an administrative term used to describe a subset of the population with kidney failure who are treated with dialysis or kidney transplantation.[72] ESRD is often the outcome used to describe the burden of kidney failure as it is easily ascertained through medical

claims and records; however use of this definition excludes those who are untreated and thus may not be representative of the total population with late stage CKD or kidney failure.[72]

Table 2. Standardized Staging of Chronic Kidney Disease and End Stage Renal Disease described by the 2002 Kidney Disease Outcomes Quality Improvement (K/DOQI) guidelines

Stages	Description	GFR (mL/min/1.73 m2)	Disease State
1	Kidney damage with normal or high GFR	≥ 90	Mild CKD
2	Kidney damage with mild decrease in GFR	60-89	Mild CKD
3	Moderate decrease in GFR	30-59	Moderate CKD
4	Severe decrease in GFR	15-29	Severe CKD
5	Kidney failure	<15	ESRD if treated

3.2.4 Markers of kidney damage

Markers of kidney damage are used, particularly in the early stages of CKD, to detect the presence of the disease. Proteinuria denotes detectable levels of protein in urine and is likely the earliest pathological marker of kidney damage in CKD, and a predictor of CKD progression.[73] Quantification of the excess excretion of albumin is frequently used as a sensitive screening and assessment of CKD.[74] Microalbuminuria is defined as an albumin to creatinine excretion ratio of 30–299 mg/g and macroalbuminuria is defined as an albumin to creatinine excretion ratio of ≥300.[75] Persistent albuminuria indicates renal damage as proteins that are normally too large to penetrate the glomerulus are increased in filtered urine and renal tubular interstitium due disturbances in endothelial cell function.[27] Albuminuria predicts the development of ESRD with individuals with albuminuria at stage 1 or 2 CKD progressing to ESRD at a higher rate than individuals with stage 3 or 4 CKD without proteinuria.[76]

In addition to estimating levels of proteins through urinalysis, urine sediment findings can suggest undiagnosed structural or glomerulonephritis, particularly hematuria, or

abnormal presence of excessive red blood cells (RBCs) in the urine.[67,77] Persistent presence of hematuria can be associated with proliferative glomerulonephritis, cystic kidney disease, kidney stones, and malignancies.[67] Although hematuria can result from a variety of causes, hematuria in the presence of proteinuria, hypertension or decreased renal function suggest glomerular bases. Among asymptomatic individuals with hematuria, the development of ESRD is 18 times more likely compared those without hematuria over 20 years of follow up, supporting the uses of urinalysis findings in the definition of kidney damage.[78] Examination of urinary sediment is a noninvasive investigative tool suggested for individuals at risk for the development of CKD and those with confirmed or suspected CKD.[67]

Imaging the kidneys may be necessary to determine the presence of kidney damage or reduced renal mass.[67] Renal ultrasonography is often used as the first-line diagnostic imaging to investigate CKD as it allows for assessment of kidney size and cortical thickness with minimal invasion and potential for adverse risks.[79] Echogenicity, the ability to reflect sound waves, is often increased for the renal cortex of individuals with renal sclerosis, interstitial fibrosis, glomerular hyalinization, and chronic kidney injury with small hyperechoic kidneys indicating CKD.[80,81] Ultrasonography has also proved useful in investigating tumors, masses, and renal cysts particularly for polycystic kidney disease and medullary cystic disease.[82] Computed tomography (CT) is often used complementary to ultrasonography follow up to examine and diagnosis complex renal cysts, renal stones, decreases in renal mass, and ureteral obstructions.[83] In addition to ultrasonography and CT testing, magnetic resonance imaging (MRI) can be particularly advantageous in the assessment of renal masses, lesions, cysts and renal vein thrombosis.[84] Abnormal imaging

results are indicative of kidney damage even in the absence of reduced GFR and are included in the definition of CKD.

3.2.5 Manifestations of disease

CKD is typically asymptomatic or presents with non-specific symptoms in its mild early stages, with clinical presentation of CKD developing as the disease progresses. Prolonged subtle symptoms can appear in advanced stages in association with CKD complications that include anemia, hypocalcemia, uremia, hyperparathyroidism, sodium retention, cardiomyopathy and hyperkalemia.[27] Manifestations of CKD (Table 3) can vary by etiology; a few major manifestations of CKD and there mechanisms are discussed below as they can contribute to decreases in QOL or disability associated with CKD and kidney failure.

Anemia due to decreases in red blood cell production induced by decreases in renal production and excretion of erythropoietin, or folate and vitamin B_{12} deficiency is a common consequence of CKD.[27] In stages 1 and 2 of CKD anemia is only present in less than 10% of the population; as CKD progresses, the prevalence of anemia increases with about 20-40% of those with stage 3 and 4 CKD experiencing anemia and by stage 5 or ESRD, about 70% of the population having developed anemia.[85,86] Decreases in the ability of blood to carry necessary levels of oxygen as a result of anemia effects morbidity and decreases quality of life (QOL) through fatigue, shortness of breath, decreased cognitive function, and physical activity limitations.[86] Anemia also contributes to increased mortality in CKD by increasing the risk for cardiac complications such as heart failure (HF) and left ventricular hypertrophy and CKD progression.[86]

Mineral and bone disorders commonly contribute to morbidity and mortality from CKD as a consequence of hyperphosphatemia, hypocalcemia, and vitamin D deficiency. Given normal kidney function the parathyroid hormone (PTH) interacts with other hormones including calcitriol to regulate levels of calcium and phosphorus, in part by regulation of renal reabsorption, and bone mineral dissolution.[87] When GFR is reduced to levels indicative of stage 3 CKD, the kidneys' ability to maintain mineral homeostasis is disrupted resulting in increased serum phosphorus, decreased serum calcium (hypocalcemia) and the excessive release of PTH.[87] Secretion of PTH decreases reabsorption of phosphorus and increases levels of calcium through renal and bone absorption.[67] By ESRD the kidneys no longer increase excretion of phosphate in urine and phosphate retention impairs vitamin D synthesis leading to hypocalcemia and secondary hyperparathyroidism.[88] In response to hypocalcemia, calcium may be released from bone causing decreases in bone quality, and increased incidence of bone fracture and bone pain.[88] Early bone abnormalities presents at stage 3 CKD with patients progressing to ESRD at four fold risk of hip fracture compared to age and sex matched controls.[89]

Soft tissue and vascular calcification can be triggered by activation of bone associated proteins in hyperphosphatemia and contribute to morbidity and mortality from CVD in CKD.[88] Increases in plasma levels of phosphate with hyperphosphatemia and enhanced secretion of PTH promote the level of calcium-phosphate product that can induce mineralization and accelerate atherosclerosis and CVD.[90,91] A second mechanism supports an active osteogenesis with the expression of proteins such as runt-related transcription factor 2 (RUNX2) being associated with the formation of vascular calcification.[92] Coronary artery calcification is common in dialysis patients with appropriately 83% of dialysis patients

having some degree of calcification[93] and calcification is estimated to be 2 to 5-fold greater in dialysis patients than comparable controls.[94] Vascular calcification contributes to the development of a 30-fold higher risk of CVD mortality among the CKD population compared to the general population and should be considered as an important predictor of CVD and target for therapies that reduce the risk of developing CVD in CKD.[95]

Table 3. Manifestation of CKD/Kidney failure and mechanisms for occurrence

Manifestation	**Mechanism**
Anemia	Decreases in erythropoietin production Decreases in erythrocyte survival Iron deficiency Folate deficiency Vitamin B_{12} deficiency
Renal osteodystrophy Mineral and bone disorders	Hyperphosphatemia Hypocalcemia Impaired renal production of 1,25-dihydroxycholecalciferol Secondary hyperparathyroidism
Soft tissue and vascular calcification	Hyperphosphatemia enhanced secretion of PTH
Neurologic symptoms	Uremia Hypertension Aluminum toxicity
Gastrointestinal symptoms	Uremic conditions
Cardiomyopathy Arrhythmias	Uremia Hypertension Fluid overload
Hypertension	Volume overload Excessive renin production
Hyperkalemia	Decreases in GFR Metabolic acidosis Excessive potassium intake Hyporeninemic hypoaldosteronism Non-steroidal anti-inflammatories (NSAIDs)

Kidney injury and decreased filtration can cause waste products of small molecular weight that are normally removed by the kidneys in urine to build up in the blood (termed uremia) causing major symptoms including fatigue, lethargy, decreases in mental alertness and anorexia.[27] Although the exact pathophysiology of uremia remains unresolved, progressive rises in blood urea nitrogen (BUN) in the presence of accumulation of other waste molecules in kidney failure are associated with uremic symptoms making BUN a useful marker of uremia.[96] Dialysis patients with BUN levels above 140 mg/dL begin to experience nausea and headaches with levels above 180 mg/dL expanding these symptoms to include weakness and lethargy.[27] Uremic syndrome is associated with uremic gastroenteritis, peripheral neuropathy, and uremic fibrinous pericarditis with clinical symptoms ranging from loss of appetite particularly in regard to protein, and attrition of taste to reduced stamina, and altered nerve function impairing memory, and concentration.[27] Although reductions in physical functioning in dialysis patients to approximately 50% of normal operation can be attributed to many of the manifestations of kidney failure, studies have ascribed much of the decrease to fatigability associated with uremia.[27]

Decreases in GFR, excessive potassium intake, medication usage or metabolic acidosis can also result in hyperkalemia usually defined as a blood potassium concentration level of 5.5 mmol/L or higher.[27] Over 98% of the body's overall potassium is intracellular, predominately in the muscles with skeleton muscles stores approximately 75% of total potassium.[27] When urinary potassium excretion is reduce or potassium excretion from the cells is increased raising potassium concentration to very high levels, severe muscle fatigue, paresthesia, weakness, and flaccid paralysis can be experienced. Hyperkalemia is also associated with cardiac manifestations, depolarization of cardiac myocytes, and ECG

changes with most patients developing serious cardiac abnormalities prior to the development of neurologic symptoms.[97]

Renal dysfunction in CKD can promote atherosclerosis, cardiomyopathy, and arrhythmias leading to a higher risk of CHD, heart failure and sudden death in those with CKD.[27] With advanced decreases in GFR, prevalence arterial stiffness, structural heart disease and arrhythmias increase, with the incidence of sudden cardiac death being five times the incidence in the general population.[27] In addition to death, associations with ischemic heart disease, electrolyte abnormalities, and HF increase disability and cost of health care among the CKD population.

3.3 Kidney disease epidemiology

3.3.1 Population burden and health care costs

CKD is a costly worldwide public health problem with high health care utilization, poor health outcomes, and increasing kidney failure prevalence. CKD (stages 1 to 4) affects an estimated 26 million or 13% (1999-2004) of US adults and results in approximately 115,000 incident cases of ESRD annually (2012).[1,2,98] Precise CKD incidence estimates in the US have been limited by the sparse availability of generalizable longitudinal cohort studies or widespread surveillance systems with multiple measurements of biochemical data to verify chronicity of disease.[27] Estimates from available longitudinal studies including ARIC and the Cardiovascular Health Study suggest that the incidence of CKD ranges between 10,350 per 1 million person-years and 13,000 per 1 million person-years, varying based on the definition of CKD used.[27] Prevalence of CKD as estimated by the National Health and Nutrition Examination Surveys (NHANES) after taking into account differences in calibration of creatinine measurement have remained relatively stable since the 1990s[27,98],

with the population distribution of eGFR exhibiting a shift towards lower eGFR levels since NHANES 1988-1994.[98] Recent estimates (2011-2014) suggest a CKD prevalence (stages 1-5) of 14.8%, with the majority of the CKD population exhibiting moderate disease or stage 3 CKD.[99]

With limited data on to burden of kidney failure over time, ESRD is often used as a surrogate endpoint. Trends of rapidly increasing incidence of ESRD in the 1980s, and 1990s have stabilized over the last decade, however, increasing survival rates contribute to an increasing prevalence of ESRD.[27,85] Fitting with this trend, the adjusted incidence rate of ESRD in 2012 (353 per million/year) was the lowest recorded incidence rate for ESRD since 1997. Improved screening, and emphasis on management of CKD, blood pressure, and glycemic control have resulted in lower incidence rates for ESRD, albeit in the presence of marked variation by geographic region, age, and race/ethnicity.[27,98] The Unites States Renal Data System (USRDS) reports 636,905 prevalent cases of ESRD at the end of 2012 with the prevalent dialysis and transplant populations being 57.4% and 77.7% larger than in 2000, respectively.[98] Increases in the prevalence of ESRD reflects advances in medical care and maintenance of patients on dialysis, as well as longer survival time among patients with kidney transplantation.[27]

Rate of rehospitalization have remained relatively unchanged over the past decade. All cause rehospitalization rates within 30 days for U.S. residents without CKD, those CKD and those with ESRD were 17.4, 24, and 33 percent respectively, reflecting a near doubled rehospitalization rate among the ESRD population compared to the general population.[98] In the Medicare database, patients with recognized CKD account for 18% of total expenditures

but only represent 9% of the patient population.[100] When ESRD is included in these estimates, CKD and ESRD combined account for 24% of the Medicare budget.[100] Estimates of the cost-effectiveness of CKD prevention suggest that $18.56 and $60.61 billion in direct health care costs could be saved in a decade if at the beginning of 2010 the yearly rate of decline in GFR decreased by 10% and 30%, respectively, in every patient with GFR of 60 mL/min/1.73 m^2 or less.[101] Decreases in blood pressure could help realize these cost savings as well as declines in disability due to CKD. As the burden on the healthcare system of treating and managing individuals with CKD continues to rise, preventing the development of incident cases of CKD and ESRD affords the best opportunity to combat kidney disease.

3.3.2 Quality of life and disability

Even in early stages of renal decline, manifestations of CKD can cause substantial decreases in the physical and mental capacity of those with CKD, leading to decreases in quality of life and increased disability. Estimates using NHANES 2006-2011 suggest that difficulty with activities of daily living was 2 to 3 times more likely in those with CKD stages 1-4 than individuals with no CKD.[102] Symptoms associated with advanced kidney disease, such as edema, fatigue, and cognitive difficulties, have a greater impact the quality of life and functional capacity in ESRD. Physical limitations resulting from diminished muscle function and CKD complications can limit the most basic daily activities of kidney failure patients including walking.[103] Research suggests that only 60% of nondiabetic and 23% of diabetic ERSD patients are able to perform any physical activity outside of self-care.[104] These limitations, in conjunction with the need for frequent dialysis, increases the burden of unemployment and depression in this population.[104]

With transplantation only available to suitable candidates, dialysis as a long-term treatment plan is often accompanied by long-term disability.[104] Measures of disability that quantify both premature mortality and time spent in states of reduced health have been developed to describe the magnitude of disability commonly reported among people with CKD and kidney failure[24] and will be used for Specific Aim 2. Disability weights, which describe disease severity ranging from 0 to 1, have not been estimated for CKD stages 1 through 3. For stage 4 CKD and kidney failure with dialysis, disability weights are estimated at 0.104 and 0.571, respectively, indicating that disability is greatly increased when dialysis is required.[25] With kidney transplantation, disability weights are considerably reduced to 0.024 with observational evidence supporting increases in psychosocial factors, employment and physical ability following transplantation.[105]

3.3.3 CKD Mortality

Despite increased screening and emphasis on management of CKD and its risk factors, CKD is the eighth leading cause of death in the United States (2010).[106] As renal function decreases, mortality rates increase with risk of death being higher than the risk of progression to ESRD. [107-110] In 2012, the adjusted mortality rate for Medicare patients age 66 or older with CKD stage 1,2, or 3 was approximately 63 deaths per 1,000 patient years compared to 78 deaths per 1,000 patient years among those with stage 4 or 5 CKD and 52 deaths per 1,000 patient years among those without CKD.[98] CKD's association with other traditional risk factors such as diabetes, hypertension, and obesity greatly increase an individuals' risk of death particularly for cardiovascular causes of death.[107,110] CKD patients without CVD or diabetes experienced an adjusted mortality rate of 47 deaths per patient year compared to 103 deaths per 1,000 patient year among individuals with both diabetes and

CVD.[98] High rates of mortality, which appear greater for men, limit the number of survivors who progress to requiring dialysis or renal transplantation.[111]

Net reductions in mortality of 28, 47, and 51% among hemodialysis, peritoneal, and transplant patients respectively since 1993 have contributed to a trend of declining ESRD mortality overall.[98] Despite these decreases in mortality, only 54% of hemodialysis patients and 65% of peritoneal dialysis patients survive past three years after initial onset of ESRD.[98] Among dialysis patients between 30-50 years of age, remaining lifetime estimates are a third of lifetime estimate for those of the same age in the general population.[98] In addition to quality of life benefits, individuals who receive a kidney transplant have the highest ESRD survival and remaining lifetime estimates at approximately 85% of those for the general population. Remaining lifespan for dialysis and transplant patients aged 45 to 49 years are 9 years and 25 years respectively and approximately 4.5 and 13 years, respectively for those aged 65 to 69 years.

3.3.4 CKD awareness and CKD screening guidelines in clinical practice settings

Screening programs are typically employed in a population when the presence of a treatable health condition of significant magnitude can be tested for in an economically balanced and safe manner to allow intervention before late stages of disease.[112] Current assessments of screening programs establish that programs should integrate education, testing, and clinical services into screening efforts, and additionally strive to provide equitable access to screening for the whole target population.[112] Such programs should also have clear benefits that outweigh associated harms.[112] In order for a screening program to effective, the interval between detection due to screening and the time at which diagnosis would have occurred without early detection should yield enough lead time in the detectable

preclinical period to provide for beneficial early treatment that improves the prognosis. Screening tests should be valid, repeatable, and easy to perform.[112,113] The criteria noted above have been widely used to determine the appropriateness of screening for population as a whole or among groups at increased risk for disease.

Given the asymptomatic nature of CKD in early stages, screening programs have been considered to identify CKD in the preclinical phase to facilitate early treatment and improving long-term outcomes. For the general asymptomatic population not at increased risk for CKD development, the U.S. Preventative Task Force (USPSTF) has concluded that insufficient evidence exists to assess whether the benefits of CKD screening outweigh the risks or harm associated with routine screening.[114] To-date, no studies have assessed the sensitivity and specificity of screening tools for CKD.[114] Furthermore, the benefits of treatment of early CKD in patients that are neither diabetic or hypertensive remain unproven.[114] False positives and unnecessary medical treatment are noted as the most likely harms associated with screening for early CKD.[114]

KDIGO does recommend CKD screening for populations at increased risk for CKD, including those with hypertension, diabetes, and CVD since clinical trials support the efficacy of treatment for these condition in reducing the progression of CKD.[57,115] Other target groups that should be evaluated for screening effectiveness include those characterized by advanced age, obesity, metabolic syndrome, smoking, those of some chronic infectious disease such as HIV, and individuals with a family history of CKD.[115] Although clinical trial data assessing the effectiveness of screening is lacking, yearly CKD screening of this high risk population is suggested, including both a urine specimen for proteinuria and a blood specimen for creatinine-based estimation of eGFR.[57,115] Although no federally supported

CKD screening programs exist, the National Kidney Foundation's Kidney Early Evaluation Program (KEEP) targets these populations at high risk of CKD for a free, voluntary screening test with measurements that include serum creatinine, albumin-creatinine, blood pressure, plasma glucose and hemoglobin.[57] The identification of a significant number of participants with previously undiagnosed hypertension, diabetes, and decreased eGFR is taken to support the utility of community-based targeted health screening programs such as KEEP.[116]

KEEP also strives to increase awareness of CKD and its relationship with CVD by providing participants with educational materials highlighting diabetes, hypertension, proteinuria and CKD[117] and physician referrals for participants with positive screening results.[57,118] Comparisons between KEEP and NHANES participants suggest that despite educational programing KEEP participants were less aware of CKD risk compared to NHANES participants, highlighting the missed educational opportunity during physicians visits for management of CKD risk factors such as diabetes and hypertension.[118] Even with the provision of clinical practice guidelines and community awareness events, national awareness of the causes, risk factors and treatment options for CKD did not improve from 1999 to 2006, and remains low.[119,120] Patient level data indicate a lack of perceived risk among individuals at increased susceptibility of disease, and a general lack of knowledge about CKD, particularly among individuals with no family history of CKD.[120] Healthcare provider data report an unacceptably low level of CKD knowledge and KDOQI guidelines for early CKD management among primary care providers, associated with suboptimal early referral and transfer of knowledge to CKD patients.[120] These deficiencies in CKD awareness

stress the importance of community, patient, and physician level public health programming to increase early awareness and intervention in those vulnerable to CKD development.[120]

National education programs sponsored by the National Institute of Diabetes and Digestive and Kidney Disease (NIDDK), such as the National Kidney Disease Education Program (NKDEP), work to improve the understanding, early detection, and management of CKD. Efforts toward this goal include maintaining a database of relevant kidney disease publications, developing and distributing CKD educational materials supporting family based interventions, facilitating identification of at risk patients, and improving care among CKD patients.[57] The NKDEP collaborates with several government, health care, and community agencies to encourage testing among at-risk populations, with programming developed and targeted specifically to reduce CKD disparities in population with increased burden of disease. For example, a focus on African Americans capitalizes on traditional family reunions and the prominent role of the church in this community, to encourage families and congregations to discuss CKD risk factors and pursue diagnostic testing. Free informational kits designed to facilitate sharing of information with lay community members are provided to volunteers who disseminate this information to their peers. NKDEP has also increased awareness and education among health professionals by providing guidance to diabetes educators and dietitians on CKD prevention and dietary therapy.[121] Continued efforts from NKDEP and other federal or community entities could aid in improving CKD awareness, identification, disparities, and care in the future.

3.3.5 CKD and ESRD Surveillance

CKD surveillance is an essential public health activity for ongoing systematic collection, analysis, interpretation and dissemination of key information including the

development and severity of disease that can be used for public health planning and evaluation of CKD management.[122] The primary role of disease surveillance is to increase knowledge so that the disease may be prevented, or harm attributable to the disease may be minimized. Several federally funded surveillance registries and surveys exist in the US to inform on CKD and its complications including the USRDS, Centers for Medicare and Medicaid Services (CMS) ESRD Network System, NHANES, and Quality Improvement Organizations (QIO).[57]

Funded by NIDDK in 1989, the USRDS is the largest national ESRD surveillance system, comprehensively charged with collecting and analyzing data on the human and fiscal burden of CKD, particularly for ESRD treatment.[123,124] At its expansion in 1999, the USRDS declared 6 main goals: 1) to design and implement a renal database, providing expertise in analyzing collected data, 2) report on the incidence, prevalence, treatment and mortality trends over time, characterized by socio-demographic variables, 3) develop and analyze aggregate data on renal disease prevention, treatment, progression, mortality and morbidity, 4) identify areas in need of more in-depth research focus, 5) evaluate cost-effectiveness of ESRD treatment and 6) disseminate collected data to other kidney disease investigators.[123] Given the role of federal funding in providing treatment for the vast majority of ESRD patients, data provided to the USRDS is supplied through mandatory reporting of renal replacement therapy (RRT), basic demographic information, and basic laboratory data on all ESRD patients.[123] The USRDS publishes an annual data report that describes updated kidney disease epidemiology statistics through figures and tables that are accessible to the general public. Several special reports sponsored by the USRDS have provided essential information

regarding nutrition therapy, end of life care, and the burden of CVD among ESRD patients.[99,125]

CMS's ESRD Network Program was mandated in 1972 to improve cost effectiveness, foster patient rehabilitation, ensure quality of care, and encourage safe renal replacement therapy among the providers of dialysis to ESRD Medicare and Medicaid beneficiaries.[126] During this time, 32 networks were developed to integrate hospitals and other health care facilities providing dialysis with the federal government to ensure coordinated delivery of reliable ESRD care to all patients. The Network Program currently consists of 18 ESRD networks, assigned to work with patients and providers in their assigned geographic region to improve quality of treatment and clinical outcomes.[126,127] Dialysis centers in each ESRD network are required to participate in ESRD networks and fund these centers through a $0.50 fee paid per treatment from their dialysis reimbursements.[126] Through this self-funding mechanism, the Networks are able to collect patient and provider level data for surveillance of ESRD and evaluate the appropriateness of patient care provided by dialysis facilities, as described in Dialysis Facility Reports.[127] The Consolidate Renal Operations in a Web-enable Network (CROWNWeb) funded through CMS (2008) provides an additional registry system that enables dialysis facilities to electronically report clinical laboratory results and treatment quality measures mandated of dialysis facilities.[127] Electronic data submitted through CROWNWeb improves patient care and quality evaluation by providing real time surveillance of clinical performance results.

While both the previous surveillance programs concentrate on ESRD, surveillance data on earlier stages of CKD is less abundant. Nationally representative samples of the NHANES cross-sectional surveys have frequently been used to describe the prevalence of

CKD and the trends in the US burden of CKD over time.[1,128] While these surveys capture demographic data and information on levels and awareness of risk factors for CKD, detailed laboratory data is only available in a subset of the population.[129] A lag also exists between collection and dissemination of data for analysis by research, limiting the availability of contemporary epidemiologic data.[129]

To provide more comprehensive passive surveillance of CKD, the CDC has developed a CKD Surveillance System to measure the burden and awareness of CKD, its risk factors, and complications in the U.S. population over time.[129] Similar to the efforts of the ESRD Network Program for data collection on ESRD, the CDC Surveillance System also collects measures needed to evaluate, monitor and implement quality improvement in health care capacity and management of CKD.[129] A comprehensive variety of existing data sources were compiled for inclusion in the surveillance system including health care data from managed care plans, government insurance plans, community health centers, registries, population surveys and cohort studies.[129] Reports developed by the CDC CKD surveillance program are disseminated to the research and medical community regularly to increase awareness of CKD and to generate a knowledgeable supportive network of stakeholders.[129]

3.4 Kidney disease risk factors

Many factors, both modifiable and non-modifiable, have been shown to increase the risk or odds of development and progression of kidney dysfunction (Figure 6). Modifiable risk factors that accelerate declines in renal function, such as diabetes and elevated blood pressure, reportedly contribute to over 70% of CKD and ESRD cases.[7] Heredity, gender, race and aging also influence the development, progression, and prognosis of CKD and highlight

groups disproportionately affected by the disease. A review of selected traditional and non-traditional risk factors contributing to CKD and kidney failure is provided below (Figure 7).

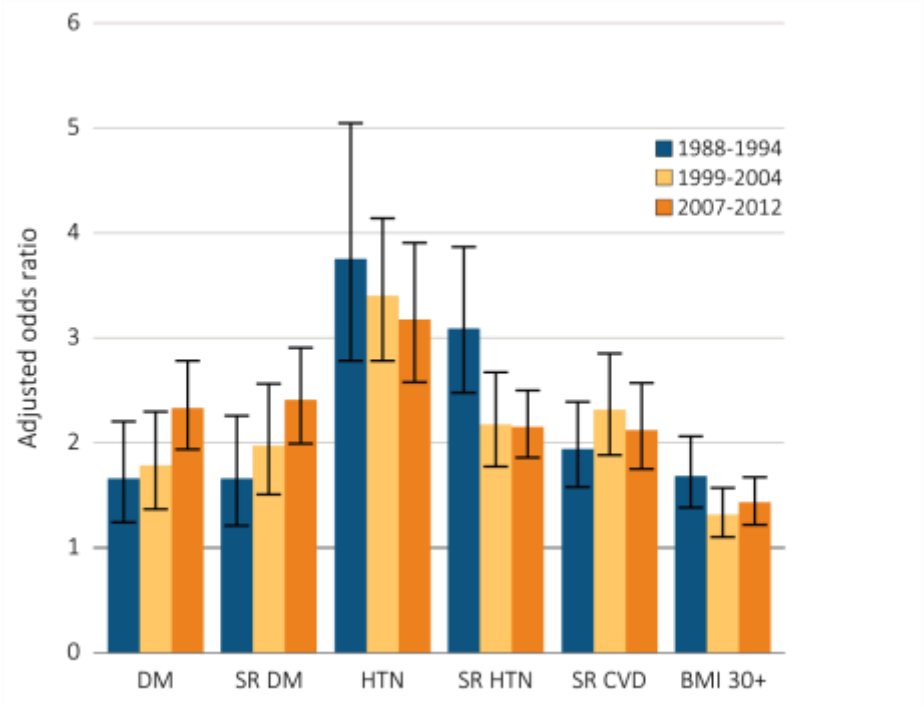


Figure 6. Adjusted odds ratios for CKD risk factors NHANES 1988-2012
Data Source: National Health and Nutrition Examination Survey (NHANES), 1988–1994, 1999-2004 & 2007–2012 participants age 20 & older; single-sample estimates of eGFR & ACR. Adj: age, sex, & race; eGFR calculated using the CKD-EPI equation. Whisker lines indicate 95% confidence intervals. Abbreviations: BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; DM, diabetes mellitus; HTN, hypertension; SR, self-report. Figure source: USRDS 2014 report

Elevated blood pressure

Hypertension, denoted by sustained elevation in blood pressure above the treatment threshold, is the most common primary diagnosis in the United States[15] and the second leading cause of CKD.[85] In the US, prevalence of high blood pressure increases with age with approximately 19.2% and 61.2% of Americans between the aged 18-59 years and ≥60 years, respectively having blood pressure measurements above the treatment thresholds defined by JNC 8.[130] Elevations in blood pressure can damage the kidney vasculature and impair glomerular filtration.[64] Even blood pressure levels that are considered "high-normal" (defined as systolic blood pressure between 130 and 139 mmHg or diastolic 85 to 89 mmHg)

are associated with a 3-fold greater risk of future development of ESRD. [10,11] The prevalence of high blood pressure increases with severity of CKD.[131] Nationally representative data from NHANES 1999-2006 estimated the prevalence of JNC 7 defined high blood pressure in the population without CKD as 23.6%, compared to 35.7% among stage 1, 52.2% among stage 2, 64.1% among 3, and 82.2% among stage 4-5 CKD populations.[132] Prevalence of hypertension also varies by cause of CKD; strong association with hypertension was reported in patients with renal artery stenosis (93%), diabetic nephropathy (87%), and polycystic kidney disease.

In combination with other CKD risk factors including dyslipidemia and diabetes, hypertension contributes to the high rate of cardiovascular events among the CKD population. CVD is the leading cause of morbidity and mortality among the CKD population, with risk of CVD increasing as GFR declines.[110,133] For example, in individuals with normal kidney function, CKD stage 1 or 2, the age-standardized baseline rate of cardiovascular events is 21 events per 1000 person-years compared to 37, 113, 218, or 366 events per 1000 person-years among people with CKD stage 3a (GFR of 45 to 59), 3b (30 to 44), 4 (15 to 29) or 5 (<15).[85,132]

Type 2 Diabetes

Diabetes, which affects approximately 9% of the US population, is the leading cause of CKD and contributes to an estimated 50% of all ERSD cases in the US.[134] Chronic hyperglycemia causes glomerular hyperfiltration leading to an increased output of urine. In response, blood vessels in the kidneys constrict to slow the loss of fluid from the body. With insufficient blood supply, the kidneys become damaged and optimal function is impaired. Diabetic nephropathy is characterized by the development of hypertension, progressive

albuminuria, and decline in GFR.[3] Between 20 to 30% of persons with diabetes develop kidney disease[135] and decline in kidney function occurs more rapidly in those with poor control of blood glucose levels.[136]

Age

Structural and functional changes in aging kidneys decrease kidney mass, renal blood flow,[137] and recovery from infections, making age a key predictor of CKD.[138,139] Arterial changes in elasticity and intimal thickening associated with advancing age resemble arteriolar nephrosclerosis attributed to hypertension even in normotensives, but is exaggerated in those with hypertension.[140] Blood pressure rises that accompany aging in Western societies have also been linked to decreases in kidney function and faster declines in renal perfusion. The number of glomeruli begins to decrease around 30 years of age and is generally reduced by 30-50% by 70 years of age. In conjunction with reduced glomerular count, GFR begins declining at age 30 and gradually declines annually by approximately 1 mL/min/y/1.73 m2, falling to an average of 70 mL/min/1.73 m2 by 70 years of age.[141] The likelihood of being diagnosed with CKD has been shown to increase with age,[1,137] with the highest likelihood being among those age 80 and older.[100] In individuals older than 65 years of age, 11% of those without hypertension or diabetes had stage 3 or worse CKD[142], and 25% of new dialysis patients are age $\geq$ 75 years.[124] With the occurrence of co-morbid conditions increasing with age preventing or delaying risk factor development could improve functional impairment, quality of life, and disability in later life.

Race and Ethnicity

The observed disparities by race in CKD progression are likely do to both modifiable lifestyle factors and genetic predisposition. With the rate of kidney decline being more rapid

in African Americans, the risk of ESRD attributed to hypertension in African Americans is observed to be approximately 5 times that of age matched white American.[143,144] In addition to an earlier occurrence and greater severity of hypertension in African Americans, other risk factors such as diabetes, high sodium intake, adiposity, and physical inactivity are disproportionately prevalent in this group.[145-147] New investigations into this disparity highlight an association between two independent sequence variants in *APOL1* and renal disease including focal segmental glomerular sclerosis and ESRD due to hypertension in African-Americans, with 50% and 10-15% of African Americans carrying at least one allele or two alleles, respectiviely.[148,149] African Americans with two alleles have up to an 18-fold higher risk of nondiabetic ESRD compared white Americans.[150]

Cigarette smoking

Like many CKD risk factors, cigarette smoking contributes to CKD through direct kidney injury and the promotion of kidney damage in patients with other CKD risk factors. Cigarette smoking is associated with decreases in GFR, and increases in serum creatinine, microalbuminuria, and proteinuria.[151,152] Smoking may also promote loss of kidney function through damage caused by vasoconstriction and increases in blood pressure.[153,154] Smokers with hypertension or diabetes experience more rapidly declining kidney function than non-smokers.[155] Experimental and observational studies suggest that smoking cessation can slow the progression of CKD, supporting the use of both the prevention of smoking initiation and of smoking cessation programs in the prevention of CKD[152,156]

Diet

In addition to the influence of dietary patterns on hypertension, diabetes and obesity, dietary protein and salt have been reported to be associated with progressive kidney damage.

The initial step in urine formation requires filtration of fluid until it is nearly free of protein. The ingestion of excessive dietary protein may result increased absorption of salt and induce a continued increased in renal hyperfiltration. Increased absorption can lead to a decrease sensitivity of the tubuloglomerular feedback mechanism, causing rises in glomerular pressure and damage to the kidneys' structure and function over time. Some theories also suggest that increases in GFR and renal blood flow due to high protein intake may result from actual growth of the kidney. Evidence from meta-analyses support the correlation between lower protein intake and a reduced rate of GFR decline for patient with reduced kidney function.[157,158] High sodium intake may also induce hyperfiltration and glomerular pressure harming the kidneys.[159]

Obesity

Obesity increases the risk of CKD through its relationship with other risk factors, but also independently shows a strong graded association with the risk of CKD and ESRD.[160,161] Obesity is posited to induce hypertension by increasing renal sodium reabsorption, stimulation of the sympathetic nervous system and the RAS complex.[151] Obesity also increases the risk of diabetes through mechanisms that induce insulin resistance. In addition to these pathways, biopsy studies have found renal lesions in obese individuals that are unrelated to diabetic nephropathy or hypertensive nephrosclerosis.[162,163] Hyperfiltration and elevations of renal plasma flow in the obese may also predispose to the development of focal segmental glomerulosclerosis and proteinuria.[163] Although the exact pathways are still being investigated, weight loss has been proven been effective in decreasing the rate of kidney function loss.[164]

Gender

The incidence of CKD and the rate of kidney disease progression differ by gender, with men experiencing a higher rate of progression of CKD and a poorer prognosis than women, independent of blood pressure levels.[165,166] Possible mechanism for the protective affect among women include smaller kidney size,[167] resistance to angiotensin II,[168] lower protein intake, and better lipid and risk factor patterning at earlier ages. The role of estrogen in the release of nitric oxide and the regulation of the RAS complex has also been cited an explanation of the better outcomes among women.[169,170] Incidence of hypertension at younger ages and poor hypertension control among men also contribute to increased duration of elevated blood pressure and its damage to kidney function.[169]

Physical inactivity

Physical inactivity is associated with the development of obesity,[171,172] elevated blood pressure,[173] and diabetes.[174,175] Among diabetics, physical activity decreases the development of renal complications[176] and in those with CKD, physical activity deceases the rate of GFR decline.[177] Studies of long-term increased physical activity have shown that physical limitations that influence quality of life for many CKD and dialysis patients could be improved with increased physical activity.[178,179]

Family history

Observational studies suggest that individuals with two or more first degree relatives affected by kidney disease have a 10-fold increase in the odds of kidney failure after adjustment for covariates.[180] Among African Americans, 26% of prevalent ESRD cases report a first- or second-degree relative with CKD or ESRD.[181] Clustering of kidney disease

within families and across racial groups suggests that genetic factors influence the predisposition, origination, and progression of ESRD,[181-183] although the contribution of shared norms and lifestyle factors cannot be ruled out. Heritability estimates for CKD reportedly vary from 20 to 80% but remain largely unexplained.[184] Large genome-wide association studies have found at least 30 loci for renal function and CKD, several of which in the SLC family of genes which encodes proteins responsible for active transport.[185] Genetic, sociocultural or environment factors clustered within families likely are associated with risk factor development[186] and increases in risk within families affected by kidney disease.

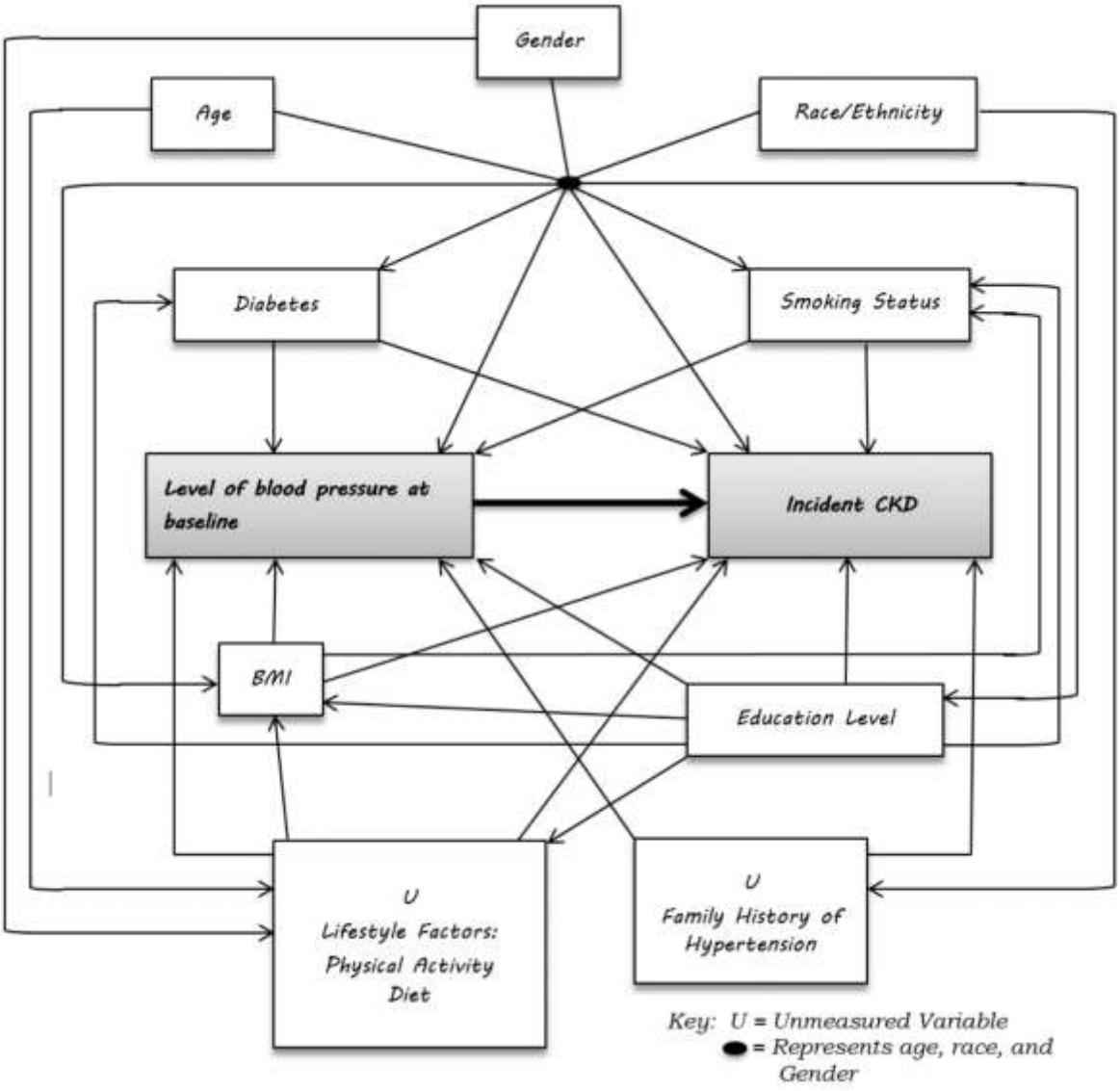


Figure 7. Directed acyclic graph representing pathways between blood pressure values at baseline and development of incident CKD

3.5 Pathophysiology

Although pathophysiologic mechanisms for kidney damage are heterogeneous, models of kidney injury commonly depict the occurrence of irreversible tubulointerstitial fibrosis, which elicits further damage and progressive deterioration of kidney function.[187] In the absence of methods to ameliorate permanent injury within the kidneys, delaying the commonly observed progression of kidney decline over time in individuals with CKD, through intervention on factors that contribute to more rapid decline, remains the focal target of treatment.[188] Once GFR has been reduced to approximately 50% of normal aptitude, a progressive loss of function occurs, regardless of the elimination of the initial cause of function loss, thus emphasizing the importance of early detection for management of CKD, a diagnosis that is often delayed due to the asymptomatic nature of the early stages of the disease.[189] Primary prevention of kidney injury through avoidance or control of factors associated with the development of CKD is a compelling approach to preserving kidney function and to prevent or delay the development of incident CKD. One of the highly prevalent risk factors that exhibit an association with increased incidence of CKD is elevated blood pressure. Lowering blood pressure and controlling hypertension has been shown to slow the progression of renal disease regardless of the initial cause of CKD.[190] Primary and secondary hypertension both play a role in renal disease, with hypertension being a cause as well as a consequence of CKD. Thus, reducing blood pressure and improving control of hypertension are essential components of strategies aimed at decreasing the burden of CKD. Blood pressure's role in the development of renal disease is discussed in more detail below.

3.5.1 Elevated blood pressure and chronic kidney disease

Both systolic and diastolic blood pressure show a graded, continuous relationship with CKD,[10,191-193] with rates of CKD increasing as blood pressure rises. Elevated blood pressure can precede the development of CKD and escalate progression of renal dysfunction by causing renal vascular damage. The disproportionately large cardiac output and rate of blood flow allocated to the kidneys as well as the extensive renal vascular system make the kidneys vulnerable to pathological changes from sustained exposure to elevated blood pressure. Despite the large burden of CKD attributed to hypertensive disease, morphologic evidence of the pathogenesis of hypertensive nephrosclerosis remains unclear.[64] Two main pathophysiologic mechanisms have been suggested as underlying the development of hypertensive nephrosclerosis: vascular and glomerular changes, and interstitial nephritis.

Vascular and glomerular changes

Elevated systemic blood pressures can initiate vascular anatomical changes such as vascular hypertrophy, intimal thickening and luminal narrowing of the kidneys' arteries and glomerular arterioles leading to CKD.[194,195] Stated simply, the force of blood flow against vessel walls is a product of cardiac output and vascular resistance.[196] As discussed in section 3.1.1, afferent and efferent arteries in the glomerulus primarily auto-regulate the range of blood pressure and volume of blood flow through vasoconstriction and vasodilation. Afferent arterioles mitigate the transmission of abnormally high blood pressure into the glomerulus by signaling contraction of smooth muscle; with coordinated efferent arteriole vasoconstriction and dilation, tension on the arterial wall is released.[27] As a result of habitual vasoconstriction, afferent arteriole smooth muscle cells hypertrophy. Under conditions of high blood pressure, blood in the arterial tree between the aortic valves and the capillaries

causes barotrauma to the smooth muscle and endothelial cell of the vessel wall.[27] Smooth muscle cells respond to barotrauma by secreting pro-inflammatory cytokines and extracellular matrix of fibrin, collagen, and lipid in the sub-intimal space. Structural and cellular changes of the arterial wall and media-to-lumen ratio, resulting from systemic high blood pressure and aging, can decrease compliance, exposing the interlobular arteries and afferent arterioles to increased blood flow pulsatility and velocity. The resulting adaptive changes expose the efferent arterioles and tubules to hypoperfusion.[27]

Arterial stiffening caused by degradation of elastic fibers in the large or medium (1 mm to 25 mm) arteries begins in early life becoming progressively severe as elastic fibers degrade with age. Increases in force of blood flow and strain on the wall can damage the endothelial cells of the tunica intima, resulting in dysfunction of the barrier between blood and the basement membrane. As barrier cells of the tunica intima begin to destruct, permeability to substances in the blood, including low-density lipoprotein (LDL), collagen and myofibroblasts, increases. In turn, LDL in the sub-intimal space attracts macrophages (which consume LDL and become foam cells), leading to inflammation, necrosis and the formation of atherosclerotic lesions. Smooth muscle cells from the tunica media migrate into the tunica intima contributing to the organization of the atheromata, and the deposition of calcium into the lesion. Fibrous lesions, intimal thickening and vascular remodeling from these processes gradually decrease the lumen radius while calcification causes the wall to become firm and non-compliant.[197] Elevated blood promotes and accelerates these pathophysiologic processes. Arterial remodeling and stiffening results in increased vascular resistance and in pulsatile blood flow reaching the muscular afferent arteriolar supplying the kidneys.[64,198]

In addition to arterial the stiffening and/or arteriosclerotic changes in the larger arteries, high blood pressure can cause smaller renal arteries (0.01 mm -1 mm) to undergo arteriolosclerosis and lose compliance, leading to hypertensive kidney disease.[199] The enhanced blood pressure gradient on the vessel wall can force circulating proteins across the tunica intima and basement membrane, into the tunica media. Hyaline arteriolosclerosis is characterized by the leakage of plasma proteins such as C3b in hyaline material across the endothelium. Accumulation of hyaline, comprised of fibrin, collagen, and lipids, and proteins thickens arteriolar wall and increases synthesis of basement membrane components by smooth muscle cells.[200] Entrapment, accumulation, and deposition of hyaline into small cortical scars or lesions in arterioles leads t glomerular atrophy by narrowing the lumen of the vessels and decreases blood flow to the glomerulus, and thus filtration.[201] Hyaline arteriolosclerosis eventually spreads throughout the glomerulus leading to chronic ischemia, nephron loss, and reduced renal size. Hyaline arteriosclerosis is accelerated by sustained elevated blood pressure leading to decreases in blood perfusion and GFR, with increased ischemic injury and nephron loss.[200]

Hyperplastic arteriolosclerosis is associated more with malignant high blood pressure and hyperglycemia than is the case for systemic high blood pressure, and presents as concentric thickening of vessel walls and narrowing of the lumen. Increased blood pressure or blood glucose diminishes the vascular wall's ability to withstand stress, allowing serum proteins and macromolecules to penetrate the basement membrane and insudate the tunica media.[201] Thickening of smooth muscle cells through rapid cell proliferation in hyperplastic arteriosclerosis is distinct as the pattern of thickening by concentric layering of cells resembles an "onion skin".[202] Concentric layering and reduplication of the basement

membrane eventually dominates the lumen space resulting in decreased blood flow and reduced GFR.[194,201]

Hypertension is also one of multiple etiologies associated with glomerulosclerosis and glomerular hypertrophy.[64] Vascular damage from high blood pressure can scar segments of the glomeruli, with increases in accumulation of glomerular collagen material that produces sclerosis of lesions.[27] As effected nephrons begin to succumb to scarring and hypoperfusion, hyperfiltration and enlargement of the remaining nephrons compensates for the decrease in filtration capacity from the loss nephrons in order to maintain a continuously high GFR.[27] Increased glomerular capillary pressure to the remaining nephrons causes both epithelial and endothelial cell damage, as well as compensatory intraglomerular hypertension and hypertrophy in the surviving glomeruli,[27] perpetuating the cycle of injury leading to greater progression of focal and segmental sclerosis. Eventually GFR diminishes as a consequence of advanced loss of surface area, hypertrophy and sclerosis.

Tubulo-interstitial diseases

Tubulo-interstitial diseases have also been proposed as a possible mechanism by which high blood pressure contributes to the burden of CKD and ESRD. Chronic ischemia and hypoxia, which can result from hypertension, are the most significant attributing factors for the development of interstitial fibrosis.[27,64,201] In interstitial fibrosis, ischemia, loss, or impairment of peritubular capillaries impairs tubular oxygen supply damaging tubular cells and epithelium.[64] Hypoxic conditions in the renal interstitium promotes destructive fibrogensis in fibroblasts and increased synthesis of extracellular matrix, further separating oxygenated blood in the remaining peritubular capillaries from tubular cells..[64,201] Once evoked, the CKD environment also stimulates atypical apoptosis of normal glomerular and

tubular epithelial cells and excessive recruitment of macrophages, perpetuating fibrosis, apoptosis, and kidney dysfunction.[64,201,203] Although the etiology remains controversial, experimental evidence supports the role of molecular and cellular mechanisms causing an inflammatory response and subsequent renal injury after the development of high blood pressure, particularly among those with salt-sensitive hypertension.[204,205] As a result of these processes, kidney and tubular atrophy and interstitial fibrosis contribute to the functional impairment of the kidneys.

3.5.2 Blood pressure elevation induced by CKD

Approximately 75% of individuals with GFR less than 30 mL/min/1.73 m2 are diagnosed with hypertension,[67] reflecting both the role of blood pressure elevation both as a leading cause and a consequence of renal disease associated with decline in kidney function. Since the kidneys play a pivotal role in the regulation on blood volume, hormone secretion, and solute concentration, renal dysfunction and renal disease can contribute to sustained blood pressure elevation through several mechanisms. Pathways to the development of blood pressure elevation resulting from kidney disease include impaired salt and water excretion, activation of the RAS complex, elevated sympathetic nervous activity, and increased arterial stiffness.[27]

Pressure natriuresis refers to increased urinary sodium excretion that occurs when arterial blood pressure is elevated.[27] As discussed in section 3.1.1, balance of fluids and electrolytes in healthy kidneys is regulated through appropriate changes in GFR, tubular reabsorption, and urinary secretion, allowing for maintenance of extracellular fluid volume. Normal natriuresis undergoes compensatory increase in sodium and water excretion in response to increases in blood pressure , thus reducing extracellular fluid, blood volume, and

normalizing blood pressure.[27,206] Severe reductions in GFR or high dietary sodium intake in CKD can impair the pressure-natriuresis relationship and allow for increased tubular sodium reabsorption and retention, and thus large extraceullular fluid expansion, despite elevated levels of blood pressure.[206] This failure to maintain normal volume homeostasis increasingly shifts the sodium excretion and blood pressure balance to higher levels of blood pressure, making high blood pressure a necessary adjustment for preserving normal levels of excretion of sodium and fluids.[27]

Functional nephron loss due to ischemia or infarction of renal tissues in CKD results in less surface area to accomplish filtration and excretion of sodium and water from sustained volumes of fluid. With permanent nephron loss, blood flow and pressure increase to aid surviving nephrons in compensating for the need to balance filtration and reabsorption of sodium and water with reduced kidney mass.[207] The remaining nephrons also undergo compensatory structural and functional changes resulting in hypertrophy and hyperfiltration, which ultimately lead to intra-glomerular hypertension and thus accelerated sclerosis of the remaining nephrons.[27]

Increased dietary sodium intake and changes in sodium reabsorption also contribute to the development of high blood pressure in CKD. In addition to sodium-fluid balance abnormalities which increase pressure under high sodium intakes, with loss of nephrons increased angiotensin II or mineralocorticoids can cause salt sensitive hypertension due to increased proximal, distal and collecting tubule reabsorption.[208] Under conditions where reabsorption is increased downstream from the macula densa, chronic increases in sodium chloride transport to the macula densa to maintain sodium balance can drastically suppress renin release thus allowing high levels of angiotensin II with high sodium intake, making

blood pressure salt sensitive.[207-209] When reabsorption is increased prior to the macula densa, increases in release of renin stimulates renal vasodilation and renal blood flow promoting increased GFR and salt-insensitive hypertension.[208] Although responses from the RAS complex allow for proper balancing of sodium intake and excretion, pressure natriuresis is shifted to higher levels of blood pressure, with severity dependent on the volume of reabsorption occurring prior to the macular densa.[210]

As discussed in section 3.1, the RAS complex is pivotal for maintaining circulating salt-water balance and normal blood pressure. When the RAS complex is functioning properly, sodium balance is maintained over a comprehensive spectrum of sodium intake levels, allowing for maintenance of near normal blood pressure through the vasocontractile properties of angiotensin II.[208] Over-production of renin, or unnecessary activation of RAS produces excess angiotensin II which acts to acutely and chronically increase blood pressure by several distinct pathways. Angiotensin II acts as an effector hormone and is very effective as a vasoconstrictor, eliciting increased peripheral vascular resistance and increased blood pressure.[211-213] In the presence of excess angiotensin II, receptor-dense efferent arterioles constrict as compensation for reduced GFR from renal injury which restores normal GFR at the expense of increasing glomerular hypertension and reducing renal blood flow.[208] Additionally, angiotensin II stimulates the reabsorption of sodium both directly and through increased release of aldosterone which can diminish the effectiveness of pressure natriuresis, requiring increases in blood pressure to maintain sodium balance.[214] Under conditions of high sodium intake, angiotensin II is suppressed, allowing for the appropriate sodium excretions needed to maintain a normal blood pressure. Hypoperfusion of damaged nephrons signals increases in secretion of renin, producing excess angiotensin and aldosterone, which

increases sodium retention, leading to initial hypertension.[215] Hypertension can be then damage the remaining nephrons by causing vasodilation, barotrauma, and glomerulosclerosis promoting additional nephron loss, reduced kidney function and perpetuation of hypertension.

The sympathetic nervous system activity is considerably increased in CKD patients, with suggestions that angiotensin II increases muscle sympathetic nerve activity (MSNA). Of note, MSNA is 2.5 times higher in dialysis patients than equivalent controls.[216] Increases in MSNA is accompanied by undue activation of the RAS complex, and thus contributes to augmented vasoconstriction, sodium retention, and hypertension. MSNA levels are also inversely associated with extracellular fluid volume[217] suggesting that rises sympathetic nervous system activity can decrease extracellular fluid, contributing to the development of hypertension.

3.6 Management of high blood pressure

While much research has been dedicated to identifying risk factors for incident CKD (Section 3.4), less evidence is available to guide or support the implementation of interventions on these risk factors to prevent the development of CKD.[57,72,218] Many observational studies identify elevated blood pressure as a risk factor for development of CKD,[219-222] and support the notion of a benefit from blood pressure reduction on the risk of CKD. Lacking randomization, evidence from observational studies is vulnerable to confounding bias and insufficient to guide interventions that lower blood pressure toward an anticipated benefit on the risk of CKD.[218] Randomized controlled trials addressing the relationship between blood pressure reductions and chronic diseases have mostly concentrated on cardiovascular outcomes, or progression from CKD to kidney failure due to

short follow up times.[218] Systematic reviews of observational and experimental studies have been most influential in the development of guidelines for the clinical management of elevated blood pressure with CKD risk reduction as their focus. Although strategies exist for the prevention of elevated blood pressure on a population level, these have not received a degree of attention consistent with their potential for the reduction of CKD. Instead, the majority of initiatives are focused on the clinical management of elevated blood pressure identified through screening for elevated blood pressure and blood pressure control in known or newly identified hypertensives.[223]

3.6.1 Elevated blood pressure guidelines

Introduction to the JNC

The Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC) provides guidance for clinicians on the detection and management of high blood pressure using periodically updated synopses of the best available scientific evidence. Before the 1960s, risks associated with levels of blood pressure below 210/100 mmHg were not clearly understood and hypertension management was clinically focused primarily on treating individuals with severe and malignant hypertension.[224] In the following decades, the development of safe, effective pharmacological agents and emerging evidence from studies such as the Framingham Heart Study and the Veterans Administration Cooperative Study highlighted the benefits of reducing hypertension, previously classified as benign, for the prevention of heart disease and stroke.[225,226] In 1972, the National Heart, Lung, and Blood Institute (NHLBI) established The National High Blood Pressure Education Program (NHBPEP) designated to increase prevention, awareness, treatment and control of hypertension.[227] To provide guidance on the management of high blood pressure, the

NHBPEP task force 1 committee produced a 1973 report entitled "Data Base For Effective Antihypertensive Therapy" which provided practical recommendations for identifying and treating those with high blood pressure.[228] Over the following 3 years, large gains were achieved in widespread efforts to expand identification high blood pressure to the community venues and new classes of medications were developed and approved treat high blood pressure, necessitating updated, streamlined guidelines.[227] The first JNC report, issued in 1977, addressed the appropriate evaluation of individuals with high blood pressure, provided a stepped-care approach for treatment and recommend monitoring of long-term control of high blood pressure.[227]

Increasing availability of evidence for the management of blood pressure and changing therapy options presents a need for continual summarization and updating of management guidelines. Since the initial JNC report, seven iterations (JNC 2-JNC 8) of blood pressure guidelines have been published by multidisciplinary experts from medicine, nursing, nutrition, pharmacy and public health chosen to contribute to the development of JNC reports. JNC guidelines over time have emphasis various aspects of hypertension management including absolute risks and benefits of treatment strategies, new combinations and dosages of antihypertensive medications and angiotensin II receptor blockers, strategies to improvement adherence to treatment, and control, lifestyle interventions, growing health care costs, and home monitoring of blood pressure.[15,23,227-229] Treatment thresholds have evolved from an emphasis on DBP in all adults to treatment based on SBP and DBP as well as comorbid conditions that increase risk among subsets of the population with high blood pressure. Although JNC guidelines do not supersede clinical judgement, particularly among

patients with multiple risk factors or diseases, succinct user friendly guidelines based on newly published evidence aids clinicians in approaching hypertension management.

2014 Guidelines for the Management of High Blood Pressure from the Eighth Joint National Committee

Newly release guidelines for the management of high blood pressure were developed in 2014 (JNC 8) by a panel of experts charged with reviewing and synthesizing available evidence on blood pressure interventions and CVD or CKD related outcomes.[23] The panel published nine recommendations that address the choice of blood pressure thresholds for initiation of therapy by age group and comorbid conditions, as well as criteria for selecting and managing antihypertensive medications (Figure 8). The 2014 Guidelines for the Management of High Blood Pressure will be used to identify participants with blood pressure above treatment initiation thresholds. Treatment thresholds are: for the general population aged ≥ 60 years, SBP ≥150 mmHg or a DBP ≥ 90 mmHg; for the general population aged <60, SBP ≥140 mmHg or a DBP ≥ 90 mmHg; for those with CKD or diabetes irrespective of age, SBP ≥140 mmHg or a DBP ≥ 90 mmHg.[23]

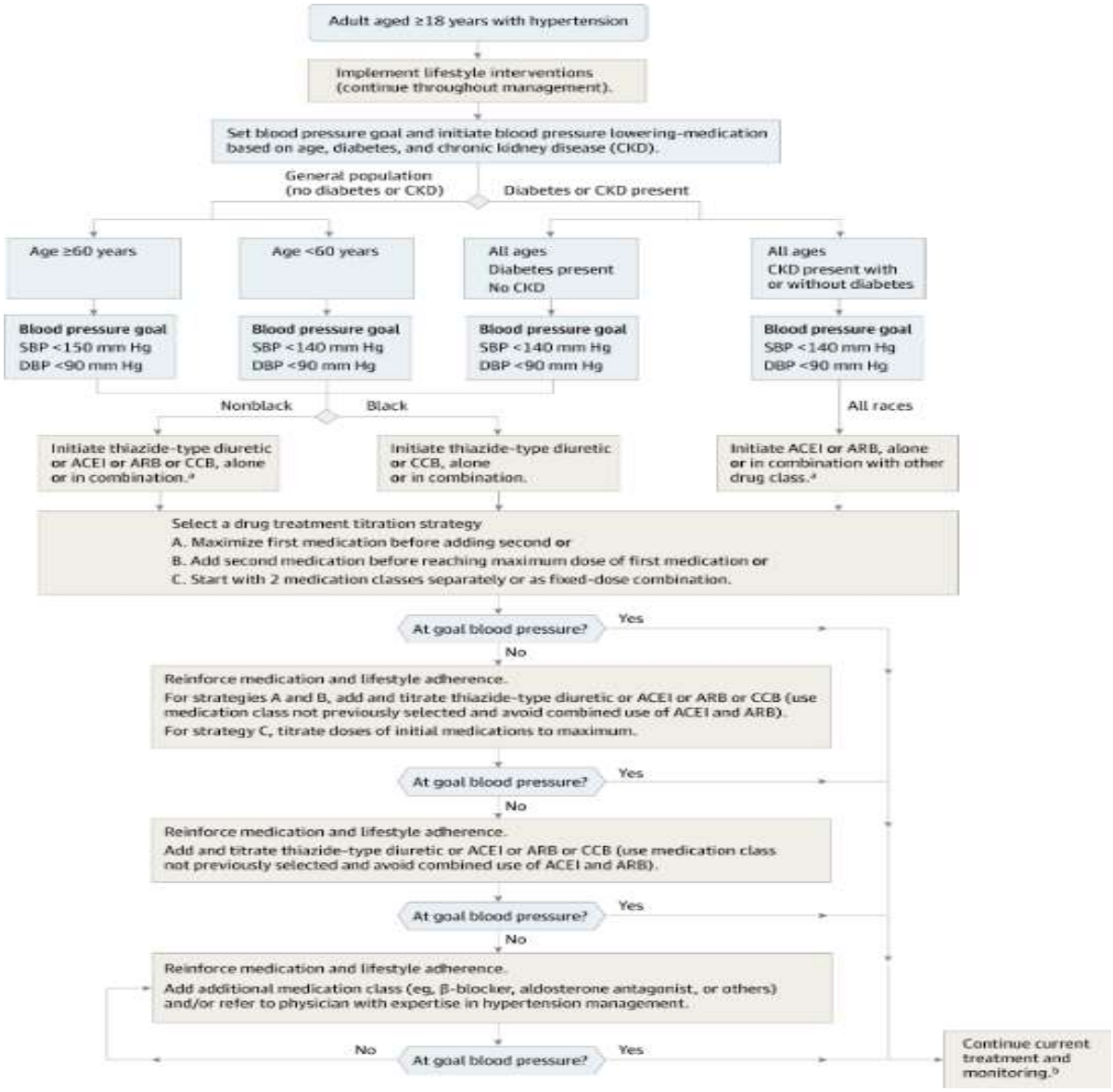


Figure 8. 2014 Guidelines for the Management of High Blood Pressure treatment algorithm for US adults

While evidence-based, the 2014 blood pressure guidelines and their use are subject to several limitations. The panel of experts limited its focus to three narrowly motivated clinical questions regarding the initiation of blood pressure-lowering therapy, the selection of optimal therapeutic agents, and the management of antihypertensive medications. [23] To answer these clinical questions the panel restricted the scope of evidence to results from accessible

randomized controlled trials, constraining the data on heterogeneous participants with diverse characteristic and comorbidities, as commonly encountered in the general population. Due to these limitations, many of the recommendations put forward in the 2014 guidelines are based on moderate, insufficient, or conflicting evidence,[23] leading the panel to make expert opinion recommendations even when the net benefit from blood pressure treatment was unclear. For example, in the absence of definitive benefits or harms from treatment of blood pressure in randomized control trials in those younger than 60 years of age, panel members made recommendations based panel member's judgement and simplified of the guidelines for implementation. [23]

Comparison of JNC 8 with the previous blood pressure guidelines: JNC 7

The 2014 blood pressure guidelines differ from its predecessor (JNC 7) in several ways. While JNC 7 clearly defined hypertension and prehypertension using SBP and DBP categories (Table 4), the 2014 blood pressure guidelines merely identified thresholds for antihypertensive treatment devoid of formal definitions for high blood pressure categorization. Randomized control trials that included individuals with normal blood pressure or prehypertension were also excluded from evidence supporting the 2014 guidelines, leaving a large subset of the population at increased risk of CKD, CVD, and mortality unaddressed by the 2014 blood pressure management strategies.[23] Emphasis on clinical recommendations as opposed to increases in risk of CKD as blood pressure increases also limits the utility of 2014 guidelines for describing risk associated with blood pressure levels below thresholds designated as requiring antihypertensive treatment. Health promoting lifestyle modifications were recommended in JNC 7 for adults with prehypertension;[15] the 2014 guidelines did not assess lifestyle intervention or address SBP or

DBP reductions in those without hypertension but rather expressed support for the 2013 Lifestyle Work Group recommendations.[23]

Table 4. Definitions of blood pressure categories defined by JNC 7

BP Category	SBP (mmHg)		DBP (mmHg)	Lifestyle Modification	Medication Recommendations
Normal	< 120	and	< 80	Encourage	No antihypertensive unless compelling indication
Prehypertension	120-139	or	80 - 89	Yes	
Hypertension, Stage 1	140-159	or	89 - 99	Yes	Yes
Hypertension, Stage 2	≥ 160	or	≥ 100	Yes	Yes

*adapted from JNC 7

Controversially, the 2014 blood pressure guidelines also raised the treatment thresholds for adults 60 years of age or older to SBP >=150 mmHg as opposed to the more proactive SBP threshold of 140 mmHg used to identify hypertension and treatment initiation under JNC 7.[15,230] Although an increased blood pressure threshold for older adults is in agreement with other international policies,[231] critics of the higher threshold note the lack of definitive evidence and the inclusion of underpowered randomized control trials that suggested no additional benefit was associated with reducing blood pressure to <140/90 mmHg compared to ≤150/90 mmHg.[230,232,233] The two main studies cited in the 2014 guidelines report data from the JATOS and VALISH study groups[234,235] in relatively healthy Japanese populations with notable low event rates and power to evaluate varying levels of control on preventing outcomes in older age groups,[233] making generalizability of these results and validity of recommendations based on them debatable.

The 2014 blood pressure guidelines further simplified the management of blood pressure by eliminating tighter control recommendation for individuals with diabetes and

CKD which were largely based on observational studies in JNC 7 (high blood pressure control threshold of 130/90 mmHg).[15] Although the 2014 statement acknowledges a few randomized control trials comparing low to moderate blood pressure control levels among high risk populations, the panel found no high quality trials that met their inclusion criteria of a randomized control trial with an entirely hypertensive population providing sufficient evidence to support recommendation of a lower goal.[23] In addition to being used as treatment thresholds, guidelines often double as performance measures introducing the increased possibility of suboptimal treatment and control under the higher thresholds particularly for those individuals at increased risk of CKD and CVD.[232,233]

Due to the limitations associated with the 2014 high blood pressure guidelines, we will also estimate the benefits of treating eligible individuals at the initiation and control thresholds for antihypertensive medications and lifestyle modifications recommendations by both JNC 7 and the 2014 blood pressure guidelines. Applying both of the most recent US blood pressure guidelines will also us to compare the potential impact of more conservative vs. proactive thresholds for initiation and control of blood pressure on the development and progression of kidney disease.

Controversy over lower blood pressure treatment thresholds

KDIGO

The 2012 Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for the Management of Blood Pressure in Chronic Kidney Disease summarized available evidence based on systematic literature reviews and provided recommendations on treatment approaches and lifestyle modifications that reduce blood pressure among those with CKD.[236] Although these guidelines are focused on defining, managing and predicting CKD progression, KDIGO guidelines recommend that CKD patients with albumin excretion

<30 mg/24 hours with office blood pressure >140/90 mmHg be treated so that blood pressure is consistently maintained at <140/90 mmHg regardless of diabetic status. For CKD patients with albumin excretion >30 mg/24 hours, treating and maintaining a blood pressure of <130/80 is suggested for blood pressure control.[37] These guidelines provide support for the benefits of lower blood pressure thresholds, consistent with those maintained by JNC 7, for slowing progression among individuals with CKD. To our knowledge, guidelines for the management of elevated blood pressure to reduce the risk of incident CKD have not been developed, largely due to the lack of research directed toward prevention of incident CKD.

Emerging evidence

Contributing information additional to that in the two latest published JNC guidelines, the Systolic Blood Pressure Intervention Trial (SPRINT), a large randomized control treatment trial designed to examine the effects of treating blood pressure lower than currently recommended goals on cardiovascular disease, has been stopped due to the significant benefit of reducing blood pressure below goal.[237] The SPRINT trial, initiated in 2009, followed 9,300 men and women in the US and Puerto Rico for 4 to 9 years, to determine whether lowering SBP to <120 among those with high blood pressure aged 50 years or older conferred a lower risk of developing CVD, kidney disease or slow age-related declines in coginition.[238] Participants were randomly assigned to either the standard group, with treatment targets of <140 mmHg, or an intensive treatment group, with treatment targets of <120 mmHg.[239] Treatments modified the dosage or type of blood pressure medications needed to achieve treatment targets in each group with the average participant receiving two and three medications in the standard and intensive groups, respectively.[239]

Results published to date suggest that achieving a SBP of <120 mmHg reduced rates of cardiovascular events, by approximately 1/3 and the risk of death by approximately 1/4, as compared to the standard target of SBP <140 mmHg.[237,239] While acknowledging a small number of renal outcomes, SPRINT found no difference in CKD progression to ESRD or a decrease in eGFR of 50% or more between the two treatment groups.[239] Furthermore, the intensive treatment group experienced incident CKD, or a decrease in the eGFR of ≥30% to a value of < 60 ml per min per 1.73 m^2 more often than the standard group (1.21% per year vs. 0.35% per year).[239] The intensive treatment group was prescribed on average a larger number of blood-pressure medications (2.8 medications for intensive group vs 1.8 in the standard group), with the use of each class of blood pressure medication being greater in the intensive-treatment group compared to the standard group.[239] Although ACE inhibitors are known to have renoprotective effectiveness beyond their effect on reducing blood pressure,[37,189] use of ACE inhibitors is also associated with initial rapid declines in eGFR that stabilize over time, ultimately resulting in less irreversible loss of nephrons and thus slower rates of progression of CKD.[72] ACE inhibitor-induced reduction in GFR resulting from decreases in intraglomerular pressure can occur in one-third to one-half of all individuals with renal stenosis.[240,241] Acute effects of increased medication use and dosage for intensive blood pressure control could potentially complicate the interpretation of incident CKD measures in this study, as estimates of GFR decline and reduced follow up time in the SPRINT trial do not differentiate medication effects from those related to actual decreases in SBP.[241] Examination of follow-up measurements collected in the SPRINT trial in the coming years is necessary to determine the long-term effects of lowering blood pressure thresholds for CKD development

A recent 2015 systematic review and meta-analysis, which included the SPRINT trial, examined the influence of type of antihypertensive medication prescribed, comorbidities, and baseline blood pressure on the relationship between blood pressure reductions and chronic disease outcomes and found a non-significant benefit of 10 mmHg reductions in SBP on kidney failure (risk ratio 0.95, 95% CI: 0.84-1.07).[242] Conversely, a meta-analysis of randomized control trials evaluating treatment targets among those with CKD concluded that a more intensive treatment regime resulted in reductions in kidney failure events.[243] Compared to standard treatment goals, more intensive blood pressure reductions lowered both the risk of the composite outcome defined as 50% decline in glomerular filtration rate with doubling of the serum creatinine level, or ESRD (hazard ratio [HR] 0.82, 95% confidence interval [CI] 0.68–0.98) and ESRD (HR 0.79, 95% CI 0.67–0.93).[243] However, stratified analysis showed intensive blood pressure treatment only benefitted individuals with proteinuria at baseline.[243] The trials reporting on adverse events included in this systematic review found no increased risk among the intensive blood pressure treatment group compared to standard treatment (RR 1.04, 95% CI 0.60–1.78).[243] Given the absence of consensus evidence supporting the benefits of lower therapeutic blood pressure control targets to yield greater reductions in CKD and kidney failure events, we will only investigate the potential benefit of treating participants to the JNC 7 and JNC 8 treatment thresholds as opposed to investigating the benefits of reducing blood pressure to lower blood pressure thresholds.

3.6.2 Awareness, treatment and control

The publishing and implementation of NHBPEP's blood pressure guidelines have made notable improvements in the public awareness, clinical treatment and control of high

blood pressure. National Health Examination Survey I (NHES I, 1960-1962) and NHANES surveys I (1971-1974) and II (1976-1980), collected before and after the mass media and physician education campaigns for improvements in detection, treatment, and follow up of high blood pressure, showed reductions in mean SBP, age-adjusted proportion of those with SBP ≥ 140 mmHg, and proportion of those with undiagnosed or untreated high blood pressure.[244] Awareness of high blood pressure among Americans has increased from approximately 50% in 1976-1980, to 81% in 2007-2008.[244,245] As appropriate identification of those with high blood pressure is a necessary first step in improved treatment and control, gains in high blood pressure awareness were paralleled with substantial improvements in treatment and control. Over the same time period from NHANES II to 2007-2008, treatment of high blood pressure improved from 31% to 73% while control of high blood pressure improved from 10% to 50%.[15,245] Over several decades, the NHBPEP committee's prioritization of high blood pressure extended these benefits to reductions in age-adjusted death rates for CVD, however, improvements are still needed particularly for high blood pressure control among those with CKD and kidney failure, emphasizing the need for primary prevention of CKD.

Awareness, treatment and control among those with CKD or kidney failure

Awareness

Among individuals with CKD, NHANES 2007-2012 estimated that 22.5% of those with high blood pressure are unaware of the condition, corresponding to a 24% decline in lack of awareness of high blood pressure compared to NHANES 1999-2004.[98] In studies where CKD awareness is relatively high, high blood pressure awareness levels are, correspondingly, much higher with estimates of awareness at 86-99% of those with high

blood pressure.[246,247] Given that detection of high blood pressure is a prerequisite for appropriate treatment and control, CKD guidelines recommend measuring blood pressure at each clinic visit.[67] Recent studies of high blood pressure awareness found that lack of awareness of high blood pressure was most prevalent among individuals who did not have a usual source of health care, or had not had a health care visit within the past year.[248] Appropriate frequent health care visits, blood pressure screening events, community based awareness programs and self-monitoring of blood pressure continue to be desirable options to increase blood pressure awareness in the CKD population.[248]

Treatment

In addition to the 22.5% unaware of their high blood pressure and thus not treated, NHANES (2007-2012) estimates that among those with CKD 6.5% of individuals with high blood pressure are aware but not treated, leaving opportunity to initiate treatment based on guideline recommendations.[132] Experimental evidence supports the benefits of treating high blood pressure among CKD and ESRD patients, with intensive blood pressure reductions providing greater protection against kidney failure events compared to standard regimens.[243] Consistent with recommendations from the American Society of Nephrology and the National Kidney Foundation, JNC 7 and 8 both recommend antihypertensive therapy for CKD patients that consists of an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin II receptor blocker (ARB) to slow CKD progression, reduce proteinuria and CVD risk.[15,23] K/DOQI's guideline 7 additionally recommends prescribing diuretics in most patients with CKD and additional medications based on an individual's CVD history or risk.[67] Despite these recommendations, valuable opportunities to treat those with elevated blood pressure, particularly among the CKD population are missed; treatment interventions

targeted to untreated populations with elevated blood pressure have the potential to reduce CKD and kidney failure events.

Control

Poor control of blood pressure is a major risk factor that accelerates CKD progression, prompting recommendations for lower blood pressure treatment thresholds and rigorous control efforts among those with CKD.[15,23,249] NHANES (2007-2012) data indicates that 43.9% of the CKD population with high blood pressure is aware and treated but not controlled to goal, while trial data suggests that elevated blood pressure remained uncontrolled in 34% of participants in spite of an average of two medications being used per participant.[85,250] Women, older adults, the obese, and those with albuminuria have higher levels of uncontrolled blood pressure and present potential targets for improved blood pressure control in the CKD population.[251] Adequate control on monotherapy is low, with uncontrolled blood pressure generally observe to decrease with increasing number of medications used to treat blood pressure.[251] In addition to increasing the number of medications used to treat elevated blood pressure, restriction of dietary sodium, use of diuretics, and night-time dosing of medications have been evaluated as complementary strategies for achieving blood pressure control among those with CKD.[251]

3.6.3 Blood pressure as a continuously distributed trait

Complementary to treatment guidelines are public health policies that account for the continuous distribution of blood pressure and the monotonic relationship of blood pressure with the risk of adverse health events. Based on these well-documented features of blood pressure,[252-254] such policies promote blood pressure reductions in the general population, not limited to thresholds that define “hypertension” or set goals for pharmacologic treatment

categorization. Approximately one third of all-cause mortality can be attributed to elevated SBP at levels designated as non-hypertensive,[255,256] indicating a need to address blood pressure management among the larger population at risk.[257-261] Although most adults in industrialized societies eventually develop elevated blood pressure, reducing population levels of blood pressure has the potential to reduce or delay elevations in blood pressure over the life course, and reduce the risk of blood pressure-related CKD. In new hypertension cases occurring in the United States 32%, 32% and 17% can be attributed to excess sodium intake, being overweight, and lack of regular exercise respectively.[262] Building on numerous observational studies, experimental studies have demonstrated the efficacy of lifestyle-based blood pressure interventions, such as increased physical activity and the Dietary Approaches to Stop Hypertension (DASH) diet, with beneficial effects for blood pressure reduction and disease prevention.[13,14,263-265] This body of evidence supports recommendations from JNC 7 and KDIGO that call for lifestyle modifications for blood pressure reduction in those with and without high blood pressure and the consideration of population-wide interventions to reduce blood pressure alongside interventions targeted to populations with high blood pressure for kidney disease reduction.[23,67]

3.6.4 Lifestyle modifications for blood pressure and CKD reduction

Modifying lifestyle factors that contribute to the development and maintenance of elevated blood pressure offers effective ways to impact a large number of individuals and range of health outcomes. The 2012 KDIGO guidelines summarize the available evidence and provide recommendations on treatment approaches and lifestyle modifications that reduce blood pressure among those with CKD.[236] Most of the evidence in the literature documenting the effect of lifestyle changes on blood pressure was conducted in the general

population, although individuals with CKD often have many of the comorbid conditions, such as CVD, diabetes, obesity and dyslipidemia present in the larger population.[188] Early trials examining the relationship between blood pressure reductions and chronic disease often methodically excluded individuals with CKD or were not equipped to meticulously measure renal outcomes, and, subsequently, few trials addressed renal endpoints.[218] With a lack of abundant, large scale randomized control trials that quantify the effect of lifestyle modification on CKD reductions, KDIGO guidelines recommendations are largely generalized from many of the well-documented dietary modifications, weight management, and physical activity interventions suggested universally or quantified for cardiovascular outcomes.[37,236] Lifestyle interventions considered here will be suitable for the general US population and those with CKD since the ARIC cohort includes both.

Elevated blood pressure is generally higher among individuals with CKD and certain modifications such as salt restriction could have greater blood pressure reducing effects in those with CKD. A population-level intervention to reduce sodium intake is likely to change blood pressure in individuals by modest magnitudes that trials may not be powered to detect. Trials reflecting significantly reduce rates of incident CKD which takes decades to develop are improbable given the size and length of follow-up for many trials.[266] Although experimental evidence from large trials with adequate follow up for salt reduction among CKD patients is limited, the processes involved in salt and water retention's effect on blood pressure levels in CKD when sodium balance is impaired could result in larger reduction on blood pressure from salt restriction than are seen in the general population.[27] A meta-analysis of experimental studies examining sodium reductions of blood pressure found a dose response relationship between decreased urinary sodium and blood pressure; although the

magnitude of blood pressure decline varied among at risk groups such as older adults, a median decline in urinary sodium of approximately 1800 mg/d or approximately ¾ of a teaspoon of salt dropped SBP/DBP by 2.0/1.0 mmHg in those without elevated blood pressure and by 5.0/2.7 mmHg in those with elevated blood pressure.[267] Trials of uncontrolled elevated blood pressure suggest reducing sodium intake by 4600 mg/d or approximately 2.25 of a teaspoon of salt has the potential to lower SBP/DBP by 22.7/9.1 mmHg.[37] Considering the current body of evidence, KDIGO guidelines recommend lowering daily sodium intake to <2 g for reducing blood pressure among those with CKD.[37]

Observational and experiments studies have documented the benefit of weight reduction on blood pressure control in the general population with limited evidence among those with CKD.[236,268,269] Trials examining the effect of diets rich in fruit and vegetables have shown reductions in weight coupled with 6.0 and 4.8 mmHg reductions in SBP and DBP, respectively, in the general population.[37] A few trials conducted in CKD populations that examined blood pressure reductions following both surgical (22.6 mmHg) and non-surgical (9.0 mmHg) weight reduction strategies, demonstrate the efficacy of achieving or maintaining a healthy weight on improving blood pressure among those with CKD. This evidence provides a strong basis for recommending weight loss among those without ideal weight levels; the mechanisms by which weight reductions are achieved must be carefully selected as many popular and commonly endorsed weight loss diets are frequently high in potassium and protein and could consequently increase risks of hyperkalemia and CKD progression, particularly after stages 1 and 2.[37,236] Overall, current evidence advocates for achieving or maintaining a healthy body weight for favorable reductions in blood pressure and CKD progression.[37]

Independent of its effect on weight reduction, physical activity has also been shown to provide beneficial effects on multitude of health conditions including CKD and ESRD.[270] Physical activity positively effects vascular structure and adaptations, endothelial function, the sympathetic nervous system and RAS, all of which contribute to elevated blood pressure and CKD.[271] A strong inverse association between physical activity and blood pressure from randomized control trials has been summarized as indicating that three to five weekly sessions of 30-60 minutes of aerobic exercise resulted in SBP reductions of 6.1 mmHg and 3.0 mmHg reductions in DBP.[37]

Recommendations from the 2013 Report of Lifestyle Management to Reduce Cardiovascular Risk

In 2008, the NHLBI partnered with the American College of Cardiology (ACC) and the American Heart Association (AHA) to form expert panels charged with summarizing the scientific literature on five topics, two of which addressed lifestyle modifications and blood pressure.[272] The working group considered results from randomized control trials, observational studies, meta-analyses, and systematic reviews on risk factors, and their respective interventions to produce the 2013 Report of Lifestyle Management to Reduce Cardiovascular Risk.[272] Although the working group concentrated on studies of CVD risk factors and outcomes, reductions in blood pressure are assumed to apply to CKD and kidney failure in a similar manner.

Table 5. Range of blood pressure reductions achievable through lifestyle interventions

Lifestyle Intervention	Population	Evidence type	Blood Pressure Reduction (SBP/DBP)
Dietary Sodium Reduction			
Reducing sodium intake that achieved a mean 24-hour urinary sodium excretion of ~2,400 mg/day, relative to ~ 3,300 mg/day[272]	Adults aged 25–75 years	RCT	2/1 mmHg
Reducing sodium intake that achieved a mean 24-hour urinary sodium excretion of ~1,500 mg/day, relative to ~ 3,300 mg/day[272]	Adults aged 25–75 years	RCT	7/3 mmHg
Counseling to reduce sodium intake by an average of 1,150 mg per day[272]	Adults aged 30–80 years	RCT	3–4/1–2 mmHg
Physical Activity			
Aerobic physical activity –average of 12 weeks duration with 3 to 4 sessions per week, lasting on average 40 minutes per session, involving moderate-to-vigorous intensity physical activity[272]	Age ≥18 years	Meta-analysis of RCTs	2–5/1–4 mmHg
Adiposity Reduction			
5% weight loss in overweight or obese adults[273]		Meta-analyses and Look AHEAD study	3/2 mmHg
Dietary interventions for weight loss over 6 to 36 months, average loss of 11-13 lbs[273]	Hypertensive adults	RCT	6/3 mmHg

Lifestyle interventions targeted to individuals with hypertension

In addition to guiding pharmacologic treatment, the 2014 blood pressure guidelines endorse the recommendations of the 2013 Lifestyle Work Group on nonpharmacological lifestyle interventions for reducing blood pressure among those at highest risk.[23] Among these recommendations (Sodium and Physical Activity, Table 5) healthcare providers are charged with counseling and providing educational materials detailing strategies to lower sodium intake to patients with hypertension.[23] This recommendation was supported by finding from The Trial of Non-pharmacologic Interventions in the Elderly (TONE) study that

showed 4 and 2 mmHg reductions in systolic/diastolic blood pressure following a mean reduction in sodium intake of 1,035 mg per day achieved through personalized registered dietitian sessions, and weekly or biweekly small group meetings.[272] Beyond counseling by health practitioners, physical activity rehabilitation centers, and clinical weights management program are also often targeted at the individual level for those with hypertension for the reduction of blood pressure and increased cardiovascular health.[274]

Population lifestyle interventions

Unlike interventions targeting individuals with hypertension that can be adequately tailored to an individual's characteristics and needs, the population-based approach largely places emphasis on promoting health activities or policies that impact the larger environment. For example, a campaign targeting the gradual reduction of sodium content in processed foods and consumer awareness of sodium intake in the United Kingdom achieved an average estimated reduction in blood pressure of 2.7/1.1 mmHg in individuals with untreated blood pressure from 2003-2011.[265] Population level reductions in adiposity and increases in physical activity could also be achieved through guidelines that limit screen time and marketing of unhealthy foods to children and adolescents,[275,276] improved access to recreation facilities and sports,[277-279] worksite or school based nutrition and physical activity programming,[117,280-282] national physical education curriculum,[283] and walkable, bike-friendly built environments.[284,285]

Eligibility and Safety Considerations

Given that all recommended lifestyle interventions (Table 5) may not apply universally or to the entire population, for purposes of this work we assume that simultaneous implementation of policies targeting a variety of lifestyle behaviors would

meaningfully address blood pressure reduction in all eligible individuals of the groups reached by such policies. For example, weight loss for blood pressure reduction is an impractical and unsafe goal for individuals who are underweight or pregnant, who therefore may be excluded from, or not engage in population level efforts to reduce adiposity, while reduction of sodium in the food supply could still favorably influence blood pressure levels in such individuals. The focus of this doctoral research is on the estimation of the potential impact on blood pressure reduction in the population, irrespective of the specific structural intervention or policy avenue used to influence the exposure.

Two vulnerable groups are commonly considered for safety concerns when considering population-wide blood pressure reductions: those with low blood pressure and the elderly. Risk to these groups can be diminished by proper formulation of population-wide blood pressure reduction strategies. Reductions in sodium, for example, have been shown to have heterogeneous effects on systolic and diastolic blood pressure based on individual characteristics such as salt sensitivity or blood pressure level. Individuals with lower blood pressure experience smaller reductions in blood pressure compared to those with elevated blood pressure for an equivalent reduction in sodium intake.[286,287] Recent findings also suggest that a small minority of the world population consumes low daily intakes of sodium, and that sodium intake at low levels is not related to blood pressure.[288,289] Collectively, these observations suggest minimal harm in utilizing sodium reduction as means to decrease blood pressure in the population.

Several large scale sodium or blood pressure reduction trials have included older adults and found no, or limited increased risk of adverse events among elderly persons. The TONE study demonstrated that lifestyle modification of sodium intake is effective in

lowering the blood pressure in the elderly with occurrence of adverse events such as dizziness or physical injury similar to the control group with usual lifesytle.[290] Results from the SPRINT trial also demonstrated that pharmacologic lowering of systolic blood pressure to below 120 mmHg resulted in similar incidences and patterns of hypotension, injurious falls, and bradycardia in participants 75 years of age or older compared to the overall cohort.[291]

Nonetheless, safety concerns must be considered when recommending population-wide blood pressure reductions by means of lifestyle modifications including sodium reductions. As discussed in section 3.6, 2014 blood pressure guidelines increased the threshold for blood pressure treatment among older adults age 60 or greater motivated by insufficient randomized control trial evidence supporting the benefit of lower thresholds in older populations. Despite controversy surrounding these guidelines and recent evidence supporting lower thresholds, clinicians in practice routinely consider attributes of individual patients in recommending lower blood pressure levels.[232] For example, among frail older adults or those with osteoporosis, postural or orthostatic hypotension can increase vulnerability to fractures and other injurious falls particularly among those with poor blood pressure control.[292] Gradual initiation and changes to blood pressure medications as well as modifications to sodium and fluid intake may be necessary to avoid adverse events in this population.[293] Although dietary sodium reduction is an effective method of treatment and prevention of high blood pressure, gustatory and olfactory dysfunction in later life can result in appetite declines necessitating the addition of flavor enhancements, such as sodium, to support diet and weight loss management.[294]

Evidence against population-wide sodium reduction programs

Our analysis is independent of the means used to reduce blood pressure by the designated decrements outlined in our aims (Chapter 2). We note however that sodium reduction is the most widely discussed population wide public health approach to blood pressure reduction.[266,267,295-297] As discussed in section 3.5.2, excess dietary intake of salt is a prominent contributor to the pathogenesis of elevation in blood pressure.[267] Animal, longitudinal, clinical and meta-analytic studies collectively provide strong evidence of a relationship between high sodium intake and elevated blood pressure and indicate that on average, blood pressure increases as salt intake increase.[295] Multiple well designed meta-analyses have provided solid evidence of a reduction in CVD events following dietary sodium restriction and have supported the long-term impact of sodium reduction on improved blood pressure measurements.

Nonetheless, some studies suggest a U or a J shaped relationship between sodium intake and outcomes signifying a higher risk of disease at lower sodium levels.[266,298] The Prospective Urban Rural Epidemiology (PURE) study is the largest (n=156,424) and likely most publicized of these studies. The PURE study estimated sodium intake by urinary excretion and found that sodium intakes (<3,000 mg per day) notably higher than the recommended maximum intake of sodium per day (<2300) were associated with increased risk of CVD and mortality.[298] While provocative, PURE study finding as well as corresponding contradictory studies of sodium reduction and disease risk are often biased by methodological weaknesses. Many of these observational studies were conducted in populations with conditions such as CVD that are recognized to influence dietary modifications following disease occurrence.[266] Estimating the relationship between low

sodium intake and outcomes in this population is thus likely to reflect an increased risk of adverse outcomes due to extant illnesses and low sodium intake in response to disease, rather than usual low sodium intake and subsequent disease.[266] This potential for reverse causation is likely reflected in the PURE study findings as those who were older, diabetic, or had prior CVD were more likely to have lower sodium intake than the other study participants.[298] Obtaining high quality 24-hour urine samples for urinary sodium excretion is often expensive and cumbersome for participants, leading many studies to rely on spot urine samples. Spot urine samples are unreliable for estimation of usual salt intake due to variation in dietary sodium intake over multiple days, and variability of spot measurements within the same subject and dietary intake level.[299] Measurements of factors such as physical activity and diet quality that impact health outcomes are often limited or missing in studies that relate sodium intake to health outcomes, allowing for residual confounding.[266] Despite these scientific limitations studies suggesting harm at low levels of sodium have garnered much public attention. The physiological basis for a minimal sodium intake suggests that less than <1000 mg of sodium (or a half of a teaspoon of salt) is needed to support normal biologic requirements.[266] Global estimates suggest that in 2010 alone, 1.65 million deaths from cardiovascular causes were attributable to sodium intakes in excess of 2000 mg per day.[288]

The breadth and quality of evidence suggesting benefits for most adults from reduced sodium intake on blood pressure and CVD has been sufficiently compelling for international and national health organizations to recommend population-wide sodium reductions.[267,295] Following an exhaustive and comprehensive review of the clinical interventions and observational studies of sodium consumption the World Health Organization (2012) recommended reductions in sodium consumption irrespective of the current level of intake

for the reduction of blood pressure and CVD.[300] The 2015–2020 Dietary Guidelines for Americans recommend < 2,300 mg of sodium per day, 1,940 and 680 mg less than the current average sodium intake for American men and women respectively.[301]

3.6.5 Relationship between blood pressure and incident CKD from risk prediction equations

Many individuals with CKD are not identified until complications lead to signs or symptoms that are often life-threatening if they present in late stages of CKD or kidney failure.[27] Risk prediction models have been developed to aid in the early identification of individuals at increased risk for developing CKD, based on risk factors identified in epidemiologic studies. Among the latter, those commonly used in clinical practice have been favored.[302] In addition to providing information on high-risk individuals who would potentially benefit the most from intervention on risk factors, risk prediction equations provide estimates of the magnitude of the relationship between specific risk factors and incident CKD in diverse population settings. Estimates of the odds of developing CKD given the presence of hypertension and other covariates included in the model (Table 6) can be obtained from such models. For elevated blood pressure identified as hypertension, β-coefficient estimates ranged from 0.45 to 0.85, corresponding to odds ratios of 1.6 to 2.3, contingent on the study population and the covariates considered. Since our aims examine the effect of blood pressure decreases on CKD in a single population-based cohort, reference to the association between hypertension and incident CKD over diverse populations will provide an external benchmark for this association estimated in our study population (Table 6).

Table 6. Summary of risk models for predicting incident chronic kidney disease

Study, Year	Study Design	Population	Endpoint	Main Findings - Adjustment factors, β coefficients, or Odds Ratios (ORs)	
O'Seaghdha,[303] 2011	Framingham Logistic External Validation in ARIC	1171 men 1319 women 229 (9%) with CKD	<60 mL/min/1.73m2	MDRD OR Age, per year 1.09(1.07-1.12) Diabetes 1.73 (1.08-2.77) Hypertension 2.10(1.51-2.94) Baseline eGFR 60-74 3.73 (2.36-5.90) 75-89 1.66 (1.05-2.62) Albuminuria 1.62 (1.04-2.53)	CKD-EPI OR Age, per year 1.10 (1.08-1.13) Diabetes 1.61 (1.02-2.56) Hypertension 2.14(1.56-2.92) Baseline eGFR 60-74 4.75 (3.10-7.28) 75-89 1.66 (1.45-3.29) Albuminuria 1.35 (0.86-2.11)
Bang,[304] 2007	NHANES Logistic	8530 Final dataset 5666	<60 mL/min/1.73m2	Age β-coefficient (SE) 50-59 1.55 (0.27) 60-69 2. 31 (0.30) >=70 3.23 (0.27) Female 0.29 (0.13) Anemia 0.93 (0.32) Hypertension 0.45 (0.21) Diabetes 0 .44 (0.20) CVD history 0.59 (0.18) CHF history 0.45 (0.22) PVD 0.74 (0.28) Proteinuria 0.83 (0.15)	Age OR 95% CI 50-59 4.7 (2.8-8.1) 60-69 10.0 (5.6-18.1) >=70 25.2 (14.8-43.0) Female 1.3 (1.04-1.7) Anemia 2.5 (1.4-4.7) Hypertension 1.6 (1.05-2.4) Diabetes 1.6 (1.05-2.3) CVD history 1.8 (1.3-2.6) CHF history 1.6 (1.02-2.4) PVD 2.1 (1.2-3.6) Proteinuria 2.3 (1.7-3.1)
Bang,[304] 2007	External validation in ARIC Logistic	12,038 Age 45-64	<60 mL/min/1.73m2	Age β-coefficient 50-59 0.30 60-69 0.86 >=70 NA Female 0.26 Anemia 1.62 Hypertension 0.85 Diabetes 0.52 CVD history 0.52 CHF history 0.58 PVD 0.65	Age OR 95% CI 50-59 1.3 (0.99-1.83) 60-69 2.4 (1.7-3.2) >=70 NA Female 1.3 (1.03-1.6) Anemia 5.1 (3.5-7.4) Hypertension 2.3 (1.9-3.0) Diabetes 1.7 (1.3-2.1) CVD history 1.7 (1.3-2.2) CHF history 1.8 (0.9-3.6) PVD 1.9 (1.4-2.7)
Kshirsagar,[305] 2008	CHS/ARIC Logistic	1,605/9,470 development data set Age 45-64	<60 mL/min/1.73m2	Age β-coefficient 50-59 0.63 (0.12) 60-69 1.33 (0.12) >70 1.46 (0.14) Female 0.12 (0.07) Anemia 0.48 (0.20) Hypertension 0.55 (0.07) Diabetes 0.33 (0.10) CVD history 0.26 (0.10)	Age OR 95% CI 50-59 1.9 (1.5-2.4) 60-69 3.8 (3.0-4.8) >=70 4.3 (3.3-5.6) Female 1.1 (1.0-1.3) Anemia 1.6 (1.1-2.4) Hypertension 1.7 (1.5-2.0) Diabetes 1.4 (1.2-1.7) CVD history 1.3 (1.1-1.6)

				CHF history 0.50 (0.25) PVD 0.41 (0.13)	CHF history 1.6 (1.0-2.7) PVD 1.5 (1.2-1.9)
Thakkinstian[306], 2011	Thailand Cross-sectional survey Logistic regresison	18 or older 3,459 subjects from CKD prevalence study Community based	CKD was defined as stages I-4	Age β-coefficient 40-59 0.6 (0.13) 60-69 1.4 (0.17) >70 2.1 (0.22) Hypertension 0.8 (0.13) Diabetes 0.9 (0.19) Kidney stone 1.0 (0.15)	Age OR 95% CI 40-59 1.8 (1.3-2.5) 60-69 4.1 (2.6-6.3) >70 8.3 (4.7-14.4) Hypertension 2.3 (1.6-3.2) Diabetes 2.5 (1.5-4.1) Kidney stone 2.8 (1.9-4.1)
Kwon,[307] 2012	K-NHANES Logistic Korean Genomic Epidemiologic study (KoGES) external validation	6565 participant age >19	<60 mL/min/1.73m2 MDRD equation	Age β-coefficient 50-59 1.16 (0.15) 60-69 1.91 (0.21) >70 2.71 (0.25) Female 0.40 (0.31) Anemia 0.94 (0.18) Hypertension 0.48 (0.14) Diabetes 0.73 (0.14) CVD history 0.60 (0.20) Proteinuria 0.48 (0.20)	Age OR 95% CI 50-59 3.19 (1.98-5.13) 60-69 6.75 (4.12-11.06) >70 15.02 (9.18-24.58) Female 1.49 (1.14-1.95) Anemia 2.57 (1.80-3.66) Hypertension 1.62 (1.10-2.40) Diabetes 2.08 (1.57-2.75) CVD history 1.83 (1.23-2.71) Proteinuria 1.62 (1.10-2.40)
Halbesma,[308] 2011	PREVEND study, median follow-up of 6.4 years Logistic	40,856	Top 20% in renal function decline and had an eGFR value <60 ml/min per 1.73 m^2	β-coefficient Baseline eGFR 0.37 Baseline $eGFR^2$ -0.003 Age (years) 0.02 Urinary albumin Excretion 0.23 CRP 0.19 SBP 0.009 Hypertension 0.44	OR 95% CI Baseline eGFR 1.45 (1.22-1.74) Baseline $eGFR^2$ 0.997 (0.996-0.998) Age (years) 1.02 (1.01-1.04) Urinary albumin Excretion 1.27 (1.11-1.48) CRP 1.21 (1.07-1.38) SBP 1.01 (1.01-1.02) Hypertension 1.56 (1.12-2.20)
Alssema,[309] 2012	Data merged from 3 different studies in the Netherlands Rotterdam Study, Hoorn, and PREVEND Logistic	Rotterdam Study 4,018 Hoorn 627 PREVEND 2,135	eGFR value <60 ml/min per 1.73 m^2 Equation developed as one assessment tool for CVD, diabetes, and CKD	Males B Coefficient OR 95% CI Age <45 ref Ref 45-49 0.91 2.5 (1.2-5.0) 50-54 1.20 3.3 (1.7-6.4) 55-59 1.57 4.8 (2.7-8.7) 60-64 2.34 10.4 (5.8-18.6) 65-69 2.66 14.3 (7.9-25.7) 70-74 3.26 25.9 (14.2-47.5) 75-85 4.29 72.8 (37.6-140.9) BMI <25 ref 25-29 0.32 1.4 (1.1-1.7) 30+ 0.87 2.4 (1.6-3.6)	Females B OR 95% CI Age Coefficient <45 ref Ref 45-49 0.69 2.0 (1.0-4.1) 50-54 1.08 2.9 (1.6-5.5) 55-59 1.54 4.7 (2.6-8.2) 60-64 1.98 7.2 (4.1-12.7) 65-69 2.55 12.8 (7.3-22.5) 70-74 3.34 28.1 (15.8-50.1) 75-85 4.06 58.2 (31.9-106.1) BMI <25 ref 25-29 0.27 1.3 (1.1-1.6) 30+ 0.52 1.7 (1.3-2.2)

				Waist (cm)				Waist (cm)	
				<94	ref			<80	ref
				94-102	0.20	1.2 (1.0-1.5)		80-87.9	0.12	1.2 (0.9-1.4)
				102+	0.19	1.2 (0.9-1.6)		88+	0.40	1.5 (1.2-1.9)
				Antihyp	0.74	2.1 (1.6-2.7)		Antihyp	0.75	2.1 (1.8-2.6)
				Smoke	0.63	1.9 (1.5-2.3)		Smoke	0.61	1.8 (1.5-2.2)
				Fam Hist				Fam Hist		
				CVD	0.09	1.1 (0.9-1.4)		CVD	0.26	1.3 (1.1-1.5)
				Fam Hist				Fam Hist		
				Diab	0.30	1.3 (1.1-1.7)		Diab	0.21	1.2 (1.0-1.5)

3.7 Public Health Significance

CKD and kidney failure affect nearly 15% of the American population with treatment for these diseases disproportionately consuming nearly 25% of the Medicare budget.[310] CKD is often asymptomatic in early stages, however as the disease progresses to kidney failure, prevalence and intensity of complications increase, as well as the diseases' contribution to premature death and disability.[85] Healthy people 2020 goals aimed for a 10% reduction in the proportion of the US population with CKD and a 10% reduction in incident ESRD cases, goals that focus research on prevention of CKD and kidney failure.[311] While environmental factors and lifestyle behaviors have a substantial influence on the development and progression of CKD and its risk factors,[69,151,155,176,312] emphasis is often placed on the clinical management of these conditions.[23,188] Preventable lifestyle modifications that are expected to have a positive impact on the disease incidence and progression across race/ethnic groups if implemented population-wide or reinforced among high risk group are often undervalued or overlooked.[272,273,313,314] A better understanding of the potential benefits associated with modification of risk factors for CKD and kidney failure at the population level as well as among high-risk groups is needed to reduce the burden of disease and disability attributable to CKD and kidney failure.

Elevated blood pressure is considered a major preventable risk factor for CKD and kidney failure with well-defined methods for its management, presenting an opportunity to intervene on the development and progression of CKD. Approximately 37% and 19% of kidney failure cases in African Americans and white Americans respectively are attributed to high blood pressure;[9] even blood pressure levels considered "high-normal" (defined as systolic blood pressure between 130 and 139 mmHg or diastolic 85 to 89 mmHg) are

associated with a 3-fold greater risk of development of kidney failure.[10,11] While lifestyle modifications and pharmacological therapies are established as effective methods to manage high blood pressure[12-20] and can prevent or slow the progression of CKD and kidney failure, the predicted population impact of various blood pressure reduction modalities on CKD and kidney failure have not, to our knowledge, been quantified.

Interventions aimed at individuals with clinically defined elevated blood pressure allow for intensive interventions capable of achieving large reductions in blood pressure among those at highest risk, consequently reducing CKD and kidney failure incidence and disability in the non-negligible segment of the population affected by elevate blood pressure. Small reductions in blood pressure across the population would result in modest reductions in individual blood pressure levels, but when applied to the population as a whole, the impact on the overall burden of CKD and kidney failure is potentially pronounced. Given the graded relationship between blood pressure and disease risk, and given the large proportion of CKD and kidney failure events in the population that occur among those not identified, treated or controlled as hypertensives, a population-based strategy is posited to achieve the largest benefit in reducing the overall burden of blood-pressure related outcomes.[259,260] While elevated blood pressure is generally managed clinically population-wide strategies are seen as complementary to the practitioner-based high-risk approaches, and are consistent with the lifestyle interventions recommended by clinical practitioners to their patients with high blood pressure, per the established clinical practice guidelines. Comparisons of the impact of population and individual level blood pressure reduction strategies are needed to enrich the discussion of efficient avenues to reduce incidence and progression of CKD and kidney failure.

Clinical significance

Evidence from the SPRINT trial demonstrated the value of controlling blood pressure to or below the level recommend by treatment guidelines suggesting that proper management of patient with elevated blood pressure could improve the suboptimal levels of blood pressure control currently documented in the US population. As CKD progresses so does the inability to control blood pressure adequately, accentuating the importance of blood control prior to the development of CKD. In the general population only approximately half of the population with elevated blood pressure is controlled to the recommended goals, leaving much room for improvement in the management strategy used to counsel, prescribe, dose and monitor the regimen used to achieve blood pressure targets. Providing estimates of CKD and kidney failure events potentially preventable through improved clinical management of patients with elevated blood pressure could motivate a review of current management practices and improvements upon these practices could be used to aid primary prevention of CKD and kidney failure.

Contrasting population-wide interventions with high-risk approaches is inherently dependent on the thresholds used to define the high-risk populations, and thus the size of the population targeted for intensive reductions. Evaluation of blood pressure thresholds for defining and treating the high-risk group is particularly timely given the growing concern over the evidence used in the 2014 guidelines to support higher blood pressure thresholds for individuals ≥ 60 years of age (discussed in section 3.6). Here, we plan to assess potential events prevented by hypothetical interventions on those with blood pressure above treatment goals who are unaware, untreated, or uncontrolled according to both JNC 7 and the 2014 guidelines.[315] Estimating the predicted reductions in CKD and kidney failure achieved under

each set of guidelines will identify the potential benefit of treating those age greater than 60 more intensively to the previous threshold of 140/90 mmHg (JNC 7) compared to the currently recommended 150/90 mmHg (JNC 8).

CHAPTER 4: RESEARCH PLAN

The proposed research will use data from the Atherosclerosis Risk in Communities (ARIC) Study, a longitudinal multi-center prospective cohort study designed to investigate the etiology and progression of CVD in 4 US communities. In additional to CVD, ARIC ancillary studies have been funded to examine a wide range of other pertinent health conditions including CKD and ESRD. Our analysis will use demographic, risk factor, medical and vital record, and validated outcome data from the main ARIC study and an ancillary study to investigate the effect of blood pressure reduction on kidney disease.

Leveraging approximately 25 years of follow up, this dissertation proposal aims to: 1) estimate the effect on the population burden CKD of interventions that reduce blood pressure by contrasting life-style based population-wide interventions with interventions that implement current clinical guidelines for blood pressure treatment and 2) Characterize the potential benefits from interventions that reduce blood pressure on disability attributed to CKD, quantified as DALYS, by contrasting life-style based population-wide interventions with interventions that implement current clinical guidelines for blood pressure treatment. Specific aims one and two will be addressed using a weighted least regression approach that allows for estimation of the number of events that can prevented by a blood pressure reducing intervention.[315]

4.1 Study population

The Atherosclerosis Risk in Communities (ARIC) study, which began in 1986, is a prospective population based study examining the etiology and natural course of cardiovascular disease, variations in patterns of medical care, risk factors, and disease progression over time. From 1987 to 1989, the ARIC cohort recruited 15,792 predominately white American and African American participants between the ages of 45 and 64, from four geographic regions in the United States, Washington County, Maryland; Forsyth County, North Carolina; Minneapolis, Minnesota; and Jackson, Mississippi.[7] Eligible households in Forsyth County were identified by area sampling. In Jackson, Minneapolis, and Washington County, age-eligible participants were identified from driver's licenses, voter registration cards, identification cards, and jury duty listings. Home interviews covering cardiovascular risk factors, socioeconomic factors, and family medical history were then administered to each potential cohort member, followed by an invitation for an extensive clinical examination. Following the baseline examination (1987-1989), the three follow-up examinations were conducted at three-year intervals through 1998 with a fifth examination (2011-2013) being funded in 2009. Participants were follow up annually through telephone calls used to assess health status and deaths in the cohort.

4.2 Exposure measurements

Essential to this analysis, the baseline and follow up examinations included sitting blood pressure measurements, anthropometry, a physical examination and an interview. Each of the four ARIC field centers were required to have a minimum of three staff members who attended a standardized training session and received certification for measuring blood

pressure.[316] Blood pressure measurement procedures were followed to ensure precise measurements were recorded. After five minutes in a resting position with no posture changes, blood pressure was measured three times using a random zero sphygmomanometer. To reduce within person variation, an average of the second and third readings was recorded for participants' blood pressure. Quality control measures required the retraining and recertification of personnel, proper maintenance of equipment, observation of measurements by a superior, and frequent staff meeting to provide feedback on measurements.[316]

4.3 Outcome Assessment

4.3.1 Incident CKD

CKD stage ≥3 will be defined by an eGFR lower than 60 mL/min/1.73m^2, using samples collected at ARIC visits 1, 2, 4 and 5, or death or hospitalization with CKD identified by ICD-9 discharge code 585.X in any position. Creatinine was measured at ARIC study visits from serum and plasma samples, as well as random urine samples, using the modified kinetic Jaffé method in serum specimens from ARIC study visits 1 and 2, plasma and urine specimens from ARIC study visit 4,[317] and both serum and urine levels of creatinine in visit 5 using the Roche enzymatic method.[318] Creatinine measurements were calibrated to the National Institute of Standards and Technology standard to account for variability amongst laboratories, assays, and methods (Table 7).[319,320] Calibration was unnecessary for visit 5 measurements. Calibrated creatinine measurements were used to estimated GFR using the CKD-EPI equation as follows:[47]

$141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa \text{ or } 1)^{-1.209} \times 0.993^{Age} \times (1.018 \text{ if female}) \times (1.159 \text{ if black})$, where κ is 0.7 if female and 0.9 if male; α is -0.329 if female and -0.411 if male; min= the minimum of Scr/κ or 1; max= the minimum of Scr/κ or 1; Scr-serum creatinine (mg/dL)

Table 7. Values used to calibrate creatinine measurements collected at ARIC visits 1, 2, 4, and 5

Visit	ARIC Variable, Serum Creatinine (mg/dL)	Calibrated Serum Creatinine (mg/dL)
1	chma09	scre_v1 = chma09 – 0.37
2	chmb08	scre_v2 = chmb08 – 0.37
4	lipd6a	scre_v4 = lipd6a + 0.11
5	chm21	scre_v5 = chm21

Table 8. ICD-9 and ICD-10 codes used to identify incident CKD stage 3 or higher

ICD-9-code	Description	ICD-10-code
582	Chronic glomerulonephritis	N03
583	Nephritis and nephropathy	
585, 585.x where x≥3	Chronic kidney disease	N18, N18.x where x≥3
586	Renal failure	N19
587	Renal sclerosis	N26
588	Disorders resulting from impaired renal function	N25
403	Hypertensive chronic kidney disease	I12
404	Hypertensive heart and kidney disease	I13
593.9	Unspecified disorder of the kidney and ureter	
250.4	Diabetes with renal complications	E10.2, E11.2, E13.2
V42.0	Kidney replaced by transplant	Z94.0
55.6	Transplant of kidney	
996.81	Complications of transplanted kidney	
V45.1	Renal dialysis status	Z99.2
V56	Admission for dialysis treatment or session	Z49
39.95	Hemodialysis	
54.98	Peritoneal dialysis	
	Encounter for adjustment and management of vascular access device	Z45.2

*Codes in red are counted as incident CKD only if a concomitant AKI code (ICD-9: 584.x, ICD-10: N17) is not present. Adapted from Derived Kidney Variables & Incident Kidney Events ARIC documentation

Due to the limitations of defining CKD based on measurement of eGFR and the potential that individuals with CKD may be less likely to attend subsequent ARIC visits, we will also use CKD events identified through surveillance. In addition to creatinine measurements at visits 1, 2, 4, and 5, incident CKD events will be identified through hospitalizations or deaths with ICD-9-CM/ICD-10 codes noted in table 8 in any position (Table 7). Hospitalizations were identified for investigation through annual telephone call and hospitalization surveillance. Deaths were also identified through annual follow-up and investigated through hospital records, death certificate searches, and coroner reports. While follow-up is ongoing, this analysis will include deaths reported through 2011.

4.3.2 Incident kidney failure

Incident kidney failure will be identified using eGFR <15 mL/minute/1.73m^2 during follow-up visit, calculated using the CKD-EPI equation and calibrations described in table 5, as well as death or hospitalization with kidney failure identified by discharge code and collected similar to methods described for CKD above (Table 8). Additionally, linkage to the USRDS national registry indicating ESRD treatment provides an avenue for identifying ARIC participants with ESRD based physician determined kidney failure from medical chart review and will be used to maximize the identification of case (Table 9). [321]

Table 9. ICD-9 and ICD-10 codes used to identify kidney failure

ICD-9-code	Description	ICD-10-code
V42.0	Kidney replaced by transplant	Z94.0
55.6	Transplant of kidney	
996.81	Complications of transplanted kidney	
V45.1	Renal dialysis status	Z99.2
V56	Admission for dialysis treatment or session	Z49
39.95	Hemodialysis	
54.98	Peritoneal dialysis	
	Encounter for adjustment and management of vascular access device	Z45.2
585.5	Chronic kidney disease stage 5	N18.5
585.6	End stage renal disease	N18.6
586	Renal failure	N19
403.01	Hypertensive chronic kidney disease, malignant, with CKD 5 or ESRD	
403.91	Hypertensive chronic kidney disease, with CKD 5 or ESRD	I12.0

*Codes in red will not be counted as incident kidney failure if: 1) for hospitalizations, a concurrent AKI code is present; 2) for deaths, if a concurrent AKI code is present without a concurrent CKD code. Adapted from Derived Kidney Variables & Incident Kidney Events ARIC documentation

4.4 Statistical analysis

We proposed the use of an additive parametric model to contrast the predicted impact of clinical and population interventions applied to different targets of elevated blood pressure eligible for interventions at baseline.[322] The effect of the decrease in blood pressure associated with these interventions will be used to estimate reductions in incident CKD and kidney failure by gender, and race[21,22] in by 10-year age categories in a population-based, bi-racial sample of middle-aged men and women (n= 15,792) from the Atherosclerosis Risk in Communities (ARIC) study.

4.4.1 Impact of reducing blood pressure on incidence of CKD and kidney failure

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

Sub Aim 1.1: Estimate reductions in incident CKD associated with decreases in blood pressure of a magnitude achievable by lifestyle modifications by gender, race and 10-year age categories.[21,22]

To estimate the number of incident CKD, and kidney failure events per 100,000 person-years (PY) potentially prevented after a population-wide 1 mmHg or 2 mmHg SBP reduction, achievable through population-wide sodium reduction strategies, we will use a least squares linear regression approach.[322] The least squares regression model will estimate racial/ethnic specific incidence rate differences (IRD) adjusted for age, gender, and diabetes mellitus given their association or role in the pathophysiology of kidney disease. Adjustment will also be made for the use of anti-hypertensive medications. These models provide

estimates of the IRDs for CKD and kidney failure associated with a 1 mmHg decrement in SBP at study baseline potentially achievable after lifestyle interventions were fully implemented;[264,265,323-325] estimates for a 2 mmHg reduction will be obtained by multiplying the SBP regression coefficient by two. Estimates of 1 to 2 mmHg are consistent with modest reductions achievable through reducing sodium content in the food supply.[326] As sensitivity analyses, we will also estimate the impact of blood pressure reductions ranging from 3-7 mmHg in the total population achievable through the implementation of other population-based lifestyle interventions on physical activity and adiposity.

Sub Aim 1.2: Estimate reductions in incident CKD associated with increases in awareness of blood pressure above goal, initiation of antihypertensive therapy, and decreases in uncontrolled blood pressure above goal in the population with hypertension, according to recommended treatment thresholds from the 2014 guidelines for the management of elevated blood pressure[23] and JNC 7, on incident CKD by gender, race, and 10-year age categories.

To evaluate interventions targeted to populations with blood pressure above goal after full implementation, we will first estimate race-, gender-, and age- (in 10 year increments) specific IRDs using the least squares regression approach[322] for the association between blood pressure above goal and incident CKD/kidney failure. Events reduced after a 10% reduction in unaware, untreated, or uncontrolled blood pressure above goal at study baseline will then be estimated in the ARIC study using the following equation: $IRD_{ijk} * (proportion_l - proportion_m)$, where *i, j,* and *k* index race, gender, and 10 year age categories, *proportion* is the race-specific proportion of blood pressure above goal estimated in NHANES,[327] pre- (*l* subscript) and post (*m* subscript)- intervention that shifted 10% of the

proportion of the population with unaware, untreated or uncontrolled blood pressure above goal to unexposed (i.e. below goal blood pressure). Results will be presented per 100,000 PY and represent a special case of the population attributable risk that considers partial, rather than complete, elimination of the risk factor. Here, we will consider partial elimination of blood pressure above goal, achieved after fully implementing interventions that decreased the proportion of the population with unaware, untreated, or uncontrolled blood pressure by 10%.[328] Age- and gender-specific results will then be collapsed by race using a case-load weighted summation method[329,330] and 95% confidence intervals will be obtained using bootstrapping.[331]

As a sensitivity analysis, we will also estimate the impact of a 10% reduction in the total population with blood pressure above goal. Hypothetical interventions that achieved a 5% and 20% reduction in the proportion of individuals with blood pressure above goal as well as the proportions of individuals with unaware, untreated, and uncontrolled blood pressure above goal will also be examined. Contemporary race-specific population projections for the number of events prevented by the population-wide and the targeted interventions will be calculated by multiplying the race specific IRD estimates by the race-specific total population aged 45 to 64 years obtained from the 2010 U.S. census. All statistical analyses will be performed with SAS 9.3 software (SAS Institute, Cary, NC) and Stata12 (StataCorp, College Station, TX).

4.4.2 Impact of reducing blood pressure on disability attributed to CKD/kidney failure

--Specific Aim #2: Characterize the potential benefits from interventions that reduce blood pressure on disability attributed to CKD by contrasting life-style based population-wide

interventions with interventions that implement current clinical guidelines for blood pressure lowering among individuals with hypertension

As direct measures of disability and functional limitations associated with CKD and kidney failure are unavailable in the ARIC cohort, disability adjusted life years (DALYs) will be used to describe the preventive burden of incident CKD and kidney associated disability. From 1990 to present day the Who Health Organization's Global Burden of Disease (GBD) project has developed and improved upon this metric used to assess and compare the population burden of hundreds of diseases ranging from acute illnesses to chronic lifelong diseases in a consistent reliable manner across diverse populations.[24,332] Considering diseases and risk factors on a common scale of severity, premature mortality, and loss of health enables prioritization of conditions for health care and research resource allocation. Moving beyond simple prevalence estimates, periodic updates of DALYs over the last three decades have provided a measure of how the harms imposed by a particular disease are changing over time.[333] DALYs combine data the burden of disability attributed to a disease measured by Years Lived with Disability (YLD) and data on premature mortality, measured by years of life lost (YLL) into a single measure that estimates the how much the experience of living with a disease deviates from ideal health.

Sub Aim 2.1: Estimate the change in burden of disability for incident CKD[24,25] – measured as YLD - attributable to population-wide blood pressure reductions of a magnitude consistent with lifestyle interventions, by gender, race, and 10-year age categories.

Sub Aim 2.2: Estimate the change in burden of disability for incident CKD[24,25] –

measured as YLD - attributable to increases in awareness of blood pressure above goal, initiating antihypertensive therapy, or decreases in uncontrolled blood pressure above goal in the population with hypertension, according to recommended treatment thresholds from the 2014 guidelines for the management of elevated blood pressure[23] and JNC 7, by gender, race, and 10-year age categories.

Estimations of YLD due to living with CKD/kidney failure and its manifestations, will calculated as $YLD = I \times DW \times L$,

where I represents the number of incident cases
DW indicates disability weights for CKD by stage and kidney failure, and
L specifies the average duration of cases of CKD or kidney failure until remission or death.[24]

Average duration of disability will be estimated by the mean survival time following the identification of incident CKD unitl remission or death by CKD stage. For the calculation YLDs attributable to blood pressure reductions, YLDs will be calculated using the total number of incident CKD and kidney failure in the population before intervention and calculated for the number of incident CKD and kidney failure events that would occur in the ARIC population following a blood pressure intervention that reduced events by the IRDs or partial population attributable risks calculated in Sub Aims 1.1 and 1.2.

Disability weights

Calculation of YLD for CKD and ESRD is dependent on the disability weight assigned to designate the severity of disability experienced as a result of living with CKD and kidney failure. Disability weights for a given medical condition conventionally range from 0 to 1, with 0 implying ideal or optimal health and 1 implying a state equivalent to death. Given concerns for the impact of social and cultural environment on one's impression

of disability, the 2010 GBD study estimated disability weights for 220 medical conditions using a multi-country (Bangladesh, Indonesia, Peru, Tanzania, and the USA) household survey and an open-access web-based survey, provided in a variety of languages, and among diverse cultures, and socioeconomic status levels in the general public.[24] Respondents were provided with a lay representation of manifestations and functional limitations associated with each condition evaluated and used these descriptions to compare health status of among hypothetical pairs of individuals experiencing various disease conditions.[24] A subset of respondents for the web based survey were asked to weigh and contrast the health benefits of diverse lifesaving or disease prevention interventions and these comparisons were used to restrict disability weights to a 0 to 1 scale. Three disability weights were estimated to describe the impact of CKD on disability, 0.105 (95% CI: 0.069-0.154) for stage 4 CKD, 0.027 (95% CI: 0.015-0.043) for ESRD with kidney transplant, and 0.573 (0.397-0.749) for ESRD on dialysis.[24] Disability weights appropriate for individuals with earlier stages of CKD or kidney failure, who did not receive treatment through dialysis or transplantation, were not assessed.

The GBD 2013 study added to the existing database created for the 2010 study by expanding the survey and protocol to four new European countries: Hungary, Italy, the Netherlands and Sweden.[25] Eligible participants in these countries were selected through existing internet panels with sample selection based on representativeness of the populations' age, gender, and education distributions.[25] In additional to clarifying lay descriptions for several conditions included in the 2010 study, the 2013 study included disability weights for 20 outcomes that were omitted in the earlier burden of disease calculations.[24,25] Disability weights for stage 4 CKD [0.104 (95% CI: 0.070-0.147)], ESRD with kidney transplant

[0.024 (95% CI: 0.014-0.039)], and ESRD on dialysis [0.571 (0.398-0.725)] were slightly reduced but highly comparable to 2010 estimates..[24,25] Replications of the GBD protocol and smaller country specific studies have resulted in a variety of disability weights assigned to CKD and ESRD. For example, a study in Iran that calculated disability weights by CKD cause, and treatment modality found increased impact on disability among those with kidney transplantation and a lower disability weight among those on peritoneal dialysis or hemodialysis compare with GBD estimates.[334]

In 2016, the GBD published updated disability weights that expanded the scope of coverage for CKD to include disability associated with stage 3 CKD and stage 4 CKD according the anemia status (Tables 10 and 11).[335] Disability weights for end-stage renal disease and stage 4 CKD without anemia remained consistent with estimates provided above by the GBD 2013 study. Disability weights for stage 3 CKD ranged from 0 for CKD stage 3 with no anemia to 0.149 for stage 3 CKD with severe anemia. Stage 4 CKD weights followed a similar patterns with the disability weight for stage 4 CKD with severe anemia representing a significantly higher burden of disability compared to stage 4 CKD with no anemia (disability weights=0.104 to 0.237 respectively; Table 11).[333]

Table 10. Definitions for Anemia status

Severity of Anemia (Hg,B g/dl)			
	Mild	Moderate	Severe
Males	12.0-12.9	9.0-11.9	6.0-8.9
Females	11.0-11.9	8.0-10.9	5.0-7.9

*Adapted from the WHO guidelines definition for anemia[333,335]

Table 11. GBD 2015 disability weights for stage 3 to stage 5 CKD by anemia severity

Health State	Lay Description	Disability weight (95% CI)
CKD Stage III without Anemia	Asymptomatic	—
CKD Stage III with mild anemia	Feels slightly tired and weak at times, but this does not interfere with normal daily activities	0.004 (0.001-0.008)
CKD stage III with moderate anemia	Feels moderate fatigue, weakness, and shortness of breath after exercise, making daily activities more difficult	0.052 (0.034-0.076)
CKD stage III with severe anemia	Feels very weak, tired, and short of breath and has problems with activities that require physical effort or deep concentration	0.149 (0.101-0.21)
CKD stage IV without anemia	Tires easily, has nausea, reduced appetite and difficulty sleeping	0.104 (0.07-0.147)
CKD stage IV with mild anemia		0.108 (0.072-0.151)
CKD stage IV with moderate anemia		0.15 (0.103-0.207)
CKD stage IV with severe anemia		0.237 (0.165-0.324)
CKD stage V	Has lost a lot of weight and has constant pain. The person has no appetite, feels nauseated, and needs to spend most of the day in bed	0.569 (0.389-0.727)
End-stage renal disease, on dialysis	Is tired and has itching, cramps, headache, joint pains, and shortness of breath. The person needs intensive medical care every other day lasting about a half a day	0.571 (0.397-0.725)
End-stage renal disease, with kidney transplant	Sometimes feels tired and down, and has some difficulty with daily activities	0.024 (0.014-0.039)

According to the GBD study, global and national estimates of YLD have consistently increased since first described in 1990 (148/100,000 PY for U.S.) to 2015 (180/100,000 PY for U.S.) (Figure 9).[336] The corresponding increase in incidence rates for CKD from approximately 3,600 to 4,200 events per 100,000 PY from 1990 to 2015 contributes heavily to the growth in YLD.[336] Both incidence rates and YLD were

significantly higher in the U.S. compared to global estimates demonstrating the large need for reducing the burden of CKD and its associated disability nationally.

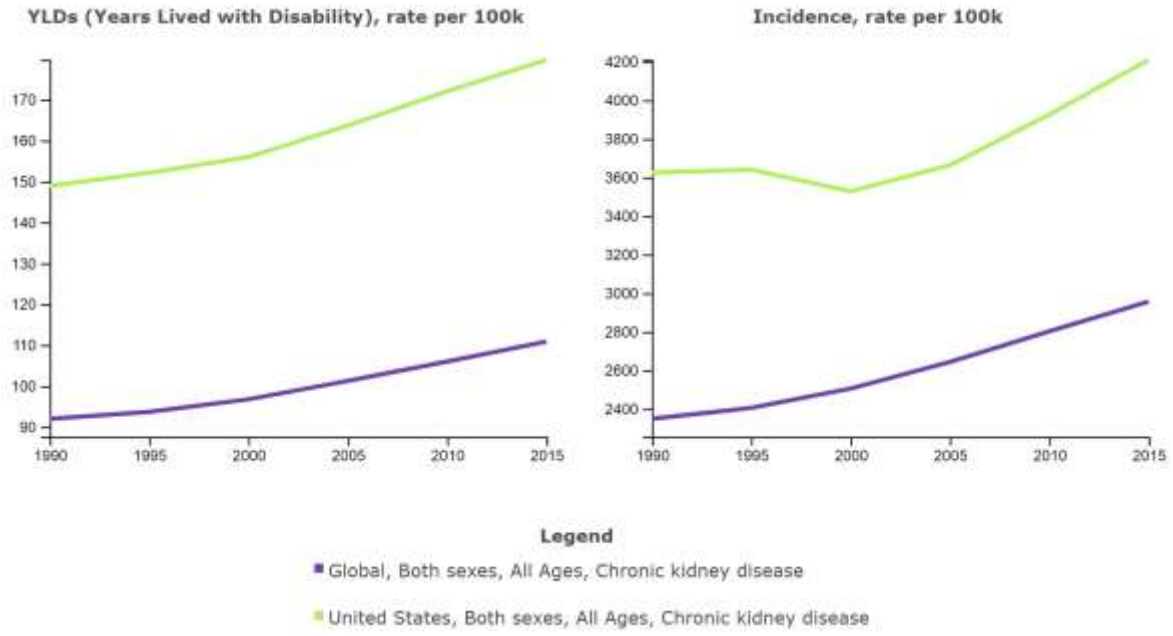


Figure 9. Trends in YLD and incidence rates per 100,000 person-years for CKD in the US and abroad (1990-2015)[336]

Sub Aim 2.3: Estimate the change in years of life lost (YLL) associated with incident CKD attributable to population-wide blood pressure reductions of a magnitude consistent with lifestyle interventions, by gender, race, and 10-year age categories.

Sub Aim 2.4: Estimate the change in years of life lost (YLL) attributable to increasing awareness of blood pressure above goal, initiating antihypertensive therapy, or decreasing uncontrolled blood pressure above goal in the population with hypertension, according to recommended treatment thresholds from the 2014 guidelines for the management of elevated blood pressure[23] and JNC 7, by gender, race, and 10-year age categories.

YLL expresses burden in terms of premature mortality and will be calculated as the number of deaths among those with CKD/kidney failure times the standard age-specific life expectancy at age of death from CKD/kidney failure in years or YLL = ∑ number deaths with CKD/kidney failure * life expectancy at age of death.[24] Individual age-, gender-, and race-specific life expectancies without CKD/kidney failure will be estimated using the 2010 US life tables.

Though YLLs for CKD were visibly lower in the U.S. compared to abroad in 1990, large growth in YLLs for CKD nationally had essentially closed this gap by 2015 (Figure 10).[336] A total of 1,080,889 YLL (rate 334/100,000 PY) for overall CKD were estimated for the US in 2015, with 45% of YLLs for the CKD attributed to hypertension. Over this same time period death rates for CKD had been consistently higher in the U.S. compared to abroad and have increased at a higher rate from 1990 to 2015 (Figure 10).[336] In 2015 the age-standardized death rate for CKD in the US was 24/100,000 PY compared to 17/100,000 PY globally.[336] This increasing death rate for CKD in the U.S. likely contributes to the growing burden of YLL among the CKD population.

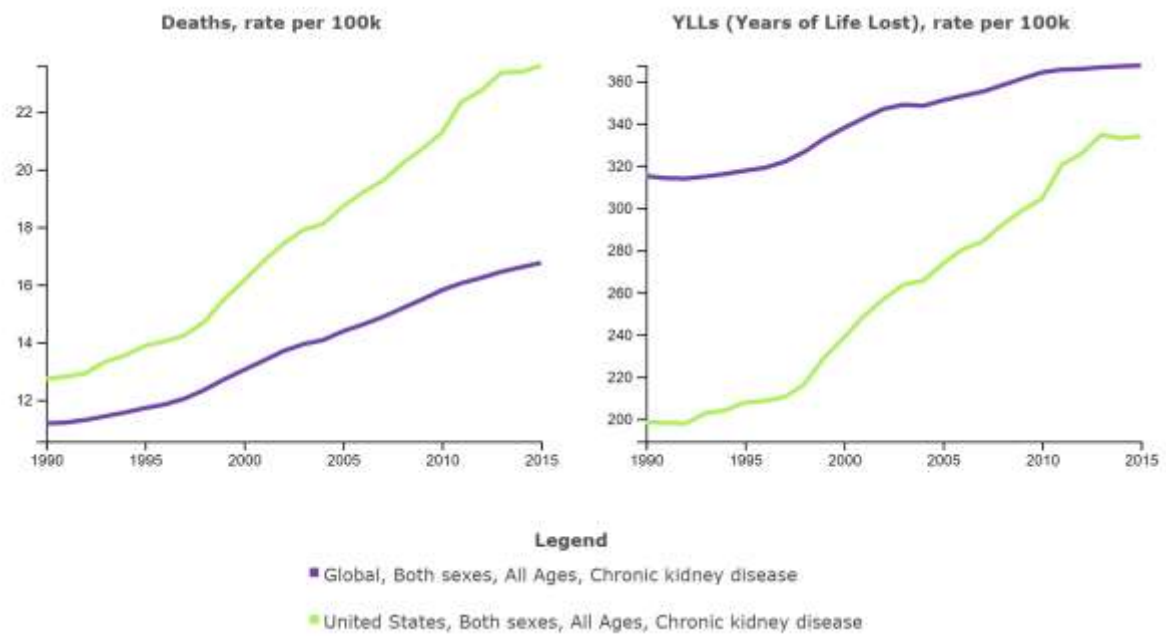


Figure 10. Death rate and years of life lost per 100,000 person-years for CKD in the US and abroad (1990-2015)[336]

Calculation of DALYS

Using estimates of YLD and YLL calculated in Aim 2, we will estimate the burden of DALYs for CKD and kidney failure[24] attributable to blood pressure reductions due to the impact of population-wide (**Sub aim 2.1 and 2.2)** or high risk strategy **(Sub Aim 2.3 and 2.4)** interventions. DALYs will be calculated as the sum of YLL and YLD before blood pressure intervention and among the remaining events after subtraction of events prevented blood pressure reductions.[24,337] Subsequently, we will contrast the potential benefits on disability attributed to CKD and kidney failure, quantified as 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 elevated blood pressure above treatment goals.

The rates of DALYs for CKD were higher globally than in the US until the late 2000s. The burden of DALYs for CKD in the U.S. increased from a rate of 347 per 100,000 PY in 1990 to approximately 520 DALYs per 100,000 PY in 2015 (Figure 11).[336] Most of the reported DALYs for CKD are contributed by YLL, reflecting the effect of early mortality in the CKD population. Given the substantial burden of DALYs from CKD in the U.S., quantifying the health impact of blood pressure interventions using disability indicators such as DALYs aids in prioritizing public health interventions by stressing the relevance of CKD in reducing health and increasing the burden of premature mortality.

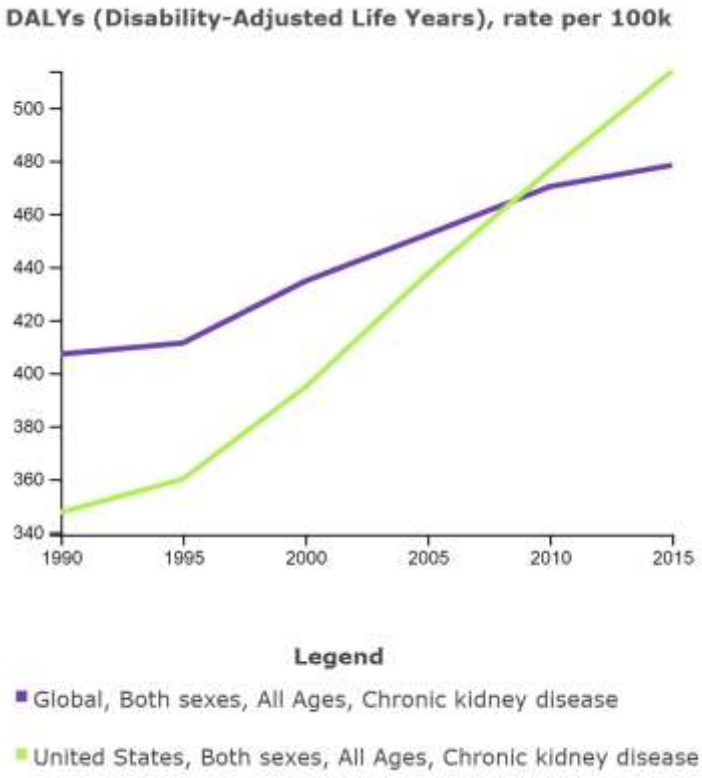


Figure 11. Trends in DALYs rates per 100,000 person-years for CKD in the US and abroad (1990-2015)[336]

CHAPTER 5: RESULTS

5.1 Prevention of Chronic Kidney Disease: Impact of Addressing the Blood Pressure Distribution, Not Just the Tail

Introduction

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).[1,2] 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 with dialysis patients experiencing adjusted all-cause mortality rates that are 6.5 to 7.9 times greater than the general population.[3] The burden of hospitalization, disability, and increased risk of all-cause mortality associated with kidney disease[4-8] call for a better understanding of the potential benefits associated with preventive reduction of CKD risk factors.

Elevated blood pressure is considered a major modifiable risk factor for CKD with well-defined approaches for its detection and management presenting an opportunity to intervene on CKD development. Approximately 37% and 19% of ESRD cases in African Americans and white Americans respectively are attributed to high blood pressure.[9] Even blood pressure levels considered "high-normal" (defined as systolic blood pressure, SBP, between 130 and 139 mmHg or diastolic blood pressure, DBP, between 85 and 89 mmHg) are associated with a 3-fold greater risk of development of ESRD.[10,11] While the efficacy of

lifestyle modifications as well as pharmacological therapies in the management of high blood pressure are established,[12-20] the predicted effects of blood pressure reductions on CKD incidence have not been quantified to our knowledge. Here we estimated the effects of population wide blood pressure reductions, achieved through lifestyle interventions, and improved management of hypertension, achieved through pharmacological interventions, to assess their potential impact on the population burden of incident CKD.

Methods

Study population

The Atherosclerosis Risk in Communities (ARIC) study is a prospective, population based investigation of the etiology and natural history of CVD and its risk factors.[7] From 1987 to 1989, ARIC investigators sampled 15,792 predominately white American and African American participants between the ages of 45 and 64 from four geographic regions in the United States: Washington County, Maryland; suburban Minneapolis, Minnesota; Forsyth County, North Carolina, and Jackson, Mississippi. The latter two communities contributed the majority of African Americans to the cohort. Physical examinations and standardized questionnaires were administered by trained study personnel at baseline and during four follow up examinations. Cohort follow-up for identification and classification of health outcomes is ongoing. The ARIC study obtained institutional review board approval from all participating institutions, and informed consent was obtained at each study visit.

The following sequential exclusions were applied: participants who reported a race other than African American or white American (n=48), participants with prevalent CKD (estimated glomerular filtration rate (eGFR) < 60 mL/minute/1.73m^2) at baseline or missing information to determine prevalent CKD (n=354, 227 African American, 127 white

American). After these exclusions, a total of 15,390 participants were available for the evaluation of incident CKD. Follow-up time was calculated from study enrollment to the first identification of CKD, loss to follow-up, death, or December 31st, 2011.

Exposure and covariate assessment

Seated blood pressure measurements were taken after a five-minute rest using a random-zero sphygmomanometer; the mean of the second and third baseline examination readings was used for analysis. We used the both the 2014 Guidelines for the Management of High Blood Pressure from the Eighth Joint National Committee (JNC 8) and JNC 7 guidelines to identify participants with blood pressure above goal. Using JNC 8 guidelines, hypertension was classified by SBP ≥150 mmHg or a DBP ≥ 90 mmHg for participants aged ≥ 60 years and SBP ≥140 mmHg or a DBP ≥ 90 mmHg, for participants aged <60.[23] Using JNC 7 guidelines, hypertension was classified by a SBP ≥140 mmHg or a DBP ≥ 90 mmHg for participants for all ages. All study participants with blood pressure levels below goal were classified as unexposed, irrespective of medication usage or history of hypertension, as they were ineligible for interventions targeted to populations with blood pressure above goal. All study participants with blood pressure measurements were eligible for the population-wide blood pressure shift. Antihypertensive medication use, race, age, diabetes and gender were assessed at study baseline.

Outcome ascertainment and definition

The eGFR for each participant was estimated from calibrated creatinine measurements using the CKD-EPI equation. Incident CKD was a composite outcome defined by at least 1 of the following conditions: (1) development of an eGFR < 60 mL/minute/1.73m^2 accompanied by 25% eGFR from baseline, using samples collected at

ARIC visits 1, 2, 4 and 5, (2) death or hospitalization with CKD identified by International Classification of Diseases (ICD) 9 or 10 discharge code 585.X in any position, and (3) linkage to the USRDS national registry indicating ESRD treatment between baseline at the end of follow up.[338] ARIC study participants were interviewed annually by phone and all hospitalizations and deaths during the preceding year were identified, abstracted, and adjudicated according to study criteria. Active surveillance of the ARIC cohort through local hospital discharge records and vital records was also used to detect hospitalizations and deaths of cohort participants and linkage to the USRDS national registry provided an avenue for identifying ARIC participants with ESRD based physician determined kidney failure from medical chart review.

Statistical Analysis

Incidence rates, stratified by race/ethnicity, were calculated by dividing the total number of CKD events by the person-years (PY) at risk. A least squares linear regression approach[322] was used to estimate the number of incident CKD events per 100,000 PY potentially prevented after a population-wide 1 mmHg or 2 mmHg reduction in SBP adjusted for age, gender, diabetes and anti-hypertensive medication use at baseline. These models provided estimates of the incidence rate difference (IRD) for CKD associated with a 1 mmHg decrement in SBP at study baseline, an increment potentially achievable after lifestyle interventions were fully implemented;[264,265,323-325] estimates for a 2 mmHg reduction were obtained by multiplying the SBP regression coefficient by two.

To evaluate interventions targeted to populations with blood pressure above goal we first estimated race-, gender-, diabetes- and age- (in five year increments) specific IRDs using the least squares regression approach[322] for the association between blood pressure

above goal and incident CKD. Reduction on the incidence rate after a 10% reduction in unaware, untreated, or uncontrolled blood pressure above goal at study baseline were then estimated in the ARIC study using the following equation: $IRD_{ijk} * (proportion_l - proportion_m)$, where *i, j,* and *k* index race, gender, and 5 year age categories, *proportion* is the race-specific proportion of blood pressure above goal estimated in NHANES,[327] pre- (*l* subscript) and post (*m* subscript)- intervention that shifted 10% of the proportion of the population with unaware, untreated or uncontrolled blood pressure above goal to unexposed (i.e. below goal blood pressure). Results were estimated per 100,000 PY and represent a special case of the population attributable risk that considers partial, rather than complete, elimination of the risk factor. Here we considered partial elimination of blood pressure above goal, achieved after fully implementing interventions that decreased the proportion of the population with unaware, untreated, or uncontrolled blood pressure by 10%.[328] Age- gender- and diabetes- specific results were then collapsed by race using a case-load weighted summation method[329,330] and 95% confidence intervals (CI) were obtained using bootstrapping.[331]

As a sensitivity analysis, we estimated the impact of interval censoring on the IRDs for both the population-wide and targeted blood pressure above goal reduction strategies. Since incident CKD was ascertained at interval ARIC study visits, the exact timing of incident CKD development is unknown. We applied follow-up time reductions of 1, 1.5, and 2 years among incident CKD cases identified at ARIC visits to estimate the impact of event times occurring prior to identification at an ARIC visit. We also examined 5-20% proportional reductions in unaware, untreated, and uncontrolled blood pressure above goal. Contemporary race-specific population projections for the number of events prevented by the

population-wide and the targeted interventions were calculated by multiplying the race specific IRDs by the race specific total population aged 45 to 64 years from the 2010 U.S. census population. All statistical analyses were performed with SAS 9.3 software (SAS Institute, Cary, NC) and Stata12 (StataCorp, College Station, TX).

Contemporary race-specific weighted proportions of unaware, untreated, and uncontrolled blood pressure above JNC 7 goal for ages 45-64 were estimated from the National Health and Nutrition Examination Survey (NHANES, 2009-12) as follows: white Americans,15.8% blood pressure above goal (42% unaware; 17% untreated; 41% uncontrolled) and African Americans 26.4% blood pressure above goal (25% unaware; 20% untreated; 55% uncontrolled). Individuals with hypertension who were aware and treated to JNC 8 or JNC 7 treatment goals were not included in the intervention group for the respective analyses.

Results

At study baseline, 15,390 (26% African American, 55% female) eligible ARIC cohort members were available for analysis (Table 12). On average, African Americans were twice as likely to have blood pressure above goal, to report the use of antihypertensive medications, or to have diabetes. As expected, more African Americans and white Americans were defined as having blood pressure above goal using JNC 7 blood pressure guidelines compared to JNC 8 guidelines. Over a mean 19.7 years of follow-up, 3,852 incident CKD events (29% African American) were identified with an incident rate of 1,476 per 100,000 PY for African Americans and 1,203 per 100,000 PY for white Americans.

After a population-wide hypothetical intervention that achieved an overall 1 mmHg decrement in SBP at study baseline, reductions of 13.4 (95% CI: 7.8-19.0) and 11.7 (95% CI:

6.2-17.3) incident CKD events per 100,000 PY in white Americans and African Americans was estimated, respectively (Table 14). The hypothetical intervention achieving the larger SBP reduction of 2 mmHg population-wide was associated with 2 times the reductions in the incident CKD for both racial groups compared to a 1mmHg reduction (Table 14). The estimated preventable CKD events following a 1 mmHg reduction in SBP were fairly comparable by race, with preventable events estimated to be slightly greater for white Americans. If applied nationwide, a hypothetical 1 mmHg shift in SBP among African American and white American populations aged 45-64 years was estimated to prevent approximately 9,996 incident CKD events annually (Table 15).

As a contrast to hypothetical SBP reductions population wide, we estimated the effect of interventions targeted to populations with blood pressure above goal that achieved a 10% proportional reduction in unaware, untreated, or uncontrolled blood pressure. These targeted blood pressure above goal intervention were applied to the corresponding (smaller) subset of the total population. For example, using JNC 7 guidelines for blood pressure, before intervention 28.3% of African Americans and 15.8% of white Americans aged 45-64 years classified as having blood pressure above goal (NHANES 2009-2012; Table 13); we therefore evaluated a targeted intervention that achieved a 10% proportional decrease in unaware blood pressure above goal (i.e. 25% to 23% among African Americans and 42% to 38% among white Americans, respectively) resulting in post interventions proportion of blood pressure above goal of 27.6% for African Americans and 15.1% for white Americans (Table 13). In contrast to results from the population-wide SBP interventions, a 10% proportional reductions in unaware, untreated, or uncontrolled blood pressure above JNC 7 goal produced the largest reduction in events for African Americans particularly for untreated

and uncontrolled blood pressure above goal (Table 13). Specifically, a 10% proportional reduction in unaware, untreated, or uncontrolled blood pressure above goal at study baseline resulted in approximately 3.2 (95% CI: 2.0-4.9), 2.8 (95% CI: 1.8-4.3), and 5.8 (95% CI: 3.6-8.8) fewer incident CKD events per 100,000 PY respectively, in African Americans and 3.1 (95% CI: 2.3-4.1), 0.7 (95% CI: 0.5-0.9), and 1.9 (95% CI: 1.3-2.4) fewer CKD events per 100,000 PY respectively in white Americans (Table 14). If 10% proportional reductions in unaware, untreated, or uncontrolled blood pressure above JNC 7 goal were achieved nationwide in African Americans and white Americans aged 45-64, approximately 2,098, 636, and 1,598 fewer incident CKD events, respectively could be prevented annually (Table 15). Notably, interventions targeted at populations with blood pressure above JNC 7 goal produced greater estimated reductions in incident CKD than interventions targeted at reductions in blood pressure above JNC 8 goal.

Sensitivity analyses to determine the degree to which length of follow-up time influences the potential reduction in incident CKD indicated less than 1 additional preventable event for up to 2 years of decreased follow up time among cases identified at ARIC study visits (Appendix 1, Supplemental Table 1). Additional analyses examining 5%-20% proportional reductions in unaware, untreated, and uncontrolled blood pressure above goal demonstrated that size of the population impacted by the intervention considerably varies the number of incident CKD events that can be prevented by targeting unaware, untreated, or uncontrolled blood pressure above JNC 8 goals (Appendix 1, Supplement Table 2).

Discussion

Predicted benefits from blood pressure reductions estimated in a biracial, population-based cohort showed that a modest population-wide 1 mmHg or 2 mmHg decrement in SBP could potentially prevent more incident CKD events per 100,000 PY than interventions that achieved a 10% proportional reduction in unaware, untreated, or uncontrolled blood pressure above goal. Although the population-wide approach estimated a similar number of CKD event reductions by race, the estimated benefits of lowering the proportion of the population with blood pressure above goal on CKD events were greater for African Americans, particularly in regards to 10% reductions in untreated, and uncontrolled blood pressure above goal.

Healthy people 2020 goals aimed for a 10% reduction in the proportion of the US population with CKD and a 10% reduction in incident ESRD cases, goals that focus research on prevention of CKD and kidney failure.[311] However, little evidence is available on population based interventions that prevent the initial development of CKD.[57,72,218] A number of observational studies have identified elevated blood pressure as a risk factor for development of CKD,[219-222] and support the notion of benefits from blood pressure reduction on the risk of CKD. Despite a strong association between elevated blood pressure and CKD, randomized control trials of antihypertensive therapy on CKD progression have failed to provide sufficient evidence of efficacy, particularly for intensive control of blood pressure .[239,339,340] Primordial prevention of CKD provides the greatest opportunity for reducing the incidence of CKD and kidney failure and will likely shape future public health initiatives as focus shifts from halting progression of CKD to preventing its development.

An exclusive focus on hypertension as opposed to blood pressure shifts to higher values constrains the opportunity to examine high-impact, population-wide blood pressure reduction approaches and the potential benefits associated with reducing blood pressure in the large segment of the population at risk for CKD. Given the monotonic (graded) relationship between blood pressure level and disease risk and the large proportion of CKD events that occurs among those whose elevated blood pressure is treated and controlled, a population-based strategy is posited to achieve the largest benefit in reducing the overall burden of blood-pressure related outcomes.[259,260] Although small reductions in blood pressure across the population resulted in modest IRD estimates, when applied to the population as a whole the impact of a 1 mmHg decrement in blood pressure population-wide on the overall burden of CKD is pronounced. Approximately 10,000 annual incident CKD events could theoretically be prevented among U.S. African American and white American populations aged 45 years or greater. Prevention-oriented lifestyle modifications are expected to have a positive impact on disease incidence and progression across race/ethnic groups if implemented population-wide, or reinforced during medical encounters among high risk groups, yet are often undervalued or unsupported as public health strategies of CKD prevention.[272,273,313,314] A better understanding of the potential benefits associated with modification of risk factors for CKD and kidney failure at the population level and among high-risk groups is needed to reduce the population burden of disease attributable to CKD.

Contrasting population-wide interventions with high-risk approaches relies on assumptions and is inherently dependent on the thresholds used to define the high-risk populations, and thus the size of the population targeted for intensive reductions. Controversially, the 2014 JNC 8 blood pressure guidelines raised the treatment thresholds for

adults 60 years of age or older to SBP >=150 mmHg as opposed to the more proactive SBP threshold of 140 mmHg used under JNC 7.[15,230] Due to this difference in treatment thresholds, 10% improvements in uncontrolled blood pressure above goal as defined by JNC 7 are expected to prevent 300 more events in the U.S. African American and white American populations aged 45 years to 64 years annually compared to a 10% reduction in blood pressure above goal defined by JNC 8 treatment guidelines. Evidence from randomized control trials of the benefit of treatment thresholds lower than JNC 7 for CKD prevention remains unclear. The Systolic Blood Pressure Intervention Trial (SPRINT), demonstrated the value of controlling blood pressure to or below the level recommend by treatment guidelines for cardiovascular outcomes with or without CKD, suggesting that proper management of patients with elevated blood pressure could improve the suboptimal levels of blood pressure control and CVD currently documented in the US population.[291] However, the group treated most intensively for blood pressure control also experienced higher risk of CKD, or a decrease in the eGFR of ≥30% to a value of < 60 ml per minute per 1.73 m^2 than the standard group, suggesting that lower treatment targets for blood pressure potentially harm levels of kidney function.[291] As future trials decipher antihypertensive medication effects on incident CKD from the effect of lower blood pressure, estimates of preventable events achieved from reduction blood pressure to lower thresholds can be appropriately interpreted and compared to the preventable burden of CKD due to blood pressure reductions under previous guidelines.

Among the clinical management approaches considered, improvements in uncontrolled blood pressure offered the greatest opportunity to prevent incident CKD. In the general population only about half of the population with elevated blood pressure is

effectively controlled to the recommended goals, leaving much room for improvement in the management strategy used to prescribe, dose and monitor the regimen used to achieve blood pressure targets. Recent clinical trial evidence demonstrates that proper management of patient with elevated blood pressure can improve the suboptimal levels of blood pressure control currently documented in the US population[291]. As CKD progresses so does the difficulty to control blood pressure, accentuating the importance of blood management prior to the development of CKD. Providing estimates of CKD events potentially preventable through reductions in uncontrolled blood pressure above goal invites a review of current blood pressure management practices, although a greater convergence among trial findings supporting the use of antihypertensive therapy for CKD prevention is needed.

The strengths of this study include the use of a large, biracial cohort with high retention and quality assurance protocols over an average of 20 years of follow up. There also are several limitations that deserve consideration. The ARIC cohort was sampled from 4 geographically defined locales and results may not be fully generalizable to the general population, particularly for African Americans who were primarily recruited from Jackson, Mississippi and Forsyth County, North Carolina; other U.S. minority groups were not represented in this study. The ARIC study was also restricted to participants aged 45-64 years at study baseline. Further, we assumed the same incidence rate reduction when calculating the number of events that could be prevented from interventions that targeted unaware, untreated, and uncontrolled blood pressure above goal. We also estimated separate intervention effects, for unaware, untreated, and uncontrolled blood pressure above goal; in practice, these interventions would likely be promoted in combination and associated with target specific IRDs.

As the focus of CKD research shifts from studying disease progression to disease prevention, modest blood pressure interventions population-wide and among the high risk population with blood pressure above goal both provide an opportunity to substantially reduce the burden of CKD. Blood pressure thresholds used to define and treat the high-risk group are evolving, making the estimation of preventable CKD events under each guideline particularly timely as an intuitive means of expressing the potential implications of blood pressure treatment thresholds on the development of kidney disease. While lowering the threshold for blood pressure treatment could increase the impact of high risk strategies on CKD prevention, small decrements in the population level of SBP offer an effective method to prevent the largest number of CKD events and should be developed as an integral component of CKD prevention strategies.

Acknowledgments

The authors thank the staff and participants of the ARIC study for their important contributions.

Funding Sources

The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C).

The authors have no relationships with industry to disclose.

Disclosures: None

Table 12. Baseline characteristics of the ARIC Study cohort (N=15,390) by race, 1987-1989.

Baseline Characteristics	African Americans (n=4,039)	White Americans (n=11,351)
Mean follow-up in years, (SD)	18.7 (7.2)	20.0 (6.4)
Mean age in years, (SD)	53.5 (5.8)	54.3 (5.7)
Diabetes	750 (18.6)	1016 (9.0)
Female, N (%)	2,488 (61.6)	5,990 (52.8)
Reported antihypertensive use, N (%)	1,597 (50.6)	2,201 (22.2)
Mean systolic blood pressure, mmHg (SD)	128.5 (21.1)	118.4 (17.0)
Mean diastolic blood pressure, mmHg (SD)	76.7 (12.2)	71.5 (10.1)
Blood pressure categories*		
Blood pressure below JNC 8 goal, N (%)	2,892 (71.6)	10,182 (89.7)
Blood pressure above JNC 8 goal, N (%)	1,146 (28.4)	1,164 (10.3)
Blood pressure below JNC 7 goal, N (%)	2,807 (69.5)	9,922 (87.5)
Blood pressure above JNC 7 goal, N (%)	1,231 (30.5)	1,424 (12.6)

*JNC&, blood pressure values that exceed thresholds for management of blood pressure defined by JNC 7; JNC 8, blood pressure values that exceed thresholds for management of blood pressure defined by JNC 8; blood pressure below goal, blood pressure values below thresholds for management of blood pressure defined by JNC 8

ARIC, Atherosclerosis Risk in Communities Study; SD, standard deviation

Table 13. Proportion of African American and white American NHANES participants aged 45-64 years with blood pressure above JNC 8 and JNC 7 goal before and after targeted interventions improving unaware, untreated, and uncontrolled blood pressure by 10%, 2009-2012

Blood pressure guidelines	Race	Proportion of participants with blood pressure above goal			
		Before invention	After 10% reduction in proportion of unaware blood pressure above goal	After 10% reduction in proportion of untreated blood pressure above goal	After 10% reduction in proportion of uncontrolled blood pressure above goal
JNC 8	African Americans	26.36	25.84	25.78	24.82
	White Americans	11.88	11.41	11.71	11.33
JNC 7	African Americans	28.31	27.60	27.74	26.75
	White Americans	15.79	15.12	15.53	15.14

Table 14. Table 3: Estimated incident CKD events reduced from population-wide or targeted hypothetical interventions that achieves a 1-2 mmHg decrement in SBP or a 10% reduction of unaware, untreated or uncontrolled blood pressure above goals, by race (N=15,390), 1987-2011, ARIC Study.

	Incident CKD events reduced* per 100,000 PYs (95% CI) by Interventions achieving reductions in BP	
Blood pressure intervention	African Americans	White Americans
Hypothetical population-wide intervention to decrease SBP		
1 mmHg decrease	11.7 (6.2-17.3)	13.42 (10.3-16.6)
2 mmHg decrease	23.5 (12.3-34.6)	26.8 (20.6-33.1)
Hypothetical intervention to reduce blood pressure (above JNC 8 treatment threshold)		
10% decrease in unaware	2.7 (1.6-4.2)	2.5 (1.8-3.3)
10% decrease in untreated	2.4 (1.4-3.7)	0.5 (0.4-0.7)
10% decrease in uncontrolled	4.9 (2.9-7.6)	1.5 (1.0-1.9)
10% decrease in all BP above goal	13.6 (8.0-21.1)	6.2 (4.4-8.2)
Hypothetical intervention to reduce blood pressure (above JNC 7 treatment threshold)		
10% decrease in unaware	3.2 (2.0-4.9)	3.1 (2.3-4.1)
10% decrease in untreated	2.8 (1.8-4.3)	0.7 (0.5-0.9)
10% decrease in uncontrolled	5.8 (3.6-8.8)	1.9 (1.3-2.4)
10% decrease in all BP above goal	16.1 (10.0-24.3)	7.8 (5.6-10.2)

*Events reduced calculated $as\ IRD_{ijk} * (proportion_l - proportion_m)$, where *i, j,* and *k* index race, gender, and 5 year age categories, *proportion* is the race-specific proportion of blood pressure above goal pre- (*l* subscript) and post (*m* subscript)- intervention, per 100,000 person years

Table 15. Estimated incident CKD events reduced from hypothetical population-wide and targeted blood pressure reduction interventions, by race, 2010 US census population ages 45-64

	Incident CKD events reduced* per 100,000 PYs (95% CI) by Interventions achieving reductions in BP	
Blood pressure intervention	African Americans US population size N=9,042,518	White Americans US population size N=57,864,260
Hypothetical population-wide intervention to decrease SBP		
1 mmHg decrease	1,351	8,645
2 mmHg decrease	2,702	17,290
Hypothetical intervention to reduce blood pressure (above JNC 8 treatment threshold)		
10% decrease in unaware	245	1,425
10% decrease in untreated	216	229
10% decrease in uncontrolled	444	846
10% decrease in all BP above goal	1,227	3,563
Hypothetical intervention to reduce blood pressure (above JNC 7 treatment threshold)		
10% decrease in unaware	291	1,807
10% decrease in untreated	256	380
10% decrease in uncontrolled	526	1,072
10% decrease in all BP above goal	1,454	4,518

*****Total 2010 US census race specific populations aged 45-64 (American Americans n= 9,042,518, white Americans n= 57,864,260) were used to calculate the by above goal blood pressure

5.2 Preventable Burden of Kidney Failure Disability Attributable to Blood Pressure: The ARIC study

INTRODUCTION

Chronic kidney disease (CKD) and kidney failure affect nearly 15% of the American population[99] and represent an increasing cause of disability adjusted life years (DALYS) and premature mortality worldwide.[85] CKD is often asymptomatic in early stages, however as the disease progresses to kidney failure, prevalence and intensity of complications and comorbidities increase. Among new dialysis patients (2005-2007), less than a quarter of the population reported being able to work for pay, with approximately 80% of the same patients having applied for disability benefits.[22] Despite recent declines in mortality rates among those with end stage renal disease (ESRD), dialysis patients younger than 80 years of age continue to have less than one third of the remaining life expectancy of their counterparts without ESRD.[99] This increasing burden of disability and premature mortality supports the need for clinical and public health efforts to reduce new cases of kidney failure, a key priority of Healthy People 2020.

Modifying the risk profile of the at-risk population could substantially reduce the burden of kidney failure and its associated disability. Elevated blood pressure is present in over 90% of dialysis patients, results in substantial morbidity,[341] and among risk factors for CKD, it is the leading contributor to mortality.[342] Intensive blood pressure lowering is protective against kidney failure events, particularly among CKD patients with proteinuria,[243] and current preventative care strategies aim to maintain stringent control of blood pressure through antihypertensive medications among those with CKD.[190,243] Moreover, lifestyle modifications that can be applied population-wide have proven to be effective in reducing blood pressure[343,344] and could substantially reduce the burden of kidney failure. Quantifying

the burden of kidney failure that could be prevented by decreasing blood pressure levels population wide and among high risk populations is of direct relevance for primary prevention, resource allocation and research prioritization of this costly and deleterious disease. Here we estimate the burden of kidney failure that can be prevented by intervening on blood pressure, based on a prolonged follow up of the Atherosclerosis Risk in Communities (ARIC) cohort.

Methods

Study population

The ARIC study is a prospective, population based investigation of the etiology and natural history of cardiovascular disease (CVD) and its risk factors.[7] From 1987 to 1989, ARIC investigators sampled 15,792 predominately white American and African American participants between the ages of 45 and 64 years from four geographic regions in the United States: Washington County, Maryland; suburban Minneapolis, Minnesota; Forsyth County, North Carolina, and Jackson, Mississippi. The latter two communities contributed the majority of African Americans to the cohort. Physical examinations and standardized questionnaires were administered by trained study personnel at baseline and during four follow up examinations.[7] Cohort follow-up for identification and classification of health outcomes is ongoing. The ARIC study obtained institutional review board approval from all participating institutions, and informed consent was obtained at each study visit.

Due to small numbers, participants who reported a race other than African American or white American (n=48) at baseline were excluded from these analyses. A total of 15,744 participants were available for the evaluation of incident kidney failure. Follow-up time was

calculated from study enrollment to the first identification of kidney failure, loss to follow-up, death, or December 31st, 2011.

Exposure and covariate assessment

Two hypothetical interventions to lower blood pressure were compared for their estimated effects on the incidence of kidney failure and the burden of deaths and disability. One intervention approach represents population-based, low intensity behavior modifications consistent with various changes in lifestyle, that based on experimental evidence are associated with reductions in habitual blood pressure levels.[173,287,290] Consistent with observed changes in lifestyle, the shifts in behaviors and routines considered here apply to large segments of the population and can reflect various messages and diverse channels. For purposes of these analyses the magnitude of blood pressure reduction attributable to this hypothetical population-wide shift in blood pressure was conservatively set at 1 mmHg, and 2 mmHg systolic blood pressure (SBP).

The alternative intervention considered is a proportional 10% reduction in individuals with blood pressure above goal per clinical guidelines for management of blood pressure. This reduction may be achieved by various extant or new programs. We used both the 2014 Guidelines for the Management of High Blood Pressure from the Eighth Joint National Committee (JNC 8) and JNC 7 to identify participants with blood pressure above goal. Using JNC 8, blood pressure above goal was classified by SBP ≥150 mmHg or a diastolic blood pressure (DBP)≥ 90 mmHg for participants aged ≥ 60 years and SBP ≥140 mmHg or a DBP ≥ 90 mmHg, for participants aged <60.[23] Using JNC 7, blood pressure above goal was classified by a SBP ≥140 mmHg or a DBP ≥ 90 mmHg for participants of all ages. All study participants with blood pressure levels below goal were classified as unexposed, irrespective

of medication usage or history of hypertension, as they were ineligible for clinical intervention targeted to populations with blood pressure above goal. All study participants with blood pressure measurements were eligible for the population-wide blood pressure shift. Seated blood pressure measurements at the ARIC baseline examination were taken after a five-minute rest using a random-zero sphygmomanometer; the mean of the second and third consecutive readings was used for analysis.[316] Antihypertensive medication use, race, age, diabetes and gender were assessed at study baseline according to a standardized protocol.[7,317]

Outcome ascertainment and definition

eGFR was estimated from calibrated creatinine measurements using the CKD-Epidemiology Collaboration equation. Incident kidney failure was a composite outcome defined by at least 1 of the following conditions 1) an ARIC study visit with an eGFR measurement of <15 mL/min/1.73 m^2 2) International Classification of Diseases (ICD) 9 or 10 codes from hospitalizations and deaths that represent kidney failure, transplantation, and dialysis; and 3) linkage to the USRDS national registry indicating ESRD treatment between baseline at the end of follow up. Disability weights for treated stage 5 CKD were those published by the Global Burden of Disease Project (2016) as 0.571.[332]

Statistical Analysis

Incidence rates, stratified by race/ethnicity, were calculated by dividing the total number of kidney failure events by the person-years at risk. A least squares linear regression approach[322] was used to estimate the number of incident kidney failure events per 100,000 person-years (PY) potentially prevented after a population-wide 1 mmHg or 2 mmHg SBP reduction adjusted for age, gender, diabetes and anti-hypertensive medication use at baseline. These models provided estimates of the incidence rate difference (IRD) for incident kidney

failure associated with a 1 mmHg decrement in SBP at study baseline;[264,265,323-325] estimates for a 2 mmHg reduction were obtained by multiplying the SBP regression coefficient by two.

To evaluate interventions that target populations with blood pressure above goal we first estimated race-, gender-, diabetes- and age- (in five year increments) specific IRDs using the least squares regression approach[322] for the association between blood pressure above goal and incident CKD. Reductions in the incidence rate after a 10% reduction in blood pressure above goal at study baseline were then estimated in the ARIC study using the following equation: $IRD_{ijk} * (proportion_l - proportion_m)$, where *i, j,* and *k* index race, gender, and 5 year age categories, *proportion* is the race-specific proportion of blood pressure above goal estimated in National Health and Nutrition Examination Survey (NHANES),[327] pre- (*l* subscript) and post (*m* subscript)- intervention that shifted 10% of the proportion of the population with blood pressure above goal to unexposed (i.e. below goal blood pressure). Results were estimated per 100,000 PY and represent a special case of the population attributable risk that considers partial, rather than complete, elimination of the risk factor. Here we considered partial elimination of blood pressure above goal, achieved after implementing interventions that decreased the proportion of the population with blood pressure above goal by 10%.[328] Age- gender-and diabetes- specific results were then collapsed by race using a case-load weighted summation method[329,330] and 95% confidence intervals (CI) were obtained using bootstrapping.[331]

Disability adjusted life years

DALYs are commonly used health metrics to quantify disability associated with a disease and measure the difference between the current health status in the population and a counterfactual where the population does not develop the disease, instead living a full life

expectancy without disability.[25] A single disease-specific DALY can be interpreted as one healthy year of life loss due that medical condition. DALYs are comprised of two measures: years of life lost (YLL) as the premature mortality in a population due to medical condition, and years of life lived with disability (YLD) that estimates the disability associated with living in the diseased state. DALYs were calculated as the sum of YLL and YLD:

$$DALYs = YLLs + YLDs$$

where:

$$YLLs = \sum \text{number of deaths} \times \text{life expectancy at age of death}$$

and:

$$YLDs = \sum \text{Number of incident cases} \times \text{disability weight} \times \text{the average duration of a case}$$

For YLL estimation the number of deaths included all deaths among those with kidney failure and life expectancy at age of death was calculated using age, race, and gender specific 2012 US life tables. Calculation of YLD for kidney failure was dependent on the disability weight assigned to designate the severity of disability experienced as a result of living with kidney failure. Disability weights for a given medical condition conventionally range from 0 to 1, with 0 implying ideal or optimal health and 1 implying a state equivalent to death. The disability weight assigned to treated stage 5 CKD by the Global Burden of Disease panel of reviewers was 0.571.[332] For YLD estimation, the disability weight (0.571) was multiplied by the number of incident kidney failure events and by the average duration of a case until death or end of follow-up. DALYs for each blood pressure reduction strategy were calculated as the difference between DALYs associated with all ARIC incident kidney failure events and DALYs associated with the number of incident kidney failure events after a given blood

pressure reduction. All statistical analyses were performed using SAS 9.4 (Cary, North Carolina) and STATA 12 (College Station, Texas).

Results

Compared with white Americans, African Americans were slightly younger, more often female, and twice as likely to have diabetes at baseline. African Americans were also twice as likely to be on antihypertensive treatment and had a higher prevalence of blood pressure above both JNC 7 and JNC 8 goals compared to white Americans (Table 16). Over a mean 20.4 years of follow up, 432 and 522 cases of kidney failure were identified in African Americans and white Americans respectively, (Tables 16 and 17). The crude incidence rate of kidney failure among African Americans (527.1/100,000) was approximately 2 times the incidence rate of kidney failure among white Americans (218.9/100,000).

A reduction of 20.1 (95% CI: 12.4-27.8) and 9.3 (95% CI: 6.0-12.5) incident kidney failure events per 100,000 PY in African Americans and white Americans, respectively was estimated to follow a population-wide hypothetical intervention that achieved an overall 2 mmHg decrement in SBP at study baseline (Table 18; Figure 12). The estimated preventable incident kidney failure events following a 2 mmHg reduction in SBP were twice as large in African Americans compared to white Americans. If applied nationwide, a hypothetical 2 mmHg shift in SBP among African American and white American aged 45-64 years was estimated to prevent approximately 7,176 incident kidney failure events annually; a more modest reduction of 1 mmHg decrement in SBP would result in approximately 3,588 incident kidney failure events annually (Table 19).

In addition to decreasing the incidence of kidney failure, a population wide reduction in SBP may impact disability and early mortality associated with kidney failure. In the ARIC

cohort, kidney failure was associated with 11,233 YLLs (47% African American) as a measure of burden of early mortality. Approximately 2,872 years of life were lived following the incident kidney failure event; multiplying this estimate by the kidney failure disability weight of 0.571 yielded 1,640 YLDs (49% African American). Together, the YLD and YLL estimates (total DALYs=12,873) indicated that, on average, African American and White American ARIC participants with kidney failure experienced 13.9 and 12.7 DALYs, the majority representing early mortality. A 2 mmHg reduction in SBP was associated with 37.5 and 14.0 fewer DALYs associated with kidney failure in African American and white American participants, respectively.

As a comparison to hypothetical population wide SBP reductions we estimated the effect of interventions that target populations with blood pressure above goal, and thus apply to this smaller set of the total population. Interventions applied population-wide included the entire eligible ARIC cohort of 15,744 participants at baseline, whereas interventions targeted to populations above JNC 7 guidelines applied to 1,229 and 1,186 African Americans and white American participants classified as having blood pressure above goal. A 10% proportional reduction in blood pressure above JNC 7 goal estimated a slightly higher reduction in kidney failure events compared to a population-wide reduction of 1 mmHg for African Americans. In contrast, a 10% reduction in blood pressure above goal resulted in approximately half the event reductions association with a 1 mmHg population wide SBP reduction for white Americans (Table 18). Specifically, a 10% proportional reduction in blood pressure above goal at study baseline resulted in approximately 12.5 (95% CI: 7.8-17.6), and 2.5 (95% CI: 1.3-3.7) fewer incident kidney failure events per 100,000 PY in African Americans and white Americans, respectively (Table 18). If a 10% proportional

reduction in blood pressure above JNC 7 goal were achieved nationwide in African Americans and white American populations aged 45-64, approximately 1,129 and 1,418 incident kidney events could be prevented annually. A 10% reduction in blood pressure above goal was associated with 23.5 and 3.9 fewer DALYs associated with kidney failure in African American and white American participants, respectively.

Discussion

Our results from a biracial, population-based cohort estimate that a modest population-wide 2 mmHg decrement in systolic blood pressure could prevent substantially more incident kidney failure events compared to interventions that achieve a 10% proportional reduction of the population with blood pressure above the treatment goal. For either hypothetical approach to blood pressure reduction, the estimated benefits of lowering blood pressure on incident kidney failure events were greater for African Americans compared to white Americans. Kidney failure was associated with premature mortality and a considerable number of years lived with disability. Both the population-wide and the blood pressure above goal interventions considered in this report were estimated to decrease the incident of kidney failure and the number of DALYs associated with kidney failure events.

We consider the two types of intervention presented in this report to be compatible, and likely complementary. Although they mostly draw on different resources and channels of funding, only clinically oriented strategies that target 'high risk' populations whose blood pressure is elevated above goal are now being implemented systematically, and on a large scale. An exclusive reliance on the high risk strategy focused on individuals whose blood pressure is above a treatment goal is insufficient to reduce the burden of disease and mortality associated with the levels of blood pressure that characterize most

contemporaneous populations.[245,332] Our results suggest considerable potential for benefit in reducing the burden of kidney failure and associated DALYs through population-wide reductions of blood pressure that are of modest magnitude, and are demonstrably attainable through modification of lifestyle or health-related behaviors. Awareness of the large predicted benefit associated with population-wide blood pressure reductions of modest magnitude is low however, to the detriment of efforts to investigate population strategies for blood pressure reduction and the primordial prevention of blood pressure elevation.

While environmental, behaviors and lifestyle factors can have a substantial influence on both the development and progression of CKD and its risk factors,[69,151,155,176,312] emphasis is often placed on lifestyle modification after CKD has developed.[23,188] The estimated reductions in incidence and associated disability across race/ethic groups following a population wide reduction in SBP support a paradigm shift not only from focusing predominately on risk factors once levels have surpassed clinical thresholds that designate them as targets for intervention but also support a shift from focusing on lifestyle factors after kidney disease has developed.[272,273,313,314] Although lifestyle modification studies for the long-term prevention of kidney failure are scarce, preventable lifestyle modifications such as increased physical activity and optimized diet quality are expected to have a positive impact on risk factors that influence the initial development of kidney failure, such as elevated blood pressure, obesity and diabetes.[264,282,344-346]

African Americans comprise of approximately a quarter of the ARIC cohort, however approximately half of the DALYs associated with incident kidney failure in this population are contributed by African Americans, reflecting the near double incidence rate of kidney failure among African Americans compared to white Americans in the ARIC cohort.

Previous studies suggest that accounting for age, the incidence rate of ESRD with hypertension listed as the primary cause is 2 to 7 fold higher among African Americans compared to white Americans.[99] The relationship between hypertension and ESRD and the higher prevalence of blood pressure above goal in African Americans contributes to explaining the considerably greater estimated benefits from blood pressure reductions on kidney failure events observed for African Americans compared to white Americans. The disproportionate burden of kidney failure among African Americans,[99] highlights the need for more widespread interventions that can benefit this population to reduce disparities in the burden of kidney failure.

Despite the large burden of disability estimated for CKD and kidney failure by the Global Burden of Disease project,[333] few studies have characterized the disability associated with kidney failure.[334] In addition to the complex manifestations of kidney failure and its associated comorbidities,[347] dialysis requires a patient to seek intensive medical care approximately three times a week, for sessions lasting nearly a half a day.[348] Symptoms of kidney failure, including extreme fatigue and the time commitment required for dialysis, restrict patients' ability to care for themselves physically and financially.[22] In addition to reductions in incidence and disability, the economic savings potentially achieved from population strategies to prevent or delay the onset of kidney failure and its sequelae of chronic conditions such as congestive heart failure, should be considered.[99,349] Estimates from USRDS 2016 show that approximately 678,383 ESRD patients accounted for $32.8 billion in direct medical costs, driven in part by the cost of $87,638 per year for the treatment of each hemodialysis patient.[99] Beyond the costs of care, benefits associated with efforts to prevent kidney failure would accrue from the increase in years of productive life and the

avoidance or delay of disability associated with kidney failure.[22,350] Analysis of the health and economic benefits associated with prevention of incident kidney failure through blood pressure reduction should thus consider population intervention approaches to achieve modest reductions in blood pressure levels.

The strengths of this study include over 20 years of follow up of a biracial, middle aged cohort with standardized examinations and assessments of risk factors, and a comprehensive surveillance of kidney failure.[7,351] Extending the traditional USRDS identification of ESRD to include diagnostic codes and eGFR measurements at ARIC visits for kidney failure identification incorporated death as a competing event in late stage CKD, prior to dialysis initiation or entry in the USRDS registry. Several limitations of our analysis should also be considered. Our calculation of DALYs considers all incident kidney failure events as treated with dialysis and thus all events are assigned a disability weight of 0.571. A sensitivity analysis classifying incident kidney failure events not identified by linkage to USRDS as untreated assigned a disability weight of 0.569,[333] which did not appreciably change our results. Furthermore, our estimated reduction in DALYs following decreases in blood pressure only decreased the number of incident events used to calculate YLD and did not impact the estimated number of deaths among those with incident kidney failure, likely underestimating the benefit of blood pressure reduction on DALYs.

A recent Kidney Disease Improving Global Outcomes (KDIGO) conference identified a need to characterize the impact of kidney failure on population health for policymakers to enable an allocation of resources for prevention.[352] Primordial and primary prevention of risk factors for kidney failure, including blood pressure, in early and middle life likely provide the greatest opportunity for reducing the incidence of kidney failure and its

associated disability. Our results suggest that modest improvements in the population level of blood pressure, and in the proportion of individuals with blood pressure above goal can decrease both the incidence of kidney failure and the number of years lost or lived with disability associated with kidney failure.

Table 16. Baseline characteristics of the Atherosclerosis Risk in Communities Study (ARIC) Study cohort (N=15,744) by race, 1987-1989.

Baseline Characteristics	**African Americans (n=4,266)**	**White Americans (n=11,478)**
Mean follow-up in years, (SD)	19.3 (7.0)	20.8 (6.0)
Mean age in years, (SD)	53.6 (5.7)	54.4 (5.7)
Diabetes	821 (19.8)	1046 (9.1)
Female, N (%)	2,635 (61.2)	6,050 (52.7)
Reported antihypertensive use, N (%)	1,728 (40.5)	2,271 (19.8)
Mean systolic blood pressure, mmHg (SD)	128.9 (21.6)	118.5 (17.0)
Mean diastolic blood pressure, mmHg (SD)	79.7 (12.3)	71.5 (10.0)
Blood pressure categories*		
Blood pressure above JNC 8 goal, N (%)	1,229 (28.9)	1,186 (10.3)
Blood pressure above JNC 7 goal, N (%)	1,324 (31.8)	1,453 (12.7)

*JNC 7, blood pressure values that exceed thresholds for management of blood pressure defined by JNC 7; JNC 8, blood pressure values that exceed thresholds for management of blood pressure defined by JNC 8; SD, standard deviation

Table 17. Incident CKD and kidney failure events and incidence rates in the ARIC study cohort (N=15,744), by race (1987-2011)

	Incident kidney failure events reduced* per 100,000 PYs (95% CI) by Interventions achieving reductions in BP	
Blood pressure intervention	**African Americans**	**white Americans**
Hypothetical population-wide intervention to decrease SBP		
1 mmHg decrease	10.5 (6.2-13.9)	4.6 (3.0-6.3)
2 mmHg decrease	20.1 (12.4-27.8)	9.3 (6.0-12.5)
Hypothetical intervention to reduce blood pressure above treatment threshold		
10% decrease in all BP above JNC 8 treatment goal	10.2 (5.8-15.0)	2.2 (1.2-3.3)
10% decrease in all BP above JNC 7 treatment goal	12.5 (7.8-17.6)	2.5 (1.3-3.7)

Table 18. Estimated incident kidney failure events reduced from population-wide intervention that achieves a 1-2 mmHg decrement in SBP, or targeted intervention that achieves a 10% reduction in blood pressure above JNC 8 or JNC 7 treatment goals, by race (N=15,744), 1987-2011, ARIC Study.

	African American			White Americans		
	Number of Events	Total Person-years	Incidence Rate per 100,000 PY	Number of Events	Total Person-Years	Incidence Rate per 100,000 PY
Incident CKD	1,115	75,547.9	1,475.9	2,737	227,556.7	1,202.8
Incident Kidney Failure	432	81,954.4	527.1	532	238,483.7	223.5

Table 19. Estimated incident kidney failure events reduced from hypothetical population-wide and targeted blood

	Incident kidney failure events reduced* per 100,000 PYs (95% CI) by Interventions achieving reductions in BP	
Blood pressure intervention	**African Americans** US population size N=9,042,518	**white Americans** US population size N=57,864,260
Hypothetical population-wide intervention to decrease SBP		
1 mmHg decrease	909	2,679
2 mmHg decrease	1,818	5,358
Hypothetical intervention to reduce blood pressure above treatment threshold		
10% decrease in all BP above JNC 8 treatment goal	921	1,251
10% decrease in all BP above JNC 7 treatment goal	1,129	1,418

*****Total 2010 US census race specific populations aged 45-64 (African American n= 9,042,518, white American n= 57,864,260) were used to calculate the population projections

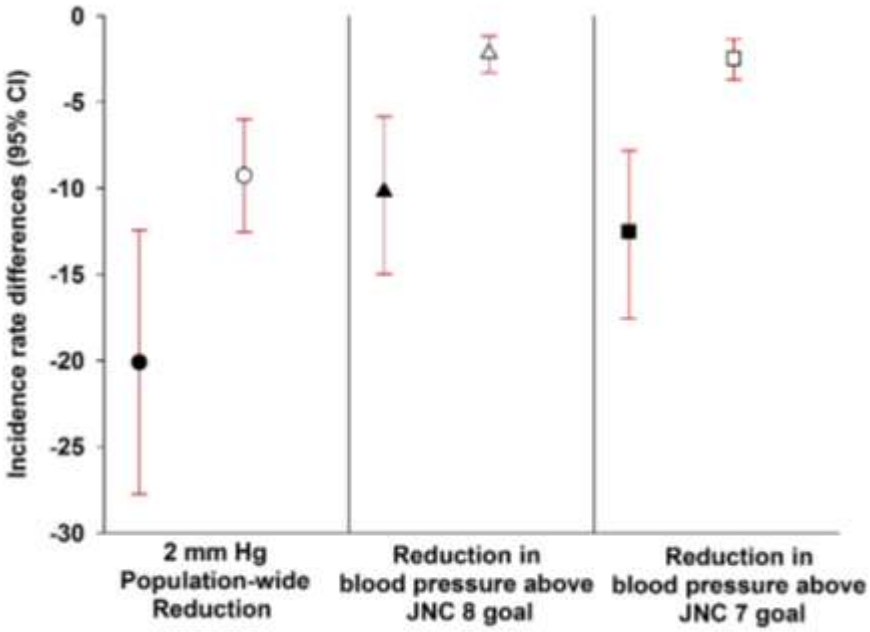


Figure 12. Incidence rate differences or estimated number of events reduced for kidney failure per 100,000 person-years associated with 2 mmHg reduction in systolic blood pressure population-wide (circle), 10% proportional reductions in blood pressure above JNC 8 (triangle) and JNC 7 treatment goal (square) in African American (black symbols) and white American (white symbols) ARIC participants, 1987-2011

CHAPTER 6: DISCUSSION

6.1 Introduction

To our knowledge, the results presented herein are the first to compare the benefits of population-wide blood pressure reduction strategies and among those with blood pressure above treatment thresholds for the prevention of CKD and kidney failure. Despite the ability of lifestyle interventions to reduce many of the risk factors for CKD, few studies have evaluated the predicted effect on incident CKD or kidney failure associated with improvements in diet quality, and physical activity.[353,354] Given that elevated blood pressure is a highly prevalent risk factor for CKD that is modifiable by well-established lifestyle modifications, this represents an opportunity to influence blood pressure levels at the population level to prevent or delay the development of CKD and kidney failure, and their associated disability. Our results comparing the impact of two pragmatic interventions on blood pressure levels hypothesized to reduce the incidence of CKD and kidney failure suggest that modest improvements both in the level of SBP and of blood pressure above goal have the potential to reduce the incidence of CKD and kidney failure substantially. African Americans, who bear a disproportionate burden of kidney failure and its associated disability, would potentially benefit from blood pressure reduction strategies more than white Americans. Further work to define the ability and cost effectiveness of lifestyle modifications to reduce the burden of CKD and kidney failure in the U.S. population is needed to define the merits of widespread implementation of population-wide lifestyle interventions for CKD prevention.

6.2 Key Findings

Three main comparisons are presented and described by this doctoral research: (1) the potential events reduced from population-level primordial prevention of elevations in blood pressure compared to the high risk approaches of treating clinical defined elevated blood pressure, (2) the benefits of reducing blood pressure on the incidence of CKD compared to incidence of kidney failure and (3) the evaluation of the impact of 10% reductions in blood pressure above treatment goals on incident CKD and incident kidney failure events, contrasting the thresholds of the two most recent blood pressure reduction guidelines (JNC 7 and 8). Each of these comparisons have public health implications that could influence the current paradigm that focuses on risk factors or diseases once they reach a clinical intervention target, to an emphasis on prevention at the population level and the clinical setting.

Population-wide reductions in SBP of 2 mmHg are predicted to preempt approximately twice the number of incident CKD and kidney failure events compared to a 10% reduction in the proportion of the population with blood pressure above both JNC 7 and JNC 8 treatment thresholds. Despite the substantial potential for CKD prevention estimated from population based interventions, only clinically oriented strategies that target 'high risk' populations whose blood pressure is elevated above goal are now being implemented systematically, and on a large scale.[355] An exclusive reliance on the high risk strategy focused on individuals whose blood pressure is above a treatment goal leaves a large subset of the population with prehypertension or high normal blood pressure without intervention, and at increased risk of disease. The persistently high levels of antihypertensive treatment combined with suboptimal control of blood pressure levels among those treated, makes an

exclusive focus on this population insufficient to reduce the burden of disease associated with the levels of blood pressure that characterize most contemporaneous populations.[245,332] The considerable potential benefits in reducing the burden of kidney failure, and associated DALYs, through population-wide reductions of blood pressure that are of modest magnitude as shown by our results are demonstrably attainable through modification of lifestyle or health-related behaviors.[264] Population strategies for blood pressure reduction and the primordial prevention of blood pressure elevation should thus be explored for their potential role in strategies used to reduce the population burden of CKD and kidney failure.

While a greater reduction in incident CKD events compared to incident kidney failure was generally predicted by both blood pressure intervention approaches considered , much of the kidney disease literature has historically been devoted to disease management among the kidney failure population with only recent efforts addressing moderate stages of CKD and CKD progression. The substantial burden of disease and disability associated with kidney failure support the high proportion of resources and awareness allocated to this debilitating disease.[99] Yet modest efforts oriented to the investigation of CKD prevention seems incongruent with the larger burden of incident CKD that could be prevented through reduction of blood pressure in the in the population. Greater scientific awareness of the potential benefits of blood pressure interventions on the development of CKD could increase the examination of risk factor prevention to favorably influence the rates of CKD incidence.

Considerably greater benefits from blood pressure reduction strategies were estimated for African Americans compared to white Americans with kidney failure as the outcome of interest compared to incident CKD. For example, after adjustment for antihypertensive use, gender, diabetes and age, a 2 mmHg decrement in SBP across the total population was

associated with fairly similar estimated event reductions for incident CKD in African American and white American participants (23.5 and 26.8 fewer incident CKD events reduced per 100,000 PY respectively). In contrast, African Americans would have twice the reduction in the number of kidney failure events compared to white Americans as a result of the same intervention (20.1 and 9.3 fewer incident kidney failure events per 100,000 PY in African Americans and white Americans, respectively). This greater benefit for kidney failure prevention among African Americans is amplified when assessing a high risk approach to blood pressure reduction. A 10% proportional decrease in the population with blood pressure above JNC 7 treatment goal was estimated to reduce almost twice the number of CKD events among African Americans compared to white Americans (16.1 and 7.8 fewer incident CKD events per 100,000 PY), and approximately five times fewer incident kidney failure events in African Americans compared to white Americans (12.5 and 2.5 fewer incident KF events per 100,000 PY). Reflecting the rapid rate of kidney decline and the higher risk of ESRD attributed to hypertension in African Americans compared to age matched white Americans[143,144] this increased benefit of kidney failure prevention through intentional blood pressure modification could increase health equity in a population disproportionately burdened with kidney failure and its associated disability.

As expected, classification of blood pressure above goal defined with the lower SBP thresholds recommended by JNC 7 compared to JNC 8 categorized a larger number of participants as having blood pressure above goal, thus establishing a larger target population for interventions aimed at reducing blood pressure. Though examination of the estimated incidence rate difference showed only modest gains in potential events reduced by implementation of interventions following JNC 7 guidelines compared to JNC 8,

extrapolation to U.S. population highlights the magnitude of CKD and kidney failure prevention achievable using the former guidelines. A 10% proportional reduction in blood pressure above goal using JNC 7 guidelines was estimated to prevent approximately an additional 1,182 and 375 incident CKD and kidney failure events annually compared to a 10% proportional reduction in JNC 8 defined blood pressure above. A threshold of 140/90 mmHg supported by the JNC 7 guideline is reasonably considered safe and effective for the generally population at risk for CKD, though guidelines are continuously evolving.[15,291] In terms of CKD preventions, modest reductions in the population with blood pressure above goal defined by JNC 7 offers the greatest benefit among those at increased risk compared to JNC 8.

6.3 Strengths

The ARIC cohort consists of a large sample of African American and white American individuals middle-aged at intake in 1987-1989, with standardized measurement of blood pressure and relevant risk factors for CKD at baseline. With a sample size of 15,744 participants and an extensive follow-up (approximately 20 years), the ARIC study enabled the ascertainment of a substantial number of incident events; specifically, 3,852 incident CKD events and 954 kidney failure events were ascertained. Events were ascertained from a variety of sources including creatinine measurements at ARIC study visits, linkage to the USRDS registry for identification of treated ESRD, and surveillance of death or hospital records for identification of ICD-9 or ICD-10 discharge coding for CKD or kidney failure in any position. The use of both USRDS and cohort or surveillance allowed for the ascertainment of kidney failure and CKD events that are untreated or censored prior to

treatment initiation, permitting the inclusion of outcomes that are often under-reported in the literature. Despite these strengths, several limitations of the available data should be noted.

6.4 Limitations

6.4.1 Limited assessment of eGFR and CKD staging

ARIC study visits one through four occurred every three years, with a fifth visit subsequently occurring about 15 years after the conclusion of the fourth. Although five ARIC visits were completed and accessible for this analysis, creatinine was not measured at visit three. The 6- and 15- year gaps in creatinine measurements between visits 2 and 4 and visits 4 and 5 may increase the likelihood of missed events. Ascertainment of events using the USRDS registry and medical records served as an additional avenue for event identification however, although events ascertained using the latter method provided little covariate or eGFR specific data at the time of event identification. For example, stage specific CKD discharge coding only became available in the early 2000s. Older coding practices that provide no patient-specific eGFR levels at time of hospitalization or stage-specific coding have proved inadequate. As a further limitation, the stage of CKD at time of diagnosis is unknown for cases identified through hospitalization.[99,356]

The KDIQO recommended definition of CKD includes a repeated measure of eGFR after 3 months to confirm chronicity of disease.[67] While confirmatory tests were not done in this cohort, the definition of CKD used in the this analysis included a 25% decline in eGFR from baseline allowing for verification a meaningful decline in eGFR over time. Confirmation of 25% decline in eGFR and thus chronicity of disease was not available for cases identified through hospital records.

The long duration of follow up is a major strength of this analysis but also contributes an important weakness. In conjunction with the normal number of glomeruli deteriorating with advancing age GFR gradually declines by approximately 1 mL/min/y/1.73 m^2 annually, falling to an average of 70 mL/min/1.73 m2 by 70 years of age. Participants with advanced age in the later ARIC visits may be classified as incident CKD based on eGFR values that reflect relatively normal eGFR decline in older age. The contribution of older participants with higher Stage 3 eGFR values to the number of incident CKD cases was not evaluated.

Outcomes of Incident CKD and Disability Associated with Incident CKD

This doctoral work originally aimed to investigate the benefits of blood pressure reduction strategies on the burden of DALYs associated with incident CKD, but limitations of our data prevented the estimation of several components of the YLL statistic. Chief among these restrictions was the limited information available to determine staging of cases of CKD at identification, as mentioned above for cases identified via hospital or death records (n=2,057). Quantifying the number of incidence cases of CKD by stage was critical to the calculation of YLL as the value assigned to the disability associated with CKD varies by stage and anemia status. As described in section 4.4, disability weights for CKD ranged from 0.004 for stage 3 CKD with mild anemia to 0.237 for stage 4 CKD with severe anemia and 0.569 for stage 5 CKD with no treatment.[333] Hemoglobin measurements needed to assess anemia status and apply the appropriate disability weight within stage of CKD was not available at all ARIC visits on the full cohort, resulting in a large number of observations with missing anemia classification. The underutilization and lack of specificity of ICD 9/10 codes for anemia precluded the use of medical records for determining anemia status of ARIC cohort members. Although multiple imputation or anemia prevalence estimates for

external sources could have been used as surrogates for missing data, lack of CKD staging in approximately half of incident CKD events devalued the usefulness of defining anemia as both measures were needed for assigning the relevant disability weight. Duration of time expended in each stage of disease was also unavailable. With no usable measures of the components required to calculate YLL for incident CKD, the disability burden described by aim 2 was restricted to kidney failure assessment.

6.4.2 Interval censoring

Interval censored of event times frequently occurs in longitudinal studies in which covariates and outcomes are only measured periodically at scheduled visits.[357,358] With episodic assessments the exact time of onset for the outcome of interest is not detected but is known to occur in the time interval between the last disease free assessment and the first observation that indicates disease.[357] In the ARIC study measurements of creatinine used to assess CKD status were only collected at visits, 1 and 2 (3 year interval), visit 4 (6 year interval between visits 2 and 4) and visit 5 (15 year interval between visits 4 and 5). In an individual with an eGFR $\geq$ 60 mL/min/1.73 m^2 at visit 2 and an eGFR that has fallen below 60 mL/min/1.73 m^2 measured visit 4, the onset of CKD transpired at some point between these exam visits, although the precise time of onset is unknown. Although timing of some outcomes such as death or renal replacement was ascertained from death or hospital records, the precise time of occurrence for CKD events is rarely exactly measured by record sources given that medical encounters infrequently coincide with a decline in eGFR to a specific threshold.[359]

Given the large censoring intervals in the ARIC cohort's consecutive eGFR measurements, it is probable that the recorded timing of CKD onset in our study is not

consistent with the actual onset of disease, and interval censoring should ideally be accounted for in this analysis.[360] We developed a maximum likelihood approach to estimate the incidence rate difference incorporating an adjustment for interval censoring (Appendix 3). While this approach was computationally sound, it failed to make proper use of the available eGFR measurements in the ARIC study. Next, we explored the use of piecewise linear equations to plot the available eGFR measurements and reverse calculated the time point at which participants likely crossed the eGFR threshold used to classify incident CKD (Appendix 3)[361]. Due to uneven follow-up time the knots used to calculate individual piecewise linear equations had to be participant specific given that visit dates for each participant varied, an issue that was further complicated by missing eGFR measurements on some participants. Lastly, we used mixed models to overcome concerns regarding unequally spaced time intervals between measurements, unequal number of measurements per participant, and reliance on individual eGFR trajectories. Despite these strengths our mixed models estimated up to 45% of African Americans and 36% of white Americans to have follow-up times that were longer than the follow-up time recorded by the ARIC study (Appendix 3).

Two popular and simpler approaches for assigning event times when the exact time of onset is interval censored are right imputation and midpoint imputation.[362] Right imputation would simply assign the time CKD was identified in the ARIC study as the time of CKD onset; this method has been commonly used in CKD analyses. When the interval between two consecutive measurements is narrow or censoring is minimal, imputation using the time of measurement as the event time may be sufficiently similar to the exact onset times. However, when interval censoring is disregarded or treated as exact times using longer

censored intervals, imputations using measurement times can create a sample that is not representative of the study population and introduce considerable bias to parameter estimates, potentially resulting in incorrect conclusion and inference errors regarding the effect of covariates on onset time.[359,363] Midpoint imputation accounts for the notion that actual onset of disease occurs in the interval bounded by measurement collections by assigning the average or midpoint of the censored interval as the event time. Midpoint imputation is therefore dependent on the amount of time between outcome measurements, which for CKD in the ARIC study ranges from 3 to 15 years. Uneven intervals bounding the onset times in our study would lead to varied assignment of midpoint event times depending on the visits at which the onset of CKD was identified. Imputing exact onset times from the interval midpoint is arbitrary and has been shown to underestimate the variance by failing to account for the inherent uncertainty regarding the exact time of declines in eGFR below <60 mL/min/1.73 m2. [364] Although interval censoring frequently occurs in studies of CKD incidence and progression, interval censoring is rarely acknowledged in analysis techniques employed in these studies or the above mentioned basic imputation methods are used to account for censored intervals.[359]

Due to the limitations in using the maximum likelihood, piecewise linear, mixed effects modelling and midpoint imputation approaches for interval censoring noted above, we used right imputation to define onset of incident CKD and kidney failure. Using right imputation to assign CKD onset times would generally underestimate incidence rates. To examine the sensitivity of our incidence rate difference estimates to interval censored outcome times for both the population-wide and targeted blood pressure above goal reduction strategies, we applied follow-up time reductions of 1, 1.5, and 2 years among incident CKD

cases identified at ARIC visits to estimate the impact of event times occurring prior to identification at an ARIC visit. Sensitivity analyses to determine the degree to which length of follow-up time influences the potential reduction in incident CKD indicated less than 1 additional preventable event for up to 2 years of decreased follow up time among cases identified at ARIC study visits (Appendix 1, supplemental table 1).

6.5 Public Health Implications and Future Directions

Physical activity, weight reduction, and sodium restriction have been shown to favorably alter several of the known risk factors for CVD and CKD, including hypertension, dyslipidemia, obesity, and diabetes and to decrease the risk for CVD.[264,326] It could be assumed that trials of blood pressure reduction through lifestyle modifications for CVD prevention would extend to CKD, yet the literature lacks direct studies of this renal outcome. A trial with sufficient statistical power to detect reductions in the initial development of CKD in the general population would require large sample size and budget, and is unlikely to be funded.[365] Few RCTs have been designed and conducted specifically to examine population wide blood pressure interventions such as sodium reduction and CKD, likely due to the practical considerations, unjustifiable expense and the questions of equipoise given the high quality of information on the benefits of salt reduction and CVD.[266] A trial of sodium reduction in the general population with an outcome of CKD may be considered unnecessary for the purposes of supporting sodium reduction policies given the strength of the existing evidence of risk associated of elevated blood pressure and CVD with excess sodium intake.[13,343,344] The literature on blood pressure intervention on CKD as an outcome is populated largely by studies assessing the benefits of a new antihypertensive medication on CKD progression or kidney failure, given the much shorter time frame needed to ascertain

late stage outcomes among those with reduce kidney function compared to the general population. Blood pressure reduction by pharmacologic intervention for incident CKD prevention among hypertensives is likewise rarely formally assessed in randomized clinical trials.

Even contemporary projections of the effects of reductions in sodium on relevant outcomes have been limited to specific cardiovascular events.[13] For example, a reduction in population-wide sodium intake of 1200 mg/dL, achievable by reducing sodium used in food production, was estimated to annually reduce coronary heart disease by 60,000 to 120,000, stroke events by 32,000 to 66,000, myocardial infarctions by 54,000 to 99,000, and deaths by 44,000 to 92,000.[13] Annual savings of 194,000 to 392,000 quality-adjusted life-years and $10 to $24 billion in healthcare costs were also estimated from reductions in CVD.[13] The exclusion of CKD from these estimates represents a missed opportunity to address the full benefits of sodium reduction at the population level and contribute information to inform national policy on this issue.

The current incomplete characterization of the effects of pressure reduction through lifestyle modification on incident CKD by large, high quality randomized controlled trials and global projections highlight the public health importance of our results. Experimental proof of benefits on the incidence of CKD from lifestyle-based population intervention desirable, but lacking. Estimation of the predicted effects of hypothetical interventions on incident CKD events that would follow reduction is blood pressure of small magnitude can bring awareness to both the substantial health benefits of lifestyle modification and to the prevention of CKD as opposed to an exclusive reliance on disease management. Blood pressure approaches that reduce the incidence of CKD would likely also have beneficial

effects on cardiovascular morbidity and ultimately the risk of mortality. Preventing the development of CKD would also reduce the risk of subsequently developing kidney failure. In this work we estimated the number incident CKD events that are reduced by attainable blood pressure decrements. Additional analyses to explore the implications of a prevented CKD event on downstream health events are warranted to describe the potential gains to be achieved through prevention of disease.

If the controversy currently surrounding blood pressure treatment goals results in altered guidelines, lower blood pressure treatment thresholds would magnify the scope of targeted intervention and reasonably result in increased prevention of CKD events. Whether lower treatment thresholds would result in treatment initiation at lower blood pressure values is unknown. Our estimates suggest that to maximize CKD prevention, JNC 7 recommendations of healthy lifestyles modifications among those with prehypertension supported by clinical and public health efforts should be expanded to all populations regardless of blood pressure levels. Such efforts could prevent the development of established hypertension and its sequela of a spectrum of adverse health outcomes that extend beyond the scope of estimates presented herein.

We consider the two types of intervention presented in this report to be compatible, and likely complementary. Our goal in presenting the superiority of population-wide approaches to blood pressure management in reducing the burden of CKD is not to intended to support recommendations favoring one preventive strategy over the other, but rather to emphasize the neglected opportunity to expand the target population beyond those at high risk. An exclusive reliance on the high risk strategy is inadequate for maximizing the yield of preventative action. To support the addition of population-wide strategies to current public

health efforts, cost analyses of each strategy for prevention of an event must be considered. Targeting those at high-risk is known to be cost-effective for disease prevention on grounds of logistics, feasibility and efficacy of interventions. Its efficacy in reducing the population burden of the blood pressure-related disease is limited, however. Characterizing the benefits and costs associated population-wide, lifestyle-based interventions for blood pressure reduction is a compelling next step that should be explored in future work.

APPENDIX 1: MANUSCRIPT 1 SUPPLEMENTAL TABLES

Supplemental Table 1: Incident CKD events reduced annually from two population-wide hypothetical blood pressure reduction interventions accounting for 1, 1.5 or 2 years of interval censored follow up time, by race, 2010 US census population age 45-64

	Incident CKD events reduced* per 100,000 PYs (95% CI) by Interventions achieving reductions in BP	
Blood pressure intervention	African Americans	White Americans
Follow up time recorded in the ARIC cohort		
1 mmHg decrease	11.7 (6.2-17.3)	13.42 (10.3-16.6)
2 mmHg decrease	23.5 (12.3-34.6)	26.8 (20.6-33.1)
1-year adjustment for interval censoring		
1 mmHg decrease	11.9 (6.2-17.5)	13.6 (10.4-16.8)
2 mmHg decrease	23.8 (12.4-35.1)	27.2 (20.8-33.5)
1.5 year adjustment for interval censoring		
1 mmHg decrease	12.0 (6.3-17.7)	13.7 (10.5-16.9)
2 mmHg decrease	23.9 (12.5-35.3)	27.3 (20.9-33.7)
2.0 year adjustment for interval censoring		
1 mmHg decrease	12.0 (6.3-17.8)	13.7 (10.5-17.0)
2 mmHg decrease	24.0 (12.6-35.5)	27.5 (21.0-33.9)

Supplemental Table 2: Estimated incident CKD events reduced from a hypothetical intervention that achieves a 5, 10 or 20% reduction of unaware, untreated or uncontrolled blood pressure above JNC 8 goals, by race (N=15,390), 1987-2011, ARIC Study.

Blood pressure category	Incident CKD events reduced* per 100,000 PYs (95% CI) by interventions achieving reductions in BP above goal					
	5% proportional reduction		10% proportional reduction		20% proportional reduction	
	African American	White American	African American	White American	African American	White American
Hypothetical intervention to reduce blood pressure above JNC 8 treatment threshold						
Unaware	1.4 (0.8-2.1)	1.2 (0.9-1.6)	2.7 (1.6-4.2)	2.5 (1.8-3.3)	5.4 (3.2-8.4)	4.9 (3.5-6.5)
Untreated	1.2 (0.7-1.9)	0.3 (0.2-0.3)	2.4 (1.4-3.7)	0.5 (0.4-0.7)	4.8 (2.8-7.4)	1.03 (0.7-1.4)
Uncontrolled	2.5 (1.5-3.8)	0.7 (0.5-1.0)	4.9 (2.9-7.6)	1.5 (1.0-1.9)	9.8 (5.8-15.3)	2.9 (2.1-3.9)
Hypothetical intervention to reduce blood pressure above JNC 7 treatment threshold						
Unaware	1.6 (1.0-2.4)	1.6 (1.1-2.0)	3.2 (2.0-4.9)	3.1 (2.3-4.1)	6.4 (4.0-9.7)	6.2 (4.5-8.1)
Untreated	1.4 (0.9-2.1)	0.3 (0.2-0.4)	2.8 (1.8-4.3)	0.7 (0.5-0.9)	5.6 (3.5-8.5)	1.3 (0.9-1.7)
Uncontrolled	2.9 (1.8-4.4)	0.9 (0.7-1.2)	5.8 (3.6-8.8)	1.9 (1.3-2.4)	11.6 (7.2-17.6)	3.7 (2.7-4.8)

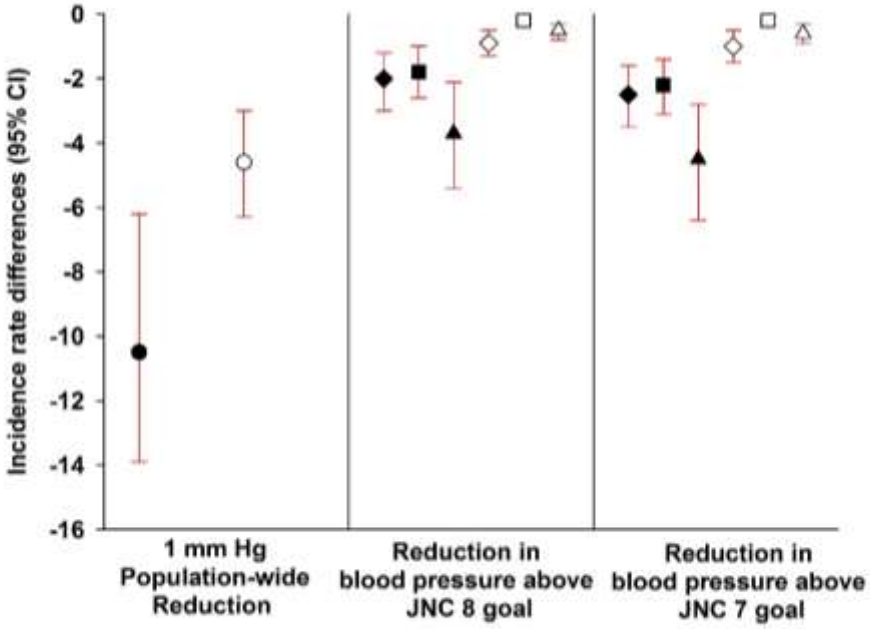
*Events reduced calculated $as\ IRD_{ijk} * (proportion_l - proportion_m)$, where *i, j,* and *k* index race, gender, and 5 year age categories, *proportion* is the race-specific proportion of blood pressure above goal pre- (*l* subscript) and post (*m* subscript)- intervention, per 100,000 person years

APPENDIX 2: MANUSCRIPT 2 SUPPLEMENTAL TABLES

Supplemental Table 1: Estimated incident kidney failure events reduced from population-wide intervention that achieves a 1-2 mmHg decrement in SBP, or targeted intervention that achieves a 10% reduction of unaware, untreated or uncontrolled blood pressure above goals, by race (N=15,744), 1987-2011, ARIC Study.

	Incident KF events reduced* per 100,000 PYs (95% CI) by Interventions achieving reductions in BP	
Blood pressure intervention	African Americans	White Americans
Hypothetical population-wide intervention to decrease SBP		
1 mmHg decrease	10.5 (6.2-13.9)	4.6 (3.0-6.3)
2 mmHg decrease	20.1 (12.4-27.8)	9.3 (6.0-12.5)
Hypothetical intervention to reduce blood pressure (above JNC 8 treatment threshold)		
10% decrease in unaware	2.0 (1.2-3.0)	0.9 (0.5-1.3)
10% decrease in untreated	1.8 (1.0-2.6)	0.2 (0.1-0.3)
10% decrease in uncontrolled	3.7 (2.1-5.4)	0.5 (0.3-0.8)
10% decrease in all BP above goal	10.2 (5.8-15.0)	2.2 (1.2-3.3)
Hypothetical intervention to reduce blood pressure (above JNC 7 treatment threshold)		
10% decrease in unaware	2.5 (1.6-3.5)	1.0 (0.5-1.5)
10% decrease in untreated	2.2 (1.4-3.1)	0.2 (0.1-0.3)
10% decrease in uncontrolled	4.5 (2.8-6.4)	0.6 (0.3-0.9)
10% decrease in all BP above goal	12.5 (7.8-17.6)	2.5 (1.3-3.7)

Figure 1: Incidence rate differences or estimated number of events reduced for kidney failure per 100,000 person-years associated with 1 mmHg reduction in systolic blood pressure population-wide (circle), 10% proportional reductions in unaware (diamond), untreated (squares), or uncontrolled (triangles) blood pressure above JNC 8 and JNC 7 treatment goal in African American (black symbols) and white American (white symbols) ARIC participants, 1987-2011



APPENDIX 3: INTERVAL CENSORING

1 Method

Consider a follow-up study with n independent subjects. For each subject i, we observe that the survival time of interest T is in (L_i, R_i), where $L_i = 0$ indicates left-censoring, and $R_i = \infty$ indicates right-censoring. We assume that the hazard function of the survival time T_i at time t is from the additive hazards model with

$$\lambda_i(t|Z_i(s), s \le t) = \lambda(t) + \beta^{\mathrm{T}} Z_i(t),$$

where $Z_i(t)$ is a set of time-dependent covariates. The observed data likelihood is

$$\begin{aligned}
L_n(\beta, \lambda) &= \prod_{L_i=0} \left(1 - \exp\left[-\int_0^{R_i} \{\lambda(t) + \beta^{\mathrm{T}} Z_i(t)\}\, dt\right]\right) \prod_{R_i=\infty} \exp\left[-\int_0^{L_i} \{\lambda(t) + \beta^{\mathrm{T}} Z_i(t)\}\, dt\right] \\
&\quad \times \prod_{L_i\neq 0, R_i\neq\infty} \left(\exp\left[-\int_0^{L_i} \{\lambda(t) + \beta^{\mathrm{T}} Z_i(t)\}\, dt\right] - \exp\left[-\int_0^{R_i} \{\lambda(t) + \beta^{\mathrm{T}} Z_i(t)\}\, dt\right]\right) \\
&= \prod_{L_i=0} \left[1 - \exp\left\{-\Lambda(R_i) - \beta^{\mathrm{T}} \int_0^{R_i} Z_i(t)dt\right\}\right] \prod_{R_i=\infty} \exp\left\{-\Lambda(L_i) - \beta^{\mathrm{T}} \int_0^{L_i} Z_i(t)dt\right\} \\
&\quad \times \prod_{L_i\neq 0, R_i\neq\infty} \left[\exp\left\{-\Lambda(L_i) - \beta^{\mathrm{T}} \int_0^{L_i} Z_i(t)dt\right\} - \exp\left\{-\Lambda(R_i) - \beta^{\mathrm{T}} \int_0^{R_i} Z_i(t)dt\right\}\right] \\
&= \prod_{L_i=0} \left[1 - \exp\left\{-\Lambda(R_i) - \beta^{\mathrm{T}} \int_0^{R_i} Z_i(t)dt\right\}\right] \prod_{R_i=\infty} \exp\left\{-\Lambda(L_i) - \beta^{\mathrm{T}} \int_0^{L_i} Z_i(t)dt\right\} \\
&\quad \times \prod_{L_i\neq 0, R_i\neq\infty} \left(\exp\left\{-\Lambda(L_i) - \beta^{\mathrm{T}} \int_0^{L_i} Z_i(t)dt\right\} \left[1 - \exp\left\{\Lambda(L_i) - \Lambda(R_i) - \beta^{\mathrm{T}} \int_{L_i}^{R_i} Z_i(t)dt\right\}\right]\right)
\end{aligned}$$

If we assume that the baseline hazards function is piecewise linear, i.e.,

$$\lambda(t) = \sum_{k=1}^{K} \lambda_k I(t_{k-1} < t \le t_k)$$

for $0 = t_0 < t_1 < \cdots < t_K = \infty$, then

$$\Lambda(t) = \sum_{k=1}^{K} \lambda_k I(t > t_{k-1})\{\min(t, t_k) - t_{k-1}\}$$

Consider a logistic regression model with log link function and no intercept

$$\log\{P(Y_i = 1)\} = X^{\mathrm{T}} \alpha,$$

where Y_i is the binary outcome, X_i is a vector of covariates, and α is the vector of regression coefficients. Then, the likelihood is of the form

$$\prod_{i=1}^{n} \{\exp(X^{\mathrm{T}}\alpha)\}^{I(Y_i=1)} \{1-\exp(X^{\mathrm{T}}\alpha)\}^{I(Y_i=0)}$$

We can artificially transform the problem of additive hazards model with interval-censored data with time-varying covariates as a logistic regression model with log link function and no intercept. Specifically, we let the covariate in the logistic regression model $X = (\widetilde{X}_1, \widetilde{X}_2)$ with $\widetilde{X}_1 = (X_{11}, \ldots, X_{1K})$ and $\widetilde{X}_2 = (X_{21}, \ldots, X_{2d})$, where d is the dimension of Z_i. The coefficient for $\widetilde{X}_1$ is equal to $(\lambda_1, \ldots, \lambda_K)$, while the coefficient for $\widetilde{X}_2$ is equal to β.

- For subject left-censored at R_i, we artificially generate one observation $Y_{i1} = 0$ with $X_{1k} = -I(R_i > t_{k-1})\{\min(R_i, t_k) - t_{k-1}\}$ and $\widetilde{X}_2 = -\int_0^{R_i} Z_i(t)dt$.
- For subject right-censored at L_i, we artificially generate one observation $Y_{i1} = 1$ with $X_{1k} = -I(L_i > t_{k-1})\{\min(L_i, t_k) - t_{k-1}\}$ and $\widetilde{X}_2 = -\int_0^{L_i} Z_i(t)dt$.
- For subject with $L_i \neq 0$ and $R_i \neq \infty$, we artificially generate two observations
  - $Y_{i1} = 1$ with $X_{1k} = -I(L_i > t_{k-1})\{\min(L_i, t_k) - t_{k-1}\}$ and $\widetilde{X}_2 = -\int_0^{L_i} Z_i(t)dt$.
  - $Y_{i2} = 0$ with $X_{1k} = I(L_i > t_{k-1})\{\min(L_i, t_k) - t_{k-1}\} - I(R_i > t_{k-1})\{\min(R_i, t_k) - t_{k-1}\}$ and $\widetilde{X}_2 = -\int_{L_i}^{R_i} Z_i(t)dt$.

The corresponding likelihood for the logistic regression model of Y_{ik} $(i = 1, \ldots, n, k = 1, 2)$ with log link function and no intercept is exactly the same as the likelihood of additive hazard model for interval-censored data with time-varying covariates. Therefore, we can obtain the estimate for $\alpha = (\lambda_1, \ldots, \lambda_K, \beta)$ using proc genmod in SAS.

2 Simulation

We generate a sequence of examination times $U_1, \ldots, U_5$, where $U_1 \sim \text{Unif}(0, 1)$ and $U_{k+1} = U_k + \text{Unif}(0, 1)$ for $k = 1, \ldots, 4$. We generate a change point $V \sim \text{Unif}(0, 5)$, and the covariate $Z(t) = B_1 I(t \leq V) + B_2 I(t > V)$ with B_1 and B_2 independent Bernoulli(0.5) random variables. We assume the baseline hazard function $\lambda(t) = 1$ and $\beta = 0.5$.

Table 1 shows the parameter estimates for the additive hazards model with $K = 5$, where the cutpoints $t_1, \ldots, t_4$ are chosen such that there are approximately equal numbers of observation times in the intervals.

Table 1: Parameter estimates for the simulated dataset

Parameter	Estimate	Std. Error	p-value
λ_1	0.933	0.126	< 0.0001
λ_2	0.938	0.342	0.006
λ_3	0.784	0.467	0.093
λ_4	0.785	0.194	< 0.0001
λ_5	0.994	0.178	< 0.0001
β	0.621	0.119	< 0.0001

Piecewise linear regression

The traditional paradigm of research on CKD development and progression has commonly employed linear regression models to approximate eGFR declines.[366,367] Assuming linearity in models of eGFR opportunely allows the slope to be interpreted clinically and academically as a rate of decline and used to estimate the timing of a patient's progression to more severe stages of CKD.[366,367] Although linearly has been shown in some studies to be consistent with the existing data, most studies using eGFR measurements have been limited to follow up times of less than 5 years and have collected few eGFR measurements per participant giving rise to both biological and measurement variability.[366,367] The assumption of linearity has not been well validated. In fact, studies have shown that eGFR trajectories in many individuals deviates from linearity with periods of accelerated or decelerated eGFR decline;[366-368] this evidence supports the use of a more complex model that intuitively allows slope to change over time as the exposures and risk factor profiles of patients changes.

Continuous piecewise linear regression is a regression model that permits multiple linear relationships and slopes to occur between the response variable (y) and the explanatory variable (x) over a range of x values.[369] In this case, follow up time can be divided into segments to allow a separate linear regression to be fitted for each interval of time. Given that eGFR measurements only occur at ARIC visits 1, 2, 4 and 5, the breakpoints or knots for partitioning intervals of time will occur at visits 2 and 4. Using two knots, our piecewise linear regression for participants attending all four ARIC visits will have three separate

regressions and corresponding slopes allowing for more variability in eGFR changes over time than would a linear model (sample plot).

Calculating piecewise linear regressions will allow for determining the date of development for CKD during the censored time interval by facilitating calculation of the time point at which eGFR crosses the threshold for CKD classification. Our piecewise linear functions will be constructed as:

$$E(y|x) = \beta_0 + \beta_1 x + \beta_2 (x - x_a) I_a + \beta_3 (x - x_b)$$

Where:

- y is the estimated glomerular filtration rate in (Units)
- x_a will represent the value of x at the first knot (a represents visit 2 at ~3 years)
- x_b will represent the value of x at the second knot (b represents visit 4 at ~9 years)
- I_a is an indicator variable equal to 1 if x>3

  0 otherwise
- I_b is an indicator variable equal to 1 if x>9

  0 otherwise

For values of x less than a (ARIC visit 2), the mean function will be

$$E(y|x) = \beta_0 + \beta_1$$

For values of x greater than a but less than b, the mean function becomes

$$E(y|x) = (\beta_0 - \beta_2 x_a) + (\beta_1 + \beta_2)$$

For values of x greater than b (visit 4), the mean function becomes, $E(y|x) = (\beta_0 - \beta_2 x_a - \beta_3 x_b) + (\beta_1 + \beta_2 + \beta_3)x$

Mixed effects model

To approximate the time at which an individual was likely to have crossed the eGFR threshold necessary to define CKD we used a linear mixed effects model. A mixed effects model utilizes both random and fixed effects in the model with random effects thus allowing for the characterization of all individual trajectories. A major advantage of linear mixed effects models are that they do not require equally spaced time intervals between measurements nor the same number of measurements per participant[359]. As a result all available information is used in the estimation process, including patients who have only one available measurement of the outcome. This optimal use of information allows more accurate estimates of the effects of risk factors on the trajectory.

REFERENCES

1. Coresh J, Selvin E, Stevens LA, et al. PRevalence of chronic kidney disease in the united states. *JAMA.* 2007;298(17):2038-2047.

2. Miller ER, Erlinger TP, Young DR, et al. Results of the Diet, Exercise, and Weight Loss Intervention Trial (DEW-IT). *Hypertension.* 2002;40(5):612-618.

3. Van Buren PN, Toto R. Hypertension in Diabetic Nephropathy: Epidemiology, Mechanisms, and Management. *Advances in Chronic Kidney Disease.* 2011;18(1):28-41.

4. Fried LF, Katz R, Sarnak MJ, et al. Kidney Function as a Predictor of Noncardiovascular Mortality. *Journal of the American Society of Nephrology.* 2005;16(12):3728-3735.

5. Hallan S, Astor B, Romundstad S, Aasarød K, Kvenild K, 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(22):2490-2496.

6. Schiffrin EL, Lipman ML, Mann JFE. Chronic Kidney Disease: Effects on the Cardiovascular System. *Circulation.* 2007;116(1):85-97.

7. Szklo M, Barnes R, Folsom A, et al. The atherosclerosis risk in communities (ARIC) study: Design and objectives. *American journal of epidemiology.* 1989;129(4):687-702.

8. Loehr LR, Rosamond WD, Chang PP, Folsom AR, Chambless LE. Heart Failure Incidence and Survival (from the Atherosclerosis Risk in Communities Study). *The American journal of cardiology.* 2008;101(7):1016-1022.

9. Appel LJ, Wright JT, Jr, Greene T, 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(8):832-839.

10. Klag MJ, Whelton PK, Randall BL, et al. Blood Pressure and End-Stage Renal Disease in Men. *New England Journal of Medicine.* 1996;334(1):13-18.

11. Crews DC, Plantinga LC, Miller ER, et al. Prevalence of Chronic Kidney Disease in Persons With Undiagnosed or Prehypertension in the United States. *Hypertension.* 2010;55(5):1102-1109.

12. Appel LJ, Moore TJ, Obarzanek E, et al. A Clinical Trial of the Effects of Dietary Patterns on Blood Pressure. *New England Journal of Medicine.* 1997;336(16):1117-1124.

13. Bibbins-Domingo K, Chertow GM, Coxson PG, et al. Projected Effect of Dietary Salt Reductions on Future Cardiovascular Disease. *New England Journal of Medicine.* 2010;362(7):590-599.

14. Eyles H, Webster J, Jebb S, Capelin C, Neal B, 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(5):555-560.

15. Chobanian AV, Bakris GL, Black HR, 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(19):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(9246):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(6):657-667.

18. Cook NR, Cutler JA, Obarzanek E, et al. Long term effects of dietary sodium reduction on cardiovascular disease outcomes: observational follow-up of the trials of hypertension prevention (TOHP). *BMJ.* 2007;334(7599):885.

19. Kelley GA, Kelley KS. Progressive Resistance Exercise and Resting Blood Pressure: A Meta-Analysis of Randomized Controlled Trials. *Hypertension.* 2000;35(3):838-843.

20. Whelton SP, Chin A, Xin X, He J. Effect of Aerobic Exercise on Blood PressureA Meta-Analysis of Randomized, Controlled Trials. *Annals of Internal Medicine.* 2002;136(7):493-503.

21. Tarver-Carr ME, Powe NR, Eberhardt MS, et al. 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(9):2363-2370.

22. Plantinga LC, Johansen K, Crews DC, et al. Association of CKD With Disability in the United States. *American Journal of Kidney Diseases.* 2011;57(2):212-227.

23. James PA, Oparil S, Carter BL, 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(5):507-520.

24. Salomon JA, Vos T, Hogan DR, et al. 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(9859):2129-2143.

25. Salomon JA, Haagsma JA, Davis A, et al. Disability weights for the Global Burden of Disease 2013 study. *The Lancet Global Health.*3(11):e712-e723.

26. Boron WF, Boulpaep EL. Saunders; 2012.

27. Brenner BM. *Brenner and Rector's the Kidney / 2 Volume Set.* Elsevier Science Health Science Division; 2007.

28. Briggs JP, Kriz W, Schnermann JB. 1 - Overview of Kidney Function and Structure. In: Weiner SJGE, ed. *National Kidney Foundation Primer on Kidney Diseases (Sixth Edition).* Philadelphia: W.B. Saunders; 2014:2-18.

29. Ricksten S-E, Bragadottir G, Redfors B. Renal oxygenation in clinical acute kidney injury. *Critical Care.* 2013;17(2):221.

30. VAN'T HOFF WG. Molecular developments in renal tubulopathies. *Archives of Disease in Childhood.* 2000;83(3):189-191.

31. Fusellier M, Desfontis JC, Madec S, et al. Effect of tepoxalin on renal function in healthy dogs receiving an angiotensin-converting enzyme inhibitor. *Journal of veterinary pharmacology and therapeutics.* 2005;28(6):581-586.

32. Persson P, Ehmke H, Kirchheim H. Influence of the renin-angiotensin system on the autoregulation of renal blood flow and glomerular filtration rate in conscious dogs. *Acta physiologica Scandinavica.* 1988;134(1):1-7.

33. Aukland K. Myogenic mechanisms in the kidney. *Journal of hypertension. Supplement : official journal of the International Society of Hypertension.* 1989;7(4):S71-76; discussion S77.

34. Norman AW, Henry HL. *Hormones.* Elsevier Science; 2014.

35. Adler S, Adrogué HJ, Allon M, et al. Contributors. In: Weiner SJGE, ed. *National Kidney Foundation Primer on Kidney Diseases (Sixth Edition)*. Philadelphia: W.B. Saunders; 2014:v-xi.

36. Stevens LALA. Assessing kidney function--measured and estimated glomerular filtration rate. *The New England journal of medicine.*354(23):2473-2483.

37. KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. *International Society of Nephrology* 2012;2(5).

38. Lawson R. How to Do a Radioisotope Glomerular Filtration Rate Study. In: Payne S, Eardley I, O'Flynn K, eds. *Imaging and Technology in Urology*: Springer London; 2012:109-112.

39. Sterner G, Frennby B, Mansson S, Nyman U, Van Westen D, Almen T. Determining 'true' glomerular filtration rate in healthy adults using infusion of inulin and comparing it with values obtained using other clearance techniques or prediction equations. *Scandinavian journal of urology and nephrology.* 2008;42(3):278-285.

40. Hsu C-y, Bansal N. Measured GFR as "Gold Standard"—All that Glitters Is Not Gold? *Clinical Journal of the American Society of Nephrology.* 2011;6(8):1813-1814.

41. Orlando R, Floreani M, Padrini R, Palatini P. Determination of inulin clearance by bolus intravenous injection in healthy subjects and ascitic patients: equivalence of

systemic and renal clearances as glomerular filtration markers. *British Journal of Clinical Pharmacology.* 1998;46(6):605-609.

42. Pline KA, Smith CL. The effect of creatine intake on renal function. *The Annals of pharmacotherapy.* 2005;39(6):1093-1096.

43. Allen PJ. Creatine metabolism and psychiatric disorders: Does creatine supplementation have therapeutic value? *Neuroscience and Biobehavioral Reviews.* 2012;36(5):1442-1462.

44. Martin E, Hine R. creatine. 'Oxford University Press'.

45. Uchino S, Uchino S. Creatinine. *Current opinion in critical care.*16(6):562-567.

46. Heymsfield SB, Arteaga C, McManus C, Smith J, Moffitt S. Measurement of muscle mass in humans: validity of the 24-hour urinary creatinine method. *The American Journal of Clinical Nutrition.* 1983;37(3):478-494.

47. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Annals of internal medicine.* 2009;150(9):604-612.

48. Froissart M, Rossert J, Jacquot C, Paillard M, Houillier P. Predictive Performance of the Modification of Diet in Renal Disease and Cockcroft-Gault Equations for Estimating Renal Function. *Journal of the American Society of Nephrology.* 2005;16(3):763-773.

49. Michels WM, Grootendorst DC, Verduijn M, Elliott EG, Dekker FW, Krediet RT. Performance of the Cockcroft-Gault, MDRD, and New CKD-EPI Formulas in Relation to GFR, Age, and Body Size. *Clinical Journal of the American Society of Nephrology : CJASN.* 2010;5(6):1003-1009.

50. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron.* 1976;16(1):31-41.

51. Florkowski CM, Chew-Harris JSC. Methods of Estimating GFR – Different Equations Including CKD-EPI. *The Clinical Biochemist Reviews.* 2011;32(2):75-79.

52. Botev R, Mallié J-P, Couchoud C, et al. Estimating Glomerular Filtration Rate: Cockcroft–Gault and Modification of Diet in Renal Disease Formulas Compared to Renal Inulin Clearance. *Clinical Journal of the American Society of Nephrology : CJASN.* 2009;4(5):899-906.

53. Munikrishnappa D. Chapter 6: Limitations of Various Formulae and Other Ways of Assessing GFR in the Elderly: Is There a Role for Cystatin C? https://www.asn-online.org/education/distancelearning/curricula/geriatrics/Chapter6.pdf. Available at. Accessed May 3, 2017.

54. Rigalleau V, Lasseur C, Perlemoine C, et al. Cockcroft-Gault formula is biased by body weight in diabetic patients with renal impairment. *Metabolism: clinical and experimental.* 2006;55(1):108-112.

55. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A More Accurate Method To Estimate Glomerular Filtration Rate from Serum Creatinine: A New Prediction Equation. *Annals of internal medicine.* 1999;130(6):461-470.

56. Levey AS, Greene T, Schluchter MD, et al. Glomerular filtration rate measurements in clinical trials. Modification of Diet in Renal Disease Study Group and the Diabetes Control and Complications Trial Research Group. *Journal of the American Society of Nephrology.* 1993;4(5):1159-1171.

57. Levey AS, Schoolwerth AC, Burrows NR, Williams DE, Stith KR, McClellan W. Comprehensive public health strategies for preventing the development, progression, and complications of CKD: report of an expert panel convened by the Centers for Disease Control and Prevention. *Am J Kidney Dis.* 2009;53(3):522-535.

58. Matsushita K, Mahmoodi BK, Woodward M, et al. Comparison of risk prediction using the ckd-epi equation and the mdrd study equation for estimated glomerular filtration rate. *JAMA.* 2012;307(18):1941-1951.

59. Bragadottir G, Redfors B, Ricksten S-E. Assessing glomerular filtration rate (GFR) in critically ill patients with acute kidney injury - true GFR versus urinary creatinine clearance and estimating equations. *Critical Care.* 2013;17(3):R108-R108.

60. Ozmen S, Kaplan MA, Kaya H, et al. Role of lean body mass for estimation of glomerular filtration rate in patients with chronic kidney disease with various body mass indices. *Scandinavian journal of urology and nephrology.* 2009;43(2):171-176.

61. Perrone RD, Madias NE, Levey AS. Serum creatinine as an index of renal function: new insights into old concepts. *Clinical chemistry.* 1992;38(10):1933-1953.

62. Levey AS, Eckardt KU, Tsukamoto Y, et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int.* 2005;67(6):2089-2100.

63. Eknoyan G. Chronic kidney disease definition and classification: the quest for refinements. *Kidney Int.* 0000;72(10):1183-1185.

64. Hill GS. Hypertensive nephrosclerosis. *Current opinion in nephrology and hypertension.* 2008;17(3):266-270 210.1097/MNH.1090b1013e3282f1088a1091f.

65. Part 4. Definition and Classification of Stages of Chronic Kidney Disease. *American Journal of Kidney Diseases.*39(2):S46-S75.

66. Rahman M, Smith MC. Chronic renal insufficiency: A diagnostic and therapeutic approach. *Archives of Internal Medicine.* 1998;158(16):1743-1752.

67. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis.* 2002;39(2 Suppl 1):S1 - 266.

68. Thomas R, Kanso A, Sedor JR. Chronic Kidney Disease and Its Complications. *Primary Care: Clinics in Office Practice.* 2008;35(2):329-344.

69. Stevens PE, Levin A. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. *Annals of internal medicine.* 2013;158(11):825-830.

70. London G, Coyne D, Hruska K, Malluche HH, Martin KJ. The new kidney disease: improving global outcomes (KDIGO) guidelines – expert clinical focus on bone and vascular calcification. *Clinical nephrology.* 2010;74(6):423-432.

71. Zhang A-H, Tam P, LeBlanc D, et al. Natural history of CKD stage 4 and 5 patients following referral to renal management clinic. *International Urology and Nephrology.* 2009;41(4):977-982.

72. Levey AS, Inker LA, Matsushita K, et al. GFR decline as an end point for clinical trials in CKD: a scientific workshop sponsored by the National Kidney Foundation and the US Food and Drug Administration. *Am J Kidney Dis.* 2014;64(6):821-835.

73. Fassett RG, Venuthurupalli SK, Gobe GC, Coombes JS, Cooper MA, Hoy WE. Biomarkers in chronic kidney disease: a review. *Kidney Int.* 2011;80(8):806-821.

74. Brosius FC, Hostetter TH, Kelepouris E, et al. REPRINT Detection of Chronic Kidney Disease in Patients With or at Increased Risk of Cardiovascular Disease: A Science Advisory From the American Heart Association Kidney and Cardiovascular Disease Council; the Councils on High Blood Pressure Research, Cardiovascular Disease in the Young, and Epidemiology and Prevention; and the Quality of Care and Outcomes Research Interdisciplinary Working Group: Developed in Collaboration With the National Kidney Foundation. *Hypertension.* 2006;48(4):751-755.

75. Redon J, Pichler G, Martinez F. Proteinuria-Microalbuminuria in Renal Damage. In: Agabiti Rosei E, Mancia G, eds. *Assessment of Preclinical Organ Damage in Hypertension*: Springer International Publishing; 2015:159-164.

76. Gansevoort RT, de Jong PE. The Case for Using Albuminuria in Staging Chronic Kidney Disease. *Journal of the American Society of Nephrology.* 2009;20(3):465-468.

77. Woolhandler S, Pels RJ, Bor DH, Himmelstein DU, Lawrence RS. Hematuria and Proteinuria. In: Goldbloom RB, Lawrence RS, eds. *Preventing Disease: Beyond the Rhetoric*. New York, NY: Springer New York; 1990:367-374.

78. Vivante A, Afek A, Frenkel-Nir Y, et al. PErsistent asymptomatic isolated microscopic hematuria in israeli adolescents and young adults and risk for end-stage renal disease. *JAMA.* 2011;306(7):729-736.

79. Davenport A. Clinical investigation of renal disease. Oxford, UK: 'Oxford University Press'.

80. Renal resistive indexes: variability in Doppler US measurement in a healthy population. *Radiology.* 1996;199(1):165-169.

81. Page JE, Morgan SH, Eastwood JB, et al. Ultrasound findings in renal parenchymal disease: Comparison with histological appearances. *Clinical Radiology.*49(12):867-870.

82. The small (less than or equal to 3.0 cm) renal parenchymal tumor: detection, diagnosis, and controversies. *Radiology.* 1991;179(2):307-317.

83. Clayman RV, Surya V, Miller RP, Reinke DB, Fraley EE. Pursuit of the renal mass. *The American journal of medicine.*77(2):218-223.

84. Balci NC, Semelka RC, Patt RH, et al. Complex renal cysts: findings on MR imaging. *American Journal of Roentgenology.* 1999;172(6):1495-1500.

85. U.S. Renal Data System. USRDS 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. *National Institutes of Health.* 2013;National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, .

86. Wish JB. 57 - Anemia and Other Hematologic Complications of Chronic Kidney Disease. In: Weiner SJGE, ed. *National Kidney Foundation Primer on Kidney Diseases (Sixth Edition).* Philadelphia: W.B. Saunders; 2014:497-506.

87. Gal-Moscovici A, Sprague SM. Role of Bone Biopsy in Stages 3 to 4 Chronic Kidney Disease. *Clinical Journal of the American Society of Nephrology.* 2008;3(Supplement 3):S170-S174.

88. Quarles LD. 55 - Bone Disorders in Chronic Kidney Disease. In: Weiner SJGE, ed. *National Kidney Foundation Primer on Kidney Diseases (Sixth Edition).* Philadelphia: W.B. Saunders; 2014:476-487.

89. Allen N, Berry JD, Ning H, Van Horn L, Dyer A, Lloyd-Jones DM. Impact of Blood Pressure and Blood Pressure Change During Middle Age on the Remaining Lifetime Risk for Cardiovascular Disease: The Cardiovascular Lifetime Risk Pooling Project. *Circulation.* 2012;125(1):37-44.

90. Guérin AP, London GM, Marchais SJ, Metivier F. Arterial stiffening and vascular calcifications in end-stage renal disease. *Nephrology Dialysis Transplantation.* 2000;15(7):1014-1021.

91. Goodman WG, Goldin J, Kuizon BD, et al. Coronary-Artery Calcification in Young Adults with End-Stage Renal Disease Who Are Undergoing Dialysis. *New England Journal of Medicine.* 2000;342(20):1478-1483.

92. Ducy P, Zhang R, Geoffroy V, Ridall AL, Karsenty G. Osf2/Cbfa1: A Transcriptional Activator of Osteoblast Differentiation. *Cell.*89(5):747-754.

93. Hujairi NMA, Afzali B, Goldsmith DJA. Cardiac calcification in renal patients: what we do and don't know. *American Journal of Kidney Diseases.* 2004;43(2):234-243.

94. Braun J, Oldendorf M, Moshage W, Heidler R, Zeitler E, Luft FC. Electron beam computed tomography in the evaluation of cardiac calcification in chronic dialysis patients. *Am J Kidney Dis.* 1996;27(3):394-401.

95. Mizobuchi M, Towler D, Slatopolsky E. Vascular Calcification: The Killer of Patients with Chronic Kidney Disease. *Journal of the American Society of Nephrology.* 2009;20(7):1453-1464.

96. Johnson WJ, Hagge WW, Wagoner RD, Dinapoli RP, Rosevear JW. Effects of urea loading in patients with far-advanced renal failure. *Mayo Clin Proc.* 1972;47(1):21-29.

97. Riggs JE. Neurologic Manifestations of Electrolyte Disturbances. *Neurologic Clinics.* 2002;20(1):227-239.

98. Saran R, Li Y, Robinson B, et al. US Renal Data System 2014 Annual Data Report: Epidemiology of Kidney Disease in the United States. *Am J Kidney Dis.* 2015;65(6 Suppl 1):A7.

99. System USRD. *2016 USRDS annual data report: Epidemiology of kidney disease in the United States.* Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases;2016.

100. Prentice RL. A Case-Cohort Design for Epidemiologic Cohort Studies and Disease Prevention Trials. *Biometrika.* 1986;73(1):1-11.

101. Trivedi H. Cost Implications of Caring for Chronic Kidney Disease: Are Interventions Cost-effective? *Advances in Chronic Kidney Disease.* 2010;17(3):265-270.

102. Plantinga LC, Johansen K, Crews DC, et al. Association of CKD with disability in the United States. *Am J Kidney Dis.* 2011;57(2):212-227.

103. Tawney KW, Tawney PJW, Kovach J. RENAL RESEARCH INSTITUTE SYMPOSIUM: Disablement and Rehabilitation in End-Stage Renal Disease. *Seminars in Dialysis.* 2003;16(6):447-452.

104. Gutman RA, Stead WW, Robinson RR. Physical Activity and Employment Status of Patients on Maintenance Dialysis. *New England Journal of Medicine.* 1981;304(6):309-313.

105. Laupacis A, Keown P, Pus N, et al. A study of the quality of life and cost-utility of renal transplantation. *Kidney Int.* 1996;50(1):235-242.

106. Jones DS, Podolsky SH, Greene JA. The Burden of Disease and the Changing Task of Medicine. *New England Journal of Medicine.* 2012;366(25):2333-2338.

107. Charytan DM, Li S, Liu J, Herzog CA. Risks of Death and End-Stage Renal Disease After Surgical Compared With Percutaneous Coronary Revascularization in Elderly Patients With Chronic Kidney Disease. *Circulation.* 2012;126(11 suppl 1):S164-S169.

108. Dalrymple LS, Katz R, Kestenbaum B, et al. Chronic kidney disease and the risk of end-stage renal disease versus death. *J Gen Intern Med.* 2011;26(4):379-385.

109. Keith DS, Nichols GA, Gullion CM, Brown JB, Smith DH. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. *Arch Intern Med.* 2004;164(6):659-663.

110. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu C-y. Chronic Kidney Disease and the Risks of Death, Cardiovascular Events, and Hospitalization. *New England Journal of Medicine.* 2004;351(13):1296-1305.

111. Nitsch D, Grams M, Sang Y, et al. *Associations of estimated glomerular filtration rate and albuminuria with mortality and renal failure by sex: a meta-analysis.* Vol 3462013.

112. Andermann A, Blancquaert I, Beauchamp S, Déry V. Revisiting Wilson and Jungner in the genomic age: a review of screening criteria over the past 40 years. *Bulletin of the World Health Organization.* 2008;86(4):317-319.

113. Rose G, Barker DJ. Epidemiology for the uninitiated. Screening. *British Medical Journal.* 1978;2(6149):1417-1418.

114. Moyer VA, on behalf of the USPSTF. Screening for chronic kidney disease: U.s. preventive services task force recommendation statement. *Annals of internal medicine.* 2012;157(8):567-570.

115. Levey ASA. Chronic kidney disease as a global public health problem: approaches and initiatives - a position statement from Kidney Disease Improving Global Outcomes. *Kidney international.*72(3):247-259.

116. Brown WW, Peters RM, Ohmit SE, et al. Early detection of kidney disease in community settings: the Kidney Early Evaluation Program (KEEP). *Am J Kidney Dis.* 2003;42(1):22-35.

117. Brown T, Summerbell C. Systematic review of school-based interventions that focus on changing dietary intake and physical activity levels to prevent childhood obesity: an update to the obesity guidance produced by the National Institute for Health and Clinical Excellence. *Obesity Reviews.* 2009;10(1):110-141.

118. Jurkovitz CT, Qiu Y, Wang C, Gilbertson DT, Brown WW. The Kidney Early Evaluation Program (KEEP): Program Design and Demographic Characteristics of the Population. *American Journal of Kidney Diseases.* 2008;51(4, Supplement 2):S3-S12.

119. Vest BM, York TR, Sand J, Fox CH, Kahn LS. Chronic Kidney Disease Guideline Implementation in Primary Care: A Qualitative Report from the TRANSLATE CKD Study. *Journal of the American Board of Family Medicine : JABFM.* 2015;28(5):624-631.

120. Plantinga LC, Tuot DS, Powe NR. Awareness of chronic kidney disease among patients and providers. *Adv Chronic Kidney Dis.* 2010;17(3):225-236.

121. Program NKDE. National Kidney Disease Education Program: Reducing Disparities. Improving Care. A Summary Report. 2008. Accessed May 2, 2017, 2017.

122. Choi BCK. The Past, Present, and Future of Public Health Surveillance. *Scientifica.* 2012;2012:26.

123. Agodoa L. United States renal data system (USRDS). *Nefrologia.* 2000;20(Suppl 5):13-16.

124. Collins AJ, Foley R, Herzog C, et al. United States Renal Data System 2007 Annual Data Report Abstract. *American Journal of Kidney Diseases.*51(1):A6-A7.

125. Kutner NG, Johansen KL, Kaysen GA, et al. The Comprehensive Dialysis Study (CDS): A USRDS Special Study. *Clinical Journal of the American Society of Nephrology : CJASN.* 2009;4(3):645-650.

126. DeOreo PB, Wish JB. Medical Director Responsibilities to the ESRD Network. *Clinical Journal of the American Society of Nephrology.* 2014.

127. Foley RN, Collins AJ. The USRDS: What You Need to Know about What It Can and Can't Tell Us about ESRD. *Clinical Journal of the American Society of Nephrology.* 2013;8(5):845-851.

128. Castro AF, Coresh J. CKD surveillance using laboratory data from the population-based National Health and Nutrition Examination Survey (NHANES). *Am J Kidney Dis.* 2009;53(3 Suppl 3):S46-55.

129. Saran R, Hedgeman E, Plantinga L, et al. Establishing a national chronic kidney disease surveillance system for the United States. *Clin J Am Soc Nephrol.* 2010;5(1):152-161.

130. Navar-Boggan A, Pencina MJ, Williams K, Sniderman AD, Peterson ED. PRoportion of us adults potentially affected by the 2014 hypertension guideline. *JAMA.* 2014;311(14):1424-1429.

131. Tedla FM, Brar A, Browne R, Brown C. Hypertension in Chronic Kidney Disease: Navigating the Evidence. *International Journal of Hypertension.* 2011;2011.

132. System USRD. USRDS 2010 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. *National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD.* 2010.

133. Chronic Kidney Disease Prognosis C. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *The Lancet.*375(9731):2073-2081.

134. Prevention CfDCa. National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States, 2014. *US Department of Health and Human Services.* 2014.

135. Nephropathy in Diabetes. *Diabetes care.* 2004;27(suppl 1):s79-s83.

136. Bash LD, Selvin E, Steffes M, Coresh J, Astor BC. Poor glycemic control in diabetes and the risk of incident chronic kidney disease even in the absence of albuminuria and retinopathy: Atherosclerosis risk in communities (aric) study. *Archives of Internal Medicine.* 2008;168(22):2440-2447.

137. Davies DF, Shock NW. AGE CHANGES IN GLOMERULAR FILTRATION RATE, EFFECTIVE RENAL PLASMA FLOW, AND TUBULAR EXCRETORY CAPACITY IN ADULT MALES. *The Journal of Clinical Investigation.* 1950;29(5):496-507.

138. Friedman SA, Raizner AE, Rosen H, Solomon NA, Sy W. Functional Defects in the Aging Kidney. *Annals of internal medicine.* 1972;76(1):41-45.

139. Weinstein JR, Anderson S. The Aging Kidney: Physiological Changes. *Advances in Chronic Kidney Disease.*17(4):302-307.

140. Davidson AJ, Talner LB, Downs WM, 3rd. A study of the angiographic appearance of the kidney in an aging normotensive population. *Radiology.* 1969;92(5):975-983.

141. Glassock RJ, Winearls C. Ageing and the Glomerular Filtration Rate: Truths and Consequences. *Transactions of the American Clinical and Climatological Association.* 2009;120:419-428.

142. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third national health and nutrition examination survey. *American Journal of Kidney Diseases.* 2003;41(1):1-12.

143. Hsu C-y, Lin F, Vittinghoff E, Shlipak MG. Racial Differences in the Progression from Chronic Renal Insufficiency to End-Stage Renal Disease in the United States. *Journal of the American Society of Nephrology.* 2003;14(11):2902-2907.

144. Duru OK, Li S, Jurkovitz C, et al. Race and Sex Differences in Hypertension Control in CKD: Results From the Kidney Early Evaluation Program (KEEP). *American Journal of Kidney Diseases.*51(2):192-198.

145. Clark LT, Ferdinand KC, Flack JM, et al. Coronary heart disease in African Americans. *Heart disease (Hagerstown, Md.).* 2001;3(2):97-108.

146. Avery CL, Holliday KM, Chakladar S, et al. Disparities in Early Transitions to Obesity in Contemporary Multi-Ethnic U.S. Populations. *PLOS ONE.* 2016;11(6):e0158025.

147. Joseph RP, Ainsworth BE, Keller C, Dodgson JE. Barriers to Physical Activity Among African American Women: An Integrative Review of the Literature. *Women & health.* 2015;55(6):679-699.

148. Genovese G, Friedman DJ, Ross MD, et al. Association of Trypanolytic ApoL1 Variants with Kidney Disease in African Americans. *Science.* 2010;329(5993):841-845.

149. Genovese G, Tonna SJ, Knob AU, et al. A risk allele for focal segmental glomerulosclerosis in African Americans is located within a region containing APOL1 and MYH9. *Kidney Int.* 2010;78(7):698-704.

150. Ojo A. Addressing the Global Burden of Chronic Kidney Disease Through Clinical and Translational Research. *Transactions of the American Clinical and Climatological Association.* 2014;125:229-246.

151. Stengel B, Tarver–Carr ME, Powe NR, Eberhardt MS, Brancati FL. Lifestyle Factors, Obesity and the Risk of Chronic Kidney Disease. *Epidemiology.* 2003;14(4):479-487 410.1097/1001.EDE.0000071413.0000055296.c0000071414.

152. Halimi J-M, Giraudeau B, Vol S, et al. Effects of current smoking and smoking discontinuation on renal function and proteinuria in the general population. *Kidney Int.* 2000;58(3):1285-1292.

153. Gambaro G, Verlato F, Budakovic A, et al. Renal impairment in chronic cigarette smokers. *Journal of the American Society of Nephrology.* 1998;9(4):562-567.

154. Ritz E, Benck U, Franek E, Keller C, Seyfarth M, Clorius J. Effects of smoking on renal hemodynamics in healthy volunteers and in patients with glomerular disease. *Journal of the American Society of Nephrology.* 1998;9(10):1798-1804.

155. Yacoub R, Habib H, Lahdo A, et al. Association between smoking and chronic kidney disease: a case control study. *BMC Public Health.* 2010;10(1):731.

156. PHISITKUL K, HEGAZY K, CHUAHIRUN T, et al. Continued Smoking Exacerbates but Cessation Ameliorates Progression of Early Type 2 Diabetic Nephropathy. *The American Journal of the Medical Sciences.* 2008;335(4):284-291 210.1097/MAJ.1090b1013e318156b318799.

157. Pedrini MT, Levey AS, Lau J, Chalmers* TC, Wang PH. The Effect of Dietary Protein Restriction on the Progression of Diabetic and Nondiabetic Renal DiseasesA Meta-Analysis. *Annals of internal medicine.* 1996;124(7):627-632.

158. Kasiske BL, Lakatua JD, Ma JZ, Louis TA. A meta-analysis of the effects of dietary protein restriction on the rate of decline in renal function. *American Journal of Kidney Diseases.* 1998;31(6):954-961.

159. Vegter S, Perna A, Postma MJ, Navis G, Remuzzi G, Ruggenenti P. Sodium Intake, ACE Inhibition, and Progression to ESRD. *Journal of the American Society of Nephrology.* 2012;23(1):165-173.

160. Hsu C-y, McCulloch CE, Iribarren C, Darbinian J, Go AS. Body Mass Index and Risk for End-Stage Renal Disease. *Annals of internal medicine.* 2006;144(1):21-28.

161. Fox CS, Larson MG, Leip EP, Culleton B, Wilson PF, Levy D. PRedictors of new-onset kidney disease in a community-based population. *JAMA.* 2004;291(7):844-850.

162. Kasiske BL, Crosson JT. REnal disease in patients with massive obesity. *Archives of Internal Medicine.* 1986;146(6):1105-1109.

163. Kambham N, Markowitz GS, Valeri AM, Lin J, D'Agati VD. Obesity-related glomerulopathy: An emerging epidemic. *Kidney Int.* 2001;59(4):1498-1509.

164. Navaneethan SD, Yehnert H, Moustarah F, Schreiber MJ, Schauer PR, Beddhu S. Weight Loss Interventions in Chronic Kidney Disease: A Systematic Review and Meta-analysis. *Clinical Journal of the American Society of Nephrology.* 2009;4(10):1565-1574.

165. NEUGARTEN J, ACHARYA A, SILBIGER SR. Effect of Gender on the Progression of Nondiabetic Renal Disease: A Meta-Analysis. *Journal of the American Society of Nephrology.* 2000;11(2):319-329.

166. Silbiger S, Neugarten J. Gender and human chronic renal disease. *Gender Medicine.* 2008;5, Supplement 1(0):S3-S10.

167. Moëll H. Size of normal kidneys. *Acta Radiologica [Old Series]*. 1956;46(5):640-645.

168. Miller JA, Anacta LA, Cattran DC. Impact of gender on the renal response to angiotensin II. *Kidney Int.* 1999;55(1):278-285.

169. Reckelhoff JF. Gender Differences in the Regulation of Blood Pressure. *Hypertension.* 2001;37(5):1199-1208.

170. Neugarten J. Gender and the Progression of Renal Disease. *Journal of the American Society of Nephrology.* 2002;13(11):2807-2809.

171. Jakicic JM, Otto AD. Physical activity considerations for the treatment and prevention of obesity. *The American Journal of Clinical Nutrition.* 2005;82(1):226S-229S.

172. Goodpaster BH, DeLany JP, Otto AD, et al. Effects of diet and physical activity interventions on weight loss and cardiometabolic risk factors in severely obese adults: A randomized trial. *JAMA.* 2010;304(16):1795-1802.

173. Huai P, Xun H, Reilly KH, Wang Y, Ma W, Xi B. Physical Activity and Risk of Hypertension: A Meta-Analysis of Prospective Cohort Studies. *Hypertension.* 2013.

174. Bao W, Tobias DK, Bowers K, et al. Physical activity and sedentary behaviors associated with risk of progression from gestational diabetes mellitus to type 2 diabetes mellitus: A prospective cohort study. *JAMA Internal Medicine.* 2014;174(7):1047-1055.

175. Hu FB, Leitzmann MF, Stampfer MJ, Colditz GA, Willett WC, Rimm EB. PHysical activity and television watching in relation to risk for type 2 diabetes mellitus in men. *Archives of Internal Medicine.* 2001;161(12):1542-1548.

176. Kriska AM, LaPorte RE, Patrick SL, Kuller LH, Orchard TJ. The association of physical activity and diabetic complications in individuals with insulin-dependent diabetes mellitus: The epidemiology of diabetes complications study—VII. *Journal of Clinical Epidemiology.* 1991;44(11):1207-1214.

177. Robinson-Cohen C, Littman AJ, Duncan GE, et al. Physical Activity and Change in Estimated GFR among Persons with CKD. *Journal of the American Society of Nephrology.* 2013.

178. Beddhu S, Baird BC, Zitterkoph J, Neilson J, Greene T. Physical Activity and Mortality in Chronic Kidney Disease (NHANES III). *Clinical Journal of the American Society of Nephrology.* 2009;4(12):1901-1906.

179. Mustata S, Groeneveld S, Davidson W, Ford G, Kiland K, Manns B. Effects of exercise training on physical impairment, arterial stiffness and health-related quality of life in patients with chronic kidney disease: a pilot study. *International Urology and Nephrology.* 2011;43(4):1133-1141.

180. Lei HH, Perneger TV, Klag MJ, Whelton PK, Coresh J. Familial aggregation of renal disease in a population-based case-control study. *Journal of the American Society of Nephrology.* 1998;9(7):1270-1276.

181. McClellan WM, Satko SG, Gladstone E, Krisher JO, Narva AS, Freedman BI. Individuals With a Family History of ESRD Are a High-Risk Population for CKD: Implications for Targeted Surveillance and Intervention Activities. *American Journal of Kidney Diseases.* 2009;53(3, Supplement 3):S100-S106.

182. Langefeld CD, Beck SR, Bowden DW, Rich SS, Wagenknecht LE, Freedman BI. Heritability of GFR and albuminuria in Caucasians with type 2 diabetes mellitus. *American Journal of Kidney Diseases.* 2004;43(5):796-800.

183. Spray BJ, Atassi NG, Tuttle AB, Freedman BI. Familial risk, age at onset, and cause of end-stage renal disease in white Americans. *Journal of the American Society of Nephrology.* 1995;5(10):1806-1810.

184. Smyth LJ, Duffy S, Maxwell AP, McKnight AJ. Genetic and epigenetic factors influencing chronic kidney disease. *American Journal of Physiology - Renal Physiology.* 2014;307(7):F757-F776.

185. Kottgen A, Pattaro C, Boger CA, et al. New loci associated with kidney function and chronic kidney disease. *Nat Genet.* 2010;42(5):376-384.

186. Speckman RA, McClellan WM, Volkova NV, et al. Obesity Is Associated With Family History of ESRD in Incident Dialysis Patients. *American Journal of Kidney Diseases.* 2006;48(1):50-58.

187. Hodgkins KS, Schnaper HW. Tubulointerstitial injury and the progression of chronic kidney disease. *Pediatric Nephrology (Berlin, Germany).* 2012;27(6):901-909.

188. Adeera L, Paul ES. Summary of KDIGO 2012 CKD Guideline: behind the scenes, need for guidance, and a framework for moving forward. *Kidney International.* 2014;85(1):49-61.

189. Zandi-Nejad K, Brenner BM. Primary and secondary prevention of chronic kidney disease. *Journal of hypertension.* 2005;23(10):1771-1776.

190. Jafar TH, Stark PC, Schmid CH, et al. Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: a patient-level meta-analysis. *Annals of internal medicine.* 2003;139(4):244-252.

191. Perry HM, Miller JP, Fornoff JR, et al. Early Predictors of 15-Year End-Stage Renal Disease in Hypertensive Patients. *Hypertension.* 1995;25(4):587-594.

192. Young JH, Klag MJ, Muntner P, Whyte JL, Pahor M, Coresh J. Blood Pressure and Decline in Kidney Function: Findings from the Systolic Hypertension in the Elderly Program (SHEP). *Journal of the American Society of Nephrology.* 2002;13(11):2776-2782.

193. Perneger TV, Nieto F, Whelton PK, Klag MJ, Comstock GW, Szklo M. A prospective study of blood pressure and serum creatinine: Results from the 'clue' study and the aric study. *JAMA.* 1993;269(4):488-493.

194. Ueno H, Kanellakis P, Agrotis A, Bobik A. Blood Flow Regulates the Development of Vascular Hypertrophy, Smooth Muscle Cell Proliferation, and Endothelial Cell Nitric Oxide Synthase in Hypertension. *Hypertension.* 2000;36(1):89-96.

195. Intengan HD, Schiffrin EL. Vascular Remodeling in Hypertension: Roles of Apoptosis, Inflammation, and Fibrosis. *Hypertension.* 2001;38(3):581-587.

196. Ando K, Fujita T. Pathophysiology of salt sensitivity hypertension. *Annals of medicine.* 2012;44 Suppl 1:S119-126.

197. Mayet J, Hughes A. Cardiac and vascular pathophysiology in hypertension. *Heart.* 2003;89(9):1104-1109.

198. Rosario RF, Wesson DE. Primary hypertension and nephropathy. *Current opinion in nephrology and hypertension.* 2006;15(2):130-134.

199. Kang DH, Kanellis J, Hugo C, et al. Role of the microvascular endothelium in progressive renal disease. *Journal of the American Society of Nephrology : JASN.* 2002;13(3):806-816.

200. Gamble CN. The pathogenesis of hyaline arteriolosclerosis. *Am J Pathol.* 1986;122(3):410-420.

201. Metcalfe W. How does early chronic kidney disease progress?: A Background Paper prepared for the UK Consensus Conference on Early Chronic Kidney Disease. *Nephrology Dialysis Transplantation.* 2007;22(suppl 9):ix26-ix30.

202. Hayden MR, Stump CS, Sowers JR. Introduction: Organ Involvement in the Cardiometabolic Syndrome. *Journal of the CardioMetabolic Syndrome.* 2006;1(1):16-24.

203. Farris AB, Colvin RB. Renal interstitial fibrosis: mechanisms and evaluation. *Current opinion in nephrology and hypertension.* 2012;21(3):289-300.

204. Mai M, Geiger H, Hilgers KF, et al. Early interstitial changes in hypertension-induced renal injury. *Hypertension.* 1993;22(5):754-765.

205. Rodriguez-Iturbe B, Johnson RJ. The role of renal microvascular disease and interstitial inflammation in salt-sensitive hypertension. *Hypertension research : official journal of the Japanese Society of Hypertension.* 2010;33(10):975-980.

206. Khawaja Z, Wilcox CS. Role of the Kidneys in Resistant Hypertension. *International Journal of Hypertension.* 2011;2011.

207. Guyton AC. Abnormal renal function and autoregulation in essential hypertension. *Hypertension.* 1991;18(5 Suppl):III49-53.

208. Lip GYH, Hall JE. *Comprehensive Hypertension.* Elsevier Health Sciences; 2007.

209. Hall JE, Mizelle HL, Hildebrandt DA, Brands MW. Abnormal pressure natriuresis. A cause or a consequence of hypertension? *Hypertension.* 1990;15(6 Pt 1):547-559.

210. Hall JE, Brands MW, Shek EW. Central role of the kidney and abnormal fluid volume control in hypertension. *J Hum Hypertens.* 1996;10(10):633-639.

211. Laragh JH, Sealey JE. Renin–Angiotensin–Aldosterone System and the Renal Regulation of Sodium, Potassium, and Blood Pressure Homeostasis. *Comprehensive Physiology*: John Wiley & Sons, Inc.; 2010.

212. Zhou M-S, Schulman IH, Raij L. Nitric oxide, angiotensin II, and hypertension. *Seminars in nephrology.*24(4):366-378.

213. Kim S, Iwao H. Molecular and cellular mechanisms of angiotensin II-mediated cardiovascular and renal diseases. *Pharmacol Rev.* 2000;52(1):11-34.

214. Hall JE, Granger JP, Smith MJ, Jr., Premen AJ. Role of renal hemodynamics and arterial pressure in aldosterone "escape". *Hypertension.* 1984;6(2 Pt 2):I183-192.

215. Brenner BM. Nephron adaptation to renal injury or ablation. *Am J Physiol.* 1985;249(3 Pt 2):F324-337.

216. Converse RL, Jacobsen TN, Toto RD, et al. Sympathetic Overactivity in Patients with Chronic Renal Failure. *New England Journal of Medicine.* 1992;327(27):1912-1918.

217. Klein IHHT, Ligtenberg G, Neumann J, Oey PL, Koomans HA, Blankestijn PJ. Sympathetic Nerve Activity Is Inappropriately Increased in Chronic Renal Disease. *Journal of the American Society of Nephrology.* 2003;14(12):3239-3244.

218. Lewis JB. Blood Pressure Control in Chronic Kidney Disease: Is Less Really More? *Journal of the American Society of Nephrology.* 2010;21(7):1086-1092.

219. Whittle JC, Whelton PK, Seidler AJ, Klag MJ. Does racial variation in risk factors explain black-white differences in the incidence of hypertensive end-stage renal disease? *Archives of internal medicine.* 1991;151(7):1359-1364.

220. Perneger TV, Nieto FJ, Whelton PK, Klag MJ, Comstock GW, Szklo M. A prospective study of blood pressure and serum creatinine: results from the'Clue'study and the ARIC study. *Jama.* 1993;269(4):488-493.

221. Rosansky SJ, Hoover DR, King L, Gibson J. The association of blood pressure levels and change in renal function in hypertensive and nonhypertensive subjects. *Archives of internal medicine.* 1990;150(10):2073-2076.

222. de Galan BE, Perkovic V, Ninomiya T, et al. Lowering Blood Pressure Reduces Renal Events in Type 2 Diabetes. *Journal of the American Society of Nephrology.* 2009;20(4):883-892.

223. Chen NAN, Hsu C-C, Yamagata K, Langham R. Challenging chronic kidney disease: Experience from chronic kidney disease prevention programs in Shanghai, Japan, Taiwan and Australia. *Nephrology.* 2010;15:31-36.

224. Friedberg CK. *Diseases of the Heart.* Saunders; 1949.

225. Kannel WB, Schwartz MJ, McNamara PM. Blood pressure and risk of coronary heart disease: The framingham study. *Chest.* 1969;56(1):43-52.

226. FREIS ED. The Veterans Administration Cooperative Study on Antihypertensive Agents. Implications for Stroke Prevention. *Stroke.* 1974;5(1):76-77.

227. THe sixth report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Archives of Internal Medicine.* 1997;157(21):2413-2446.

228. REport of the joint national committee on detection, evaluation, and treatment of high blood pressure. *JAMA.* 1977;237(3):255-261.

229. Pogue VA, Ellis C, Michel J, Francis CK. New Staging System of the Fifth Joint National Committee Report on the Detection, Evaluation, and Treatment of High Blood Pressure (JNC-V) Alters Assessment of the Severity and Treatment of Hypertension. *Hypertension.* 1996;28(5):713-718.

230. Wright JJT, Fine LJ, Lackland DT, Ogedegbe G, Dennison Himmelfarb CR. Evidence Supporting a Systolic Blood Pressure Goal of Less Than 150 mm Hg in Patients Aged 60 Years or Older: The Minority ViewSystolic Blood Pressure Goal for Patients Aged 60 Years or Older. *Annals of internal medicine.* 2014;160(7):499-503.

231. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Journal of hypertension.* 2013;31(7):1281-1357.

232. Peterson ED, Gaziano J, Greenland P. Recommendations for treating hypertension: What are the right goals and purposes? *JAMA.* 2014;311(5):474-476.

233. Hernandez-Vila E. A Review of the JNC 8 Blood Pressure Guideline. *Texas Heart Institute Journal.* 2015;42(3):226-228.

234. Ogihara T, Saruta T, Rakugi H, et al. Target blood pressure for treatment of isolated systolic hypertension in the elderly: valsartan in elderly isolated systolic hypertension study. *Hypertension.* 2010;56(2):196-202.

235. Principal results of the Japanese trial to assess optimal systolic blood pressure in elderly hypertensive patients (JATOS). *Hypertension research : official journal of the Japanese Society of Hypertension.* 2008;31(12):2115-2127.

236. Taler SJ, Agarwal R, Bakris GL, et al. KDOQI US Commentary on the 2012 KDIGO Clinical Practice Guideline for Management of Blood Pressure in CKD. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 2013;62(2):201-213.

237. National Institutes of Health tNH, Lung, and Blood Institute Landmark NIH study shows intensive blood pressure management may save lives. 2015; http://www.nhlbi.nih.gov/news/press-releases/2015/landmark-nih-study-shows-

intensive-blood-pressure-management-may-save-lives. Accessed September 25, 2015.

238. Ambrosius WT, Sink KM, Foy CG, et al. The design and rationale of a multicenter clinical trial comparing two strategies for control of systolic blood pressure: The Systolic Blood Pressure Intervention Trial (SPRINT). *Clinical Trials.* 2014;11(5):532-546.

239. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *New England Journal of Medicine.* 2015;373(22):2103-2116.

240. Izzo JLJL. Angiotensin-converting enzyme inhibitors. *The journal of clinical hypertension (Greenwich, Conn.).* 2011;13(9):667-675.

241. van de Ven PJ, Beutler JJ, Kaatee R, Beek FJ, Mali WP, Koomans HA. Angiotensin converting enzyme inhibitor-induced renal dysfunction in atherosclerotic renovascular disease. *Kidney Int.* 1998;53(4):986-993.

242. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *The Lancet.*

243. Lv J, Ehteshami P, Sarnak MJ, et al. Effects of intensive blood pressure lowering on the progression of chronic kidney disease: a systematic review and meta-analysis. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne.* 2013;185(11):949-957.

244. Dannenberg AL, Drizd T, Horan MJ, Haynes SG, Leaverton PE. Progress in the battle against hypertension. Changes in blood pressure levels in the United States from 1960 to 1980. *Hypertension.* 1987;10(2):226-233.

245. Egan BM, Zhao Y, Axon R. US trends in prevalence, awareness, treatment, and control of hypertension, 1988-2008. *JAMA.* 2010;303(20):2043-2050.

246. Sarafidis PA, Li S, Chen SC, et al. Hypertension awareness, treatment, and control in chronic kidney disease. *The American journal of medicine.* 2008;121(4):332-340.

247. Muntner P, Anderson A, Charleston J, et al. Hypertension Awareness, Treatment, and Control in Adults With CKD: Results From the Chronic Renal Insufficiency Cohort (CRIC) Study. *American Journal of Kidney Diseases.* 2010;55(3):441-451.

248. Wozniak G, Khan T, Gillespie C, et al. Hypertension Control Cascade: A Framework to Improve Hypertension Awareness, Treatment, and Control. *The Journal of Clinical Hypertension.* 2015:n/a-n/a.

249. Ravera M, Re M, Deferrari L, Vettoretti S, Deferrari G. Importance of Blood Pressure Control in Chronic Kidney Disease. *Journal of the American Society of Nephrology.* 2006;17(4 suppl 2):S98-S103.

250. Calhoun DA, Jones D, Textor S, et al. Resistant Hypertension: Diagnosis, Evaluation, and Treatment: A Scientific Statement From the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. *Circulation.* 2008;117(25):e510-e526.

251. Judd E, Calhoun DA. Management of Hypertension in CKD: Beyond the Guidelines. *Advances in chronic kidney disease.* 2015;22(2):116-122.

252. Port S. Systolic blood pressure and mortality. *The Lancet.*356(9230):683.

253. Lew EA. High blood pressure, other risk factors and longevity: the insurance viewpoint. *The American journal of medicine.* 1973;55(3):281-294.

254. Kannel WB, Vasan RS, Levy D. Is the Relation of Systolic Blood Pressure to Risk of Cardiovascular Disease Continuous and Graded, or Are There Critical Values? *Hypertension.* 2003;42(4):453-456.

255. Stamler J, Stamler R, Neaton JD. Blood Pressure, Systolic and Diastolic, and Cardiovascular RisksUS Population Data. *Archives of Internal Medicine.* 1993;153(5):598-615.

256. Chobanian AV, Bakris GL, Black HR, et al. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension.* 2003;42(6):1206-1252.

257. Emberson J, Whincup P, Morris R, Walker M, Ebrahim S. Evaluating the impact of population and high-risk strategies for the primary prevention of cardiovascular disease. *European Heart Journal.* 2004;25(6):484-491.

258. Tobin MD, Sheehan NA, Scurrah KJ, Burton PR. Adjusting for treatment effects in studies of quantitative traits: antihypertensive therapy and systolic blood pressure. *Statistics in Medicine.* 2005;24(19):2911-2935.

259. Vasan RS, Larson MG, Leip EP, et al. Impact of High-Normal Blood Pressure on the Risk of Cardiovascular Disease. *New England Journal of Medicine.* 2001;345(18):1291-1297.

260. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *The Lancet.* 2002;360(9349):1903-1913.

261. Mason PJ, Manson JE, Sesso HD, et al. Blood Pressure and Risk of Secondary Cardiovascular Events in Women: The Women's Antioxidant Cardiovascular Study (WACS). *Circulation.* 2004;109(13):1623-1629.

262. Hypertension IoMUCoPHPtRaC. A Population-Based Policy and Systems Change Approach to Prevent and Control Hypertension. https://www.ncbi.nlm.nih.gov/books/NBK220087/ doi: 10.17226/12819. Accessed May 11, 2017, 2017.

263. Arroll B, Beaglehole R. Does physical activity lower blood pressure: A critical review of the clinical trials. *Journal of Clinical Epidemiology.* 1992;45(5):439-447.

264. Dickinson HO, Mason JM, Nicolson DJ, et al. Lifestyle interventions to reduce raised blood pressure: a systematic review of randomized controlled trials. *Journal of hypertension.* 2006;24(2):215-233.

265. He FJ, Pombo-Rodrigues S, MacGregor GA. Salt reduction in England from 2003 to 2011: its relationship to blood pressure, stroke and ischaemic heart disease mortality. *BMJ Open.* 2014;4(4).

266. Webster J, Waqanivalu T, Arcand J, et al. Understanding the science that supports population-wide salt reduction programs. *The Journal of Clinical Hypertension.* 2017:n/a-n/a.

267. Appel LJ, Frohlich ED, Hall JE, et al. The Importance of Population-Wide Sodium Reduction as a Means to Prevent Cardiovascular Disease and Stroke: A Call to Action From the American Heart Association. *Circulation.* 2011;123(10):1138-1143.

268. Neter JE, Stam BE, Kok FJ, Grobbee DE, Geleijnse JM. Influence of Weight Reduction on Blood Pressure: A Meta-Analysis of Randomized Controlled Trials. *Hypertension.* 2003;42(5):878-884.

269. Harsha DW, Bray GA. Weight Loss and Blood Pressure Control (Pro). *Hypertension.* 2008;51(6):1420-1425.

270. Pate RR, Pratt M, Blair SN, et al. Physical activity and public health: A recommendation from the centers for disease control and prevention and the american college of sports medicine. *JAMA.* 1995;273(5):402-407.

271. Cornelissen VA, Fagard RH. Effects of Endurance Training on Blood Pressure, Blood Pressure–Regulating Mechanisms, and Cardiovascular Risk Factors. *Hypertension.* 2005;46(4):667-675.

272. Eckel RH, Jakicic JM, Ard JD, et al. 2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular RiskA Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology.* 2014;63(25_PA).

273. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *Circulation.* 2013.

274. Kargarfard M, Rouzbehani R, Basati F. Effects of Exercise Rehabilitation on Blood Pressure of Patients after Myocardial Infarction. *International Journal of Preventive Medicine.* 2010;1(2):124-130.

275. Robinson TN. Reducing children's television viewing to prevent obesity: A randomized controlled trial. *JAMA.* 1999;282(16):1561-1567.

276. Harris JL, Pomeranz JL, Lobstein T, Brownell KD. A Crisis in the Marketplace: How Food Marketing Contributes to Childhood Obesity and What Can Be Done. *Annual Review of Public Health.* 2009;30(1):211-225.

277. Hannon C, Cradock A, Gortmaker SL, et al. Play Across Boston: a community initiative to reduce disparities in access to after-school physical activity programs for inner-city youths. *Preventing chronic disease.* 2006;3(3):A100.

278. Moore LV, Diez Roux AV, Evenson KR, McGinn AP, Brines SJ. Availability of recreational resources in minority and low socioeconomic status areas. *American journal of preventive medicine.* 2008;34(1):16-22.

279. Powell LM, Slater S, Chaloupka FJ, Harper D. Availability of physical activity-related facilities and neighborhood demographic and socioeconomic characteristics: a national study. *American journal of public health.* 2006;96(9):1676-1680.

280. Nicoll G, Zimring C. Effect of innovative building design on physical activity. *Journal of public health policy.* 2009;30 Suppl 1:S111-123.

281. Herman CW, Musich S, Lu C, Sill S, Young JM, Edington DW. Effectiveness of an incentive-based online physical activity intervention on employee health status. *Journal of occupational and environmental medicine / American College of Occupational and Environmental Medicine.* 2006;48(9):889-895.

282. Anderson LM, Quinn TA, Glanz K, et al. The effectiveness of worksite nutrition and physical activity interventions for controlling employee overweight and obesity: a systematic review. *American journal of preventive medicine.* 2009;37(4):340-357.

283. Donnelly JE, Greene JL, Gibson CA, et al. Physical Activity Across the Curriculum (PAAC): A randomized controlled trial to promote physical activity and diminish overweight and obesity in elementary school children. *Preventive Medicine.* 2009;49(4):336-341.

284. Ewing R, Schmid T, Killingsworth R, Zlot A, Raudenbush S. Relationship between urban sprawl and physical activity, obesity, and morbidity. *American journal of health promotion : AJHP.* 2003;18(1):47-57.

285. Li F, Harmer P, Cardinal BJ, et al. Built environment and 1-year change in weight and waist circumference in middle-aged and older adults: Portland Neighborhood Environment and Health Study. *American journal of epidemiology.* 2009;169(4):401-408.

286. Midgley J, Matthew A, Greenwood CT, Logan A. Effect of reduced dietary sodium on blood pressure: A meta-analysis of randomized controlled trials. *JAMA.* 1996;275(20):1590-1597.

287. Sacks FM, Svetkey LP, Vollmer WM, et al. Effects on Blood Pressure of Reduced Dietary Sodium and the Dietary Approaches to Stop Hypertension (DASH) Diet. *New England Journal of Medicine.* 2001;344(1):3-10.

288. Mozaffarian D, Fahimi S, Singh GM, et al. Global Sodium Consumption and Death from Cardiovascular Causes. *New England Journal of Medicine.* 2014;371(7):624-634.

289. Mente A, O'Donnell MJ, Rangarajan S, et al. Association of Urinary Sodium and Potassium Excretion with Blood Pressure. *New England Journal of Medicine.* 2014;371(7):601-611.

290. Appel LJ, Espeland MA, Easter L, Wilson AC, Folmar S, Lacy CR. Effects of reduced sodium intake on hypertension control in older individuals: Results from the trial of nonpharmacologic interventions in the elderly (tone). *Archives of Internal Medicine.* 2001;161(5):685-693.

291. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *New England Journal of Medicine.*0(0):null.

292. Gangavati A, Hajjar I, Quach L, et al. Hypertension, Orthostatic Hypotension, and the Risk of Falls in a Community-Dwelling Elderly Population: The Maintenance of Balance, Independent Living, Intellect, and Zest in the Elderly of Boston Study. *Journal of the American Geriatrics Society.* 2011;59(3):383-389.

293. Figueroa JJ, Basford JR, Low PA. Preventing and treating orthostatic hypotension: As easy as A, B, C. *Cleveland Clinic journal of medicine.* 2010;77(5):298-306.

294. Boyce JM, Shone GR. Effects of ageing on smell and taste. *Postgraduate Medical Journal.* 2006;82(966):239-241.

295. Appel LJ, Angell SY, Cobb LK, et al. Population-wide sodium reduction: the bumpy road from evidence to policy. *Annals of epidemiology.* 2012;22(6):417-425.

296. Mohan S, Campbell NRC, Willis K. Effective population-wide public health interventions to promote sodium reduction. *Canadian Medical Association Journal.* 2009;181(9):605-609.

297. Coxson PG, Cook NR, Joffres M, et al. Mortality Benefits From US Population-wide Reduction in Sodium Consumption Novelty and Significance. *Projections From 3 Modeling Approaches.* 2013;61(3):564-570.

298. O'Donnell M, Mente A, Rangarajan S, et al. Urinary Sodium and Potassium Excretion, Mortality, and Cardiovascular Events. *New England Journal of Medicine.* 2014;371(7):612-623.

299. McLean RM. Measuring Population Sodium Intake: A Review of Methods. *Nutrients.* 2014;6(11):4651-4662.

300. WHO. Sodium intake for adults and children. 2012; http://apps.who.int/iris/bitstream/10665/77985/10661/9789241504836_eng.pdf. Available at. Accessed May 11, 2017, 2017.

301. DeSalvo KB, Olson R, Casavale KO. Dietary guidelines for americans. *JAMA.* 2016;315(5):457-458.

302. Echouffo-Tcheugui JB, Kengne AP. Risk Models to Predict Chronic Kidney Disease and Its Progression: A Systematic Review. *PLoS Med.* 2012;9(11):e1001344.

303. O'Seaghdha CM, Lyass A, Massaro JM, et al. A Risk Score for Chronic Kidney Disease in the General Population. *The American journal of medicine.* 2012;125(3):270-277.

304. Bang H, Vupputuri S, Shoham DA, et al. Screening for occult renal disease (scored): A simple prediction model for chronic kidney disease. *Archives of Internal Medicine.* 2007;167(4):374-381.

305. Kshirsagar AV, Bang H, Bomback AS, et al. A simple algorithm to predict incident kidney disease. *Arch Intern Med.* 2008;168(22):2466-2473.

306. Thakkinstian A, Ingsathit A, Chaiprasert A, et al. A simplified clinical prediction score of chronic kidney disease: a cross-sectional-survey study. *BMC nephrology.* 2011;12:45.

307. Kwon KS, Bang H, Bomback AS, et al. A simple prediction score for kidney disease in the Korean population. *Nephrology (Carlton, Vic.).* 2012;17(3):278-284.

308. Halbesma N, Jansen DF, Heymans MW, Stolk RP, de Jong PE, Gansevoort RT. Development and validation of a general population renal risk score. *Clin J Am Soc Nephrol.* 2011;6(7):1731-1738.

309. Alssema M, Newson RS, Bakker SJ, et al. One risk assessment tool for cardiovascular disease, type 2 diabetes, and chronic kidney disease. *Diabetes care.* 2012;35(4):741-748.

310. Friedman EA, Friedman AL. Payment for donor kidneys: Pros and cons. *Kidney Int.* 2006;69(6):960-962.

311. [Internet] HP. Chronic Kidney Disease Objectives http://www.healthypeople.gov/2020/topics-objectives/topic/chronic-kidney-disease/objectives. Accessed November 9, 2015.

312. Stengel B. Age, blood pressure and smoking effects on chronic renal failure in primary glomerular nephropathies. *Kidney Int.* 2000;57(6):2519 - 2526.

313. Lachat C, Otchere S, Roberfroid D, et al. Diet and Physical Activity for the Prevention of Noncommunicable Diseases in Low- and Middle-Income Countries: A Systematic Policy Review. *PLoS Med.* 2013;10(6):e1001465.

314. National High Blood Pressure Education Program Working Group report on hypertension in diabetes. *Hypertension.* 1994;23(2):145-158.

315. Campbell W, Ganna A, Ingelsson E, Janssens ACJW. Prediction impact curve is a new measure integrating intervention effects in the evaluation of risk models. *Journal of Clinical Epidemiology.*

316. Manual 11: Sitting blood pressure 2015; http://www.cscc.unc.edu/aric/visit/Sitting_Blood_Pressure_and_Postural_Changes_in_Blood_Pressure_and_Heart_Rate.2_11.pdf.

317. Manual 10: Clinical Chemistry Determinations Version 2.0. 1991; http://www.cscc.unc.edu/aric/visit/Clinical_Chemistry_Determinations.2_10.pdf.

318. Atherosclerosis Risk in Communities Carotid MRI Study Manual 5 Lipid and Lipoprotein Determinations 2005 http://www.cscc.unc.edu/carmri/protocol/UNLICOMMManual5LipidsandLipidDeterminations05212005.pdf.

319. Coresh J, Astor BC, McQuillan G, et al. Calibration and random variation of the serum creatinine assay as critical elements of using equations to estimate glomerular filtration rate. *Am J Kidney Dis.* 2002;39(5):920-929.

320. Eckfeldt JH, Chambless LE, Shen YL. Short-term, within-person variability in clinical chemistry test results. Experience from the Atherosclerosis Risk in Communities Study. *Archives of pathology & laboratory medicine.* 1994;118(5):496-500.

321. Rebholz CM, Rebholz CM, Coresh J, Ballew SH, McMahon B. Kidney Failure and ESRD in the Atherosclerosis Risk in Communities (ARIC) Study: Comparing Ascertainment of Treated and Untreated Kidney Failure in a Cohort Study. *American journal of kidney diseases.*66(2):231-239.

322. Xu Y, Cheung YB, Lam KF, Tan SH, Milligan P. A Simple Approach to the Estimation of Incidence Rate Difference. *American journal of epidemiology.* 2010;172(3):334-343.

323. Eckel RH, Jakicic JM, Ard JD, et al. 2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2013.

324. Jafar TH, Islam M, Hatcher J, et al. Community based lifestyle intervention for blood pressure reduction in children and young adults in developing country: cluster randomised controlled trial. *BMJ (Clinical research ed.).* 2010;340:c2641.

325. Zhou B, Wang HL, Wang WL, Wu XM, Fu LY, Shi JP. Long-term effects of salt substitution on blood pressure in a rural North Chinese population. *J Hum Hypertens.* 2013;27(7):427-433.

326. Eckel RH, Jakicic JM, Ard JD, et al. 2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular RiskA Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology.* 2014;63(25_PA).

327. Nwankwo T YS, Burt V, Gu Q. Hypertension among adults in the United States: National Health and Nutrition Examination Survey, 2011–2012. *National Center for Health Statistics* no 133.

328. Cook NR, Cohen J, Hebert PR, Taylor JO, Hennekens CH. IMplications of small reductions in diastolic blood pressure for primary prevention. *Archives of Internal Medicine.* 1995;155(7):701-709.

329. Loehr LR, Rosamond WD, Poole C, et al. The Potentially Modifiable Burden of Incident Heart Failure Due to Obesity: The Atherosclerosis Risk in Communities Study. *American journal of epidemiology.* 2010;172(7):781-789.

330. Morgenstern H, Bursic E. A method for using epidemiologic data to estimate the potential impact of an intervention on the health status of a target population. *Journal of Community Health.* 1982;7(4):292-309.

331. Greenland S. Interval estimation by simulation as an alternative to and extension of confidence intervals. *International Journal of Epidemiology.* 2004;33(6):1389-1397.

332. Collaborators USBoD. The state of us health, 1990-2010: Burden of diseases, injuries, and risk factors. *JAMA.* 2013;310(6):591-606.

333. Kassebaum NJ, Arora M, Barber RM, et al. Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *The Lancet.*388(10053):1603-1658.

334. Nafar M, Mousavi SM, Mahdavi-Mazdeh M, et al. Burden of chronic kidney disease in Iran: a screening program is of essential need. *Iranian journal of kidney diseases.* 2008;2(4):183-192.

335. Kassebaum NJ, Jasrasaria R, Naghavi M, et al. A systematic analysis of global anemia burden from 1990 to 2010. *Blood.* 2014;123(5):615-624.

336. Evaluation IfHMa. Global Health Data Exchange GBD Results tool. 2017; http://ghdx.healthdata.org/gbd-results-tool. Accessed May 16, 2017, 2017.

337. Steenland K, Armstrong B. An Overview of Methods for Calculating the Burden of Disease Due to Specific Risk Factors. *Epidemiology.* 2006;17(5):512-519 510.1097/1001.ede.0000229155.0000205644.0000229143.

338. Bash LD, Coresh J, Kottgen A, et al. Defining incident chronic kidney disease in the research setting: The ARIC Study. *American journal of epidemiology.* 2009;170(4):414-424.

339. Xie X, Atkins E, Lv J, et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. *The Lancet.*387(10017):435-443.

340. Appel LJ, Wright JTJ, Greene T, et al. Intensive Blood-Pressure Control in Hypertensive Chronic Kidney Disease. *New England Journal of Medicine.* 2010;363(10):918-929.

341. Bansal N, McCulloch CE, Rahman M, et al. Blood Pressure and Risk of All-Cause Mortality in Advanced Chronic Kidney Disease and HemodialysisNovelty and Significance. *The Chronic Renal Insufficiency Cohort Study.* 2015;65(1):93-100.

342. Wang H, Naghavi M, Allen C, et al. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. *The Lancet.*388(10053):1459-1544.

343. Cook NR, Cutler JA, Obarzanek E, et al. Long term effects of dietary sodium reduction on cardiovascular disease outcomes: observational follow-up of the trials of hypertension prevention (TOHP). *BMJ : British Medical Journal.* 2007;334(7599):885-885.

344. Aburto NJ, Ziolkovska A, Hooper L, Elliott P, Cappuccio FP, Meerpohl JJ. *Effect of lower sodium intake on health: systematic review and meta-analyses.* Vol 3462013.

345. Ricardo AC, Anderson CA, Yang W, et al. Healthy Lifestyle and Risk of Kidney Disease Progression, Atherosclerotic Events, and Death in CKD: Findings From the Chronic Renal Insufficiency Cohort (CRIC) Study. *American Journal of Kidney Diseases.*65(3):412-424.

346. Foster MC, Hwang S-J, Massaro JM, Jacques PF, Fox CS, Chu AY. Lifestyle Factors and Indices of Kidney Function in the Framingham Heart Study. *American journal of nephrology.* 2015;41(0):267-274.

347. Chapter 1: Definition and classification of CKD. *Kidney International Supplements.* 2013;3(1):19-62.

348. Stokes JB. Consequences of Frequent Hemodialysis: Comparison to Conventional Hemodialysis and Transplantation. *Transactions of the American Clinical and Climatological Association.* 2011;122:124-136.

349. Segall L, Nistor I, Covic A. Heart Failure in Patients with Chronic Kidney Disease: A Systematic Integrative Review. *BioMed Research International.* 2014;2014:21.

350. Schofield D, Shrestha RN, Cunich MM, et al. Economic costs of chronic disease through lost productive life years (PLYs) among Australians aged 45–64 years from 2015 to 2030: results from a microsimulation model. *BMJ Open.* 2016;6(9).

351. Rebholz CM, Coresh J, Ballew SH, et al. Kidney Failure and ESRD in the Atherosclerosis Risk in Communities (ARIC) Study: Comparing Ascertainment of Treated and Untreated Kidney Failure in a Cohort Study. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 2015;66(2):231-239.

352. Jha V, Arici M, Collins AJ, et al. Understanding kidney care needs and implementation strategies in low- and middle-income countries: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. *Kidney International.* 2016;90(6):1164-1174.

353. Howden EJ, Leano R, Petchey W, Coombes JS, Isbel NM, Marwick TH. Effects of Exercise and Lifestyle Intervention on Cardiovascular Function in CKD. *Clinical Journal of the American Society of Nephrology.* 2013.

354. Teng H-L, Yen M, Fetzer S, Sung J-M, Hung S-Y. Effects of Targeted Interventions on Lifestyle Modifications of Chronic Kidney Disease Patients. *Western Journal of Nursing Research.* 2013;35(9):1107-1127.

355. James PA, Oparil S, Carter BL, 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(5):507-520.

356. Cipparone CW, Withiam-Leitch M, Kimminau KS, Fox CH, Singh R, Kahn L. Inaccuracy of ICD-9 Codes for Chronic Kidney Disease: A Study from Two Practice-based Research Networks (PBRNs). *Journal of the American Board of Family Medicine : JABFM.* 2015;28(5):678-682.

357. Zhang Z, Sun J. Interval censoring. *Statistical Methods in Medical Research.* 2010;19(1):53-70.

358. Allison PD. *Survival analysis using SAS [electronic resource] : a practical guide.* Cary, NC: SAS Institute; 2010.

359. Boucquemont J, Heinze G, Jager KJ, Oberbauer R, Leffondre K. Regression methods for investigating risk factors of chronic kidney disease outcomes: the state of the art. *BMC nephrology.* 2014;15:45.

360. Grams ME, Rebholz CM, McMahon B, et al. Identification of incident CKD stage 3 in research studies. *Am J Kidney Dis.* 2014;64(2):214-221.

361. Paweł K, Leon B. Linear Regression Modeling of Interval-censored Survival Times Based on a Convex Piecewise-linear Criterion Function. *Biocybernetics and Biomedical Engineering.* 2012;32(3):69-78.

362. Zhang W, Zhang Y, Chaloner K, Stapleton JT. Imputation methods for doubly censored HIV data. *Journal of statistical computation and simulation.* 2009;79(10):1245-1257.

363. Pantazis N, Kenward MG, Touloumi G. Performance of parametric survival models under non-random interval censoring: A simulation study. *Computational Statistics & Data Analysis.* 2013;63:16-30.

364. Hsu C-H, Taylor JMG, Long Q, Alberts DS. Analysis of Colorectal Adenoma Recurrence Data Subject to Informative Censoring. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology.* 2009;18(3):712-717.

365. Campbell KL, Palmer SC, Johnson DW. Improving Nutrition Research in Nephrology: An Appetite for Change. *American Journal of Kidney Diseases.*69(5):558-560.

366. Zhong Y, Muñoz A, Schwartz GJ, Warady BA, Furth SL, Abraham AG. Nonlinear Trajectory of GFR in Children before RRT. *Journal of the American Society of Nephrology.* 2014;25(5):913-917.

367. Li L, Astor BC, Lewis J, et al. Longitudinal Progression Trajectory of GFR Among Patients With CKD. *American Journal of Kidney Diseases.* 2012;59(4):504-512.

368. O'Hare AM, Batten A, Burrows NR, et al. Trajectories of Kidney Function Decline in the 2 Years Before Initiation of Long-term Dialysis. *American Journal of Kidney Diseases.* 2012;59(4):513-522.

369. Ryan SE. *A tutorial on the piecewise regression approach applied to bedload transport data [electronic resource] / Sandra E. Ryan, Laurie S. Porth.* Fort Collins, CO: U.S. Dept. of Agriculture, Forest Service, Rocky Mountain Research Station; 2007.