BLOOD PRESSURE, DIETARY SODIUM INTAKE, AND KIDNEY FUNCTION IN U.S. ADULTS

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DEDICATION

In the end, it is family to which we are tethered for all of the truly important things in life. My father, Ligie, always told me that I could do anything if I set my mind to it. Both of my parents (my mother, Lorene) taught me to pay attention to detail and work hard. They often reminded me that nothing worth having comes easily. How apropos!

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Mindful of your place in my heart and my life, dear family, I dedicate this dissertation to each of you – to those who have gone, those who are present, and those yet to come.

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ABSTRACT

BLOOD PRESSURE, DIETARY SODIUM INTAKE, AND KIDNEY FUNCTION IN U.S. ADULTS

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High blood pressure is an independent predictor of cardiovascular disease and is associated with a higher risk of end-stage kidney disease. Whereas healthy kidneys can handle a high dietary sodium load before reaching a blood pressure (BP) threshold, a salt-sensitive increase in BP occurs when kidney function is reduced. However, the presence of confounders may influence the ability to demonstrate the BP response. The purpose of this research was to compare dietary sodium exposure and systolic BP (SBP) and diastolic BP (DBP) of U.S. adults according to kidney function level while accounting for potential confounders using NHANES data from 2003-2014. A causal framework approach was used to choose potential confounders of the dietary sodium-to-BP relationship.

The mean (standard error [SE]) age was 47.3 (0.2) years, 49.4% (n=14,094) were male, 69.9 (n=13,199) were non-Hispanic White. Body mass index was ≥ 25 kg/m^2 in 68.4% (n=19,442) and 13.6% (n=5,001) had evidence of diabetes. Hypertension (BP >140/90 mmHg or taking antihypertensive agents) was evident in 35.3% (n=11,373) yet only 26.7% (n=8,786) reported taking antihypertensive agents. The mean (SE) estimated glomerular filtration rate (eGFR) was 85.1 (0.4) ml/min/1.73m^2. The mean (SE) dietary sodium was 3,526 (16) mg/day or 8.8 (0.1) grams of salt/day. The mean (SE) SBP was 122.4 (0.2) mmHg and DBP was 70.9 (0.2) mmHg. BP was <120/80mmHg in 46.6% (n=12,180). After conditioning on demographic and clinical variables, the dietary sodium exposure-to-BP relationship was negligible: -0.04mmHg decrease in SBP for every 200mg increase in dietary sodium (p=.018) and 0.02mmHg increase in DBP for every 200mg increase in dietary sodium, p=.200). Stated differently, a 1mmHg decrease in SBP for every 5g increase in dietary sodium or 12.7g increase in NaCl and a 1mmHg increase in DBP for every 10g increase in dietary sodium or 25.4 g NaCl.

This study demonstrated that a clinically relevant relationship between dietary sodium intake on the day prior to blood pressure measurements and systolic and diastolic blood pressure was not apparent. Several demographic and clinical characteristics (kidney function, gender, race, income but not

education, BMI, evidence of diabetes) influence the dietary sodium-to-blood pressure relationship.

Chapter I

INTRODUCTION

Background of the Problem

Progressive increases in blood pressure are associated with a higher risk of heart diseases, stroke, and kidney failure. High blood pressure is an independent predictor of the development of atherosclerosis and cardiovascular disease (Aatola et al., 2010). Results from the Framingham Heart Study indicate that a 10 mmHg increase in systolic blood pressure (SBP) relates to a 1.22-increased risk for coronary heart disease (S. Franklin, Khan, Wong, Larson, & Levy, 1999; S. S. Franklin & Wong, 2013). Furthermore, people with hypertension (defined as blood pressure >140/90 mmHg) are more likely to have diabetes, dyslipidemias, or both in addition to kidney disease; each of these conditions relate to an increased cardiovascular risk (Plantinga et al., 2010; "U.S. Renal Data System," 2016).

Whereas the prevalence of hypertension is lower in the United States (U.S.) compared to other countries, the cost remains high at approximately $50 billion per year, which is attributable to absence from work and the cost of medications and health services to treat the condition (Nwankwo, Yoon, Burt, & Gu, 2013). Additionally, hypertension is noted to be a contributing factor in more than 1,100 deaths per day in the U.S. (Nwankwo et al., 2013). It affects

an estimated 70 million adults in the U.S. and is most common in African Americans (41.2%) compared to other racial groups (24.9% of non-Hispanic Asians; 25.9% of Hispanics, and 28.0% of non-Hispanic whites (Nwankwo et al., 2013; Yoon, Fryar, & Carroll, 2015). Between 2009-2010 and 2011-2012, awareness of, or treatment for, hypertension in the U.S. remained stagnant (Nwankwo et al., 2013). From 2011 to 2014, only 53% of people with hypertension were considered to have controlled blood pressure (Yoon et al., 2015).

The data on blood pressure in U.S. adults are principally available due to a federally funded program conducted across the nation since the late 1950s known as the National Health and Nutrition Examination Survey [NHANES ("About the National Health and Nutrition Examination Survey," 2017)]. The NHANES currently samples the population every year and includes a comprehensive collection of dietary, medical, biochemical, socioeconomic and demographic data. The NHANES provides insight on the prevalence of high blood pressure, as well as factors like dietary sodium intake, that contribute to high blood pressure. Additionally, over the last 15 years, data from NHANES have been utilized to inform on the prevalence of kidney dysfunction in the U.S., which had previously been unknown (Coresh et al., 2005; Coresh et al., 2007). The availability of information on blood pressure, dietary sodium intake, and kidney function in NHANES could be an important aid for describing the kidney's role in handling dietary sodium and

influencing blood pressure. Examination of the blood pressure, dietary sodium and kidney function relationship through using NHANES data may improve the evaluation of blood pressure goals and the role of dietary sodium in adults.

The Kidney Connection to Blood Pressure

High blood pressure and kidney disease are intertwined. Renin, a dominant blood pressure hormone, is an enzyme produced by and stored in kidney tissue that is released during reduced blood flow to the kidney glomerular apparatus (Elliott, Peixoto, & Bakris, 2016). Renin attracts another hormone, angiotensinogen (generated in the liver), and cleaves it to angiotensin I, then angiotensin-converting enzyme (ACE) produces angiotensin II (Lu, Cassis, Kooi, & Daugherty, 2016). Angiotensin II is the most potent of these products and is a vasoconstrictor. The vasoconstriction triggers the release of aldosterone (a mineralocorticoid from adrenal glands) to increase sodium absorption in the kidney proximal tubules, resulting in increased blood volume and blood pressure. This system is known as the RAAS or renin-angiotensin-aldosterone system. A feature of the RAAS in blood pressure control is the phenomenon known as pressure natriuresis (Lawton, DiBona, Kopp, & Luft, 2016). As dietary sodium increases, the extracellular volume increases, and blood pressure rises temporarily. The kidney senses the increase in volume and immediately increases sodium

excretion to control the pressure. Thus, dietary sodium is an important contributor to maintenance of adequate blood volume to assure organ perfusion. However, high dietary sodium has also been attributed to the progressive increase in blood pressure. High dietary sodium intake inhibits sodium transport in the kidney. Expanded blood volume increases pressure in the vasa recta (the straight arterioles in the kidney medulla) which accounts for ~10% of renal blood flow. This increase in pressure leads to release of digitalis-like substances (ouabain and marinobufagenin) that also act as vasoconstrictors. These vasoconstrictors inhibit the sodium-potassium adenosine triphosphatase (Na^+-K^+-ATPase) pump resulting in increased natriuresis (Anderson et al., 2008). In addition to their role in regulating blood pressure, these Na^+-K^+-ATPase inhibitors also regulate cardiovascular and renal function, further establishing an intricate relationship between cardiac and renal function (Hamlyn & Blaustein, 2016; R. J. Johnson, Bakris, & Rodriguez-Iturbe, 2016; Lawton et al., 2016).

Salt Sensitivity

Healthy kidneys can handle a high dietary sodium load before reaching the blood pressure threshold (Guyton, 1991). However, when kidney function (i.e., glomerular filtration rate, GFR) is reduced, or when angiotensin II, other vasoconstrictors, or aldosterone are high, sodium handling becomes abnormal and results in a salt-sensitive increase in blood pressure. Salt

sensitivity leads to progressive increases in blood pressure, even in people without hypertension (Barba et al., 2007; Gu et al., 2013). However, the blood pressure response to salt is variable and the kidney's ability to maintain the extracellular concentration of sodium is tight. Therefore, a renin-angiotensin response to changes in dietary sodium intake is likely a signal that kidney dysfunction causes high blood pressure (Elliott et al., 2016; Stolarz-Skrzypek & Staessen, 2015). In the U.S., it is estimated that nearly 29 million adults have reduced kidney function and 74% of those have hypertension ("U.S. Renal Data System," 2016). Fewer than one-half of people who have chronic kidney disease (CKD) are aware of having the condition (Plantinga, Boulware, Coresh, & et al., 2008; "U.S. Renal Data System," 2016). Of those with CKD who have hypertension, 43.8% are treated but have uncontrolled hypertension ("U.S. Renal Data System," 2016). The role of salt sensitivity in the non-response or poor response to treatment is unknown and no estimate of the prevalence of salt sensitivity in the CKD or general population is currently available. Salt sensitivity is more common in African Americans than Caucasians and is exacerbated by hypertension (Weinberger, 1996). Genetic polymorphisms may be involved in the regulation of sodium excretion (Ehret, Munroe, Rice, & al., 2011; R. J. Johnson et al., 2016). Such an association is evident by the blood pressure increase in response to salt loading and salt sensitivity in African American families (Rayner et al., 2012), and in people with diabetes (Yazdanpanah et al., 2007) or with CKD (Meng, Fu, Zhang,

Han, & Yang, 2014). However, this appears to account for only 20-30% of primary hypertension. Some researchers have also proposed that the genetic polymorphisms associated with salt sensitivity may have evolved as a survival mechanism (Franco & Oparil, 2006; Kusche-Vihrog & Oberleithner, 2012; Lev-Ran & Porta, 2005; Weinberger, Fineberg, Fineberg, & Weinberger, 2001). People with the ability to regulate volume may have survived volume-depleting illnesses, which may be the association of the salt sensitivity of African Americans and other ethnicities (Katsuya, Ishikawa, Sugimoto, Rakugi, & Ogihara, 2003; Richardson, Freedman, Ellison, & Rodriguez, 2013), yet they live to develop hypertension. Genetic polymorphisms may also impart an endothelial dysfunction that is involved in salt sensitivity (Feng, Dell'Italia, & Sanders, 2017), which may be further exacerbated by high dietary sodium. Furthermore, recent discoveries may shed light on how some people seem resistant to salt effects on blood pressure by an ability to store salt in reservoirs in the skin (Titze & Luft, 2017). The exact mechanisms of salt sensitivity and salt resistance, however, remain unknown (Williams, Nicholas, Vaziri, & Norris, 2014). Considering that the defect in sodium handling by the kidney may be an early signal of kidney dysfunction, the prevalence of kidney disease as currently defined could be higher than recent estimates (Elliott et al., 2016). However, there is no consensus on a unified method of assessing salt sensitivity (Galletti & Strazzullo, 2016; Theodore W Kurtz, DiCarlo, Pravenec, & Morris, 2017) and kidney disease is currently

identified as having reduced filtration or urinary markers of kidney damage (eg, presence of casts in the urine, proteinuria, or nephrocalcinosis) (Kidney Disease: Improving Global Outcomes Workgroup, 2013). Additionally, the unknown prevalence of salt sensitivity may confound the ability to detect associations between dietary sodium intake and the blood pressure response in general population studies. However, the fact that high dietary sodium intake can lead to high blood pressure makes dietary sodium an important target for public health policies.

Dietary Sodium Restriction for Blood Pressure and Kidney Disease

The standard first line of treatment for high blood pressure and kidney disease is to reduce dietary sodium intake (Go et al., 2014; Kidney Disease: Improving Global Outcomes Workgroup, 2012). The recommendations from the Academy of Nutrition and Dietetics Evidence Analysis Library (AND EAL) state that for people with CKD a dietary sodium restriction to <2,400 mg/day (or <6 g salt/day) is supported by *fair evidence* ("Chronic kidney disease," 2010). However, practice guidelines from the Kidney Disease Improving Global Outcomes (KDIGO) workgroup on blood pressure management in CKD recommend a dietary sodium of <2,000 mg/day (or <5 g salt/day) to aid in blood pressure control. The KDIGO guidelines state that most clinicians support this recommendation, but the quality of evidence for the recommendation is *low, Grade C* (Kidney Disease: Improving Global

Outcomes Workgroup, 2012). Acknowledging the lack of randomized controlled trials (RCTs) in CKD for dietary sodium restriction, the KDIGO workgroup suggested that whereas blood pressure and albuminuria appear to respond to dietary sodium restriction in patients with CKD, adults with salt wasting may experience hypovolemia or electrolyte abnormalities (Kidney Disease: Improving Global Outcomes Workgroup, 2012). Thus, people with CKD should have frequent monitoring to avoid adverse consequences of dietary sodium restriction (Kidney Disease: Improving Global Outcomes Workgroup, 2012).

Notably, the majority of drug classifications for the treatment of hypertension prescribed to patients with or without CKD include a statement to limit dietary sodium ("Cozaar [package insert]," 2015; "Hytrin [package insert]," 2009; "Norvasc [package insert]," 2016; "Prinivil [package insert]," 2015; "Tekturna [package insert]," 2015; "TOPROL-XL [package insert]," 2014) ("Loniten [package insert]," 2015), but no specific recommendation is provided as to the amount of dietary sodium. Dietary sodium was not evaluated in the pivotal trials for approval of these drugs. Nevertheless, patients undergoing treatment for hypertension and for CKD may decrease their dietary sodium intake upon their physician’s advice or upon reading the instructions for using the drug. Importantly, however, animal studies have demonstrated that blocking the RAAS pathway, which is the mechanism of action for many antihypertensive agents, increases the “liking” for sodium

(Morris, Na, & Johnson, 2008; Roper, 2015; Shigemura et al., 2013). An increased desire for or interest in dietary sodium has also been demonstrated in humans and animals exposed to diuretics, which helps to control blood pressure through increased sodium excretion by the kidney and increased angiotensin-binding sites. The increased interest in sodium is partially explained by the presence of angiotensin II receptors on taste cells (Shigemura et al., 2013). Thus, while patients taking medications for treating high blood pressure are advised to decrease dietary sodium, it is also possible that altering the angiotensin II pathway may result in an increased appetite for sodium.

In addition to those organizations previously mentioned above, several medical associations and voluntary health organizations (e.g., American College of Cardiology, American Heart Association, National Kidney Foundation) advocate for lowering the dietary sodium of U.S. consumers. The most recent guidelines from a multidisciplinary task force representing cardiovascular physicians, pharmacists, nurses and physician assistants recommends that prevention of elevated blood pressure (defined as 120-129 mmHg systolic and <80 mmHg diastolic) and treatment of hypertension (defined as ≥130 mmHg systolic and ≥80 mmHg diastolic) should include a dietary sodium goal of <1,500 mg/day or at least a reduction of 1,000 mg/day (Whelton et al., 2018).

Two U.S. government agencies (the Departments of Health and Human Service (HHS) and Agriculture) have also recognized dietary sodium as a contributing factor in high blood pressure and recommend a reduction in dietary sodium intake (“A global brief on hypertension”, 2013; *Dietary Guidelines for Americans, 2015-2020*, 2015). These U.S. agencies have recommended for decades that Americans should consume less dietary sodium (*Dietary Guidelines for Americans 2005*, 2005; *Dietary Guidelines for Americans, 2010*, 2010; *Dietary Guidelines for Americans, 2015-2020*, 2015). However, in 1989-1991, dietary sodium intake was 2,852 mg/day (Tippett et al., 1995) and a report from Hoy, Goldman, Murayi, Rhodes, and Moshfegh (2011) indicated that in 2007 dietary sodium was 3,330 mg/day. In the U.S., data from NHANES provide the estimate that the current average dietary sodium intake of people over one year of age is 3,440 mg/day (8.6 g of salt; (*Dietary Guidelines for Americans, 2015-2020*, 2015). Thus, advancements in efforts to lower overall dietary sodium intake in the U.S. appear to be failing.

Unless food was directly provided to participants, large cohort studies of hypertension prevention have demonstrated participants' difficulty in achieving the stated goals for dietary sodium (Kumanyika et al., 2005; Sacks et al., 2001). These investigators and others have postulated that a contributor to the participants' inability to obtain the dietary sodium goal is the significant amount of sodium added to processed foods (IOM [Institute of Medicine], 2010; Kumanyika et al., 2005; Mattes & Donnelly, 1991). The

WHO report (2007) stated that most sources of dietary salt in European and North American countries came from processed foods and foods provided by restaurants and caterers. In contrast, in African and Asian countries most dietary salt was added in cooking at home (2007). Global recommendations for dietary sodium vary by country and range from general salt avoidance to specific guidelines of <2,000 mg/day of sodium intake (5 g/day of salt) (2007). In the U.S., the current dietary sodium limit recommended by the *Dietary Guidelines for Americans* is <2,300 mg/day (<5.8 g/day of salt) in all adults to improve blood pressure (*Dietary Guidelines for Americans, 2015-2020*, 2015). The US Dietary *Guidelines for Americans* were developed for disease prevention, not for treating disease. However, as stated "Regardless of an individual's current health status, almost all people in the United States could benefit from shifting choices to better support healthy eating patterns. Thus, the *Dietary Guidelines for Americans* may be used or adapted by medical and nutrition professionals to encourage healthy eating patterns to patients." (*Dietary Guidelines for Americans, 2015-2020*, 2015).

To aid consumers' ability to achieve the dietary guideline target, the U.S. Food and Drug Administration (FDA) recently issued a non-binding draft guidance for industry on sodium reduction in commercially processed or prepared foods ("Draft Guidance for Industry: Voluntary Sodium Reduction", 2016). The FDA guideline is intended to assist food manufacturers, food

service programs, and restaurants in planning for an overall decrease in added sodium that would aid Americans in achieving the dietary guidelines.

The NHANES contains the largest repository of data on dietary intake available in the U.S. The average dietary sodium intake in the U.S. of 3,440 mg/day [8.6 g of salt/day (Hoy et al., 2011)] or, more recently 3,409 mg/day (Quader et al., 2017), is greater than 1,000 mg (2.5 g of salt) higher than the U.S. recommendation (*Dietary Guidelines for Americans, 2015-2020*, 2015) and almost 2,000 mg (5 g of salt) higher than the most recent American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines recommendations (Whelton et al., 2018). The periods examined for the reports on average dietary sodium intake were 2007-2010, a 4-year cycle of the NHANES by Hoy et al. (2011), and 2013-2014, a 2-year cycle of NHANES by Quader et al. (2017). However, a 2- or 4-year cycle is not sufficient to capture the prevalence or impact of kidney function on dietary sodium intake and blood pressure because the number of people in the lower levels of kidney function is inadequate to allow for sub-setting the data to examine these smaller groups (C. Johnson, Paulose-Ram, & Ogden, 2013). Additionally, the presence of these conditions (CKD or taking antihypertensive medications) in the NHANES data may negatively skew current estimates of dietary sodium intake in the U.S. Thus, an evaluation of a larger set of NHANES data may provide information needed to advance the understanding

of the relationships between blood pressure, dietary sodium intake and kidney function.

Research Purpose and Implications

The purpose of this research was to assess whether a relationship between dietary sodium and systolic and diastolic blood pressures could be demonstrated, either as a simple relationship or if accounting for kidney disease and other key demographic and clinical characteristics would demonstrate a relationship. The study explored comparisons between the dietary sodium and the systolic and diastolic blood pressures of U.S. adults using NHANES data. Since a lower dietary sodium intake is recommended for people with CKD and those who have hypertension or take antihypertensive medications, adjusting for the presence of these conditions in the NHANES data set may alter the current estimates of the mean dietary sodium of U.S. healthy adults. Furthermore, the anticipated adjustment in the estimated mean sodium intake would provide a more realistic approximation of the magnitude of dietary sodium reduction needed to meet the Healthy People 2020 goals for dietary sodium and blood pressure control in adults. Information on the dietary sodium intake of U.S. adults, after controlling for key demographic and clinical characteristics, may contribute to nationwide program development and implementation for reduced sodium intake and to future research for prevention of high blood pressure in the U.S. Information

on the dietary sodium intake of adults at different levels of kidney function may also provide insight for program development on the healthcare management of people at different stages of kidney disease. To the knowledge of this investigator, no systematic reports of dietary sodium intake of adults according to level of kidney function have been provided in the literature. Knowledge of the dietary sodium by level of kidney function may help in designing research and making programmatic recommendations. Moreover, as the global effort to reduce dietary sodium increases (World Health Organization, 2007, 2016), sharing information through dissemination may contribute to methods used by other countries in their approach to measuring and assessing the extent of the high dietary sodium problem. As a result, the research was expected to improve the understanding of dietary sodium intake in nonpregnant adults with and without reduced kidney function and the relationship between dietary sodium and systolic and diastolic blood pressure.

Problem Statement

In U.S. nonpregnant adults, as represented by data from NHANES 2003-2014, whose kidney function is estimated and who have completed a 24-hour dietary recall, what is the relationship between blood pressure and dietary sodium intake on the day prior to blood pressure measurement when

accounting for levels of kidney function and key demographic and clinical characteristics?

Research Subproblems

In U.S. nonpregnant adults, as represented by data from NHANES 2003-2014, whose kidney function is estimated and who have completed a 24-hour dietary recall on the day prior to blood pressure measurement:

1. What are their key
    a. Demographic characteristics (age, sex, race and ethnicity, education level, income status)?
    b. Clinical characteristics (albumin-to-creatinine ratio, body mass index, diabetes status, number and type of antihypertensive agents used, kidney disease awareness, kidney function level, smoking status)?
2. What is their dietary sodium intake and systolic and diastolic blood pressure?
3. What is the relationship between dietary sodium intake and key
    a. demographic and
    b. clinical characteristics?
4. What is the relationship between systolic and diastolic blood pressure and key
    a. demographic and
    b. clinical characteristics?

5. What is the relationship between dietary sodium intake and systolic and diastolic blood pressure?
6. What is the relationship between dietary sodium intake and systolic and diastolic blood pressure when controlling for key demographic and clinical characteristics?

Hypotheses

1. Dietary sodium
    a. The mean dietary sodium intake of U.S. nonpregnant adults is lower in people taking antihypertensive agents than in adults not taking antihypertensive agents.
    b. The mean dietary sodium intake of U.S. nonpregnant adults is lower in people with reduced kidney function than in adults with normal kidney function.
    c. The mean dietary sodium intake of U.S. nonpregnant adults with normal kidney function is higher than 3,440 mg/day.
2. Dietary sodium and blood pressure
    a. There is no relationship between dietary sodium intake on the day prior to blood pressure measurement and systolic and diastolic blood pressure in U.S. nonpregnant adults when controlling for key demographic and clinical characteristics.

Operational Definitions

Demographic Characteristics

Demographic characteristics are statistical descriptors of a population that may include age, sex, and other characteristics (U.S. National Library of Medicine, 2018b). For the purpose of this study, demographic characteristics included age, sex, race and ethnicity, and socioeconomic status.

Education level – the highest level of education achieved at the time of the interview ("What are education levels?," 2018). For the purpose of this study, education level was the highest level of education completed as reported to the NHANES interviewer. Education level was categorized as less than a High School diploma; High School diploma or General Education Development test; Some college or an Associate degree; a college degree or higher.

Ethnicity – a group of people who share common background, such as culture, language or religion (Cornell & Hartmann, 2006). For the purpose of this study, ethnicity was used to describe U.S. adults who classify themselves as being of Hispanic or non-Hispanic ethnicity as defined by the U.S. Census Bureau (U.S. Census Bureau, 2017a).

Income status, annual – the total income for the NHANES participant family during the previous calendar year ("NHANES 2003-2004," 2004). For the purpose of this study, annual income reported to the NHANES interviewer

("NHANES 2003-2004," 2004). Annual income status was categorized as less than $20,000; $20,000 to less than $45,000; $45,000 to less than $75,000; or greater than $75,000.

Race – a group of people defined by itself or others as distinct by perceived common physical characteristics held to be inherent (M. James, 2016). For the purpose of this study, race was considered as American Indian or Alaskan Native, Black or African American, Native Hawaiian or Other Pacific Islander, and White, according to the U.S. Census definition (U.S. Census Bureau, 2017b).

U.S. nonpregnant adult – An adult is a person who is physically mature (Merriam-Webster, 2017). For the purpose of this study, this term was defined as sample persons in the NHANES database who were ≥20 years of age and, if female, were not pregnant at the time of sampling.

Clinical Characteristics

Clinical characteristics are distinguishing medical features. For the purpose of this study, clinical characteristics included diabetes status, body mass index, kidney function level, and biomarkers of kidney damage (e.g., albumin-to-creatinine ratio or categories of proteinuria).

Albumin-to-creatinine ratio (ACR) – a method of assessing protein in an on-the-spot or “spot” urine specimen and quantifying it to the amount of creatinine in the specimen (Kidney Disease: Improving Global Outcomes

Workgroup, 2013). For the purpose of this study, ACR was the urinary albumin concentration divided by the urinary creatinine concentration, reported in mg albumin/g creatinine (Kidney Disease: Improving Global Outcomes Workgroup, 2013).

Antihyperglycemia agents – medications used to lower the blood glucose level (U.S. National Library of Medicine, 2018e). NHANES participants were asked if they took a medication during the last month that required a prescription. Those who respond affirmatively were asked to show the interviewer the container; if no container was available, the participant verbally provided the name of the medication. For the purpose of this study, antihyperglycemia agents were those categorized in the NHANES database, using the Lexicon Plus® database (Cerner Multum, Inc, Denver, CO), as Metabolic Agents or Antidiabetic Agents. These medications included alpha-glucosidase inhibitors, amylin analogs, antidiabetic combinations, biquanides, dipeptidyl peptidase 4-inhibitors, incretin mimetics, insulin, meglitinides, sulfonylureas, and thiazolidinediones. For the purpose of this study, the presence of hyperglycemia agents was one component of determining diabetes status.

Antihypertensive agents – medications used to treat the condition of high blood pressure or hypertension (U.S. National Library of Medicine, 2018a). NHANES participants were asked if they took a medication during the last month that required a prescription. Those who responded affirmatively

were asked to show the interviewer the container; if no container was available, the participant verbally provided the name of the medication. For the purpose of this study, antihypertensive agents were those categorized in the NHANES database, using the Lexicon Plus® database (Cerner Multum, Inc., Denver, CO), as Cardiovascular Agents, excluding those with a second level category of inotropic agent or miscellaneous cardiovascular agents (because these two agents could not further be identified as to function) or the use of vasopressors. The Cardiovascular Agents included medications for pulmonary hypertension; aldosterone receptor antagonists; angiotensin II inhibitors; angiotensin converting enzyme inhibitors; anti-adrenergics, centrally acting; anti-adrenergics, peripherally acting; anti-anginals; anti-arrhythmics; anti-hypertensive combinations; beta-adrenergic blocking agents; calcium channel blocking agents; diuretics; and renin inhibitors.

Body mass index (BMI) – an estimate of fat mass from the ratio of height to weight (World Health Organization, 1998). For the purpose of this study, BMI was calculated as the ratio of weight in kilograms and the squared height in meters (kg/m^2).

BMI classification – groupings of the BMI intended to demonstrate deviations from normal BMI for health risk assessment and for research purposes (World Health Organization, 1998). For the purpose of this study, BMI classification was categorized as according to the WHO definition (World Health Organization, 1998):

- Underweight, BMI <18.5 kg/m^2
- Normal range, BMI 18.5-24.9 kg/m^2
- Overweight, BMI 25-29.9 kg/m^2
- Obese, BMI ≥ 30.0 kg/m^2

Diabetes status – Diabetes is a group of disorders characterized by hyperglycemia and glucose intolerance (U.S. National Library of Medicine, 2018c). For the purpose of this study, diabetes status was the presence of evidence for diabetes, defined as 1) a documented diagnosis of diabetes within the NHANES questionnaire data (“Have you ever been told by a doctor or health professional that you have diabetes or sugar diabetes?” ("NHANES 2003-2004 survey questionnaires: sample person questionnaire - diabetes," 2004)) or 2) taking antihyperglycemia agents or 3) having a fasting glucose ≥ 126 mg/dL (7.0 mmol/L) after fasting for ≥ 8 hours, or 4) having a glycosylated hemoglobin ≥ 6.5% ("2. Classification and diagnosis of diabetes," 2017).

Estimated glomerular filtration rate (eGFR) – an estimate of the functional status of the kidney, which utilizes a biomarker (e.g., serum creatinine) as a surrogate for kidney function and demographic factors (e.g., age, sex, race) to estimate or approximate the filtration rate (Levey et al., 2009). For the purpose of this study, eGFR was calculated from the Chronic Kidney Disease-Epidemiology consortium equation, shown below:

$GFR = 141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] or 1.159 [if black], where Scr is serum creatinine, κ is 0.7 for females

and 0.9 for males, **α** is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/**κ** or 1, and max indicates the maximum of Scr/**κ** or 1 (Levey et al., 2009). For participants who indicated having dialysis in the previous 12 months, an eGFR of 10 ml/min/1.73m^2 was applied.

Kidney disease awareness – Kidney disease awareness is defined as a "Yes" response to either or both of the following questions in the NHANES data set: "Have you ever been told by a doctor or other health professional that you had weak or failing kidneys? Do not include kidney stones, bladder infections, or incontinence." or "In the past 12 months, have you received dialysis (either hemodialysis or peritoneal dialysis)?" ("NHANES 2003-2004 survey questionnaires: sample person questionnaire - kidney conditions," 2004).

Kidney function – the totality of excretory, metabolic and endocrine functions of the kidney (Kidney Disease: Improving Global Outcomes Workgroup, 2013). For the purpose of this study, kidney function was estimated by eGFR as excretory function and grouped into 15 ml/min/1.73m^2 increments, from less than 15 to greater than 105 ml/min/1.73m^2, as recommended by the Kidney Disease Improving Global Outcomes Workgroup on CKD (Kidney Disease: Improving Global Outcomes Workgroup, 2013). Any participant who reported having had dialysis treatment in the previous 12 months was assigned an eGFR of 10ml/min/1.73m^2 and categorized in the less than 15 ml/min/1.73m^2 kidney function level group.

Normal kidney function – defined as eGFR ≥90 ml/min/1.73m^2 without evidence of kidney damage (e.g., albuminuria) (Kidney Disease: Improving Global Outcomes Workgroup, 2013). For the purpose of this cross-sectional study having only one assessment of eGFR and only one assessment of kidney damage was not applied, as is recommended by the KDIGO guidelines (Kidney Disease: Improving Global Outcomes Workgroup, 2013).

Proteinuria – the presence of protein in the urine (U.S. National Library of Medicine, 2018f). For the purpose of this study, proteinuria was albuminuria quantified by using a spot urinary albumin-to-creatinine ratio (ACR) of 30 mg/g or higher (Kidney Disease: Improving Global Outcomes Workgroup, 2013). The following nomenclature identified the level of proteinuria:

- Normal, ACR < 10 mg/g;
- Normal to mildly increased, ACR 10-29 mg/g;
- Moderately increased, microalbuminuria, ACR from 30 to 300 mg/g;
- Severely increased, macroalbuminuria, ACR > 300 mg/g.

Smoking status – definition of smoking. For the purpose of this study, smoking status was categorized (Choi, Park, Kim, & Lim, 2015) as

- Never smoked – someone who stated they did not currently smoke cigarettes and had not smoked cigarettes in the past

- Former smoker – someone who stated they had smoked in the past and had smoked no cigarettes in the previous 30 days
- Current smoker – someone who stated they were currently smoking and had smoked cigarettes during the previous 30 days (Choi et al., 2015)

Reduced kidney function – defined as having an eGFR less than 90 ml/min/1.73m^2 (Kidney Disease: Improving Global Outcomes Workgroup, 2013).

Blood Pressure

Blood pressure is a measure of the pressure (in millimeters of Hg; mmHg) exerted on the blood vessel walls by the pumping action of the heart (MedlinePlus, 2017). Blood pressure is usually measured using a sphygmomanometer at the brachial artery and reported as the highest pressure following systole of the left ventricle (systolic blood pressure) and the minimum pressure of diastole (diastolic blood pressure) (MedlinePlus, 2017). NHANES uses certified blood pressure examiners, trained and certified by Shared Care Research and Education Consulting, Inc. (Stateline, NV). Blood pressure was taken after sitting for 5 minutes and measured three consecutive times. A fourth blood pressure reading was taken if one of the first three measurements was interrupted or incomplete. For the purpose of this study, the variable “blood pressure” was the average of the blood

pressure readings obtained by NHANES examiners. Blood pressure was averaged and reported separately for systolic and diastolic blood pressure. Systolic and diastolic blood pressures were each considered outcome variables in this study.

Blood pressure category – defined as cut points of blood pressure for hypertension in the U.S. by Mozaffarian, Benjamin, Go, Arnett, Blaha, Cushman, …Turner (2015). For the purpose of this study using NHANES data from 2003-2014, the blood pressure categories were:

- A: <120 mmHg systolic and <80 mmHg diastolic
- B: 120-139 mmHg systolic or 80-89 mmHg diastolic
- C: 140-159 mmHg systolic or 90-99 mmHg diastolic
- D: ≥160 mmHg systolic or ≥100 mmHg diastolic

Clinically relevant blood pressure relationship – defined as the minimum clinically important difference in a variable associated with another variable or a treatment (Man-Son-Hing et al., 2002). For the purpose of this study where a large proportion of the participants had normal kidney function and were not taking antihypertensive agents, a variable having a clinically relevant blood pressure relationship was the amount of that variable associated with a blood pressure (systolic or diastolic) difference that could be measured by a sphygmomanometer (e.g., ≥1 mmHg).

High blood pressure awareness – High blood pressure awareness is defined as a “Yes” response in the NHANES data set to the following

question: “Have you ever been told by a doctor or other health professional that you had hypertension, also called high blood pressure?” ("NHANES 2003-2004 survey questionnaires: sample person questionnaire - blood pressure," 2004) by sample persons who had blood pressure >140/90 mmHg or were taking antihypertensive agents.

Hypertension status – Hypertension is defined as a persistently high blood pressure (U.S. National Library of Medicine, 2018d). For the purpose of this study, hypertension status was the average of up to four measurements of SBP that was either ≥ 140 or diastolic blood pressure (DBP) that was ≥ 90 mmHg (Chobanian et al., 2003) or taking antihypertensive agents. The definition follows the recommendations for national surveillance of hypertension proposed by the Centers for Disease Control and Prevention and the National Heart, Lung, and Blood Institute of the National Institutes of Health, as reported by Crim et al. (2012) and Mozaffarian et al. (Mozaffarian et al., 2015). These recommendations represent the vintage during which the NHANES data were collected (2003-2014) for use in the current report.

Dietary Sodium

Dietary sodium is the amount of sodium in the diet (U.S. National Library of Medicine, 2018g). For the purpose of this study, dietary sodium was the reported intake of dietary sodium sources in units of mg/day as obtained from the first of a possible two 24-hour dietary recalls in NHANES ("What we

eat in America, DHHS-USDA dietary survey integration," 2015). Interviewers used visual aids to assist participants with the recall of dietary intake (e.g., grids, glasses, household spoons, mounds, bottles, bowls, thickness strips, boxes; each of various sizes and shapes), as well as a food model booklet containing pictures of foods, while applying a uniform methodology for obtaining the information known as the U. S. Department of Agriculture's Automated Multiple-Pass Method (AMPM) for 24-hr recall (Raper, Perloff, Ingwersen, Steinfeldt, & Anand, 2004). At the end of the interview, participants were asked what type of salt they used, if they used salt at the table, if salt was used in food preparation in their household and with what frequency salt was used in food preparation. The sodium variable in NHANES was adjusted for salt used in preparing foods in surveys between 1985 and 2008 by a downward adjustment for those who indicated they did not or only rarely used salt added at the table or in cooking. In 2009 forward, the questions continued to be asked but the adjustment in the dietary sodium variable was no longer applied because a validation study using 24-hour urinary sodium excretion compared to the dietary recall determined that the AMPM for 24-hour dietary recall accurately provides dietary sodium information without requiring the salt adjustment (Rhodes et al., 2013). The first 24-hour dietary recall reflects the dietary sodium on the day prior to having blood pressure measured. The total dietary sodium reported was Winsorized to avoid allowing outliers to have undue influence on the mean

dietary sodium, yet not lose them in the analysis. Winsorizing a variable is a method of handling outliers by assigning them the highest data point not considered to be an outlier (Salkind, 2010). For the purpose of this study, the total dietary sodium on the day prior to blood pressure measurement was considered the exposure variable.

Delimitations

This study utilized NHANES datasets 2003-2004, 2005-2006, 2007-2008, 2009-2010, 2011-2012, and 2013-2014. Sample persons or participants were limited to those who were 20 years of age or older at the time of sampling, were not pregnant, and had both the medical examination (including all parameters required for kidney function assessment) and submitted a 24-hour dietary recall that was assessed to be reliable.

Chapter II

LITERATURE REVIEW

Introduction to Related Literature

The latest edition of the federally mandated *U.S. Dietary Guidelines for Americans* specifies that a healthy eating pattern limits sodium to <2,300 mg/day (<100 mmol/day or <5.8 g salt/day; (*Dietary Guidelines for Americans, 2015-2020*, 2015). However, the guideline for 2015-2020 (*Dietary Guidelines for Americans, 2015-2020*, 2015) is less targeted for dietary sodium than in previous editions (*Dietary Guidelines for Americans 2005*, 2005; *Dietary Guidelines for Americans, 2010*, 2010). The current dietary guidelines no longer advise a further reduction to 1,500 mg of sodium/day for special subgroups: African Americans, people 51 years of age and older, and people with hypertension, diabetes, or chronic kidney disease. The reason for the change was due to a lack of clear evidence that such a population recommendation would be safe and efficacious (IOM [Institute of Medicine], 2013). However, it should be noted that the cardiology guidelines continue to recommend a dietary sodium intake <1,500 mg/day to prevent elevated blood pressure and for treatment of hypertension (Whelton et al., 2018).

A recent examination of evidence for the recommendation by a special subcommittee of the National Academy of Medicine (NAM, formerly known as

the Institute of Medicine or IOM) concluded that there was some evidence, albeit inconsistent evidence, of increased morbidity and mortality when dietary sodium was <2,300 mg/day (IOM [Institute of Medicine], 2013). Large prospective cohort studies have observed a J-shaped curve for the association between urinary sodium excretion (a biomarker of dietary sodium intake) and cardiovascular disease mortality or all-cause mortality (Mente et al., 2016; O'Donnell, Yusuf, Mente, & et al., 2011). A report representing 113,118 participants of four prospective cohort studies (Anand et al., 2012; Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) Investigators et al., 2008; Teo et al., 2013; The ONTARGET Investigators, 2008) indicated a higher rate of cardiovascular events and death in people with hypertension who consume a high sodium diet (7,000 mg sodium/day or 17.5 g of salt) compared to a moderate sodium diet (<3,000 mg sodium/day or 7.5 g of salt) (Mente et al., 2016). The investigators stated that people with a dietary sodium <3,000 mg/day with or without hypertension have an increased risk of cardiovascular events or death. Graudal, Jurgens, Baslund & Alderman (2014) also reported this curve as a U-shaped curve of dietary sodium and mortality in a meta-analysis. However, without a RCT, it will remain unknown as to whether the changes seen in observational studies reflect a causal relationship between dietary sodium and blood pressure or cardiovascular disease outcomes. Furthermore, the range of safe sodium intake has not been well studied. A

major limitation of many studies available was “inconsistent and inadequate sodium intake assessment” (IOM [Institute of Medicine], 2013).

The NAM report was published in 2013 and evaluated the literature published since 2003 (IOM [Institute of Medicine], 2013). A search of literature published since the NAM special subcommittee report on the topic of blood pressure and dietary sodium for the gold standard of evidence, which are RCTs, was conducted for the current study. The purpose of the literature search was to explore whether new findings support a linear relationship between dietary sodium intake and blood pressure, whether new studies offer any clarity to the question of the appropriate dietary sodium restriction, and include studies conducted in adults with kidney disease. Therefore, studies evaluating dietary sodium and blood pressure in adult healthy volunteers, adults with high blood pressure, or adults with kidney disease were included in the literature search.

Bibliographical Methods

The literature search was conducted using electronic databases (Medline/PubMed from 1945 to November 2018, the Cochrane Library, the University of York Centre for Reviews and Dissemination) and a search of dissertations using www.dissertation.com. Systematic reviews (SRs) and meta-analyses were reference-mined for relevant articles not appearing in the main literature search results (Figure 1 and Appendix A). Citations from

related articles appearing in PubMed or in major textbooks or professional practice guidelines on the topic of blood pressure and dietary sodium were also captured, if relevant.

Criteria for the final review of records included articles on dietary sodium reported from food records or urine sodium with a comparison to blood pressure or change in blood pressure in adults. For articles pertaining to kidney disease, a measure of kidney function or kidney damage was also required. If the search returned more than one article from a single study, the original article was preferred. However, if an article with post hoc analyses was more pertinent to the research question, the article was reviewed but not included in the final qualitative synthesis unless the study planned a priori to report the finding (i.e., was powered to the endpoint).

The criteria of *blood pressure* and *dietary sodium* were initially searched together, and *kidney disease* was combined in the second search series (Figure 1, Appendix A Table A1). Blood pressure was searched as a Medical Subjects Heading (MeSH) term as well as free text ("blood pressure") and combined using the Boolean operator "OR". *Dietary sodium* and *sodium-restricted diet* were searched as MeSH terms and as free text and also included *dietary salt*, *dietary sodium chloride*, *salt reduction*, *dietary sodium reduction*. These dietary terms were searched using the Boolean operator "OR". The *blood pressure* and *dietary sodium* searches were then combined using the Boolean operator "AND" to restrict the search to only those

publications using both topics. Combining these terms in the Medline search resulted in 7,186 records (Figure 1, Appendix A Table A1). The search was further restricted to *randomized, controlled trials* (as MeSH or as free text) to capture only those records with highest levels for evidence and restricted from records identified as review articles using the Boolean operator “NOT”; this action returned 612 records. Since the NAM has recently reviewed this body of literature for evidence (IOM [Institute of Medicine], 2013) the current search was further restricted to articles published in the last seven years (since 2011), resulting in 170 abstracts to screen.

Kidney disease was searched as the MeSH term *Kidney* in order to include records of all levels of kidney function. *Glomerular filtration rate* was included as both a MeSH term and free text in addition to “*kidney function*” in order to capture records that examined kidney function. These terms were combined with the Boolean operator “OR”. When combined with the *blood pressure* and *dietary sodium* search, the search including *Kidney* resulted in 148 records, 51 of which were published in the last seven years (Figure 1). Each of these records appears in the *blood pressure* and *dietary sodium* search.

A total of 123 full text articles were reviewed and 22 met the criteria for inclusion in the study (Figure 1).

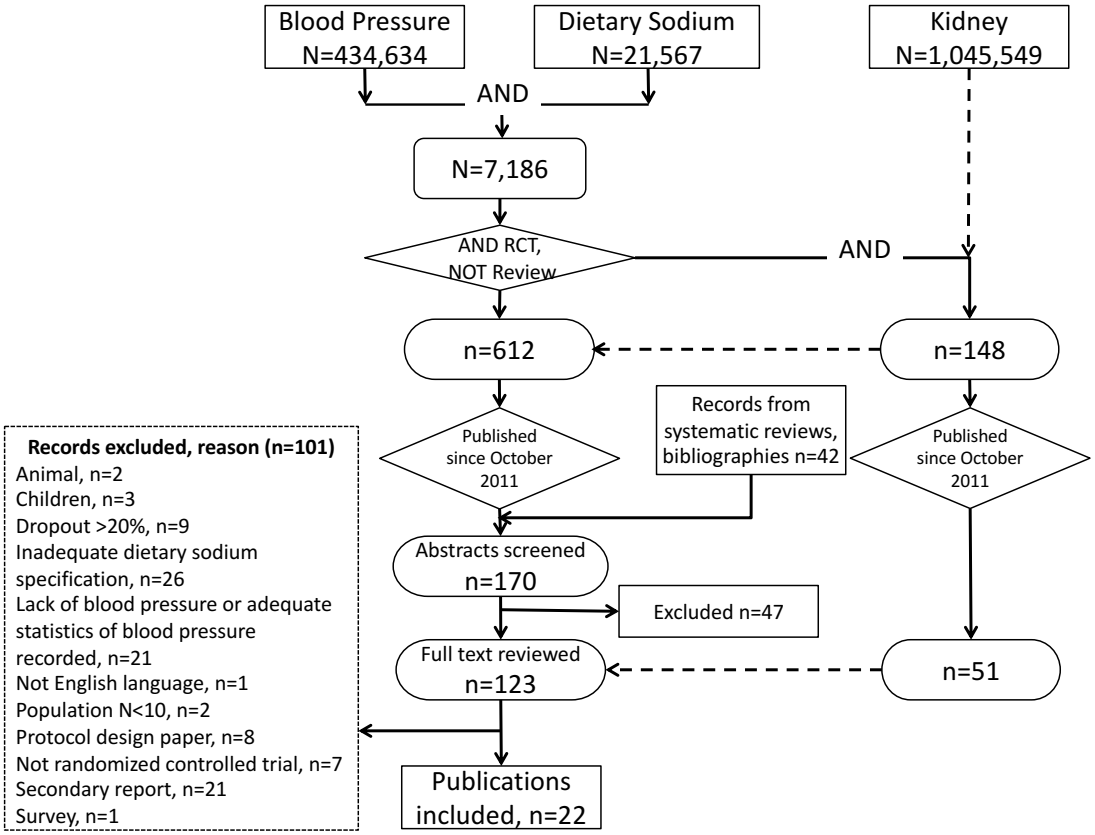

Figure 1. Flow of articles reviewed pertaining to blood pressure, dietary sodium, and kidney function.

The Cochrane Library and the Centre for Reviews and Dissemination were searched for SRs. Searching the Cochrane Library was performed using the MeSH terms *Blood Pressure* AND *Sodium, Dietary* OR *Diet, Sodium-Restricted* with the free text terms *blood pressure*, *dietary sodium*, *dietary sodium chloride*, *sodium-restricted diet*, *salt reduction*, *dietary sodium reduction*, and *systematic review* resulted in 35 SRs, 18 of which were published in the last seven years and 17 of which were Cochrane Reviews (Appendix A Table A2).

The search of the Centre for Reviews and Dissemination (www.york.ac.uk/crd) for the MeSH terms *Blood Pressure* AND *Sodium Chloride, Dietary* OR *Sodium, Dietary* and the free text *blood pressure, dietary sodium, sodium-restricted diet, salt reduction,* and *dietary salt* resulted in 32 records from 1996 to 2013 (Appendix A Table A3). No SRs were captured that also included the terms used for *kidney* and *glomerular filtration rate*. Records from 2011 forward included 12 SRs. Of these 12 records, six were included in the Cochrane search. The remaining six publications were evaluated for potential additional RCTs to add to the body of literature for the current study.

The search for dissertations on this topic resulted in two records: one from 2014 published as a thesis from a student at the University of Maryland (Nothwehr, 2014) and one from 2016 published as a dissertation from a student at Rutgers University (Osei, 2016).

A review of textbooks and practice guidelines provided material and guidance on the topic and were reference-mined for relevant citations. Major textbooks included chapters on hypertension from *Brenner & Rector's The Kidney* (Elliott et al., 2016), *Comprehensive Clinical Nephrology* (R. J. Johnson et al., 2016; Lawton et al., 2016), *National Kidney Foundation's Primer on Kidney Diseases* (Wilcox, 2014), and *Modern Nutrition in Health and Disease* (Appel, 2014). Guidelines incorporated into the report include the *2015-2020 Dietary Guidelines for Americans* (*Dietary Guidelines for*

Americans, 2015-2020, 2015), the Food and Drug Administration's Draft Guidance for Industry on "Voluntary Sodium Reduction Goals" ("Draft Guidance for Industry: Voluntary Sodium Reduction", 2016), the Eighth Joint National Committee's "2014 Evidence-based Guideline for the Management of High Blood Pressure in Adults" (P. A. James et al., 2014), the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines report "2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of high Blood Pressure in Adults: Executive Summary" (Whelton et al., 2018), the Kidney Disease Improving Global Outcomes (KDIGO) "Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease" (Kidney Disease: Improving Global Outcomes Workgroup, 2012), "KDIGO 2012 Practice Guideline for the Evaluation and Management of Chronic Kidney Disease" (Kidney Disease: Improving Global Outcomes Workgroup, 2013), and the Academy of Nutrition and Dietetics Evidence Analysis Library on Chronic Kidney Disease ("Chronic kidney disease," 2010), Hypertension ("Hypertension," 2015), and Sodium ("Sodium," 2014).

Blood Pressure and Dietary Sodium in Healthy Volunteers

In healthy volunteers, nine RCTs met the search criteria set forth for the current study (Table 1). Six studies evaluated healthy volunteers who

were < 40 years of age (Allen et al., 2014; Cavka et al., 2015; Lennon-Edwards et al., 2014; Rorije et al., 2018; Selvarajah et al., 2017; Wenner et al., 2011), one study included healthy volunteers up to 70 years of age (Blanch, Clifton, Petersen, & Keogh, 2015), and two studies included healthy volunteers who were approximately 50 years of age (Carey et al., 2012; Wang et al., 2014). The increase in dietary sodium to test the blood pressure response ranged from a 6- to a 40-fold increase and none of the trials matched in sodium dose. The length of each test cycle studied was as short as a single meal in a study by Blanch, et al. (2015), five days in a study by Allen et al. (2014), eight days in the study by Rorije et al. (2018) and seven days in the remainder of studies reviewed in a healthy volunteer population (Carey et al., 2012; Cavka et al., 2015; Lennon-Edwards et al., 2014; Selvarajah et al., 2017; Wang et al., 2014; Wenner et al., 2011) (Table 1).

Allen et al. (2014) randomized 70 healthy adult volunteers in a crossover fashion to three different levels of dietary sodium: 10, 150, and 400 mmol/day (a 40-fold increase in dietary sodium; Table 1). No statistically significant increase occurred in the SBP and a statistically significant decrease occurred in the DBP at the higher sodium level. Carey et al. (2012) also evaluated a large difference in dietary sodium using a crossover design (Table 1). A 30-fold increase in the dietary sodium resulted in no change in SBP or DBP in salt-resistant participants. However, salt-sensitive participants (n = 34, 18% and all were Caucasian) experienced a statistically significant

increase in SBP (15 mmHg) and DBP (9 mmHg) on the higher sodium regimen. Salt sensitivity may have also influenced the results from Allen, et al. (2014) because, as reported, 19 (27%, race proportion not provided) of the participants in that trial were noted to be salt-sensitive; however, the results were not reported separately. One other study reviewed demonstrated an assessment of salt sensitivity of the participants enrolled. In the study by Lennon-Edwards et al. (2014), participants were excluded from analysis if they exhibited salt sensitivity (Table 1). A total of three (7%) of the participants were deemed salt-sensitive. The results in salt-resistant participants indicated that neither the SBP nor DBP changed significantly between the low sodium (20 mmol Na/d) vs very high sodium (300-350 mmol Na/day) diet.

In a randomized, double-blind, parallel study design (i.e., two independent groups), Cavka et al. (Cavka et al., 2015) demonstrated that the participants in the low sodium diet group (approximately 50 mmol Na/day, a 30% decrease from their baseline) experienced a statistically significant decrease in SBP and DBP (Table 1). However, the SBP and DBP of those in the high sodium arm (approximately 250 mmol Na/day, an 83% increase from their baseline) did not change. In another randomized, controlled, open-label, crossover study, Rorije et al. (2018) demonstrated that a mean dietary sodium intake of 19 mmol/day for eight days followed by an acute bolus of

normal saline, a 1-week washout period, and an 8-day mean dietary sodium of 391 mmol/day did not effect a change in SBP or DBP (Table 1).

Two of the nine studies reported an increase in the SBP and DBP of adult healthy volunteers in response to a sodium challenge (Selvarajah et al., 2017; Wang et al., 2014). In a randomized, crossover design, stratified by sex, Selvarajah et al. (2017) observed a statistically significant increase in day time and evening SBP and evening DBP in women but not in men after a dietary sodium challenge (70 to 200 mmol). Interestingly, the blood pressure was not different in the office measurements between the two study diet periods in men or in women (Table 1). Of further interest from the Selvarajah et al. study (2017), was the measurement of Na:K in skin biopsies between the study periods. They observed that only men experienced an increase in skin Na:K during the high sodium diet period, which may suggest a salt-resistant state in the men in this study. The other study demonstrating an increased blood pressure in response to a high sodium diet used a randomized, sequential study design (Wang et al., 2014) and demonstrated a statistically significant higher blood pressure when increasing from a low sodium diet (approximately 50 mmol Na/day or 1,200 mg Na) to a high sodium diet (300 mmol Na/day or 7,000 mg Na; Table 1).

None of the nine studies examined reported a plan for identifying potential adverse effects of the experiments. Thus, no adverse effects were reported. However, the body of evidence may be improved if future studies

also collect and report the events in a systematic way. For example, the blood pressure response could also have been recorded categorically to indicate the proportion of people in the studies who moved from normal blood pressure (<120/80 mmHg) to blood pressure of 120-139/80-89 mmHg or beyond. Similarly, the number of people experiencing hypotension should have been recorded. A listing of potential adverse events in the "vascular disorders" category of the Common Terminology Criteria for Adverse Events (https://safetyprofiler-ctep.nci.nih.gov) provides other terms that might have occurred in some individuals in these studies (e.g., flushing or "gastrointestinal disorders" such as constipation) that would be important in capturing the potential effects of manipulating the blood pressure through dietary sodium and are largely missing from the research in this field.

In summary, the nine studies performed since 2012 in healthy volunteers from four different countries did not demonstrate an increased blood pressure in response to an increased dietary sodium dose except in those who exhibit salt sensitivity. In this series of nine studies, Allen, et al. (2014), Carey, et al. (2012), and Lennon-Edwards, et al. (2014) identified salt sensitivity using a blood pressure response method, and the range was 7-27% of the people studied, which is within the range of previous reports. Selvarajah et al. (2017) used a novel method of assessing skin levels of Na:K and found that the men in their study appeared to be salt-resistant compared to the women in the study. However, the studies reporting on salt sensitivity

were not racially diverse. Additionally, none of the studies evaluated dietary sodium at levels recommended by the U.S. Dietary Guidelines for Americans (*Dietary Guidelines for Americans, 2015-2020*, 2015) and none reported an evaluation of adverse events. Whereas the study designs were good quality RCTs in healthy volunteers, reporting of adverse events, including a dose of dietary sodium in the range of interest, improving on the diversity of participants enrolled, and studies using longer duration in the diet arms remain desirable.

Table 1.
Description of articles on randomized controlled trials of blood pressure and dietary sodium in healthy volunteers

Author, citation	Design/ Characteristics	Location/ Recruit-ment	N (% com-pleted)	Diet, Intervention	UNa, mmol/ day	Mean Blood Pressure, mmHg	
						SBP	DBP
Allen et al. Dietary sodium influences the effect of mental stress on heart rate variability. J Hypertens 2014;32:374-382	RCT, crossover; 1 mo washout between diets; 5-day duration of each diet. Age, 18-38 y M/F, 26/44 BMI, 24 ± 3 kg/m^2 No meds allowed except oral contraceptives. *Salt sensitivity* defined as SBP ≥ 5 mmHg increase on HdNa.	Rochester, MN U.S. Recruited from a genetic data-base	70 (100); Note: 19/70 (27%) were SS	LdNa = 10 mmol/day	21 ± 1.7	116 ± 1.4	70 ± 1.2
				NdNa = 150 mmol/day	110 ± 3.8	117 ± 1.3	67 ± 0.9
				HdNa = 400 mmol/day	327 ± 12.8	116 ± 1.4 *p* = .80	67 ± 1.0 *p* = .042

Author, citation	Design/ Characteristics	Location/ Recruit-ment	N (% com-pleted)	Diet, Intervention	UNa, mmol/ day	Mean Blood Pressure, mmHg	
						SBP	DBP
Blanch N, et al. Effect of sodium and potassium supplementation on vascular and endothelial function: a randomized controlled trial. Am J Clin Nutr 2015;101:939-946	RCT, crossover, DB; 7-day washout between diets; 1-meal duration of each diet. Age, 18-70 y M/F, NR BMI, 18-30kg/m^2 SBP < 130, DBP < 90 Stable weight x6mo No HTN, HLP No CS, NSAID	Adelaide Australia Recruited from adver-tisement and personal contact	39/49 (80)	Baseline, ND	ND	115 ± 8	71 ± 6
				LdK (3 mmol), LdNa (6 mmol)	ND	113 ± 1	70 ± 1
				LdK (3 mmol), HdNa (65 mmol)	ND	112 ± 1	69 ± 1
				HdK (38 mmol), HdNa (65 mmol)	ND	114 ± 1 Meal xTime *p* = .49	71 ± 1 Meal xTime *p* = .05

Author, citation	Design/ Characteristics	Location/ Recruit-ment	N (% com-pleted)	Diet, Intervention	UNa, mmol/ day	Mean Blood Pressure, mmHg	
						SBP	DBP
Carey RM et al. Salt sensitivity of blood pressure is associated with polymorphisms in the sodium-bicarbonate cotransporter. Hypertension 2012;60:1359-1366	RCT, crossover; No washout between diets; 7-day duration of each diet. *Salt sensitivity* defined as MAP ≥ 7 mmHg increase on HdNa. NT: Age, 45.0 ± 13.9 y M/F, 43/87 BMI, 24.1 ± 2.9 kg/m^2 HTN: Age, 52.4 ± 12.3 y M/F, 29/26; BMI, 25.8 ± 2.9 kg/m^2 All Caucasian	Charlottesville, VA U.S. Recruited from a genetic database	130 NT (100) 55 HTN (100). Note: 17 (13.1) NT were SS; 17 (30.9) HTN were SS; Total SS, 34 (18)	Baseline, ND	ND	118.9 ± 11.6	75.5 ± 7.1
				LdNa = 10 mmol/day			
				SS	18.6 ± 6.2	118.6 ± 11.5	70.3 ± 5.2
				SR	17.4 ± 7.4 *p* = .31	119.2 ± 15.4 *p* = .85	74.1 ± 9.0 *p* = .019
				HdNa = 300 mmol/d			
				SS	226.3 ± 37.8	133.5 ± 11.6	79.4 ± 7.6
				SR	218.8 ± 57.3	120.1 ± 13.2	71.7 ± 8.9
					p = .52 SR diff from SS	*p* < .001 SR diff from SS SS LdNa vs HdNa, *p* < .0001 SR LdNa vs HdNa, *p* = NS	*p* < .001 SR diff from SS SS LdNa vs HdNa, *p* < .0001 SR LdNa vs HdNa, *p* = NS

Author, citation	Design/ Characteristics	Location/ Recruit-ment	N (% com-pleted)	Diet, Intervention	UNa, mmol/ day	Mean Blood Pressure, mmHg	
						SBP	DBP
Cavka A, et al. The role of cyclo-oxygenase-1 in high-salt diet-induced microvascular dysfunction in humans. J Physiol 2015;593:5313-5324	RCT, parallel, SB; 7-day duration. Age, 20 ± 2 y M/F, 0/54 BMI, (LdNa), 22.9 ± 3.6 vs BMI (HdNa), 22.1 ± 2.6 kg/m^2, p = NS Race, NR	Croatia Recruited from adver-tisement at Faculty of Medicine of the University	54 (100)	LdNa, Baseline (n=24), ND	118.7 ± 56	105 ± 10	69 ± 9
				LdNa, <2.3g salt/day + placebo	82.6 ± 43.1 *p* < .05 vs LdNa Baseline	100 ± 9 *p* < .05 vs LdNa Baseline	66 ± 7 *p* < .05 vs LdNa Baseline
				HdNa, Baseline (n=30), ND	126.8 ± 45.2	105 ± 9	71 ± 8
				HdNa, 14 g salt/day (usual diet + 5.85 g salt twice daily)	232.0 ± 91.4 *p* < .05 vs HdNa Baseline	105 ± 10 *p* = NS vs HdNa Baseline	71 ± 7 *p* = NS vs HdNa Baseline

Author, citation	Design/ Characteristics	Location/ Recruit-ment	N (% com-pleted)	Diet, Intervention	UNa, mmol/ day	Mean Blood Pressure, mmHg			
						SBP		DBP	
Lennon-Edwards S, et al. Salt loading has a more deleterious effect on flow-mediated dilation in salt-resistant men than women. Nutr Met Cardio Dis 2014;24:990-995	RCT, crossover; 7-day run-in; No washout between diets; 7-day duration of each diet. *Salt-resistance* defined as ≤ 5 mmHg change in MAP on HdNa. Salt-sensitive (n = 3) excluded from analysis (3/38, 7.9%) No medications or obesity allowed. See Diet column for characteristics	Newark, DE U.S. Recruit-ment plan not des-cribed	30 (86)	Baseline (run-in) =100 mmol/day		M	F	M	F
						120 ± 3	114 ± 3 *p* = NR	76 ± 3	70 ± 3 *p* = NR
				LdNa =20 mmol/day		117 ± 3	109 ± 3 *p* < .05 MvF	63 ± 2	64 ± 2 *p* = NS MvF
				HdNa=300-350 mmol/day		119 ± 2	111 ± 3 *p* < .05 MvF; *p* = NS LdNa v HdNa	65 ± 1	66 ± 2 *p* = NS MvF; *p* = NS LdNa v HdNa
				Characteristics: M F Age, 29 ± 2 31 ± 2 BMI, 23.8 24.5 kg/m^2 ± 0.7 ± 0.7					

Author, citation	Design/ Characteristics	Location/ Recruit-ment	N (% com-pleted)	Diet, Intervention	UNa, mmol/ day	Mean Blood Pressure, mmHg	
						SBP	DBP
Rorije NMG, et al. Microvascular permeability after an acute and chronic salt load in healthy subjects. Anesthesiology 2018;128:352-60	RCT, crossover 8-day diet period for LdNa and for HdNa, 1-week washout Day 8 of LdNa included an acute bolus of normal saline (5mmol Na/liter body water) 24-hr urine at days 3, 6, 8 of each diet period Males: 12 Age: 23 (range 18-31) y BP <140/90mmHg	The Neth-erlands Recruited at an academic medical center	12 (100)	LdNa<50mmol/d Saline infusion HdNa>200mm/d	19 341	117 (112-122) 116 (111-120) 118 (115-122) *p*=NS	58 (55-62) 58 (56-61) 58 (54-61) *p*=NS

Author, citation	Design/ Characteristics	Location/ Recruit-ment	N (% com-pleted)	Diet, Intervention	UNa, mmol/ day	Mean Blood Pressure, mmHg			
						SBP		DBP	
Selvarajah V, et al. Novel mechanism for buffering dietary salt in humans: effects of salt loading on skin sodium, vascular endothelial growth fact C, and blood pressure. Hypertension. 2017;70:930-937	RCT, crossover; 7-day run-in, 7-day wash-out between diet periods; Age, 18-50 y M/F (age): 24 (28±2 y) / 24 (32±2 y); BMI: males 22.7, females 23.9 Race, all Caucasian except 2 males and 1 female (race not reported)	Cam-bridge, UK/ advertise-ment	48 (100)	Baseline, 7-day run-in on 70 mmol dNa	M: 102±12 F: 85±10	M: 123±2	F: 116±2	M: 67±2	F: 72±2
				LdNa (Placebo), 7-days on 70 mmol dNa	M: 86±10 F: 60±7	O: 120±2 Amb: 124±1	O: 114±2 Amb: 118±1	O: 71±2 Amb: 76±2	O: 73±2 Amb: 75±2
				HdNa, 7 days on 200 mmol dNa	M: 222±17 *p*<.001 F: 227±20 *p*<.001	O: 119±2 *p*=.85 Amb: 125±2 *p*=.32	O: 114±2 *p*=.72 Amb: 121±2 *p*=.02	O: 71±2 *p*=.98 Amb: 76±2 *p*=.34	O: 73±1 *p*=.75 Amb: 76±2 *p*=.33

Author, citation	Design/ Characteristics	Location/ Recruit-ment	N (% com-pleted)	Diet, Intervention	UNa, mmol/ day	Mean Blood Pressure, mmHg	
						SBP	DBP
Wang Y, et al. Effect of salt intake and potassium supplementation on serum renalase levels in Chinese adults. Medicine 2014;93:e44	RCT, sequential; 3-day baseline, 7-day duration of each diet; Age, 50.9 ± 1.3 M/F, 21/21 BMI, 23.5 ± 0.4 kg/m^2 HTN, 4 (9.5)	Xi'an, China Recruited from a rural commu-nity in Northern China	42 (100)	Baseline, NR	173.8 ± 10.1	110.7 ± 2.2	72.6 ± 1.3
				LdNa=3g NaCl/day	101.4 ± 6.0	108.7 ± 1.8	73.5 ± 1.0
				HdNa=18g NaCl/day	253.2 ± 9.5	117.3 ± 2.7*	77.7 ± 1.3*
				HdNa+K=18g NaCl/day + 4.5g KCl/day	269.5 ± 13.3	107.5 ± 1.9**	72.2 ± 1.3**
						*p < .05 vs LdNa	**p < .05 vs HdNa

Author, citation	Design/ Characteristics	Location/ Recruit-ment	N (% com-pleted)	Diet, Intervention	UNa, mmol/ day	Mean Blood Pressure, mmHg	
						SBP	DBP
Wenner MM, et al. Celecoxib does not alter cardiovascular and renal function during salt loading. Clin Exp Pharmacol Physiol 2011;38:543-549	RCT, crossover, DB. 3-day run-in, No washout between diets; 7-day duration of each diet. Age, 35 ± 2 y M/F, 10/2 BMI, 27 ± 1 kg/m^2	Newark, DE U.S. Recruit-ment not described	12 (100)	Baseline, NR	FENa (%)	117 ± 4	68 ± 2
				LdNa=20 mmol Na/day	0.05 ± 0.01	119 ± 2	71 ± 2
				HdNa=350 mmol Na/day	1.02 ± 0.06 $p < .05$	122 ± 3 p = NS	70 ± 2 p = NS
				Note: each subject completed all 3 phases twice (stated in Methods but not mentioned in stats).			

Note. Amb = ambulatory, BMI = body mass index, DB = double-blind, DBP = diastolic blood pressure, F = females, HdNa = high sodium diet; HdK = high potassium diet, HTN = hypertension (blood pressure ≥140/≥90 mmHg), LdK = low potassium diet, LdNa = low sodium diet, M = males, MAP = mean arterial pressure, ND = not done, NR = not reported, NdNa = normal or usual sodium intake, NT = normotensive, O = office, RCT = randomized controlled trial, SB = single-blind, SBP = systolic blood pressure, SR = salt-resistant, SS = salt-sensitive, UNa = urinary sodium

Blood Pressure and Dietary Sodium in Adults with Prehypertension or Hypertension

In adults with prehypertension or hypertension (Table 2), eight RCTs published between 2012 and November 2018 met criteria for review (Gijsbers et al., 2015; Gilbert, Nian, Yu, Luther, & Brown, 2013; Irwan et al., 2016; Jablonski, Racine, et al., 2013; Mallamaci et al., 2013; Nakano et al., 2016; Pinjuh Markota, Rumboldt, & Rumboldt, 2015; Whitt-Glover et al., 2013). Four of these reports were double-blind, crossover studies: three where salt tablets were compared to placebo (Gijsbers et al., 2015; Jablonski, Fedorova, et al., 2013; Mallamaci et al., 2013) and one where a drug was compared to placebo when the diet was low in sodium or high in sodium (Gilbert et al., 2013). However, only low sodium placebo and high sodium placebo periods were of interest to the current study. The other four studies were randomized, parallel designs where dietary sodium education was tested (Irwan et al., 2016; Nakano et al., 2016; Pinjuh Markota et al., 2015; Whitt-Glover et al., 2013). Each of these studies evaluated patients with mild to moderately elevated blood pressure who were, on average, 40 to > 60 years of age. Four trials studied the diet for one month or longer: Gijsbers et al. (2015) and Jablonski, Fedorova et al. (2013) evaluated diets continuing for four weeks while the remaining Pinjuh Markota et al. (2015) studied two months and Nakano et al. (2016) and Whitt-Glover et al. (2013) conducted studies for three months. The remaining studies evaluated the dietary sodium changes

over two weeks (Mallamaci et al., 2013) or less (Gilbert et al., 2013; Irwan et al., 2016).

Other than age, hypertension status, and type of RCT described above, heterogeneity was apparent among these studies for the amount of dietary sodium or capsules evaluated and whether or not urinary sodium was measured. In this population, however, six (Gijsbers et al., 2015; Gilbert et al., 2013; Jablonski, Racine, et al., 2013; Mallamaci et al., 2013; Nakano et al., 2016; Pinjuh Markota et al., 2015) of the eight studies indicated a statistically significant decrease in SBP associated with the lower dietary sodium regimen. Irwan et al. (2016) and Whitt-Glover et al. (2013) did not demonstrate a significant difference in blood pressure in their education intervention studies. The study conducted by Irwan et al. (2016) evaluated dietary sodium intervention for only three weeks. The dietary sodium results trended downward but did not reach statistical significance. Whitt-Glover et al. (2013) reported a pilot feasibility study of 25 patients in an under-resourced, urban area in an attempt to adapt the DASH-type diet to foods available within the community. Blood pressure trended downward in the intervention group during the 12-week study period but was not statistically significant.

In other education intervention studies, Pinjuh Markota et al. (2015) randomized 150 patients taking a mean of 2.1 ± 0.9 antihypertensive agents per day to a dietary education intervention. No adjustment in blood pressure medication dose was allowed during the study. After two months, the

intervention group demonstrated a statistically significant decrease in urinary sodium ($p < .0001$), which was also statistically significantly lower than controls ($p = .011$) where no change in urinary sodium was observed ($p = .15$). Furthermore, their SBP and DBP also decreased significantly over time ($p < .0001$) but did not change in the control group ($p = NS$). Similarly, the educational intervention study by Nakano et al. (2016) demonstrated a statistically significant decrease in urinary sodium in the low sodium group and statistical significance for the difference in urinary sodium excretion between the low sodium and control groups. However, only the low sodium diet group experienced a significant decrease in SBP and there was no difference in the SBP change between the low sodium and control diet groups.

In the double-blind, crossover studies, Gijsbers et al., (2015) studied 36 participants with untreated hypertension using a standard diet (117 mmol Na/day or 2,700mg Na/day) plus a placebo compared to a diet of the same sodium with the addition of tablets at a dose of 234 mmol of Na/day (5,700mg Na/day). The urinary sodium almost doubled during the period using salt tablets compared to placebo ($p < .001$) and the SBP and DBP increased ($p < .001$). Ninety percent of the foods consumed by these participants were supplied by the study. Gastrointestinal side-effects were recorded by eight participants in the placebo phase and 19 participants during the sodium phase of the diets studied, which represents a 30.6% risk difference.

Jablonski et al. (2013) studied a low sodium diet (56 mmol Na/day or 1,300 mg/day) plus a placebo and a low sodium diet (57 mmol Na/day) plus 10 sodium tablets totaling 157 mmol Na/day (or 3,600mg Na/day) in a crossover fashion in 17 participants (Table 2). They compared the salt tablet period to the baseline diet of 136 mmol Na/day (3,100 mg Na/day). Blood pressure was statistically significantly higher during the higher sodium period ($p < .01$). Five of the participants were taking antihypertensive agents during the study without dose changes. No mention of adverse event data collection was supplied in this report.

Using a 10-fold increase in the sodium dose for 2 weeks, Mallamaci et al. (2013) evaluated 32 patients with untreated hypertension (Table 2). They found an almost 7-fold increase in the urinary sodium, a mean increase in SBP of 12 mmHg ($p < .001$), and a mean increase in DBP of 3 mmHg ($p = .004$) compared to the low sodium diet. The investigators did not report on adverse events.

Beginning with a 3-week washout period to discontinue antihypertensive agents, Gilbert et al. (2013) evaluated adults consuming a low sodium diet (10 mmol/day or 230 mg/day) for six days or a high sodium diet (200 mmol/day or 4,600 mg/day) plus either fenofibrate or a placebo for six days (Table 2). Only the low sodium and high sodium plus placebo periods were of interest in the current study. The investigators then determined which participants were salt-sensitive, defined as ≥ 5 mmHg

increase in mean arterial pressure on the high sodium diet (n = 14, 41%) or salt-resistant (n = 17, 59%), and evaluated these groups separately. The participants who were deemed salt-sensitive experienced a significant increase in blood pressure after six days on the high sodium diet plus placebo ($p < .05$). The participants who were deemed salt-resistant experienced a non-significant drop in blood pressure after six days on the high sodium diet plus placebo (p = NS). Of note, this study reported that 10 participants were black; five were salt sensitive and five were not. No mention of adverse event data collection was supplied in this report.

In summary, five of eight RCTs evaluating blood pressure response to dietary sodium in prehypertensive or hypertensive adults (Gijsbers et al., 2015; Gilbert et al., 2013; Irwan et al., 2016; Mallamaci et al., 2013; Pinjuh Markota et al., 2015) demonstrated a statistically significant higher SBP during higher sodium exposure compared to lower sodium exposure. Of these, only Gilbert et al. (2013) also reported on the response of participants according to salt sensitivity where the mean blood pressure response was not statistically significantly different in salt-resistant participants. These eight studies from six different countries were of short duration and were not designed to provide information on safety, with one exception. The study by Gijsbers et al. (2015) suggests that 5,700 mg/day of dietary sodium is associated with gastrointestinal side-effects and increased blood pressure in prehypertensive and hypertensive participants, compared to 2,700 mg/day.

None of these studies evaluated the dietary sodium recommendations of the U.S. Dietary Guidelines for Americans (*Dietary Guidelines for Americans, 2015-2020*, 2015). In prehypertensive and hypertensive patients, well-designed studies examining the dose of dietary sodium associated with the best blood pressure and safety outcomes remain desirable.

Table 2.
Description of randomized controlled trials on blood pressure and dietary sodium of adults with pre-hypertension or hypertension

Author, abbreviated citation	Design/ Characteristics	Location /Recruit-ment	N (% com-pleted)	Diet, Intervention	UNa, mmol/ day	Mean Blood pressure, mmHg SBP	DBP
Gijsbers L, et al. Effects of sodium and potassium supplement-ation on blood pressure and arterial stiffness: a fully controlled dietary intervention study. J Hum Hypertens 2015;29:592-598	RCT, crossover, DB;1-week run-in; No washout between diets; 4-week duration of each diet. Stratified by sex and SBP 130-139 or ≥140 mmHg. Age, 65 (47-80) y BMI, 27.2 kg/m^2 M/F, 24/12 Untreated HTN; 90% of food and beverages supplied by research institute; all Caucasian.	Wagen-ingen, The Nether-lands Recruit-ment by local advertise-ment	36 (97)	Control, dNa=2,700mg (or 2,433mg Na and 2,506mg K + cellulose capsules x8/day	105.1 ± 39.7	125.1 ± 15.0	72.3 ± 7. 7
				dNa, Control diet + 371mg Na capsules x8/day or 2,968mg total)	202.9 ± 54.8 p < .001 dNa vs control	132.9 ± 17.6 p < .001 dNa vs control	79.2 ± 8.9 p < .001 dNa vs control
				dK, Control diet + 353mg K capsules x8/day or 2,824mg total)	96.5 ± 39.0 p = .29 dK vs control	125.1 ± 15.0 p = .10 dK vs control	72.3 ± 7.7 p = .77 dK vs control

Author, abbreviated citation	Design/ Characteristics	Location /Recruit-ment	N (% com-pleted)	Diet, Intervention	UNa, mmol/ day	Mean Blood pressure, mmHg SBP		DBP	
Gilbert K, et al. Fenofibrate lowers blood pressure in salt-sensitive but not salt-resistant hyperten-sion. J Hypertens 2013;31:820-829	RCT, crossover, DB; 3-week washout period, followed by 6-day LdNa diet, then two 6-day HdNa diet periods (HdNa+Placebo or HdNa+Fenofibrate) with 1-week washout period. *Salt sensitivity* defined as increase in MAP ≥5 mmHg on HdNa. SS (n = 14, 41%): Age, 42.1 ± 11.8 M/F, 9/5; Race, W/B, 9/5; BMI, 29.9 ± 6.6 kg/m^2; SR (n=17, 59%): Age, 45.7 ± 11.4 M/F, 6/11; Race, W/B, 12/5; BMI, 29.3 ± 4.8 kg/m^2	Nashville TN U.S. Recruit-ment not des-cribed	31 Note: authors do not describe number of people enrolled	LdNa, 10 mmol/day	ND	SS 124.0 ± 8.8	SR 135.6 ± 13.2 $p < .05$ vs SS	SS 77.8 ± 5.5	SR 79.5 ± 9.1
				HdNa, 200 mmol/day + placebo	ND	139.4 ± 10.9 $p < .05$ vs LdNa	132.2 ± 13.8 p = NS vs LdNa	86.1 ± 8.5 $p <$ .05 vs LdNa	77.1 ± 9.8 p = NS vs LdNa $p <$ .05 vs SS
				HdNa, 200 mmol/day + fenofibrate, 160mg	ND	136.8 ± 12.6 p = NS vs LdNa	134.5 ± 10.2 $p < .05$ vs LdNa	82.4 ± 5.8 $p <$ .05 vs HdNa +Pbo, vs LdNa	78.9 ± 11.1

Author, abbreviated citation	Design/ Characteristics	Location /Recruit-ment	N (% com-pleted)	Diet, Intervention	UNa, mmol/ day	Mean Blood pressure, mmHg SBP	DBP
Irwan AM, et al. Develop-ment of the salt-reduction and efficacy maintenanc e program in Indonesia. Nurs Health Sci 2016;18(4): 519-532	RCT, parallel; baseline and two 1-week visits (total of 3); Untreated HTN; Control: Age, 66.1 ± 5.7 y M/F, 5/12 BMI, 21.6 ± 3.9 kg/m^2 Intervention 1: Age, 67.9 ± 6.9 y M/F, 7/6 BMI, 22.6 ± 3.3 kg/m^2 Intervention 2: Age, 65.8 ± 5.9 M/F, 5/10 BMI, 23.5 ± 3.3 kg/m^2	Ma-kassar, Indo-nesia Recruit-ment from health clinic for older adults	45/51 (88) Control: 17 Interven-tion 1: 13 Interven-tion 2: 15	Control, dNa: Baseline, 3.2 ± 4.1g salt Visit 1, 2.4 ± 3.7g salt Visit 2, 2.6 ± 3.1g salt, *p* = .74 #1 (salt-redn, HTN training): Baseline, 3.2 ± 3.3g Visit 1, 1.1 ± 1.5 g Visit 2, 3.8 ± 2.7g, *p* = .039 #2 (salt-redn. HTN training + self-efficacy, maintenance: Baseline, 2.9 ± 4.8g Visit 1, 1.8 ± 2.3 g Visit 2, 2.1 ± 3.2 g, *p* = .68	5.9 ± 2.8 6.9 ± 2.9 7.4 ± 2.2 *p* = .17 8.6 ± 3.2 7.2 ± 3.2 7.7 ± 2.0 *p* = .13 7.5 ± 2.6 6.4 ± 2.4 6.9 ± 2.4, *p* = .10	144.8 ± 21.1 143.5 ± 16.9 138.5 ± 19.3 *p* = .5 147.5 ± 17.3 142.3 ± 16.2 138.1 ± 15.6 *p* = .22 145.5 ± 30.5 136.2 ± 23.3 137.8 ± 21.5 *p* = .037	85.2 ± 10.2 87.3 ± 7.5 85.7 ± 10.6 *p* = .58 88.0 ± 12.8 85.6 ± 8.9 85.2 ± 5.3 *p* = .22 87.5 ± 15.5 85.1 ± 9.1 83.1 ± 9.8 *p* = .20

Author, abbreviated citation	Design/ Characteristics	Location /Recruit-ment	N (% com-pleted)	Diet, Intervention	UNa, mmol/ day	Mean Blood pressure, mmHg SBP	DBP
Jablonski KL, et al. Dietary sodium restriction reverses vascular endothelial dysfunction in middle-aged/older adults with moderately elevated systolic blood pressure. J Am Coll Cardiol 2013;61:335-343	RCT, crossover, DB; 4-week duration of each diet. Age, 62 ± 7 y M/F, 11/6 Non-Hispanic white, 88% Asian, 12%	Boulder, CO U.S. Recruit-ment not des-cribed	17 (85)	Baseline, 3-day diet record: 136 ± 48 mmol Na/day	ND	138 ± 7	83 ± 7
				LdNa, 3-day diet record: 56 ± 15 mmol Na/day + placebo tablets	ND	128 ± 10 $p < .01$ vs Baseline	79 ± 6
				HdNa, 3-day diet record: 57 ± 12 mmol Na/day + 10 mmol slow-release tablets x10/day	ND	140 ± 15	82 ± 6

Author, abbreviated citation	Design/ Characteristics	Location /Recruit-ment	N (% com-pleted)	Diet, Intervention	UNa, mmol/ day	Mean Blood pressure, mmHg SBP	DBP
Mallamaci F, et al. Procalcitonin and the inflammatory response to salt in essential hyperten-sion: a randomized cross-over clinical trial. J Hypertens 2013;31:1424-1430	RCT, crossover, DB; 2-week duration of each diet with 1-week washout between Age, 48 ± 9 y Males 72% HTN, untreated: n = 21 HTN, treated, medications discontinued 4 weeks, n = 11	Reggio Calabria, Italy First blood pressure evalua-tion in BP clinic	32 (100)	LdNa, 10-20 mmol/day Na + placebo tablets HdNa, 10-20 mmol/day Na + 180 mmol Na tablets/day	28 ± 18 193 ± 35 *p* = NR	128 ± 10 136 ± 9 *p* < .001	83 ± 7 86 ± 7 *p* = .004

Author, abbreviated citation	Design/ Characteristics	Location /Recruit-ment	N (% com-pleted)	Diet, Intervention	UNa, mmol/ day	Mean Blood pressure, mmHg SBP	DBP
Nakano M et al. Effect of Intensive Salt-Restriction Education on Clinic, Home, and Ambulatory Blood Pressure Levels in Treated Hyperten-sive Patients During a 3-Month Education Period. J Clin Hypertens. 2016;18”385-392	Randomized, open-label; 3 months duration. Age, 58 ± 13 y Males 38% HTN, treated 86%	Tochigi, Japan	101 (94)	LdNa = <2,400 mg Na+; education provided by nutritionist;			
				Baseline	147 ± 54	136 ± 12	83 ± 10
				12 weeks	116 ± 50	132 ± 14	82 ± 9
					p = .002	*p* = .048	*p* = .32
				change	-30 ± 65	-3.6 ± 1.8	NR
				NdNa = Na+ precautions provided by MD;			
				Baseline	139 ± 50	135 ± 14	82 ± 12
				12 weeks	147 ± 58	136 ± 12	83 ± 11
					p = .034	*p* = .54	*p* = .59
				change	6 ± 56	1.1 ± 1.8	NR
					LdNa vs NdNa: *p* < .01	LdNa vs NdNa; *p* = .66	LdNa vs NdNa: NR

Author, abbreviated citation	Design/ Characteristics	Location /Recruit-ment	N (% com-pleted)	Diet, Intervention	UNa, mmol/ day	Mean Blood pressure, mmHg SBP	DBP
Pinjuh Markota N, et al. Emphasized warning reduces salt intake: a randomized controlled trial. J Am Soc Hypertens 2015;9:214-220	RCT, parallel 3 visits (0, 1 mo, 2 mo) Control: Age 59.3 ± 12 y M/F, 37/37 BMI 26.4 ± 2.5 HTN RX, n = 2.1 ± 0.9 Intervention: Age, 59.4 ± 13 M/F, 36/40 BMI, 26.1 ± 3.0 kg/m^2 HTN Rx, n = 2.2 ± 1.0 All, p = NS	Split, Croatia Recruit-ed from family medicine practice unit at 3 sites (Mostar, Bosnia, Herz-egovina)	150 (87.7)	Control, salt reduction education using handouts	Baseline 207.1 ± 71.0		
					1mo: 203.4 ± 59.9	142.2 ± 18.4	84.3 ± 9.8
					2mo: 200.4 ± 58.5 p = .15	143.3 ± 18.5 p = .58	83.2 ± 8.9 p = .37
				Intervention, salt reduction handout + warning stickers to place on home salt containers	Baseline: 211.2 ± 85.3	142.9 ± 20.6	84.7 ± 10.3
					1mo: 182.6 ± 62.6	138.5 ± 17.2	81.4 ± 8.5
					2mo: 176.4 ± 54.5 p < .0001	137.6 ± 16.1 p < .0001	81.8 ± 8.5 p < .0001

Author, abbreviated citation	Design/ Characteristics	Location /Recruit-ment	N (% com-pleted)	Diet, Intervention	UNa, mmol/ day	Mean Blood pressure, mmHg SBP		DBP	
Whitt-Glover MC, et al. Translating the dietary approaches to stop hypertension (DASH) diet for use in under-resourced, urban African American commun-ities, 2010. Prev Chronic Dis 2013;10:120088	RCT, parallel; open-label pilot feasibility study; 12 weeks on study. Age, 50.7 ± 7.9 M/F, 3/22 BMI, 35.9 kg/m^2 HTN meds, n = 19	Winston-Salem, NC U.S. Recruit-ment by advertise-ments, mailings, referrals	25 (100)	Control: handouts Intervention: 10 education sessions (2 individual, 8 group)		Con-trol	Inter-vention	Con-trol	Inter-vention
				Baseline	ND	127.4 ± 15.9	132.0 ± 18.7	76.0 ± 12.9	80.4 ± 13.6
				6 weeks	ND	ND	129.2 ± 21.3	ND	79.7 ± 12.4
				12 weeks	ND	131.5 ± 16.8	128.4 ± 20.1	80.4 ± 12.2	76.5 ± 9.3
				Note: Confidence to improve dietary habits, $p < .05$ for Intervention v Control			*p* for effect = .41		*p* for effect = .18

Note. BMI = body mass index, DB = double-blind, DBP = diastolic blood pressure, dNa = dietary sodium, HdNa = high sodium diet, HTN = hypertension (blood pressure ≥140/≥90 mmHg), K = potassium, LdK = low potassium diet, LdNa = low sodium diet, MAP = mean arterial pressure, ND = not done, NR = not reported, HdK = high potassium diet, NdNa = normal or usual sodium intake, NT = normotensive, RCT = randomized controlled trial, RN = registered nurse, SB = single-blind, SBP = systolic blood pressure, SR = salt-resistant, SS = salt-sensitive, UNa = urinary sodium

Blood Pressure and Dietary Sodium in Adults with Kidney Disease

Five RCTs were performed in adults with CKD between 2012 and November 2018 (Table 3). The patients in these studies were receiving pharmaceutical therapy for blood pressure control and attempts were made to standardize the treatment, either by switching all to a certain therapeutic agent prior to randomization or allowing no alteration in the therapy during the dietary evaluation period. de Vries et al. (2016) studied kidney transplant recipients.

Hwang et al. (2014) evaluated two types of dietary sodium education in 245 adults with eGFR ≥30 ml/min and a marker of kidney damage (Table 3). After receiving an angiotenson II receptor blocker (olmesartan medoxomil) for 8 weeks, participants were randomized to receive either 1) a low sodium diet (< 100 mEq Na/day, < 2,300 mg/day) with conventional education, described as two education sessions in the outpatient clinic over the remaining eight weeks of the study or 2) the low sodium diet with intensive education, described as weekly 30-minute phone sessions with a dietitian. The participants in the intensive education group demonstrated a statistically significant decrease in 24-hour urinary sodium excretion (158 mmol Na/day or 3,634 mg/day to 122 mmol Na/day or 2,806 mg/day; a 22.8% decrease) but the conventional education group experienced only a 7.6% drop in urinary sodium from baseline (p = NS). SBP and DBP, on the other hand, did not change in either group during the 8-week period. The adverse event of

hypotension was recorded but not reported in the publication, except to mention that no participants withdrew from the study due to hypotension.

In another parallel-groups RCT, de Brito-Ashurst et al. (2013) evaluated intensive diet intervention in 48 adults with eGFR < 60ml/min who also had prehypertension or hypertension (Table 3). Patients at extremes of BMI (< 20 or > 35 kg/m^2) were excluded. Those who had hypertension were taking angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics or a combination of these. The control group received a low sodium diet sheet at the renal clinic (routine care) and the intervention group received extensive training with a dietitian to lower the sodium used in cooking by 50%. The participants in the intervention group received phone calls every 2 weeks to reinforce the diet. After six months, 24-hour urinary sodium excretion decreased by 46% in the intervention group ($p < .001$) compared to only 5% in the control group ($p < .001$), representing a 41% effect difference favoring dietitian intervention. SBP was decreased in only the intervention group and was reported as the between-group difference in change in SBP: -8 (95% CI -5 to -11) mmHg ($p < .001$) favoring the intervention group. No plans to collect adverse events were reported.

The study involving kidney transplant recipients was a randomized crossover, unblinded study of diet intervention delivered by research physicians (de Vries et al., 2016) (Table 3). Participants had a kidney transplant for at least one year, had blood pressure >120/80 and less than

160/100 mmHg, were taking either an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker for blood pressure control and had stable immune suppression. The low sodium diet period was targeted at 50 mmol Na/day (1,200 mg) and the normal sodium diet period was targeted at 150 mmol Na/day (3,500 mg); each diet period was six weeks in length. Outcome measures were obtained every three weeks (five times, including baseline) and included systolic and diastolic blood pressure, urinary sodium excretion, and body weight. A statistically significant difference in mean (95% CI) SBP (-11 [-14 to -7] mmHg) and DBP (-7 [-10 to -5] mmHg) was observed during the low sodium diet period ($p < 0.001$). Mean (95% CI) urinary sodium excretion also decreased significantly (-77 [-110 to -44] mmol/day; $p < .001$) as well as body weight (-2 [-3 to -1) kg; $p < .001$). One person experienced no change in blood pressure and one person experienced an increase in blood pressure during the low sodium diet period. These investigators reported on the adverse event of orthostatic hypotension: one person experienced hypotension of a severity that required study withdrawal (this person's data were not included in the report) and five others (22.7%) reported orthostatic hypotension that responded to a decrease in antihypertensive agents.

The remaining two studies in this review of patients with CKD were randomized crossover studies where the sodium intake was manipulated using salt tablets or placebo (Kwakernaak et al., 2014; McMahon et al., 2013). McMahon et al. (2013) evaluated 20 adults with stage 3 or 4 CKD,

where nine (45%) had diabetes and were taking angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, α- or β-blockers, calcium antagonists, diuretics or a combination of these for blood pressure management (Table 3). These participants required a mean of three antihypertensive agents for blood pressure management. The diet duration was two weeks with a 1-week washout period between the diets. The low sodium diet period was 60-80 mmol Na/day (1,400 to 1,800mg Na/day) with placebo tablets and the high sodium diet period consisted of a 60-80 mmol Na/day diet plus an additional 120 mmol of sodium (2,670 mg/day) as slow-release tablets. Compared to the high sodium diet period, the low sodium diet period resulted in a 93 mmol/day difference in the decrease in 24-hour urinary sodium ($p < .001$), a 9.7 mmHg difference in the decrease in SBP ($p < .001$), and a 3.9 mmHg difference in the decrease in DBP ($p < .01$). Additionally, the maximum SBP was 199 ± 27 in the low sodium diet period compared to 213 ± 26 mmHg in the high sodium diet period, representing a 14 mmHg decrease ($p = .04$). No mention of adverse event data collection was provided in the published report.

Kwakernaak et al. (2014) enrolled 45 adults with type 2 diabetes mellitus into a randomized crossover study and at least one of the following three defined measures of albuminuria as an assessment of kidney damage: by sex (if female) ≥ 3.5 mg/mmol creatinine, (if male) ≥ 2.5 mg/mmol creatinine or >30 mg albumin/day or > 20 mg/L of urinary albumin (Table 3). A

stable creatinine clearance > 30 ml/min was also required. The study was designed to evaluate the influence of a low sodium diet (defined as 50 mmol Na/day, 1,200 mg Na/day) vs. regular sodium diet (defined as 200 mmol Na/day or 4,600 mg Na/day) on the effect of hydrochlorothiazide or placebo while taking an ACE inhibitor. Each period of this 4-way study design continued for six weeks with no washout between periods. The placebo period tests the difference of the low sodium and regular sodium diet periods in these patients with type 2 diabetes and reduced kidney function. At the end of the low sodium diet period, 24-hour urinary sodium excretion was 148 ± 65 mmol Na/day (3,400 mg Na/day) and increased to 224 ± 73 mg Na/day (5,200 mg Na/day; a 1.5-fold increase) in the regular sodium period. While taking an ACE inhibitor during each period, SBP increased from 141 ± 16 mmHg in the low sodium diet period without the diuretic to 147 ± 16 mmHg (p = .008) in the regular sodium diet period without the diuretic. Similarly, DBP increased from 79 ± 10 to 82 ± 10 mmHg (*p* = .0067) between the two diet periods without the diuretic. These investigators reported orthostatic side effects during the dietary sodium restriction period and the diuretic treatment period (both 11% of participants) and in 27% of participants during the combined low dietary sodium and diuretic treatment period. No serious adverse events occurred.

In summary, adults with CKD who were enrolled in these studies tended to be older, have comorbidities, and were already taking

antihypertensive agents. Nevertheless, a blood pressure response to change in dietary sodium was evident in all but one of the studies (Hwang et al., 2014). In that study, the targeted dietary sodium of <2,300mg/day was not achieved as judged by end of study urinary sodium excretion of 122 mmol/day instead of 100 mmol/day. This may have contributed to missing the blood pressure endpoint. Additionally, only Hwang et al. (2014) specifically evaluated the dietary sodium intake recommended by the U.S. Dietary Guidelines for Americans (a cut-point of 2,300 mg Na/day). However, McMahon et al. (2013) evaluated dietary sodium <2,300 mg/day (specifically, 1,800 mg/day). Three studies reported adverse events, but their methods were different, thus negating the opportunity to combine results. Kwakernaak et al. (2014) reported that 11% of participants taking an ACEi experienced orthostatic side effects during the low sodium diet period (1,200 mg Na/day) that increased to 27% when the diuretic was added. de Vries et al. (2016) reported orthostatic hypotension in 22.7% of participants that responded to medication adjustments. Improved study designs of dietary sodium and blood pressure in kidney disease are needed and should include information on adverse events at different dietary sodium doses during the short term (at least six weeks) and long-term (at least one year).

Table 3.
Description of randomized controlled trials on blood pressure and dietary sodium intake of adults with chronic kidney disease

Author, abbreviated citation	Design/ Characteristics	Location /Recruit-ment	N (% com-pleted)	Diet, Intervention	UNa, mmol/day	Mean Blood Pressure, mmHg	
						SBP	DBP
de Brito-Ashurst I, et al. The role of salt intake and salt sensitivity in the manage-ment of hyper-tension in South Asian people with chronic kidney	RCT, parallel; Statistician blinded; Bangladeshi origin living in UK, eGFR < 60, Mean BP > 130/80 x2 visits or taking HTN meds. No dialysis, BMI < 20 or > 35. Control: usual care LdNa diet (UdNa) sheet from clinic. Intervention: LdNa prepared 2 traditional meals: 1 usual salt, 1 50%	London, UK	48 (85.7)	Control Baseline End of study change (6 mo) Intervention Baseline End of study change (6 mo)	 259 ± 47.1 -13 (-18 to -8) p < .0001 263 ± 54.0 -122 (-140 to -105) *p* < .0001	 156.0 ± 10.7 149.3 ± 15.2 Difference from control: -8 (-5 to -11) *p* = .0003 Daytime: 9 (95% CI -3	

Author, abbreviated citation	Design/ Characteristics	Location /Recruit-ment	N (% com-pleted)	Diet, Intervention	UNa, mmol/day	Mean Blood Pressure, mmHg	
						SBP	DBP
disease. Heart 2013;99:1256-1260	salt reduction. Twice monthly phone calls.					to -5); nighttime: -12 (95% CI -16 to -10) LdNa vs UdNa (graphed in Figure 3).	

Characteristics:

Term	Cont-rol	Inter-ven-tion
Age, y	60.7 ± 12.0	55.7 ± 15.1
M/F	14/9	14/11
BMI, kg/m^2	27.1 ± 5.2	26.6 ± 5.4
DM, n (%)	14 (60)	17 (68)

Author, abbreviated citation	Design/ Characteristics	Location /Recruit-ment	N (% com-pleted)	Diet, Intervention	UNa, mmol/day	Mean Blood Pressure, mmHg	
						SBP	DBP
De Vries et al. Effects of dietary sodium restriction in kidney transplant recipients treated with renin-angiotensin-aldosterone system blockade: a randomized clinical trial. Am J Kidney Dis. 2016;67: 936-944	RCT, crossover; unblinded: two 6wk diet periods, no washout. Diet order assigned randomly. Inclusions: >18 yrs old ≥1 yr post-transplant. eGFR ≥30 BP ≥120/80 and <180/100 mmHg taking ACEi or ARB; stable immune suppression regimen. Age, 58 ± 8 M/F, 11/11 BMI, 27.7 ± 3.6 kg/m^2	Groning-gen and Amster-dam, Nether-lands	25 (88)	Baseline:		138 ± 15	85 ± 9
				LdNa target: 50mmol/d (1,200mg Na)	87 ± 56	129 ± 12	79 ± 8
				NdNa target: 150mmol/d (3,600mg Na)	164 ± 50 p < .001	140 ± 14 p <.001	86 ± 8 p <.001
				Adverse events: Orthostatic hypotension LdNa: n=5, plus 1 who was withdrawn due to severity of hypotension and not analyzed NdNa: n=0	Efficacy outcome: BP decrease	n=20	n=20

Author, abbreviated citation	Design/ Characteristics	Location /Recruit-ment	N (% com-pleted)	Diet, Intervention	UNa, mmol/day	Mean Blood Pressure, mmHg	
						SBP	DBP
Hwang JH, et al. Effects of intensive low-salt diet education on albuminuria among nondiabetic patients with hypertension treated with olmesartan: a single-blinded randomized, controlled trial. Clin J Am Soc Nephrol 2014;9:2059-2069	RCT, parallel, SB; age 19-75y, HTN w/ or w/o medications, MDRD eGFR ≥30, ACR ≥30 >2x; 8-wk run in period with LdNa training, all HTN meds switched to non-RAASi and diuretics. At week 8, randomized to conventional education (LdNaC) or intensive education (LdNaI). Age, 49.5 ± 13.3 y M/F, 122/123 BMI, 25.4 kg/m^2 CrCl, 80.8 ± 34.1 ml/min	Seoul, South Korea	245 (91.1)	Control: LdNaC (< 100 mEq Na/day)		SBP	DBP
				Week 8	155.1 ± 5.5	122.7 ± 1.2	74.1 ± 0.9
				Week 16	146.0 ± 4.9 *p* = .10	122.6 ± 1.3 *p* = .95	74.8 ± 0.9 *p* = .37
				Intervention: LdNaI (< 100 mEq Na/day + weekly 30-min call w/dietitian)			
				Week 8	158.2 ± 5.7	122.4 ± 1.2	73.9 ± 0.9
				Week 16	122.2 ± 5.0 *p* < .001	121.2 ± 1.3 *p* = .38	73.6 ± 0.9 *p* = .80
				Note: blinding not described except in the title of the study.			

Author, abbreviated citation	Design/ Characteristics	Location /Recruit-ment	N (% com-pleted)	Diet, Intervention	UNa, mmol/day	Mean Blood Pressure, mmHg	
						SBP	DBP
Kwakernaak AJ, et al. Effects of sodium restriction and hydrochlorothiazide on RAAS blockade efficacy in diabetic npehropathy: a randomised clinical trial. Lancet Diab Endo 2014;2:385-395	RCT, crossover, DB. Only T2DM w/ nephropathy (> 30 mg/day). ≥ 18yr old, CrCl ≥ 30 w/< 6 ml/min decline over previous yr. No SBP ≥ 180, DBP ≥ 110 or overt nephrotic syndrome. Intervention: drug double-blind, diet open-label. Max dose of ACEi titrated over 6 wks and maintained in all participants. Age, 65 ± 9 y M/F, 38/7; BMI, 32 ± 5; eGFR, 65 ± 25; DM, n (%) 45 (100)	Groningen, Netherlands Recruited from internal medicine and nephrology clinics of 3 medical centers	45 (93.8)	Intervention LdNa (50 mmol Na/day) + Placebo for 6wks followed by LdNa + HCTZ for 6wks			
				Placebo	148 ± 65	141 ± 16	79 ± 10
				HCTZ	164 ± 73	129 ± 14	72 ± 8
					$p < .001$	$p < .001$	$p < .001$
				Control: NdNa (200 mmol Na/day) + HCTZ for 6wks followed by HdNa + Placebo for 6wks			
				Placebo	224 ± 73	147 ± 16	82 ± 10
				HCTZ	224 ± 73	135 ± 16	76 ± 9
						$p < .001$	$p < .001$
				All took ACEi targeted to maximum dose, 40mg during all periods.	Diet effect, placebo, LdNa: ACR=393 (258-599) vs HdNa: 711 (485-1043), $p = .0002$	Diet effect, placebo, $p = .008$ HCTZ, $p = .0009$	Diet effect, placebo, $p = .0067$, HCTZ, $p = .0055$

Author, abbreviated citation	Design/ Characteristics	Location /Recruit-ment	N (% com-pleted)	Diet, Intervention	UNa, mmol/day	Mean Blood Pressure, mmHg	
						SBP	DBP
McMahon EJ, et al. A randomized trial of dietary sodium restriction in CKD. J Am Soc Nephrol 2013;24:2096-2103	RCT, crossover, DB; 1-wk run-in, 1-wk washout between diets, each diet, 2-wk; BP 130-169/ ≥ 70, Stage 3 or 4 CKD; no salt wasting CKD, no meds having ≥ 20 mmol/d Na. Age, 68.5 ± 11.0 M/F, 15/5 BMI, 29.3 ± 4.1 Diabetes, n (%) 9 (40) Anti-HTN medications, n = 3.15 ± 1.09	Wool-loong-abba, Australia	20 (80)	Baseline	126 (IQR, 78, 188)	151.3 ± 13.3	81.7 ± 7.8
				HdNa (60-80 mmol Na/day diet) + 120 mmol Na slow-release capsules/day	168 (95%CI, 146-219)	154.6 ± 11.9	83.3 ± 9.0
				LdNa (60-80 mmol Na/day) + placebo	75 (95%CI, 58-112) mean change 93 (95% CI 88, 107) $p < .001$.	144.9 ± 13.1; mean change 9.7 (4.5 to 14.8) $p < .001$.	79.4 ± 9.4; mean change 3.9 (1.3 to 6.4), $p < .01$.

Note. ACEi = angiotensin converting enzyme inhibitors, ACR = urinary albumin-to-creatinine ratio, BMI = body mass index, CrCl = creatinine clearance, DB = double-blind, DBP = diastolic blood pressure, dNa = dietary sodium, HCTZ = hydrochlorothiazide, HdNa = high sodium diet, HTN = hypertension (blood pressure ≥140/≥90 mmHg), K = potassium, LdK = low potassium diet, LdNa = low sodium diet, MAP = mean arterial pressure, ND = not done, NR = not reported, HdK = high potassium diet, NdNa = normal or usual sodium intake, NT = normotensive, RCT = randomized controlled trial, RN = registered nurse, SB = single-blind, SBP = systolic blood pressure, Una = urinary sodium

The current review demonstrates some of the issues with the RCTs in the area of blood pressure and dietary sodium. Most trials are inadequate in length to determine outcomes and only a very few even attempt to collect or report on adverse events, which is a fundamental requirement for determination of safety. Fully powered, well-designed RCTs are still needed on the controversial topic of dietary sodium and restrictions in the healthy volunteer, prehypertension and hypertensive, and kidney disease populations. More research is necessary to identify the range of dietary sodium that is safe and efficacious for the target population of healthy adults, patients with elevated blood pressure or with hypertension, and patients with CKD.

The last studies in the review of literature from 2012 to November 2018 were a thesis from a student at the University of Maryland (Nothwehr, 2014) and a dissertation from Rutgers University (Osei, 2016). Nothwehr (2014) utilized data from NHANES 2007-2010 to evaluate the relationship between food insecurity and dietary sodium and potassium intake and hypertension. The report indicated that the mean (95% CI) dietary sodium intake of U.S. nonpregnant adults was 3,038 (3,006-3,072) mg/day and was lower in people with hypertension (3,048 mg/day, 95% CI 2,984-3,112 mg/day) compared to normotensive participants (3,319 mg/day, 95% CI 3,251-3,388 mg/day; $p <$ .0001). Osei (2016) utilized NHANES 2005-2014 to demonstrate that 54% of U.S. adults consume more than 2,300mg of sodium/day and that adults with

high blood pressure consume less sodium than those without high blood pressure.

Participants in the study of NHANES data without evidence of hypertension may have a higher dietary sodium intake than the amount previously reported from NHANES data (*Dietary Guidelines for Americans, 2015-2020*, 2015). Using NHANES data, Nothwehr (2014) and Osei (Osei, 2016) demonstrated that the dietary sodium intake is lower in people with hypertension than without hypertension. In an earlier NHANES study, Moore et al. (2012) found that decreasing levels of kidney function were associated with a lower dietary protein intake (Moore et al., 2012) and lower dietary energy intake (Moore, 2011) than those with normal kidney function, which may suggest a concomitant lower sodium intake. It was anticipated that the current study would provide information regarding the influence of kidney function on the estimated dietary sodium intake and SBP and DBP relationships of U.S. adults representing the general public. A framework of the progression of kidney function is provided (Figure 2) to illustrate the prevalence of reduced kidney function and kidney disease in U.S. nonpregnant adults. Currently, it is estimated that more than 14% of U.S. adults have reduced kidney function ("U.S. Renal Data System," 2016), which could influence interpretations of the dietary sodium intake and blood pressure relationship.

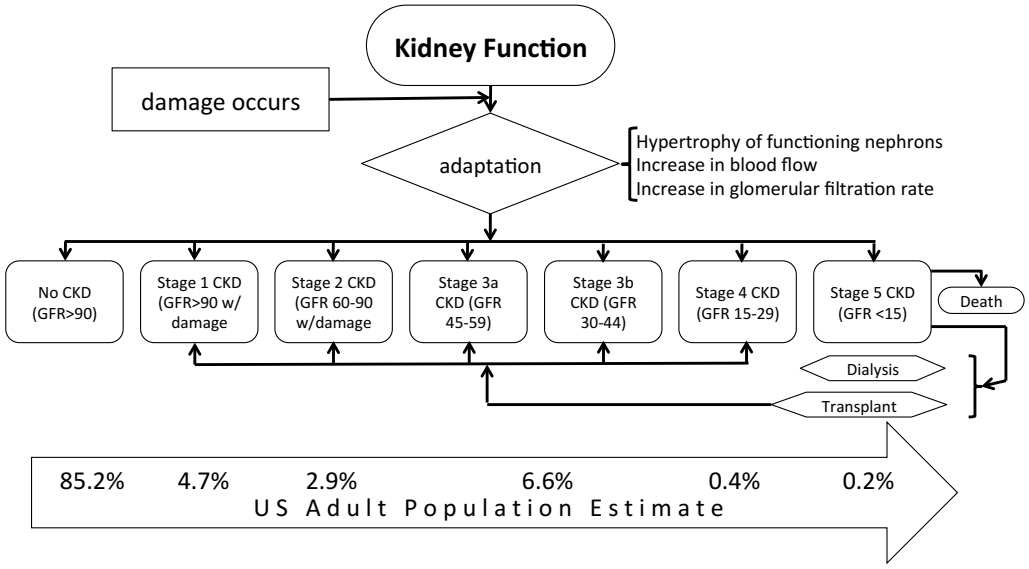

Figure 2. A conceptual framework of the progression of kidney disease and the projected population estimate.
The diagram is provided to illustrate the prevalence of kidney disease in the population. Adapted from Curtin RB et al. (Curtin, Becker, Kimmel, & Schatell, 2003) and United States Renal Data System ("U.S. Renal Data System," 2016).

It was hoped that the current evaluation of NHANES, accounting for the level of kidney function, may provide information on the estimate of the adult population above the NAM recommendation and *Dietary Guidelines for Americans* for dietary sodium while describing their blood pressure.

Theoretical Framework

The study examined the relationships between systolic and diastolic blood pressure, dietary sodium, and kidney function (Figure 3). As identified by several evidence-based clinical practice guidelines, causal relationships between blood pressure and dietary sodium exist and are influenced by many

factors, including kidney function ("Hypertension," 2015; P. A. James et al., 2014; Kidney Disease: Improving Global Outcomes Workgroup, 2013).

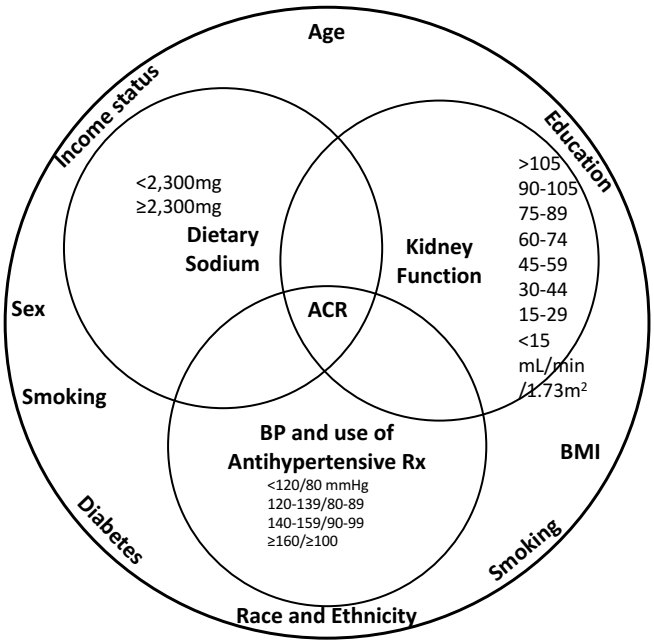

Figure 3. A theoretical framework of the interconnection between blood pressure, dietary sodium, and kidney function.
The analysis for this study examined the relationships between blood pressure, dietary sodium, and kidney function. The additional variables were expected to influence the relationships. ACR=albumin-to-creatinine ratio, BMI=body mass index, BP=blood pressure, Rx=prescription

Demographic and clinical characteristics may also influence the relationship between dietary sodium, blood pressure and kidney function. As depicted in the theoretical framework (Figure 3), these variables are age, sex, diabetes status, race and ethnicity, education and income status (considered to be socioeconomic factors), body mass index, antihypertensive agents and other variables. Their potential influence on the relationship between dietary sodium, blood pressure, and kidney function is summarized below.

Age is associated with both kidney function and hypertension (Bolignano, Mattace-Raso, Sijbrands, & Zoccali, 2014; Glassock & Rule, 2012) and also influences food choice (Rehm, Peñalvo, Afshin, & Mozaffarian, 2016). In general, men eat more food than women, which could translate to a mean difference in dietary sodium intake (Mozaffarian et al., 2015). Men also have a higher mean blood pressure than women through age 45, but women have a higher blood pressure than men after age 65 (Mozaffarian et al., 2015). Having diabetes mellitus is associated with a higher blood pressure and recommendations to lower dietary sodium ("American Diabetes Association standards of medical care in diabetes — 2016," 2016). Racial and ethnic differences exist in the prevalence of hypertension and in dietary sodium (Guo, He, Zhang, & Walton, 2012; Jackson, Coleman King, Zhao, & Cogswell, 2016; Lackland, 2014). Compared to people with higher socioeconomic status, people with a lower socioeconomic status have a higher blood pressure and reportedly consume 14% higher dietary sodium (Cundiff, Uchino, Smith, & Birmingham, 2015; de Mestral et al., 2017; Leng, Jin, Li, Chen, & Jin, 2015). Smoking has been associated with a higher dietary sodium intake (Choi et al., 2015), blood pressure (Farsalinos et al., 2016) and an increased eGFR (Ogna et al., 2016). Overweight and obesity are associated with higher blood pressure (Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration [BMI Mediated Effects] et al., 2014; Kidney Disease: Improving Global Outcomes

Workgroup, 2012; Middlemiss et al., 2016) and recommendations for people with mild to moderate CKD are to maintain a healthy weight for blood pressure control and reduced cardiovascular risk (Kidney Disease: Improving Global Outcomes Workgroup, 2012). Antihypertensive agents influence the blood pressure outcome but have also been demonstrated to influence kidney function. Notably, antihypertensive agents also influence dietary sodium intake (Morris et al., 2008; Na, Morris, & Johnson, 2012; Roper, 2015).

Additional factors influence blood pressure but were not covered in this study. Some additional factors include physical activity (Rayner, Charlton, & Lambert, 2016); dietary potassium (Adrogué & Madias, 2013; Graham, McCance, Young, & Mullan, 2014), calcium, magnesium, and fats (Rayner et al., 2016); alcohol use (Rayner et al., 2016); caffeine (Rayner et al., 2016); and stress (Trudel-Fitzgerald, Gilsanz, Mittleman, & Kubzansky, 2015).

Need for the Study

The literature reviewed for this study indicates that a dietary sodium influence on blood pressure exists but is most apparent in people who are salt sensitive (Carey et al., 2012; Gilbert et al., 2013; Lennon-Edwards et al., 2014), who have prehypertension or hypertension (Gijsbers et al., 2015; Gilbert et al., 2013; Jablonski, Racine, et al., 2013; Pinjuh Markota et al., 2015), or who have kidney disease (de Brito-Ashurst et al., 2013; Kwakernaak et al., 2014; McMahon et al., 2013). Furthermore, the

relationship is likely biased by the presence of other demographic and clinical variables that mask the influence dietary sodium may have on blood pressure. A better understanding of the dietary sodium relationship to systolic and diastolic blood pressure in adults is possible through a more thorough evaluation than currently exists.

The hypotheses for this study indicate that accounting for kidney function would reveal a higher dietary sodium intake than is currently reported in U.S. adults. It is of further importance to explore the range of dietary sodium intake in U.S. adults to more fully understand the magnitude of change required to reduce the sodium intake to currently recommended levels in the U.S.

Chapter III

METHODS

Research Design

The study was an observational study of dietary intake the day prior to blood pressure measurement using NHANES data. NHANES is a cross-sectional evaluation of the health and nutrition status of residents in the U.S.

Study Sample

The study sample comprised adults over the age of 20 years who had completed the interview, medical examination, and dietary interview components of NHANES during 2003 through 2014 and who met the participant selection criteria below.

The National Health and Nutrition Examination Survey

NHANES is a program of the National Center for Health Statistics in the Centers for Disease Control and Prevention ("About the National Health and Nutrition Examination Survey," 2017). The program that began in the 1960's in the U.S. consists of a series of personal interviews, and physical examinations. All participants are noninstitutionalized civilian residents of the U.S. To be representative of the U.S. population, the program over-samples

people over the age of 60 years, African Americans and Hispanics. Trained interviewers record information collected from preselected participants based on a complex, multistage probability sample (Figure 4) rather than simple random sampling. This methodology for participant selection allows the ability to oversample underrepresented population subgroups, which is necessary to be symbolic of the U.S. population ("About the National Health and Nutrition Examination Survey," 2017; "National Health and Nutrition Examination Survey: analytic guidelines, 2011-2012," 2013).

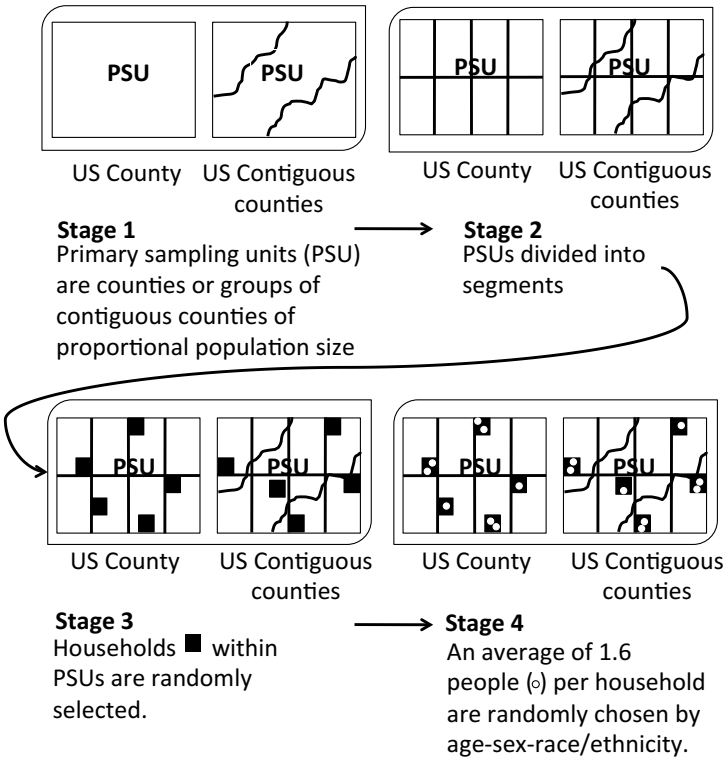

Figure 4. Multi-stage, cluster sampling design used in the National Health And Nutrition Examination Survey.
PSU=primary sampling unit. Adapted from C Johnson, et al. (2013)

Survey Cycles

The survey period was from the continuous NHANES era, a period that began in 1999 and uses an annual selection of approximately 5,000 participants of all ages and all 50 states. The data are released in 2-year cycles. The cycles selected for this study were from 2003 through 2014. From 1999-2006, NHANES oversampled non-Hispanic blacks, Mexican-Americans, low-income whites, and adolescents from 12-19 years of age. From 2007-2010, the program continued to oversample non-Hispanic blacks and low-income whites and included oversampling of all Hispanics and people over the age of 80 years. From 2011-2014, oversampling also included non-Hispanic, non-black Asians.

Participant Selection Criteria

Inclusion criteria: Participants ≥ 20 years of age, who reliably completed the dietary interview, the mobile examination component of NHANES 2003-2004, 2005-2006, 2007-2008, 2009-2010, 2011-2012, or 2013-2014, who provided the data elements for estimating kidney function, and who did not meet any of the exclusion criteria were included.

Exclusion criteria: Participants < 20 years of age or who were determined to be pregnant, reported being pregnant, or from whom it was not possible to determine if they were pregnant at the time of the mobile examination component were excluded from the analysis.

Data Collection

Since 2-year data sets would not be powered to test the hypothesis involving associations with decreased kidney function multiple 2-year cycles were combined. It was estimated that six 2-year cycles (2003-2014) would have adequate representation to provide the proportionality desired for the proposed research. Combining cycles requires an adjustment to the sampling weights (Mirel et al., 2013); the proportion of the 2-year sampling weight that represents the 1/nth number of cycle years (e.g., six 2-year cycles require an adjustment to the sampling weight of 1/6 * 2-year weight). NHANES provides weights for each component of the survey (eg, the interview, the mobile examination, the dietary interview). The sampling weight corresponding to the least number of completers of combined components should be used for analyses. For this study, the sampling weight used was the dietary interview sampling weight for the day 1 dietary interview after adjusting for the six 2-year cycles. Of note, NHANES also provides sampling weights for the fasting variable. However, the fasting variable was only used in assessing diabetes status; therefore, no adjustment in sampling weights was performed based upon the fasting variable.

Data files were downloaded from the Centers for Disease Control and Prevention website (www.cdc.gov/nchs/nhanes.htm) onto the researcher's personal computer using Google Chrome Version 49.0.2623.112 (Google, Mountain View, CA) web browser and JMP® Pro version 13.1.0 (SAS

Institute, Cary, NC) to organize the data files. Data files were built using each cycle participant's sequence number (SEQN) to match to related files. All variables were combined prior to joining cycles. Variables were checked across each cycle for nomenclature prior to stacking since some cycle years named a variable differently than other cycle years. The variables used are listed in Table 4.

The data set included all NHANES participants, even those who did not meet criteria for the study. Commands within the statistical software package (e.g., the STAT and DOMAIN statements in SAS Survey, version 9.4, SAS Institute, Cary, NC) were used to subset the data to include the intended group described by the inclusion and exclusion criteria. The purpose of this approach was to provide appropriate variance estimation as is recommended for NHANES (C. Johnson et al., 2013).

Table 4.
Study variables

Category of variables	Listing of variables to be used
Demographic	Age, sex, race and ethnicity, education level, income status
Clinical	Albumin-to-creatinine ratio, body mass index, diabetes status, high blood pressure awareness, number and type of antihypertensive agents, kidney disease awareness, kidney function level, and smoking status
Test	Dietary sodium intake and systolic and diastolic blood pressure

Independent Variables

Independent variables were dietary sodium and eGFR. The dietary intake day 1 interview occurred at the mobile examination center and reflects the dietary intake during the 24-hour period prior to the medical examination. All seven days of the week were exhibited in the NHANES data set. Dietary sodium intake was assessed as a scale (continuous) variable, reported in total mg/day and also as 200 mg increments and grams of salt (sodium chloride, NaCl). Dietary sodium was transformed into a binomial variable to evaluate the proportion of U.S. nonpregnant adults consuming the level of dietary sodium set forth in the *Dietary Guidelines for Americans* (*Dietary Guidelines for Americans, 2015-2020*, 2015) as < 2,300 mg/day or higher than the guideline. eGFR was assessed as a scale (continuous) variable, reported in ml/min/1.73m^2 and was also categorized into 15 ml/min/1.73m^2 groups (<15, 15-29, 30-44, 45-59, 60-74, 75-89, 90-105, > 105

ml/min/1.73m^2) (Kidney Disease: Improving Global Outcomes Workgroup, 2013).

Dependent Variables

The main outcome variable was blood pressure, assessed as both systolic and diastolic blood pressure. NHANES measured blood pressure after the participant was sitting for 5 minutes for three consecutive times. A fourth blood pressure reading was taken if one of the first three measurements was interrupted or incomplete. All measurements were recorded as a scale (continuous) variable in mmHg. The average of these blood pressure measurements was determined and reported as separate variables: SBP and DBP. Blood pressure was also assigned to categories (Chobanian et al., 2003; Crim et al., 2012): A: < 120 mmHg systolic and < 80 mmHg diastolic, B: 120-139 mmHg systolic or 80-89 mmHg diastolic, C: 140-159 mmHg systolic or 90-99 mmHg diastolic, or D: ≥ 160 mmHg systolic or ≥ 100 mmHg diastolic. Blood pressure was further categorized as ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic and used in the assignment of high blood pressure (Chobanian et al., 2003; Crim et al., 2012). The blood pressure variables (the continuous variables of SBP and of DBP and two categorical variables: blood pressure categories and the category of ≥140/≥90 mmHg or below) were used in separate analyses.

Power Analysis

The NHANES database is a closed database, and the selected cycles represent > 60,000 people. Therefore, an a priori power analysis was not considered necessary. A post hoc power analysis was not performed.

Privacy and Confidentiality of Data

All NHANES data files were de-identified prior to public release. Individual participant data was only identified by the participant identification (or sequence) code, SEQN. No Protected Health Information was released on the public files of NHANES data sets.

Institutional Review Board Approval

The institutional review board (IRB) of Rutgers University Health Sciences – Newark had oversight of the study. Participants in NHANES were fully consented by the survey interviewers prior to any study-related activity. Protocols used in NHANES were approved by the National Center for Health Services Research Ethics Board ("NCHS Research Ethics Review Board (ERB) Approval. National Health and Nutrition Examination Survey," 2012); for this study, Protocol #98-12, #2005-06, and #2011-17 was used. The consent forms were stored by the NCHS and not available to individual investigators. The data accessed for this study was de-identified, publicly-available data. Therefore, an exempt review and waiver of a local informed

consent for the study was requested of and provided by the Rutgers University eIRB, Health Sciences IRB - Newark (Study ID Pro20170001674; Appendix B). As the investigator for the current study is employed by, and would be using software and equipment of, the Houston Methodist Hospital in Houston, TX for this study, an approval of the Houston Methodist Research Institute IRB was also sought; a waiver for this study as non-human subjects research was provided (Appendix B).

Statistical Analysis

NHANES is a complex, multistage probability sample designed to represent the U.S. noninstitutionalized civilian population. Since NHANES is not a simple random sample (every member of the population is not equally likely to be included in the study), the variance analyses must account for the fact that people within each cluster (or primary sampling unit, Figure 4) are more similar to each other than people in other clusters and the fact that the selection of the clusters was stratified (specifying data collection from special subgroups). One method of accounting for correlation between people within a cluster that is induced by the study design is Taylor Series Linearization (*SAS/STAT(r) 9.2 User's Guide: Survey Data Analysis (Book Excerpt)*, 2009) and was used in the analyses for the study. The 2010 U.S. Census was the referent for determining prevalence estimates ("Age and sex composition in the United States: 2010," 2016).

Variable Assumptions

Normality of continuous variables

Attempts to transform the variables displaying nonparametric distributions (e.g., by log normalization, Box-Cox transformation, as appropriate) were made prior to statistical analysis. However, as the sample size for this study was large, it was not deemed necessary to display normal distributions (Lumley, Diehr, Emerson, & Chen, 2002).

Outliers

Outliers were retained because 1) they represent real-world data, 2) the NHANES project is rigorous in checking for accuracy of data such that data entry errors, laboratory errors ("NHANES, MEC laboratory procedures manual," 2013), incomplete dietary intake assessments ("NHANES, 2013-2014 data documentation, codebook, and frequencies. Dietary interview - total nutrient intakes, first day (DRITOT_H)," 2016; "NHANES, MEC In-person dietary interviewers procedures manual," 2014) or blood pressure measurement equipment malfunction were unlikely to be the cause of an outlier ("NHANES, 2013-2014 Data Documentation, Codebook, and Frequencies - Blood Pressure," 2015), and 3) the NHANES 2003-2014 cycles provide data on thousands of US non-pregnant adults, a number of participants large enough that the outliers were not expected to have a strong influence on the results. Additionally, the outcome variable blood pressure

was expected to be physiologically higher in lower kidney function level groups. Removing outliers would ultimately unequally impact the lower kidney function level groups.

Missing Data

Missing data in NHANES is, sometimes, the result of a participant who completes the interview portion but not the mobile examination component. The sample weights of the interview and examination portions of the survey adjust for this nonresponse (C. Johnson et al., 2013; "National Health and Nutrition Examination Survey: analytic guidelines, 2011-2012," 2013). However, if an item was missing (e.g., a participant refused to have their blood pressure measured or was unable to provide enough blood for all of the laboratory tests), this was considered a component non-response and was not adjusted by the sample weights.

According to the NHANES Analytical Guideline, if the outcome variable of interest is missing for more than 10% of the participants, further adjustment in the sample weights may be necessary, or imputation for missing variables may need to be considered (C. Johnson et al., 2013). Furthermore, any response coded as “refused” or “don’t know” is treated as missing data. In the current study, the primary analyses were carried out using the data from only those participants with complete data (no imputation). However, socio-demographic characteristics were compared between those missing blood pressure and those with complete blood pressure data. The study planned

that if >10% of eligible participants in any of the kidney function level groups had missing blood pressure or those with missing blood pressure differed from those within their respective kidney function level group who have complete data with respect to potential biasing factors (Figure 5), mean imputation would be utilized. If necessary, mean imputation would be performed within each kidney function level group by assigning the mean blood pressure value of the group to those with missing blood pressure. The rationale for imputing the blood pressure data by the kidney function level was that using an overall mean blood pressure would bias the kidney function level group effect since blood pressure rises as kidney function level decreases. The imputation analysis, if needed, would be compared to the primary analyses as a form of sensitivity analysis. However, no variables had >10% missingness and the method of imputation was not required.

Variable Selection Criteria

The study evaluated the relationship of dietary sodium intake to systolic and diastolic blood pressure while considering the role of kidney function. Rather than follow an “agnostic” statistical approach, the study evaluated relationships using a causal framework approach, where models were built according to theoretical or empirical relationships in an attempt to reduce bias of estimated effects (Glymour & Greenland, 2008; Szklo & Nieto, 2014a). For example, considerations for whether X should change Y, Y

should change X, whether X and Y share common factors (confounding), or a third variable causes or is influenced by X and Y (collider bias) are some of the main foci under a causal framework approach (Glymour & Greenland, 2008). A confounder variable distorts the relationship between the exposure and outcome. Conditioning (i.e., stratifying on, adjusting for, including in a model, etc.) on a collider variable introduces selection bias if the variable is caused by both the exposure (X) and the outcome (Y). Awareness of and proper handling of these relationships a priori helps to reduce bias. In the current study, evaluating kidney function as a continuous variable might have masked the dietary sodium and blood pressure relationship. The variables noted in the conceptual framework (Figure 2) formed the backdrop of the analytical plan; namely, the relationship between dietary sodium and blood pressure by evaluating kidney function, age, education, BMI, race, diabetes, sex, and income status. These variables were available in NHANES and used in drawing directed acyclic graphs (DAGs; Figure 5) to explore the potential relationships with dietary sodium or blood pressure. To aid in organizing the DAGs, relationships involving dietary sodium and blood pressure were considered to have social or behavioral associations or biologic associations. The rationale employed for separating the graphs by social or behavioral or biologic relationships was that some relationships may be overlooked if strictly considering only biologic associations. For example, it was not expected that a variable such as race would have biological associations to

dietary sodium, but ethnic groups may have different social norms for food selections and preparation that would impact dietary sodium.

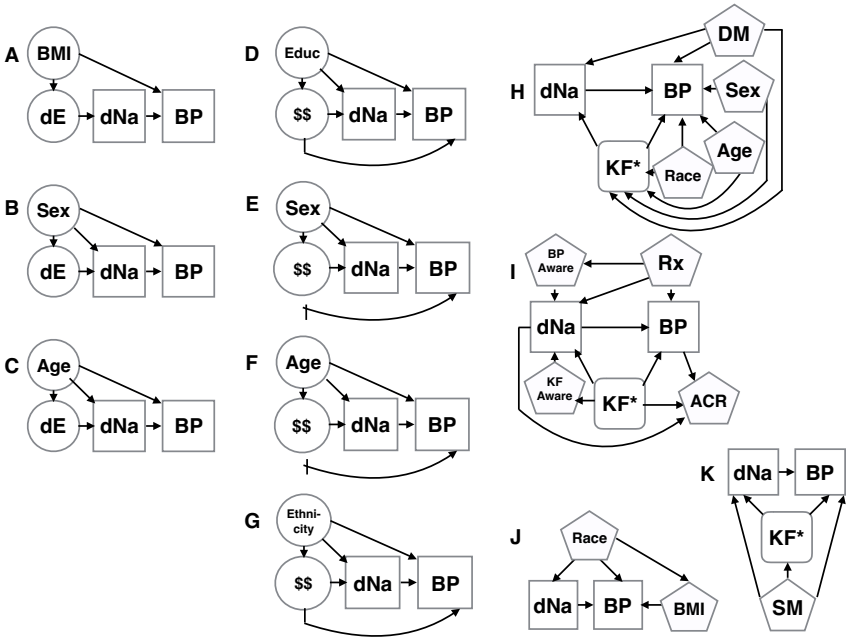

Figure 5. A series of directed acyclic graphs depicting social or behavioral (circle) and biological (pentagon) factors associated with the relationship between dietary sodium and blood pressure. The triangular path between dietary sodium, blood pressure, and kidney function is the relationship of primary interest.

$$=income, ACR=albumin-to-creatinine ratio, BMI=body mass index, BP=blood pressure, dE=dietary energy, dNa=dietary sodium, Educ=education, KF=kidney function, Rx=medications, SM=smoking

Kidney function is represented by an estimation equation that uses race (black vs non-black), age, sex and a biomarker (serum creatinine). A) BMI is a confounder of dE and BP; dE is on the causal pathway between BMI and dNa but not between dNa and BP. B) Sex is a confounder of dE, dNa, and BP; dE is on the causal pathway between Sex and dNa but not between dNa and BP. C) Age is a confounder of dE, dNa, and BP; dE is on the causal pathway between Age and dNa but not between dNa and BP. D) Educ is a confounder of $$, dNa, and BP; $$ is on the causal pathway between Educ and dNa but not between dNa and BP. E) Sex is a confounder of $$, dNa, and BP; $$ is on the causal pathway between Sex and dNa but not between dNa and BP. F) Age is a confounder of $$, dNa and BP and $$ is on the causal pathway between Age and dNa but not between dNa and BP. G) Ethnicity is a confounder of $$, dNa and BP; $$ is on the causal pathway between Ethnicity and dNa but not between dNa and BP. H) DM is a confounder of dNa, BP, and KF; Sex, Race and Age are confounders of KF and BP; KF is a confounder of dNa and BP. I) KF is a confounder of dNa and BP; Rx is a confounder of BP aware, dNa and BP; BP aware is on the causal pathway between Rx and dNa; KF aware is on the causal pathway between KF and dNa; ACR is a collider variable between KF and BP and between KF and dNa. J) Race is a confounder of dNa, BP and BMI; BMI is on the causal pathway between Race and BP. K) Smoking is a confounder of dNa, BP, and KF

Variables that were considered as having influence on only dietary sodium or only blood pressure (e.g., kidney disease awareness or blood pressure awareness) or were only represented in the causal pathway (e.g., dietary energy) were omitted from statistical models (Figure 6) because they would not confound the dietary sodium-to-blood pressure pathway. Another variable excluded was albumin-to-creatinine ratio because it was determined to be a collider variable between kidney function and blood pressure; the albumin-to-creatinine ratio is influenced by both dietary sodium and blood pressure (Figure 5) (Kidney Disease: Improving Global Outcomes Workgroup, 2012; Slagman et al., 2011). The variables for race (black vs non-black), sex and age are used in the estimation equation to determine the variable for kidney function (Levey et al., 2009) and may be collinear with the kidney function variable. Therefore, placing them in a model together may cloud the interpretation of the importance of each individual predictor. Therefore, multicollinearity between the variables sex, age, and race with the kidney function variable was checked prior to analysis using a correlation limit of 0.6. If multicollinearity was not demonstrated, the remaining variables demonstrating confounding on dietary sodium and blood pressure (sex, age, race, education, income, diabetes, blood pressure medications, and BMI) would be adjusted in the model for assessing the relationship between dietary sodium and blood pressure with kidney function as an effect modifier. Confounders of the dietary sodium and blood pressure relationship were also

expected (see the DAG in Figure 6) to confound the relationship between kidney function and blood pressure, as well as the relationship between kidney function and dietary sodium. However, one exception exists in the latter relationship. It was not anticipated that a behavioral or biological confounding by blood pressure medications exists between kidney function and dietary sodium because blood pressure medications would not influence the kidney function and dietary sodium relationship.

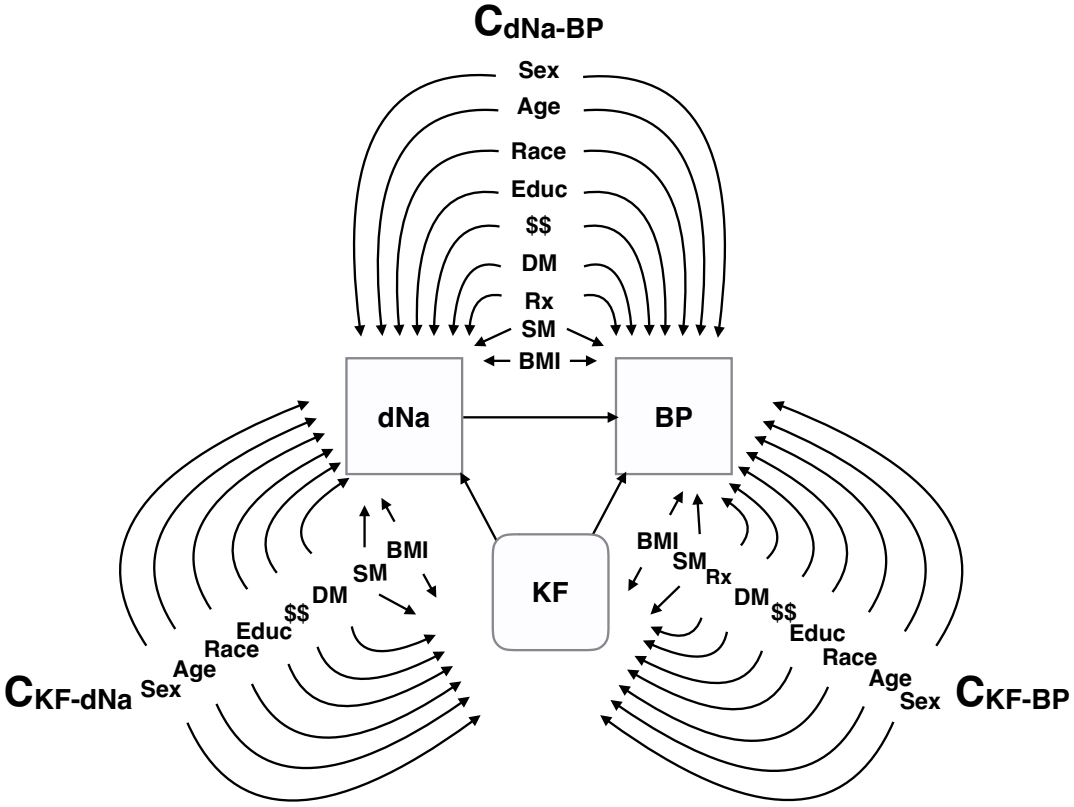

Figure 6. Conceptual model: Atypical directed acyclic graph depiction of factors associated with the relationship between dietary sodium and blood pressure that are modified by kidney function. The graph is atypical because it only depicts the relationships of factors associated with the three main variables and does not depict all potential confounding relationships within the factors.

$$=income; BMI=body mass index; BP=blood pressure, C_{dNa-BP}=confounder of dNa to BP; C_{KF-BP}=confounder of KF to BP; C_{KF-dNa}=confounder of KF to dNa; DM=diabetes mellitus; dNa=dietary sodium intake, Educ=education, KF=kidney function, Rx=blood pressure medications, SM=smoking

KF was represented by a validated estimation equation that uses Race (Black vs non-Black), Age, Sex and a biomarker (serum creatinine).

KF was grouped by 15mL/min increments from <15 to >105mL/min/1.73m^2. Since race, sex, and age are already adjusted in the KF equation, if multicollinearity was observed between race, sex, or age and KF, no additional adjustment would be taken for these variables.

Considering the totality of relationships described, the variables used in the model were determined to be dietary sodium, blood pressure (systolic

and diastolic), kidney function, sex, age, race, education, income status, diabetes status, antihypertensive agents, smoking, and BMI. Other variables (e.g., ACR, blood pressure awareness, and kidney function awareness) were summarized for the purpose of describing the population being examined in the proposed study since they did not meet the criteria required by the DAG approach. In this model, dietary sodium was considered the exposure variable and was not adjusted for dietary quality (e.g., nutrient density of dietary sodium).

Model Assumptions

Diagnostic procedures (such as plotting the residuals against predicted values of the dependent variable) were performed to assess for linearity of the predictors in the dependent variable, normality of the dependent variable, multicollinearity, and homogeneity of variance. Transformation of independent variables was considered if doing so improved the model.

Assessing the ancestry of the variables used in the DAGs was used as a method of checking for conditional independence between the predictor variables. Within pairs of variables suspected of lacking independence, the variable expected to have the stronger influence on the dependent variable would be retained in the model. This theoretical approach was checked against a standard statistical test for collinearity where the variable pairs

demonstrating Pearson correlation ≥ 0.6, with the variable having the higher relationship to the dependent variable being retained in the model.

Absence of outliers in the solution is desirable in multiple regression analysis. However, outliers were expected in the current study and, given the large number of participants in the dataset, outliers were anticipated to be informative. Thus, outliers in the solution may describe the types of cases that are not well predicted by the model.

Large sample size concerns

The potential for large sample sizes to demonstrate statistical significance is of particular importance in the current study. The inference of statistical significance when clinical relevance is not present may be expected in studies with large sample sizes because the statistical significance is determined by the standard error which becomes smaller as the sample size increases (Lin, Lucas Jr, & Shmueli, 2013). With large sample sizes, it may be more appropriate to focus on effect sizes and clinical relevance rather than *p*-values alone when interpreting the findings.

Research Aims

Research aim 1: To test whether the dietary sodium intake of U.S. non-pregnant adults varies by use of antihypertensive agents and kidney function

and whether adults with normal kidney function have a dietary sodium intake of 3,440 mg/day.

Research aim 2: To demonstrate that a simple dietary sodium and blood pressure relationship does not exist and to test whether a relationship between dietary sodium and systolic and diastolic blood pressure could be demonstrated when accounting for kidney disease and other key demographic and clinical characteristics.

The statistical analysis plan is described below with granularity on the separation of the aims and hypotheses into subproblems or questions that delineate the steps used for building the model. The planned analytical approach for each hypothesis is described in the appropriate subproblem. All analyses account for the complex survey design using SAS Survey v 9.4 (SAS Institute, Cary, NC) and the Taylor series linearization.

Analysis by Subproblem

In U.S. nonpregnant adults, as represented by data from NHANES 2003-2014, whose kidney function is estimated and who have completed a 24-hour dietary recall on the day prior to blood pressure measurement:

Subproblem 1

What are their key

a. Demographic characteristics (age, sex, race and ethnicity, education level, income status)?

b. Clinical characteristics (albumin-to-creatinine ratio, body mass index, diabetes status, number and type of antihypertensive agents used, kidney disease awareness, kidney function level, smoking status)?

Variables were reported using descriptive statistics (mean, standard error of the mean, median, and range) or frequency distributions (number and proportion of participants in each category), as appropriate (Table 5). Of note, non-Mexican American Hispanic ethnicity was combined with other races because NHANES did not oversample from this subgroup during the 2003-2014 period and no distinction was made for Asians because NHANES did not begin oversampling this race group until 2011 (C. Johnson et al., 2013).

Table 5.
Subproblem 1 - descriptors and analytical plan for describing demographic and clinical characteristics of the U.S. nonpregnant adults in NHANES 2003-2014.

Subproblem	Variable	Analysis	Dependent Y	Y variable type
1a.i	Age	Mean, SEM, Median, Range	Age, years	Continuous
1a.ii	Sex	Frequency distribution (number, proportion)	1 = male 2 = female	Categorical
1a.iii	Race and ethnicity	Frequency distribution (number, proportion)	1 = non-Hispanic black 2 = Mexican American 3 = Other race or ethnicity 4 = non-Hispanic white (ref)	Categorical

Subproblem	Variable	Analysis	Dependent Y	Y variable type
1a.iv	Education level	Frequency distribution (number, proportion)	0 = < HS diploma 1 = HS diploma/GED 2 = Some college or AA degree 3 = ≥ College degree (ref)	Categorical
1a.v	Income status	Frequency distribution (number, proportion)	0 = <$20,000 1 = $20,000 to < $45,000 or > $20,000 2 = $45,000 to < $75,000 3 = ≥ $75,000 (ref)	Categorical
1b.i	ACR	Mean, SEM, Median, Range	ACR, mg/g	Continuous
1b.ii	BMI	Mean, SEM, Median, Range	BMI, kg/m^2	Continuous
1b.iii	BMI category	Frequency distribution (number, proportion)	1 = <18.5 2 = ≥30 3 = 25.0 to ≤30 4 = 18.5 to <25 kg/m^2	Categorical
1b.iv	Diabetes status[a]	Frequency distribution (number, proportion)	1 = No 2 = Yes	Categorical
1b.v	Number of antihypertensive agents used	Mean, SEM, Median, Range	Number	Continuous
1b.vi	Number of antihypertensive agents used	Frequency distribution (number, proportion)	1 = 1 2 = 2 3 = > 2 4 = none	Categorical
1b.vii	Type of antihypertensive agents used	Frequency distribution (number, proportion)	1 = diuretics 2 = RAAS blockers 3 = diuretics and RAAS blockers	Categorical

Subproblem	Variable	Analysis	Dependent Y	Y variable type
			4 = Other antihypertensive agents 5 = No antihypertensive agents	
1b.viii	Kidney disease awareness	Frequency distribution (number, proportion)	1 = No 2 = Yes	Categorical
1b.ix	eGFR	Mean, SEM, Median, Range	eGFR, ml/min/1.73m^2	Continuous
1b.x	Kidney function level	Frequency distribution (number, proportion)	0 = <15 1 = 15 to <30 2 = 30 to <45 3 = 45 to <60 4 = 60 to <75 5 = 75 to <90 6 = 90 to 105 7 = ≥105 (ref) ml/min/1.73m^2	Categorical
1b.xi	Smoking status	Frequency distribution (number, proportion)	0 = Former smoker 1 = Current Smoker 2 = Never smoker	Categorical

Note. AA = associate degree, ACR = urinary albumin-to-creatinine ratio, BMI = body mass index, eGFR = estimated glomerular filtration rate, HS = high school, GED = General Equivalency Development, ref = reference group, SEM = standard error of the mean

[a]Diabetes status: presence of evidence for diabetes defined as 1) a documented diagnosis of diabetes within the NHANES questionnaire data ("Have you ever been told by a doctor or health professional that you have diabetes or sugar diabetes?" or 2) taking antihyperglycemia agents or 3) having a fasting glucose ≥ 126 mg/dL (7.0 mmol/L) after fasting for ≥ 8 hours, or 4) having a glycosylated hemoglobin ≥ 6.5%.

Subproblem 2

What is their dietary sodium intake and systolic and diastolic blood pressure?

Variables were reported using descriptive statistics (mean, standard error of the mean, median, and interquartile range) or frequency distributions (number and proportion of participants in each category), as appropriate (Table 5).

A wide range of dietary sodium was expected in this data set. Dietary sodium was Winsorized at the top 0.5% of the distribution to reduce the effect of potentially spurious outliers while retaining them in the data set [personal communication from the Office of Dietary Supplements, National Institutes of Health, Johanna Dwyer, DSc and Regan Bailey, PhD; (Bailey et al., 2013)]. Dietary sodium intake was reported as a continuous variable (mg/day in 200 mg increments and in 1 g/day increments of NaCl) and as a categorical variable using the 2015-2020 Dietary Guidelines recommended sodium intake cut point of < 2,300 mg/day or ≥ 2,300 mg/day (*Dietary Guidelines for Americans, 2015-2020*, 2015) to indicate the prevalence of U.S. nonpregnant adults who met the dietary guideline (Table 6). Whereas the Dietary Guidelines for Americans are not intended to be used to treat disease, applying the cut point recommended by the guideline in the current analysis may help to demonstrate the proportion of subpopulations who meet or exceed the Dietary Guidelines for Americans. Additionally, given the low level

of evidence in current kidney disease-specific guidelines for dietary sodium [ranging from <2,000 mg/day to <2,400 mg/day; ("Chronic kidney disease," 2010; Kidney Disease: Improving Global Outcomes Workgroup, 2012)], the Dietary Guidelines cut point may also be considered informative for Americans cut point may also be considered informative for kidney disease.

Dietary sodium was also captured as sodium density (mg of sodium/1,000 kcal) to demonstrate the quality of the overall dietary intake with respect to dietary sodium (Willett, Howe, & Kushi, 1997). However, dietary sodium density was not considered a marker of dietary sodium exposure.

In addition to the continuous variables for SBP and DBP, blood pressure was reported as the proportion of the U.S. nonpregnant adult population having blood pressure within the categories recommended by the American Heart Association, the Centers for Disease Control and Prevention, and the National Heart, Lung, and Blood Institute for use in surveillance (Crim et al., 2012; Mozaffarian et al., 2015) during the NHANES cycle periods used in the current study. High blood pressure awareness (yes or no), hypertension status (yes or no), and taking antihypertensive agents (yes or no) were analyzed as dichotomous variables and reported as frequency distributions (Table 6).

Table 6.
Subproblem 2 – descriptors and analytical plan for the question: what is their dietary sodium intake and systolic and diastolic blood pressure?

Subproblem	Analysis	Dependent Y	Y variable type
2a.i	Mean, SEM, Median, IQR	Dietary sodium, mg/day	Continuous
2a.ii	Frequency distribution (number, proportion)	Dietary sodium: < 2,300 mg or ≥ 2,300 mg	Categorical
2a.iii	Mean, SEM, Median, IQR	Dietary sodium density, mg sodium/1,000 kcal/day	Continuous
2a.iv	Mean, SEM, Median, IQR	SBP, mmHg	Continuous
2a.v	Mean, SEM, Median, IQR	DBP, mmHg	Continuous
2a.vi	Frequency distribution (number, proportion)	1 = D, ≥ 160 mmHg systolic or ≥ 100 mmHg diastolic 2 = C, 140-159 mmHg systolic or 90-99 mmHg diastolic 3 = B, 120-139 mmHg systolic or 80-89 mmHg diastolic 4 = A, <120 mmHg systolic and <80 mmHg diastolic	Categorical
2a.vii	Frequency distribution (number, proportion)	High blood pressure awareness: 1 = Yes 2 = No	Categorical
2a.viii	Frequency distribution (number, proportion)	Hypertension (≥ 140 mmHg systolic or ≥ 90 mmHg diastolic): 1 = Yes 2 = No	Categorical

Note. DBP = diastolic blood pressure, IQR = interquartile range, SBP = systolic blood pressure, SEM = standard error of the mean

Subproblem 3

What is the relationship between dietary sodium intake and key

a. demographic and

b. clinical characteristics?

Hypothesis 1a. The mean dietary sodium intake of U.S. nonpregnant adults is lower in people taking antihypertensive agents than in people not taking antihypertensive agents.

Hypothesis 1b. The mean dietary sodium intake of U.S. nonpregnant adults is lower in people with reduced kidney function than in U.S. nonpregnant adults with normal kidney function.

Hypothesis 1c. The mean dietary sodium intake of U.S. nonpregnant adults with normal kidney function is higher than 3,440 mg/day.

Demographic (Table 7, 3a.i – 3a.v) and clinical characteristics (Table 7, 3b.i – 3b.xiii) were compared to dietary sodium in mg/day.

Continuous variables were compared to dietary sodium by bivariate regression analyses to report the direction and size of the relationship between dietary sodium and each of the continuous demographic and clinical characteristics (Table 7). The size and direction of the relationship was reported as the Pearson product moment correlation (r, either positive or negative; effect size was small = 0.1, medium = 0.3, or large = 0.5 (Cohen, 1992)); Type-I error was set at α <0.05.

Categorical variables were compared to dietary sodium by either t-test for variables with two categories or one-way independent analysis of variance (ANOVA) for variables having more than two categories (Table 7). In the latter circumstance, a Bonferroni correction was applied to the *p*-value to account for family-wise error based upon the number of categories in each variable by taking the quotient of the critical *p*-value and the number of categories in each variable; 95% Confidence Intervals were also reported. The mean dietary sodium intake of adults with normal kidney function (e.g., >90 ml/min/1.73m^2) was assessed using a one-sample t-test to determine the difference of the dietary sodium intake (mg/day) and the stated estimate of 3,440 mg/day (*Dietary Guidelines for Americans, 2015-2020*, 2015). Type 1 error was set at α<0.05 and 95% Confidence Intervals were reported.

The demographic (Table 7, 3c.i – 3c.v) and clinical characteristics (Table 7, 3d.i – 3d.xi) was compared to the dietary sodium cutpoint at 2,300 mg/day using logistic regression for continuous predictor variables or Chi-square or a Loglinear chi-square for individual categorical variables, as appropriate. Type 1 error was set at α<0.05 and adjusted by Bonferroni correction for variables having more than two categories as described above; 95% Confidence Intervals were reported.

Table 7.
Subproblem 3 – descriptors and analytical plan for the question: what is the relationship between dietary sodium intake and key demographic and clinical characteristics? The plan includes analyses for Research Aim 1 (Hypotheses 1a – 1c).

Subproblem	Analysis	Independent X	X variable type	Dependent Y	Y variable type
3a.i	Bivariate regression	Age, years	Continuous	Dietary sodium, mg/day	Continuous
3a.ii	t-test	Sex: 1 = male 2 = female	Categorical	Dietary sodium, mg/day	Continuous
3a.iii	One-way analysis of variance, Bonferroni correction	Race and ethnicity: 1 = non-Hispanic black 2 = Mexican American 3 = Other race or ethnicity 4 = non-Hispanic white (ref)	Categorical	Dietary sodium, mg/day	Continuous
3a.iv	One-way analysis of variance, Bonferroni correction	Education level: 0 = < HS diploma 1 = HS diploma/GED 2 = Some college or AA degree 3 = ≥ College degree (ref)	Categorical	Dietary sodium, mg/day	Continuous
3a.v	One-way analysis of variance, Bonferroni correction	Income status: 0 = <$20,000 1 = $20,000 to < $45,000 or > $20,000 2 = $45,000 to < $75,000 3 = ≥ $75,000 (ref)	Categorical	Dietary sodium, mg/day	Continuous

Subproblem	Analysis	Independent X	X variable type	Dependent Y	Y variable type
3b.i	Bivariate regression	ACR, mg/g	Continuous	Dietary sodium, mg/day	Continuous
3b.ii	Bivariate regression	BMI, kg/m^2	Continuous	Dietary sodium, mg/day	Continuous
3b.iii	One-way analysis of variance, Bonferroni correction	BMI category: 1 = <18.5 2 = ≥30 3 = 25.0 to ≤30 4 = 18.5 to <25 kg/m^2	Categorical	Dietary sodium, mg/day	Continuous
3b.iv	t-test	Diabetes status: 1 = No 2 = Yes	Categorical	Dietary sodium, mg/day	Continuous
3b.v	t-test	High blood pressure awareness: 1 = Yes 2 = No	Categorical	Dietary sodium, mg/day	Continuous
3b.vi	One-way analysis of variance, Bonferroni correction	Number of antihypertensive agents used: 1 = 1 2 = 2 3 = > 2 4 = none	Categorical	Dietary sodium, mg/day	Continuous
3b.vii	One-way analysis of variance, Bonferroni correction	Type of antihypertensive agents used: 1 = diuretics 2 = RAAS blockers 3 = diuretics and RAAS blockers 4 = Other antihypertensive agents 5 = No antihypertensive agents		Dietary sodium, mg/day	Continuous

Subproblem	Analysis	Independent X	X variable type	Dependent Y	Y variable type
3b.viii	t-test	Kidney disease awareness: 1 = No 2 = Yes	Categorical	Dietary sodium, mg/day	Continuous
3b.ix	One-way analysis of variance, Bonferroni correction	Smoking status: 0 = Former Smoker 1 = Current Smoker 2 = Never smoker	Categorical	Dietary sodium, mg/day	Continuous
3b.x Hypothesis 1a	One-way analysis of variance, Bonferroni correction	Taking antihypertensive agents: 1 = Yes 2 = No	Categorical	Dietary sodium, mg/day	Continuous
3b.xi Hypothesis 1b	One-way analysis of variance, Bonferroni correction	Kidney function level: 0 = <15 1 = 15 to <30 2 = 30 to <45 3 = 45 to <60 4 = 60 to <75 5 = 75 to <90 6 = 90 to 105 7 = ≥105 (ref) ml/min/1.73m^2	Categorical	Dietary sodium, mg/day	Continuous
3b.xiii Hypothesis 1c	One-sample t-test, difference from 3,440mg sodium	Normal kidney function: eGFR >90 ml/min/1.73m^2	Continuous	Dietary sodium, mg/day	Continuous
3c.i	Logistic regression	Age, years	Continuous	Dietary sodium, < 2,300 mg/day or ≥ 2,300 mg/day	Categorical

Subproblem	Analysis	Independent X	X variable type	Dependent Y	Y variable type
3c.ii	Chi-square	Sex: 1 = male 2 = female	Categorical	Dietary sodium, < 2,300 mg/day or ≥ 2,300 mg/day	Categorical
3c.iii	Loglinear	Race and ethnicity: 1 = non-Hispanic black 2 = Mexican American 3 = Other race 4 = non-Hispanic white (ref)	Categorical	Dietary sodium, < 2,300 mg/day or ≥ 2,300 mg/day	Categorical
3c.iv	Loglinear	Education level: 0 = < HS diploma 1 = HS diploma/GED 2 = Some college or AA degree 3 = ≥ College degree (ref)	Categorical	Dietary sodium, < 2,300 mg/day or ≥ 2,300 mg/day	Categorical
3c.v	Loglinear	Income status: 0 = <$20,000 1 = $20,000 to < $45,000 or > $20,000 2 = $45,000 to < $75,000 3 = ≥ $75,000 (ref)	Categorical	Dietary sodium, < 2,300 mg/day or ≥ 2,300 mg/day	Categorical
3d.i	Logistic regression	ACR, mg/g	Continuous	Dietary sodium, < 2,300 mg/day or ≥ 2,300 mg/day	Categorical

Subproblem	Analysis	Independent X	X variable type	Dependent Y	Y variable type
3d.ii	Logistic regression	BMI, kg/m^2	Continuous	Dietary sodium, < 2,300 mg/day or ≥ 2,300 mg/day	Categorical
3d.iii	Loglinear	BMI category: 1 = <18.5 2 = ≥30 3 = 25.0 to ≤30 4 = 18.5 to <25 kg/m^2	Categorical	Dietary sodium, < 2,300 mg/day or ≥ 2,300 mg/day	Categorical
3d.iv	Loglinear	Diabetes status: 1 = Yes 2 = Not possible to determine 3 = No	Categorical	Dietary sodium, < 2,300 mg/day or ≥ 2,300 mg/day	Categorical
3d.v	Chi-square	High blood pressure awareness: 1 = Yes 2 = No	Categorical	Dietary sodium, < 2,300 mg/day or ≥ 2,300 mg/day	Categorical
3d.vi	Loglinear	Number of antihypertensive agents used: 1 = 1 2 = 2 3 = > 2 4 = none	Categorical	Dietary sodium, < 2,300 mg/day or ≥ 2,300 mg/day	Categorical
3d.vii	Loglinear	Type of antihypertensive agents used: 1 = diuretics 2 = RAAS blockers 3 = diuretics and RAAS blockers		Dietary sodium, < 2,300 mg/day or ≥ 2,300 mg/day	Categorical

Subproblem	Analysis	Independent X	X variable type	Dependent Y	Y variable type
		4 = Other antihypertensive agents 5 = No antihypertensive agents			
3d.viii	Chi-square	Kidney disease awareness: 1 = No 2 = Yes	Categorical	Dietary sodium, < 2,300 mg/day or ≥ 2,300 mg/day	Categorical
3d. ix	Loglinear	Smoking status: 0 = Former smoker 1 = Current Smoker 2 = Never smoker	Categorical	Dietary sodium, < 2,300 mg/day or ≥ 2,300 mg/day	Categorical
3d.x	Chi-square	Taking antihypertensive agents: 1 = Yes 2 = No	Categorical	Dietary sodium, < 2,300 mg/day or ≥ 2,300 mg/day	Categorical
3d.xi	Loglinear	Kidney function level: 0 = <15 1 = 15 to <30 2 = 30 to <45 3 = 45 to <60 4 = 60 to <75 5 = 75 to <90 6 = 90 to 105 7 = ≥105 (ref) ml/min/1.73m^2	Categorical	Dietary sodium, < 2,300 mg/day or ≥ 2,300 mg/day	Categorical

Note. AA = associate degree; ACR = urinary albumin-to-creatinine ratio; BMI = body mass index; eGFR = estimated glomerular filtration rate; HS = high school; GED = General Equivalency Development; ref = reference group; SEM = standard error of the mean

Subproblem 4

What is the relationship between systolic and diastolic blood pressure and key

a. demographic and
b. clinical characteristics?

The mean SBP and DBP was reported for demographic (Table 8, 4a.i – 4a.v) and clinical characteristic (4b.i – 4b.xii) variables. For continuous variables, SBP and DBP were each evaluated by bivariate regression analysis to report the relationship between blood pressure and each of the continuous demographic and clinical characteristics (Table 8). For the categorical variables, the mean and standard error of the mean SBP and DBP were reported using either t-test for variables with two categories or one-way independent analysis of variance (ANOVA) for variables having more than two categories (Table 8). In the latter circumstance, a Bonferroni correction was applied to the *p*-value to account for family-wise error based upon the number of categories in each variable by taking the quotient of the critical *p*-value and the number of categories in each variable. For example, race and ethnicity was reported using four categories (non-Hispanic white, non-Hispanic black, Hispanic, and Other). Thus, the modified *p*-value for a Type 1 error would be 0.05/4 or 0.0125 for the relationship between SBP or DBP and race and ethnicity.

The blood pressure category variable was evaluated using an ordinal logistic (or proportional odds) regression for continuous predictor variables or Loglinear chi-square for individual categorical variables (Table 8, 4c.i – 4c.v for demographic and 4d.i – 4d.xii for clinical characteristics). Type-I error was set at α<0.05 and 95% Confidence Intervals were reported.

Table 8.
Subproblem 4 – descriptors and analytical plan for the question: what is the relationship between blood pressure and key demographic and clinical characteristics?

Sub-problem	Analysis	Independent X	X variable type	Dependent Y	Y variable type
4a.i	Bivariate regression	Age, years	Continuous	SBP and DBP, mmHg	Continuous
4a.ii	t-test	Sex: 1 = male 2 = female	Categorical	SBP and DBP, mmHg	Continuous
4a.iii	One-way analysis of variance, Bonferroni correction	Race and ethnicity: 1 = non-Hispanic Black 2 = Mexican American 3 = Other race 4 = non-Hispanic white (ref)	Categorical	SBP and DBP, mmHg	Continuous
4a.iv	One-way analysis of variance, Bonferroni correction	Education level: 0 = < HS diploma 1 = HS diploma/GED 2 = Some college or AA degree 3 = ≥ College degree (ref)	Categorical	SBP and DBP, mmHg	Continuous
4a.v	One-way analysis of variance, Bonferroni correction	Income status: 0 = <$20,000 1 = $20,000 to < $45,000 or > $20,000	Categorical	SBP and DBP, mmHg	Continuous

Sub-problem	Analysis	Independent X	X variable type	Dependent Y	Y variable type
		2 = $45,000 to < $75,000 3 = ≥ $75,000 (ref)			
4b.i	Bivariate regression	ACR, mg/g	Continuous	SBP and DBP, mmHg	Continuous
4b.ii	Bivariate regression	BMI, kg/m^2	Continuous	SBP and DBP, mmHg	Continuous
4b.iii	One-way analysis of variance, Bonferroni correction	1 = <18.5 2 = ≥30 3 = 25.0 to ≤30 4 = 18.5 to <25 kg/m^2	Categorical	SBP and DBP, mmHg	Continuous
4b.v	One-way analysis of variance	Diabetes status: 1 = Yes 2 = Not possible to determine 3 = No	Categorical	SBP and DBP, mmHg	Continuous
4b.vi	t-test	High blood pressure awareness: 1 = Yes 2 = No	Categorical	SBP and DBP, mmHg	Continuous
4b.vii	One-way analysis of variance, Bonferroni correction	Number of antihypertensive agents used: 1 = 1 2 = 2 3 = > 2 4 = none	Categorical	SBP and DBP, mmHg	Continuous
4b.viii	One-way analysis of variance, Bonferroni correction	Type of antihypertensive agents used: 1 = diuretics 2 = RAAS blockers	Categorical	SBP and DBP, mmHg	Continuous

Sub-problem	Analysis	Independent X	X variable type	Dependent Y	Y variable type
		3 = diuretics and RAAS blockers 4 = Other antihypertensive agents 5 = No antihypertensive agents			
4b.ix	t-test	Kidney disease awareness: 1 = No 2 = Yes	Categorical	SBP and DBP, mmHg	Continuous
4b.x	One-way analysis of variance, Bonferroni correction	Smoking status: 0 = Former smoker 1 = Current Smoker 2 = Never smoker	Categorical	SBP and DBP, mmHg	Continuous
4b.xi	One-way analysis of variance, Bonferroni correction	Taking antihypertensive agents: 1 = Yes 2 = No	Categorical	SBP and DBP, mmHg	Continuous
4b.xii	One-way analysis of variance, Bonferroni correction	Kidney function level: 0 = <15 1 = 15 to <30 2 = 30 to <45 3 = 45 to <60 4 = 60 to <75 5 = 75 to <90 6 = 90 to 105	Categorical	SBP and DBP, mmHg	Continuous

Sub-problem	Analysis	Independent X	X variable type	Dependent Y	Y variable type
		7 = ≥105 (ref) ml/min/1.73 m^2			
4c.i	Ordinal logistic regression	Age, years	Continuous	Blood pressure category: 1 = D, ≥ 160 mmHg systolic or ≥ 100 mmHg diastolic 2 = C, 140-159 mmHg systolic or 90-99 mmHg diastolic 3 = B, 120-139 mmHg systolic or 80-89 mmHg diastolic 4 = A, <120 mmHg systolic and <80 mmHg diastolic	Categorical
4c.ii	Logistic regression	Sex: 1 = male 2 = female	Categorical	Blood pressure category: 1 = D, ≥ 160 mmHg systolic or ≥ 100 mmHg diastolic 2 = C, 140-159 mmHg systolic or 90-99 mmHg diastolic 3 = B, 120-139 mmHg systolic or 80-89 mmHg diastolic 4 = A, <120 mmHg systolic and <80 mmHg diastolic	Categorical

Sub-problem	Analysis	Independent X	X variable type	Dependent Y	Y variable type
4c.iii	Logistic regression	Race and ethnicity: 1 = non-Hispanic Black 2 = Mexican American 3 = Other race 4 = non-Hispanic White (ref)	Categorical	Blood pressure category: 1 = D, ≥ 160 mmHg systolic or ≥ 100 mmHg diastolic 2 = C, 140-159 mmHg systolic or 90-99 mmHg diastolic 3 = B, 120-139 mmHg systolic or 80-89 mmHg diastolic 4 = A, <120 mmHg systolic and <80 mmHg diastolic	Categorical
4c.iv	Logistic regression	Education level: 0 = < HS diploma 1 = HS diploma/GED 2 = Some college or AA degree 3 = ≥ College degree (ref)	Categorical	Blood pressure category: 1 = D, ≥ 160 mmHg systolic or ≥ 100 mmHg diastolic 2 = C, 140-159 mmHg systolic or 90-99 mmHg diastolic 3 = B, 120-139 mmHg systolic or 80-89 mmHg diastolic 4 = A, <120 mmHg systolic and <80 mmHg diastolic	Categorical
4c.v	Logistic regression	Income status: 0 = <$20,000	Categorical	Blood pressure category: 1 = D, ≥ 160 mmHg	Categorical

Sub-problem	Analysis	Independent X	X variable type	Dependent Y	Y variable type
		1 = $20,000 to < $45,000 or > $20,000 2 = $45,000 to < $75,000 3 = ≥ $75,000 (ref)		systolic or ≥ 100 mmHg diastolic 2 = C, 140-159 mmHg systolic or 90-99 mmHg diastolic 3 = B, 120-139 mmHg systolic or 80-89 mmHg diastolic 4 = A, <120 mmHg systolic and <80 mmHg diastolic	
4d.i	Ordinal logistic regression	ACR, mg/g	Continuous	Blood pressure category: 1 = D, ≥ 160 mmHg systolic or ≥ 100 mmHg diastolic 2 = C, 140-159 mmHg systolic or 90-99 mmHg diastolic 3 = B, 120-139 mmHg systolic or 80-89 mmHg diastolic 4 = A, <120 mmHg systolic and <80 mmHg diastolic	Categorical
4d.ii	Ordinal logistic regression	BMI, kg/m^2	Continuous	Blood pressure category: 1 = D, ≥ 160 mmHg systolic or ≥ 100 mmHg diastolic	Categorical

Sub-problem	Analysis	Independent X	X variable type	Dependent Y	Y variable type
				2 = C, 140-159 mmHg systolic or 90-99 mmHg diastolic 3 = B, 120-139 mmHg systolic or 80-89 mmHg diastolic 4 = A, <120 mmHg systolic and <80 mmHg diastolic	
4d.iii	Logistic regression	BMI category: 1 = <18.5 2 = ≥30 3 = 25.0 to ≤30 4 = 18.5 to <25 kg/m^2	Categorical	Blood pressure category: 1 = D, ≥ 160 mmHg systolic or ≥ 100 mmHg diastolic 2 = C, 140-159 mmHg systolic or 90-99 mmHg diastolic 3 = B, 120-139 mmHg systolic or 80-89 mmHg diastolic 4 = A, <120 mmHg systolic and <80 mmHg diastolic	Categorical
4d.iv	Logistic regression	Diabetes status: 1 = Yes 2 = No	Categorical	Blood pressure category: 1 = D, ≥ 160 mmHg systolic or ≥ 100 mmHg diastolic 2 = C, 140-159 mmHg systolic or 90-99 mmHg diastolic	Categorical

Sub-problem	Analysis	Independent X	X variable type	Dependent Y	Y variable type
				3 = B, 120-139 mmHg systolic or 80-89 mmHg diastolic 4 = A, <120 mmHg systolic and <80 mmHg diastolic	
4d.v	Logistic regression	High blood pressure awareness: 1 = Yes 2 = No	Categorical	Blood pressure category: 1 = D, ≥ 160 mmHg systolic or ≥ 100 mmHg diastolic 2 = C, 140-159 mmHg systolic or 90-99 mmHg diastolic 3 = B, 120-139 mmHg systolic or 80-89 mmHg diastolic 4 = A, <120 mmHg systolic and <80 mmHg diastolic	Categorical
4d.vi	Logistic regression	Number of antihypertensive agents used: 1 = 1 2 = 2 3 = > 2 4 = none	Categorical	Blood pressure category: 1 = D, ≥ 160 mmHg systolic or ≥ 100 mmHg diastolic 2 = C, 140-159 mmHg systolic or 90-99 mmHg diastolic 3 = B, 120-139 mmHg systolic or 80-89 mmHg diastolic	Categorical

Sub-problem	Analysis	Independent X	X variable type	Dependent Y	Y variable type
				4 = A, <120 mmHg systolic and <80 mmHg diastolic	
4d.vii	Logistic regression	Type of antihypertensive agents used: 1 = diuretics 2 = RAAS blockers 3 = diuretics and RAAS blockers 4 = Other antihypertensive agents 5 = No antihypertensive agents	Categorical	Blood pressure category: 1 = D, ≥ 160 mmHg systolic or ≥ 100 mmHg diastolic 2 = C, 140-159 mmHg systolic or 90-99 mmHg diastolic 3 = B, 120-139 mmHg systolic or 80-89 mmHg diastolic 4 = A, <120 mmHg systolic and <80 mmHg diastolic	Categorical
4d.viii	Logistic regression	Kidney disease awareness: 1 = Yes 2 = No	Categorical		
4d.ix	Logistic regression	Smoking status: 0 = Former smoker 1 = Current Smoker 2 = Never smoker	Categorical	Blood pressure category: 1 = D, ≥ 160 mmHg systolic or ≥ 100 mmHg diastolic 2 = C, 140-159 mmHg systolic or 90-99 mmHg diastolic 3 = B, 120-139 mmHg systolic or	Categorical

Sub-problem	Analysis	Independent X	X variable type	Dependent Y	Y variable type
				80-89 mmHg diastolic 4 = A, <120 mmHg systolic and <80 mmHg diastolic	
4d.x	Logistic regression	Taking antihypertensive agents: 1 = Yes 2 = No	Categorical	Blood pressure category: 1 = D, ≥ 160 mmHg systolic or ≥ 100 mmHg diastolic 2 = C, 140-159 mmHg systolic or 90-99 mmHg diastolic 3 = B, 120-139 mmHg systolic or 80-89 mmHg diastolic 4 = A, <120 mmHg systolic and <80 mmHg diastolic	Categorical
4d.xi	Logistic regression	Kidney function level: 0 = <15 1 = 15 to <30 2 = 30 to <45 3 = 45 to <60 4 = 60 to <75 5 = 75 to <90 6 = 90 to 105 7 = ≥105 (ref)	Categorical	Blood pressure category: 1 = D, ≥ 160 mmHg systolic or ≥ 100 mmHg diastolic 2 = C, 140-159 mmHg systolic or 90-99 mmHg diastolic 3 = B, 120-139 mmHg systolic or 80-89 mmHg diastolic 4 = A, <120 mmHg systolic	Categorical

Sub-problem	Analysis	Independent X	X variable type	Dependent Y	Y variable type
		ml/min/1.73 m^2		and <80 mmHg diastolic	

Note. AA = associate degree, ACR = urinary albumin-to-creatinine ratio, BMI = body mass index, eGFR = estimated glomerular filtration rate, HS = high school, GED = General Equivalency Development, ref = reference group, SEM = standard error of the mean

Subproblem 5

What is the relationship between dietary sodium intake and systolic and diastolic blood pressure?

Linear Regression

The relationship between dietary sodium intake and blood pressure was evaluated using three separate analyses (Table 9, 5a.i). The first two analyses utilized dietary sodium intake in mg/day (also reported as 200 mg increments of sodium and in 1 g increments of NaCl) and SBP and DBP in millimeters of Hg, both as continuous variables, using simple linear regression. R^2 (the ratio of the model sum of squares to the total sum of squares) was used to assess the size of the relationship between dietary sodium intake and blood pressure where SBP was the outcome variable in the first analysis and DBP was the outcome variable in the second analysis. The statistical significance of the relationship between dietary sodium intake and blood pressure was demonstrated by a *b*-value (the value representing the change in blood pressure resulting from a one-unit change in dietary sodium) that was significantly different from 0 using a t-statistic test with α <0.05. A clinically relevant relationship would be the amount of dietary sodium associated with a blood pressure (systolic or diastolic) difference that could be measured by a sphygmomanometer (e.g., ≥1 mmHg).

Logistic Regression

The third evaluation utilized dietary sodium intake (mg/day) as a single independent predictor when blood pressure was evaluated as blood pressure categories (A, <120 mmHg systolic and <80 mmHg diastolic; B, 120-139 mmHg systolic or 80-89 mmHg diastolic; C, 140-159 mmHg systolic or 90-99 mmHg diastolic, or D, ≥ 160 mmHg systolic or ≥ 100 mmHg diastolic; Table 9, 5b.i). The analysis was performed using ordinal logistic regression, of the type known as proportional odds or cumulative logit, with the lower blood pressure category (systolic <120 mmHg and diastolic <80 mmHg) as the reference (Hosmer Jr, Lemeshow, & Sturdivant, 2013). Measures of effect were reported as odds ratios with 95% Confidence Intervals. The proportional odds model fit was tested comparing log-likelihood values of the proportional and multinomial logistic regression models in a Loglinear chi-square test.

Table 9.
Subproblem 5 – descriptors and analytical plan for the question: what is the relationship between dietary sodium intake and systolic and diastolic blood pressure?

Sub-problem	Analysis	Independent X	X variable type	Dependent Y	Y variable type
5a.i	Simple linear regression, t statistic	Dietary sodium, mg/day	Continuous	SBP and DBP, mmHg	Continuous
5b.i	Ordinal logistic regression	Dietary sodium, mg/day	Continuous	Blood pressure category: 1 = D, ≥ 160 mmHg systolic or ≥ 100 mmHg diastolic 2 = C, 140-159 mmHg systolic or 90-99 mmHg diastolic 3 = B, 120-139 mmHg systolic or 80-89 mmHg diastolic 4 = A, <120 mmHg systolic and <80 mmHg diastolic	Categorical

Note. DBP = diastolic blood pressure, ref = reference group, SBP = systolic blood pressure

Subproblem 6

What is the relationship between dietary sodium intake and systolic and diastolic blood pressure when controlling for key demographic and clinical characteristics?

Hypothesis 2a. There is no statistically significant relationship between dietary sodium intake and blood pressure in U.S. nonpregnant adults when controlling for key demographic and clinical characteristics.

Multiple Regression

For exploration of the relationship of dietary sodium intake to blood pressure as the continuous variable of SBP and as DBP, a multiple regression model was applied (Field, 2013) using the key demographic and clinical characteristic variables described in the DAG (Figure 6 and Table 10) (Szklo & Nieto, 2014b). Dietary sodium was entered into the model first, followed by kidney function level using dummy variables to represent each kidney function level where the highest level (>105 ml/min/1.73m^2) was the reference group. The remaining variables were entered as groupings of demographic and clinical characteristics (a hierarchical approach). The procedure was repeated for assessing the relationship of dietary sodium to blood pressure as the continuous variable of DBP.

Table 10.
Subproblem 6 – descriptors and analytical plan for the question: what is the relationship between dietary sodium intake and systolic and diastolic blood pressure when controlling for key demographic and clinical characteristics? The plan includes analysis for Research Aim 2, Hypothesis 2a.

Subproblem	Analysis	Independent X	X variable type	Dependent Y	Y variable type
6a.i Hypothesis 2a	Multiple regression	Model entry order: 1. Dietary sodium, mg/day 2. Kidney function level group (>105 ml/min/1.73m^2 is ref) 3. Demographic (sex, age, race and ethnicity, education level, income status) 4. Clinical (diabetes status, taking antihypertensive agents, smoking status, BMI [kg/m^2])	Continuous and categorical (using dummy variables for variables having >2 categories)	SBP and DBP, mmHg	Continu-ous

Note. DBP = diastolic blood pressure, SBP = systolic blood pressure

Sensitivity Analysis

A sensitivity analysis was performed substituting blood pressure category for the continuous blood pressure variable to both confirm findings and depict the categories of blood pressure that might have stronger relationships to dietary sodium (Table 11).

Table 11.
Descriptors and analytical plan for sensitivity analyses of the relationship between dietary sodium and blood pressure in U.S. nonpregnant adults from NHANES 2003-2014.

Analysis	Independent X	X variable type(s)	Dependent Y	Y variable type
Multinomial logistic regression	Model entry order: 1. Dietary sodium <2,300 mg/day or ≥2,300 mg/day 2. Kidney function level group (> 105 ml/min/1.73m2 is ref) 3. Demographic variables 4. Clinical variables	Continuous and categorical	Blood pressure category: 1 = D, ≥ 160 mmHg systolic or ≥ 100 mmHg diastolic 2 = C, 140-159 mmHg systolic or 90-99 mmHg diastolic 3 = B, 120-139 mmHg systolic or 80-89 mmHg diastolic 4 = A, <120 mmHg systolic and <80 mmHg diastolic	Categorical, 4 groups

Chapter IV

RESULTS AND FINDINGS

Sample Selection

The NHANES 2003-2014 cycles included data on 61,083 participants who were 0-85 years of age. The distribution of participation from each two-year cycle of NHANES was: 16.6% (n=10,118) from 2003-2004, 16.9% (n=10,348) from 2005-2006, 16.6% (n=10,149) from 2007-2008, 17.3% (n=10,537) from 2009-2010, 16.0% (n=9,756) from 2011-2012, and 16.7% (n=10,175) from 2013-2014. The applied inclusion and exclusion criteria reduced the sample to 45.8% of the total NHANES sample for the period (Figure 7). The main exclusion was age <20 years (45.2%, n=27,581). Another 1,442 were excluded because they did not have a blood pressure measurement (outcome variable). Diastolic blood pressure was recorded as “0” in 135 participants; since a diastolic blood pressure of “0” is not physiologically possible, these participants were excluded from the analytic data set. The final sample for the current study was 27,943 non-pregnant adults.

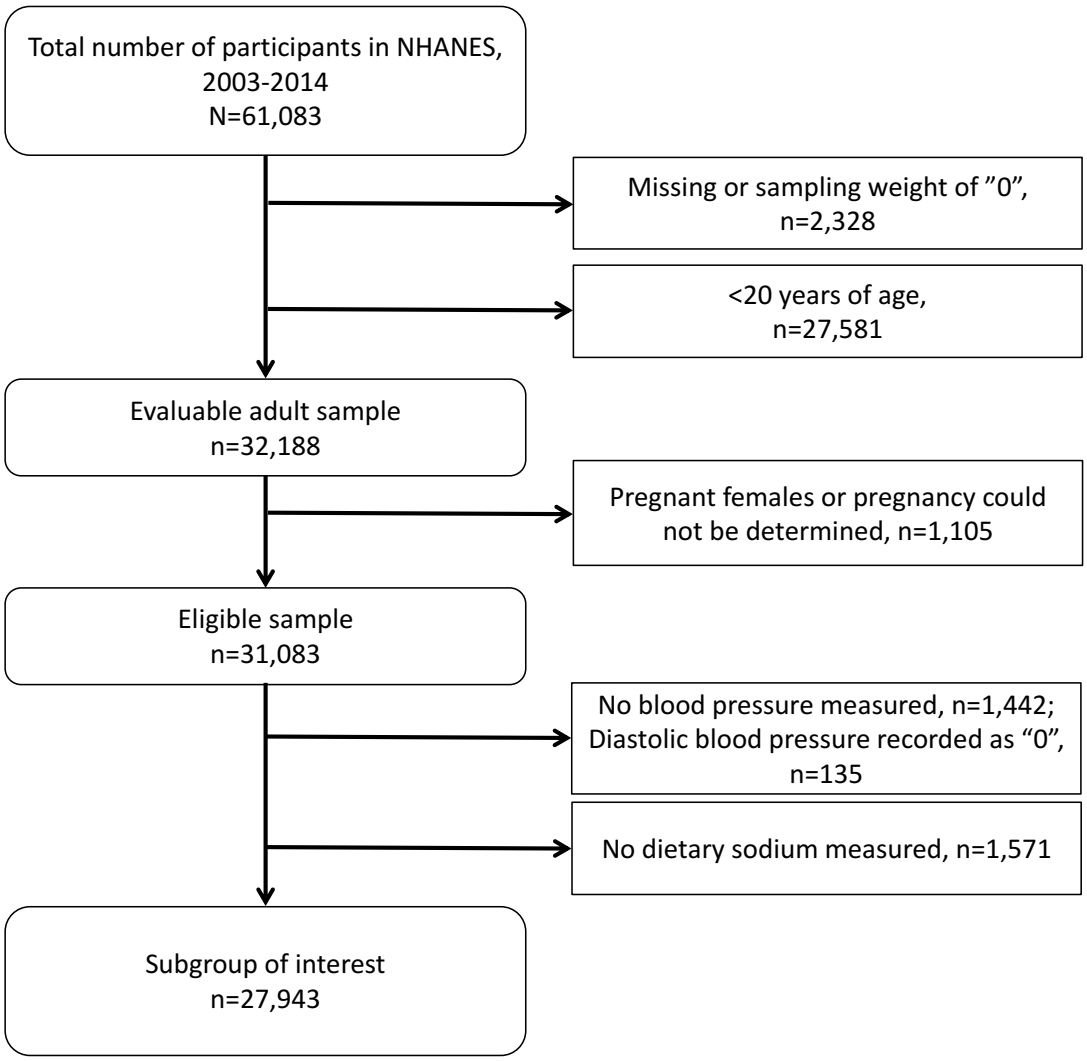

Figure 7. Disposition of participants in NHANES 2003-2014 for inclusion in the study of the relationship between dietary sodium and blood pressure in U.S. nonpregnant adults.

Normality of continuous variables

Normality was absent in each of the continuous variables. Neither log normalization nor Box-Cox transformations successfully normalized the variables. Therefore, transformations were not applied and, as proposed

(Lumley et al., 2002), were not considered a threat to the analysis of this large dataset.

Outliers

The continuous variable with the most extreme outliers was dietary sodium, a main predictor variable. Distribution analysis revealed dietary sodium intakes as low as zero and as high as 21,399 mg (right-skewed) on the day prior to having blood pressure measured. Each 2-year cycle of NHANES used in the analysis was singularly evaluated to determine whether the unusually high dietary sodium intakes might represent a single cycle. The upper 0.5% of dietary sodium for each 2-year cycle was approximately 11,000 mg/day or higher (2003-2004: 10,472 mg/day; 2005-2006: 11,208 mg/day; 2007-2008, 11,150 mg/day; 2009-2010: 10,437 mg/day; 2011-2012: 11,197 mg/day; 2013-2014: 11,551 mg/day) and represented 139 participants. The majority of these were male (87%, n=121), and median age was 36 years. By design, outliers were intended to be retained in the dataset. However, to avoid allowing these outliers to have undue influence on the mean dietary sodium, yet not lose them in the analysis, the dietary sodium variable was Winsorized at 11,000 mg/day (Salkind, 2010).

Missing Data

Survey-weighted chi-square analyses were run for all planned variables against the outcome variable of blood pressure to determine if demographic differences existed between those missing the outcome variable and those who had blood pressure measured. No missing data were observed for age, gender, race or ethnicity, or use of antihypertensive agents. Adults who did not have a blood pressure measurement (n = 1,071) were 1.36 times more likely to have less than a high school education (95% CI, 1.19-1.55; $p < .001$) and 23% less likely to have a college degree or greater (95% CI, 0.65-0.90; $p = .001$) than adults who did have their blood pressure measured. Similarly, adults who did not have a blood pressure measurement were 1.33 times more likely to have an annual income < $20,000 (95% CI, 1.17-1.52; p < .001) and 41% less likely to have an annual income > $75,000 (95% CI, 0.50-0.71; p < .001). No differences in the likelihood for having blood pressure measured were observed for the smoking variable. These findings suggest there was a statistically significant but small difference in the studied population and the overall U.S. nonpregnant adult population.

No variable had 10% or more missing data; therefore, no imputation was required. An estimate of kidney function was missing in 2.6% (n=1,353), education was missing in 0.08% (n=26), income was missing in 1.6% (n=879), BMI was missing in 0.5% (n=279), fasting status preventing assessment of evidence of diabetes was missing in 0.4% (n=264), and an

overall 3.5% (n=1,126) could not be evaluated for evidence of diabetes due to missing glucose or glycosylated hemoglobin variables. Smoking status was missing in 0.1% (n=54).

Other adjustments

The estimation of kidney function from the CKD-Epi equation utilizes the serum creatinine measured on the day of the medical examination. Since the day of medical examination may occur on a day after a dialysis treatment for those who have indicated they receive dialysis treatments, a lower serum creatinine would lead to an eGFR estimation that would be falsely high. Therefore, an eGFR of 10 ml/min/1.73m^2 was assigned for participants who indicated having had dialysis in the previous year.

Post hoc analyses

People who take antihypertensive agents have different characteristics and blood pressure outcomes than people who do not take antihypertensive agents. Whereas the category of taking vs not taking antihypertensive agents was a planned covariate, and known effect modifier, it was decided that displaying the characteristics and performing analytics with these as separate groups would be informative. Therefore, the planned analyses were also performed for these subpopulations and provided in Appendix C. Since too few participants having eGFR < 15 ml/min/1.73m^2 were available after

subgrouping by use of antihypertensive agents, participants having this lowest eGFR were combined with the next level of eGFR into a subgroup labeled eGFR < 30 ml/min/1.73m^2 in the post hoc analyses. All other analytics were identical to the planned analyses.

Research Subproblems

In U.S. nonpregnant adults, as represented by data from NHANES 2003-2014, whose kidney function was estimated and who completed a 24-hour dietary recall on the day prior to blood pressure measurement:

Subproblem 1

What were their key

a. Demographic characteristics (age, sex, race and ethnicity, education level, income status)?
b. Clinical characteristics (albumin-to-creatinine ratio, body mass index, diabetes status, number and type of antihypertensive agents used, kidney disease awareness, kidney function level, smoking status)?

The mean (SE) age of the population was 47.3 (0.2) years and 49.4% (n=14,094) were male (Table 12). Non-Hispanic White was the major race reported (69.9%, n=13,199). A college degree or higher was reported by 27.4% (n=6,018) of the population while 17.3% (n=7,343) reported not completing a high school education. Similarly, 30.4% (n=6,044) reported an annual family income ≥ $75,000 while 19.4% (n=7,063) reported < $20,000 in annual income.

Body mass index was ≥ 25 kg/m^2 in 68.4% (n=19,442) of the U.S. adult population and 13.6% (n=5,001) had evidence of diabetes (Table 11). Evidence of hypertension was present in 35.3% (n=11,373) yet only 26.7% (n=8,786) reported taking antihypertensive agents for blood pressure control. The most common antihypertensive agent classes included diuretics (2.3% of the population, n=720), renin-aldosterone inhibitors, calcium channel blockers, beta blockers or combinations of these agents (12.7% of the population, n=4,086). The albumin-to-creatinine (ACR) ratio, a marker of kidney damage, was elevated at a mean (SE) of 30.4 (1.5) mg/g; however, only 9.2% (n=3,382) had ACR >30 mg/g. The mean (SE) eGFR was 85.1 (0.4) ml/min/1.73m^2 and 16.6% (n=4,839) had eGFR < 60 ml/min/1.73m^2. Only 52.7% (n=14,860) of the population reported never smoking and 20.9% (n=5,585) reported currently smoking.

Table 12.
Demographic and clinical characteristics of U.S. nonpregnant adults in NHANES 2003-2014

Parameter	Result						
	M	*SE*	*Med*	IQR	*n*	Population, %	Group, %
Number of participants					27,943	68.7	
Age (years)	47.3	0.2	47	[33, 60]			
Gender							
Males					14,094	33.9	49.4
Females					13,849	34.8	50.6
Race and ethnicity							
Non-Hispanic White					13,199	48.0	69.9
Non-Hispanic Black					5,862	7.7	11.1
Mexican American					4,525	5.6	8.2
Other race or ethnicity					4,357	7.4	10.8
Education level							
Less than HS diploma					7,343	16.4	17.3
HS or equivalent					6,545	22.3	23.6
Some college					8,011	30.0	31.7
College degree or higher					6,018	26.0	27.4
Income status, annual							
<$20,000					7,063	13.4	19.4
$20,000 to <$45,000					9,041	20.4	29.7
$45,000 to <$75,000					4,916	14.0	20.5
$75,000 or higher					6,044	20.9	30.4
BMI (kg/m^2)	28.6	0.1	27.6	[24.0, 32.0]			
BMI category							
<18.5					433	1.1	1.6
18.5 to <25.0					7,789	21.2	30.0
25 to <30					9,344	23.8	33.5
≥30					10,098	24.7	34.9
Evidence of diabetes					5,001	9.3	13.6
Evidence of hypertension					11,373	27.9	35.3
Sys. blood pressure ≥140 or Dias. ≥90 mmHg					5,508	13.2	16.6

Parameter	Result						
	M	*SE*	*Med*	IQR	*n*	Population, %	Group, %
Awareness of hypertension					10,029	28.0	31.9
Taking antihypertensive agents					8,786	18.3	26.7
Number of antihypertensive agents used	0.5	0.0	0	[0, 1]			
Distribution of antihypertensive agents used							
None					19,157	50.3	73.3
1					4,489	10.0	14.5
2					2,540	5.2	7.5
3 or more					1,757	3.2	4.7
Type of antihypertensive agents							
None					19,157	50.3	73.3
Diuretics alone					720	1.6	2.3
Set A					4,086	8.7	12.7
Set B					3,266	6.5	9.5
Set C					714	1.5	2.2
ACR (mg/g)	30.4	1.5	6.4	[4.2, 11.4]			
ACR category (mg/g)							
<10					18,137	53.1	70.5
10-<30					6,049	15.3	20.3
30-300					2,812	6.0	7.9
>300					570	1.0	1.3
Kidney disease awareness					808	2.0	2.1
Dialysis in previous year					81	0.0	6.7
eGFR[a] (ml/min/1.73m^2)	85.1	0.4	86.1	[66.6, 103.7]			
Kidney function level[a] (ml/min/1.73m^2)							
<15 or dialysis					117	0.2	0.2
15-29					301	0.6	0.7
30-44					1,240	3.0	3.6
45-59					3,181	10.1	12.2
60-74					4,503	16.4	19.8
75-89					4,936	15.6	18.8

Parameter	Result						
	M	*SE*	*Med*	IQR	*n*	Population, %	Group, %
90-105					5,627	18.0	21.6
105 or higher					6,685	19.2	23.1
eGFR[a] <60 ml/min/1.73m^2					4,839	13.8	16.6
Smoking status							
Current smoker					5,585	19.6	20.9
Former smoker					7,444	24.8	26.4
Never smoker					14,860	50.0	52.7

Note. ACR = urinary albumin-to-creatinine ratio; BMI = body mass index; eGFR = estimated glomerular filtration rate; Group % = survey weighted subpopulation proportion; HS = High school; IQR = interquartile range; *Med* = median; NHANES = National Health and Nutrition Examination Survey; Population % = survey weighted population proportion; Set A. = renin-aldosterone inhibitors, calcium channel blockers, beta blockers or any combination of these; Set B. = diuretics plus renin-aldosterone inhibitors, calcium channel blockers, or beta blockers; Set C. = any other antihypertensive agent or any combination of three drugs

[a]Estimated glomerular filtration rate using the CKD-Epi equation (Levey et al., 2009)

A subgroup of participants in this study were prescribed antihypertensive agents and they exhibited differences from participants who were not prescribed antihypertensive agents. The participants who were prescribed antihypertensive agents were approximately 30 years older ($p < .05$) and a higher proportion were female than male ($p < .05$; Appendix C, Table C1). A higher proportion of participants who were prescribed antihypertensive agents were non-Hispanic White and non-Hispanic Black, had a high school or less education, had an annual family income < $45,000, and had evidence of diabetes (all $p < .05$) than those who were not prescribed antihypertensive agents. Additionally, participants who were prescribed antihypertensive agents had an average eGFR that was 20 ml/min/1.73m^2 lower than participants who were not prescribed antihypertensive agents ($p < .05$).

Subproblem 2

What was their dietary sodium intake and systolic and diastolic blood pressure?

The mean (SE) dietary sodium for the population was 3,526 (16) mg/day or 8.8 (0.1) grams of salt/day (Figure 8 and Appendix Table D1). Only 25.5% (n=7,984) met the Dietary Guidelines of <2,300 mg sodium per day (Appendix Table D1). Dietary sodium was statistically significantly and positively correlated with dietary energy intake (r = .778, a large effect size; B=1.412 (0.02), 95%CI: 1.37, 1.44; $p < .001$). A display of dietary intake (kilocalories/day, dietary sodium density in mg/1,000 kcal/day, and dietary sodium in mg/day, in mEq/day, and as grams of salt (NaCl) per day) is shown in Figure 8.

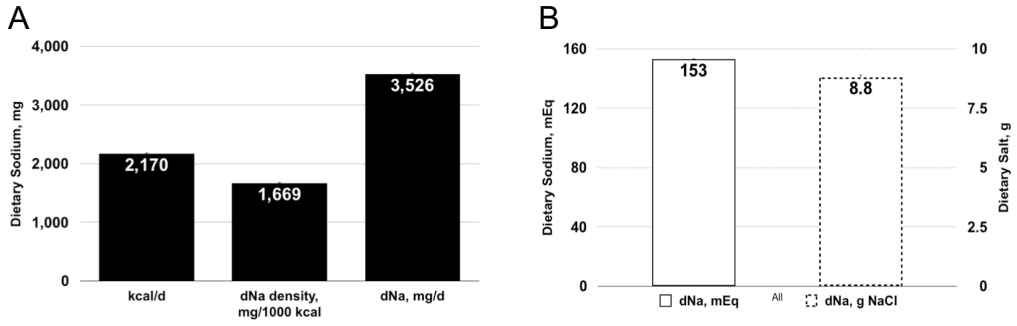

Figure 8. Dietary energy and sodium of U.S. non-pregnant adults in NHANES 2003-2014.
A, dietary energy in kcal/day, dietary sodium (dNa) density in mg/1,000 kcal/day, dietary sodium in mg/day; B, dietary sodium in mEq/day and as grams of salt (NaCl); NHANES = National Health and Nutrition Examination Survey

The dietary sodium intake of participants according to their kidney function is provided in Appendix E. Briefly, the highest group mean of dietary sodium was reported by participants with kidney function in the 45-59 and 60-74 ml/min/1.73m^2 groups: 3,647 (54) and 3,779 (39) mg/day, respectively. However, as kidney function further decreased, the dietary sodium also decreased: 2,638 (137) mg/day for participants with kidney function <15 ml/min/1.73m^2 or having dialysis.

In participants who were not prescribed antihypertensive agents, the median dietary sodium peaked at 3,734 mg/day (IQR = 2,713 to 4,905) in adults whose kidney function level was 45-59 ml/min/1.73m^2. However, for those who were prescribed antihypertensive agents, the kidney function level group with the highest dietary sodium intake was 90-105 ml/min/1.73m^2 at a median dietary sodium of 3,030 mg/day (IQR, 2,066 to 4,242) Appendix E, Tables E1 to E3).

The mean (SE) systolic blood pressure was 122.4 (0.2) mmHg and diastolic blood pressure was 70.9 (0.2) mmHg (Figure 9 and Appendix Table D1). A blood pressure <120 mmHg systolic and <80mmHg diastolic (considered to be normal blood pressure) was observed in 46.6% (n=12,180) of the population while 11.9% (n=4,203) had a blood pressure ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic (considered to be hypertension).

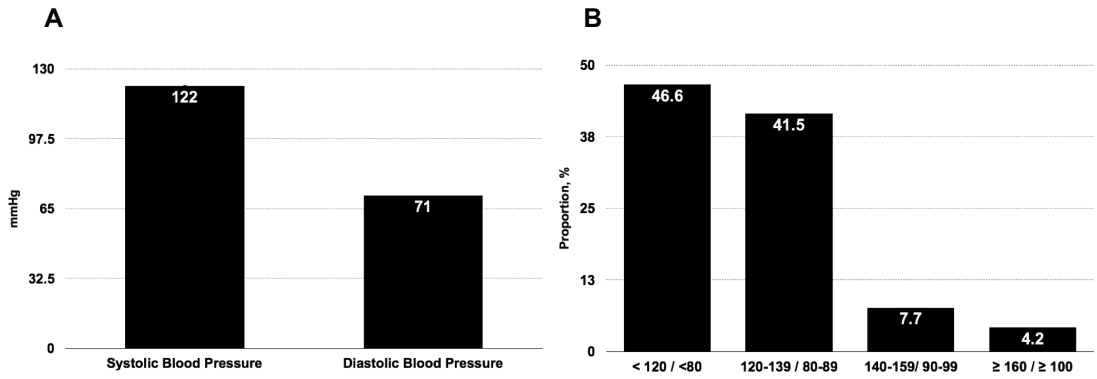

Figure 9. Mean systolic and diastolic blood pressure (A) and proportion of U.S. adults having <120 / <90 mmHg, n=12,180; 120-139 / 80-89 mmHg, n=11,560; 140-159 / 90-99 mmHg, n=2,616; or ≥ 160 / ≥ 100 mmHg, n=1,587 in U.S. non-pregnant adults in NHANES 2003-2014. NHANES = National Health and Nutrition Examination Survey

Blood pressure depicted by whether or not participants were prescribed antihypertensive agents (Appendix C) demonstrated that a blood pressure in the normal range was observed in only 28.0% (n=2,243) of those who were prescribed antihypertensive agents for high blood pressure and in only 53% (n= 9,937) of participants not having antihypertensive agents prescribed for high blood pressure (Appendix C Figure 1 and Appendix Table C2). Stated differently, 72% of participants prescribed antihypertensive agents had a blood pressure >120/80 mmHg and 47% of participants who were not prescribed antihypertensive agents had a blood pressure >120/80 mmHg.

Subproblem 3

What was the relationship between dietary sodium intake and key

a. demographic and

b. clinical characteristics?

As age increased, a statistically significant but small decrease in dietary sodium occurred (Table 13). Other demographic and clinical characteristics with a statistically significant negative relationship to total dietary sodium exposure were non-Hispanic Black race vs non-Hispanic White race, having less than some college education vs a college education or higher, having less than an annual income of $75,000 vs more than $75,000, having a BMI less than 18.5 kg/m^2 vs a normal BMI (18.5 to <25 kg/m^2), having prescribed antihypertensive agents vs no antihypertensive agents, being aware of having high blood pressure, and having kidney function less than 45 ml/min/1.73m^2 vs having kidney function >105 ml/min/1.73m^2. The greatest decrease in dietary sodium compared to the referent group was observed in participants with eGFR < 30 ml/min/1.73m^2 (-847 and -778 mg/day for < 15 ml/min/1.73m^2 and 15-29 ml/min/1.73m^2, respectively vs >105 ml/min/1.73m^2; r = .098, a small effect size; p < .001). The next greatest decrease in dietary sodium was observed in participants taking a diuretic alone vs no antihypertensive agents (-664 mg/day; r = .099, a small effect size; p < .001).

Male participants consumed almost 1,200 mg/day more dietary sodium than females (r = 0.338, a medium effect size; $p < .001$; Table 12). Participants with 120-139 mmHg systolic or 80-89 mmHg diastolic blood pressure consumed a mean (SE) of 139 (28) mg/day more dietary sodium than participants with normal blood pressure (<120 mmHg systolic and <80 mmHg diastolic; r = .086, a small effect size; $p < .001$). Participants whose eGFR was 45 – 74 ml/min/1.73m^2 reported significantly more dietary sodium than participants with eGFR > 105 ml/min/1.73m^2 (r = .098, a small effect size; $p < .001$). Smoking was also associated with a higher dietary sodium: former smokers consumed 80 mg/day more and current smokers consumed 109 mg/day more dietary sodium than never smokers (r = .027, a small effect size; $p < .05$).

With the exception of male gender (r = .338), all effect sizes were small ($r \approx 0.1$) for the relationship of demographic and clinical characteristics to dietary sodium intake.

Hypothesis 1a. The mean dietary sodium intake of U.S. nonpregnant adults is lower in people taking antihypertensive agents than in people not taking antihypertensive agents.

In participants who were not prescribed antihypertensive agents (Appendix C, Table C3), the variables with highest effect sizes for correlation with dietary sodium were gender, age, and kidney function (r = .345, .140, and .113, respectively; all $p < .001$). The correlations were similar for those

who were prescribed antihypertensive agents (r = .316, .222, and .086 for gender, age, and kidney function, respectively; all $p < .001$) but BMI was also important (r = .106, $p < .001$). Participants who were not prescribed antihypertensive agents who were categorized as overweight or obese consumed 292 and 475 mg/day, respectively, more dietary sodium than those with a normal BMI ($p < .001$). Except for gender with a medium effect size ($r \approx .3$), all effect sizes were small ($r \approx 0.1$) in both groups (prescribed or not prescribed antihypertensive agents).

Participants taking antihypertensive agents consumed 3,253 mg sodium (8.1 g NaCl) compared to 3,624 mg sodium (9.1 g NaCl) in participants not taking antihypertensive agents (Appendix Table C2); mean (SE) difference: -372 (29) mg sodium, [95% CI -429, -314], $p < .001$.

Hypothesis 1b. The mean dietary sodium intake of U.S. nonpregnant adults is lower in people with reduced kidney function than in U.S. nonpregnant adults with normal kidney function.

Participants with eGFR < 60 ml/min/1.73m^2 consumed 3,470 mg sodium (8.7 g NaCl) compared to 3,550 mg sodium (8.9 g NaCl) in participants with eGFR ≥ 60 ml/min/1.73m^2 (Table 13 and Appendix Table E1); mean (SE) difference: -80 mg (44), [95% CI -167, 7], p = .070. The comparison changed, however, if consideration was made for use of antihypertensive agents. Participants who were not using antihypertensive agents reported a higher dietary sodium if eGFR < 60 ml/min/1.73m^2 (3,844

mg sodium or 9.6 g NaCl) compared to participants with eGFR ≥ 60 ml/min/1.73m^2 (3,612 mg sodium or 9.0 g NaCl); mean (SE) difference: 232 (70) mg sodium, [95% CI 94, 370], p = .001. In contrast, those who reported using antihypertensive agents reported a lower dietary sodium if eGFR < 60 ml/min/1.73m^2 (3,175 mg sodium or 7.9 g NaCl) compared to participants with eGFR ≥ 60 ml/min/1.73m^2 (3,315 mg sodium or 8.3 g NaCl); mean (SE) difference: -140 (55) mg sodium, [95% CI - 249, - 31], p = .012.

The key demographic and clinical characteristics were also evaluated for relationship with dietary sodium density (Appendix F). All of the variables had effect size < .1 when correlated to dietary sodium density. Eight variables with statistical significance when dietary sodium was evaluated as mg/day were no longer statistically significant when dietary sodium was evaluated as dietary sodium density: gender, income between $45,000 to < $75,000, taking a diuretic alone, the continuous variable of eGFR, the eGFR categories 30 to 44, 45 to 59, 60 to 74 ml/min/1.73m^2, and being a former smoker. Only three variables without statistical significance with dietary sodium in mg/day became statistically significant when correlated with dietary sodium density: Mexican American ethnicity, other race or ethnicity, and having some college education.

Table 13.
The relationship between key demographic and clinical characteristics and dietary sodium in mg/day intake in U.S. nonpregnant adults in NHANES 2003-2014

Variable	n	*r*	*B*	*SE*	95% CI	*p*-value
Age, years	27,943	.184	-19.25	0.8	[-20.83, -17.67]	<.001
Gender, males vs females referent	14,094	.338	1199.19	25.84	[1147.87, 1250.50]	<.001
Race, ethnicity; Non-Hispanic White referent	13,199	.035				<.001
Non-Hispanic black	5,862		-198.07	41.63	[-280.73, -115.42]	<.001
Mexican American	4,525		-31.15	47.06	[-124.58, 62.29]	.510
Other	4,357		-40.57	38.25	[-116.51, 35.37]	.292
Education, College degree or higher referent	6,018	.072				<.001
Less than HS	7,343		-376.63	44.00	[-463.90, -289.35]	<.001
HS or equivalent	6,545		-137.92	43.03	[-223.36, -52.48]	.002
Some college or AA	8,011		-74.80	39.90	[-154.03, 4.42]	.064
Income, $75,000/year or higher referent	6,044	.090				
<$20,000	7,063		-374.00	48.39	[-470.08, -277.91]	<.001
$20,000 to <$45,000	9,041		-342.08	40.98	[-423.45, -260.71]	<.001
$45,000 to <$75,000	4,916		-122.18	44.52	[-210.57, -33.79]	.007
ACR (mg/g)	27,568	.022	-0.16	0.04	[-0.25, -0.08]	<.001
BMI (kg/m^2)	27,664	.030	8.11	2.10	[3.94, 12.27]	<.001
BMI category, 18.5-24.9 kg/m^2 referent	7,789	.028				<.001
<18.5	433		-227.92	106.53	[-439.45, -16.39]	.035
25.0 to <30.0	9,344		56.82	42.39	[-27.34, 140.98]	.183
≥30.0	10,098		88.81	41.60	[6.22, 171.41]	.035
Diabetes status, No evidence referent	21,816	.050				<.001
Yes	5,001		-226.85	40.59	[-307.44, -146.25]	<.001
High blood pressure awareness	10,029	.065	-245.13	32.31	[-309.28, -180.98]	<.001
Taking antihypertensive agents, None referent	8,786	.009	-371.75	29.04	[-429.41, -314.08]	<.001

Variable	n	*r*	*B*	*SE*	95% CI	*p*-value
Number of antihypertensive agents used, None referent	19,157	.097				<.001
1	4,489		-499.95	54.57	[-608.30, -391.61]	<.001
2	2,540		-467.15	49.37	[-565.18, -369.13]	<.001
3 or more	1,757		-281.26	40.78	[-362.23, -200.28]	<.001
Type of antihypertensive agent used, None referent	19,157	.099				<.001
Diuretics alone	720		-663.30	71.80	[-805.87, -520.73]	<.001
Set A	4,086		-321.76	46.07	[-413.23, -230.29]	<.001
Set B	3,266		-418.05	41.98	[-501.41, -334.68]	<.001
Set C	714		-150.75	100.89	[-351.07, 49.57]	.139
Blood pressure category, 120/80 mmHg referent	12,180	.086				<.001
120-139 mmHg sys. or 80-89 mmHg dias.	11,560		139.14	27.94	[83.66, 194.61]	<.001
140-159 mmHg sys. or 90-99 mmHg dias.	2,616		-326.32	45.40	[-416.46, -236.18]	<.001
≥ 160 mmHg sys. or ≥ 100 mmHg dias.	1,587		-411.27	60.47	[-531.33, -291.22]	<.001
eGFR (ml/min/1.73m^2)	26,590	.012	-0.84	0.56	[-1.95, 0.27]	.007
Kidney disease awareness	808	.047	-571.46	88.50	[-747.18, -395.74]	<.001
Kidney function level, >105ml/min/1.73m^2 referent	6,685	.098				<.001
<15 or dialysis	117		-846.99	135.38	[-1115.79, -578.19]	<.001
15 to 29	301		-778.38	82.64	[-942.46, -614.31]	<.001
30 to 44	1,240		-417.77	71.08	[-558.89, -276.65]	<.001
45 to 59	3,181		163.27	58.15	[47.82, 278.72]	.006
60 to 74	4,503		293.79	48.26	[197.97, 389.61]	<.001
75 to 89	4,936		-46.51	46.56	[-138.97, 45.94]	.320
90 to 105	5,627		21.56	41.92	[-61.68, 104.80]	.608

Variable	n	*r*	*B*	*SE*	95% CI	*p*-value
Evidence of CKD	4,839	.017	-80.13	43.72	[-166.94, 6.68]	.070
Smoking status, Never smoker referent	14,860	.027				<.001
Former smoker	7,444		79.79	36.81	[6.69, 152.88]	.033
Current smoker	5,585		108.75	46.85	[15.73, 201.77]	.022

Note. AA = Associate of Arts degree; ACR = albumin-to-creatinine ratio; *B* = parameter estimate; BMI = body mass index; CI = confidence interval; dias. = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HS = high school; NHANES = National Health and Nutrition Examination Survey; *r* = correlation coefficient; *SE* = standard error of the mean; Set A. = renin-aldosterone inhibitors, calcium channel blockers, beta blockers or any combination of these; Set B. = diuretics plus renin-aldosterone inhibitors, calcium channel blockers, or beta blockers; Set C. = any other antihypertensive agent or any combination of three drugs; sys. = systolic blood pressure. Student's t-test or One-way Analysis of Variance, as appropriate
[a]Estimated glomerular filtration rate using the CKD-Epi equation (Levey et al., 2009)

Hypothesis 1c. The mean dietary sodium intake of U.S. nonpregnant adults with normal kidney function is higher than 3,440 mg/day.

A normal eGFR (considered to be ≥ 90ml/min/1.73m^2) was observed in 37.2% (n=12,312) of the study population. The mean (SE) difference from 3,440 mg dietary sodium was 56 (22) mg/day or 0.14 g NaCl/day (t=2.57, 95% CI= [12.77, 98.97], *p* <.001) using a one-sample t-test. The difference was higher in participants who reported not taking antihypertensive agents: 76 (21) mg/day compared to those who reported taking antihypertensive agents (-166 (60) mg/day; p < .001).

To further elucidate the relationships of demographic and clinical characteristics to dietary sodium intake, data were analyzed to depict the odds of exceeding the Dietary Guidelines (< 2,300 mg/day) for sodium. As reported in subproblem 2 (Appendix Table D1), only 27.2% met the guideline for dietary sodium < 2,300 mg/day. Age was associated with a slightly higher odds for exceeding the dietary sodium guidelines (OR, 1.017; [95% CI, 1.015, 1.019]; *p* < .001; Table 14) while males had almost three-fold higher odds for exceeding the dietary sodium guidelines than females (OR = 2.99; [95% CI, 2.77, 3.22] *p* < .001). Participants with eGFR 60-74 ml/min/1.73m^2 had increased odds of exceeding the dietary sodium guideline over that of participants with eGFR > 105 ml/min/1.73m^2 (OR = 1.24; [95% CI, 1.12, 1.38] *p* < .001) and participants having an annual income of $45,000 to < $75,000

had higher odds for exceeding the guideline than those whose income was ≥ $75,000 (OR = 1.17; [95% CI, 1.05, 1.30] $p < .001$).

In contrast, non-Hispanic Black participants were 23% less likely to exceed the dietary sodium guidelines than non-Hispanic Whites (OR = 0.77; [95% CI, 0.70, 0.85] $p < .001$). Participants with less than a high school education were 37% less likely to exceed the dietary sodium guideline than those with a college degree or higher (OR = 0.63; [95% CI, 0.58, 0.68] $p < .001$) and those making < $45,000 annual income were also statistically significantly less likely to exceed the dietary guidelines than those making ≥ $75,000.

Participants who were prescribed antihypertensive agents were less likely to exceed the dietary sodium guideline than those not prescribed antihypertensive agents (Table 14 and Appendix C, Table C4). Similarly, participants at the lower levels of kidney function (eGFR < 45 ml/min/1.73m^2) were less likely to exceed the dietary guideline for sodium. No statistically significant differences were observed for smoking status and the odds of exceeding the dietary sodium guidelines.

Table 14.
The relationship between key demographic and clinical characteristics and dietary sodium < 2,300 or ≥ 2,300 mg/day in U.S. nonpregnant adults in NHANES 2003-2014; odds for exceeding the U.S. dietary guideline of < 2,300 mg sodium/day

Variable	n	*OR*	95% CI	*p*-value
Age, years	27,943	1.017	[1.015, 1.019]	<.001
Gender				
Males	14,094	2.99	[2.77, 3.22]	<.001
Females referent	13,849	1.00		
Race or ethnicity				
Non-Hispanic Black	5,862	0.77	[0.70, 0.85]	<.001
Mexican American	4,525	0.93	[0.84, 1.05]	.233
Other Latin or Other races	4,357	0.97	[0.86, 1.07]	.604
Non-Hispanic White referent	13,199	1.00		
Education				
Less than HS	7,343	0.63	[0.58, 0.68]	<.001
HS or equivalent	6,545	1.05	[0.77, 1.42]	.781
Some college	8,011	1.11	[1.03, 1.21]	.008
College degree or higher referent	6,018	1.00		
Income				
<$20,000	7,063	0.65	[0.60, 0.72]	<.001
$20,000 to <$45,000	9,041	0.90	[0.82, 0.98]	.020
$45,000 to <$75,000	4,916	1.17	[1.05, 1.30]	.005
≥ $75,000 referent	6,044	1.00		
BMI (kg/m^2)	27,664	0.99	[0.98, 1.00]	<.001
BMI category (kg/m^2)				
<18.5	433	0.65	[0.48, 0.87]	.005
18.5 to < 25.0 referent	7,789	1.00		
25.0 to < 30	9,344	1.07	[0.98, 1.16]	.146
≥ 30	10,098	1.08	[0.99, 1.17]	.072
Evidence of diabetes	5,001	0.82	[0.74, 0.91]	<.001
Awareness of hypertension	10,029	0.75	[0.69, 0.82]	<.001
Taking antihypertensive agents	8,786	0.68	[0.63, 0.75]	<.001
Number of antihypertensive agents used	27,943			
None referent	19,157	1.00		
1	4,489	0.77	[0.70, 0.86]	<.001

Variable	n	*OR*	95% CI	*p*-value
2	2,540	0.73	[0.64, 0.83]	<.001
3 or more	1,757	0.65	[0.56, 0.76]	<.001
Type of antihypertensive agent used				
None, referent	19,157	1.00		
Diuretics alone	720	0.57	[0.45, 0.71]	<.001
Set A	4,086	0.76	[0.68, 0.86]	<.001
Set B	3,266	0.69	[0.63, 0.76]	<.001
Set C	714	1.11	[0.87, 1.42]	.387
ACR (mg/g)	27,568	1.00	[1.00, 1.00]	.011
Kidney disease awareness	808	0.58	[0.46, 0.73]	<.001
Kidney function level[a]				
<15 or dialysis	117	0.36	[0.22, 0.61]	<.001
15 to 29	301	0.46	[0.36, 0.58]	<.001
30 to 44	1,240	0.62	[0.53, 0.73]	<.001
45 to 59	3,181	1.12	[0.99, 1.27]	.069
60 to 74	4,503	1.24	[1.12, 1.38]	<.001
75 to 89	4,936	0.94	[0.86, 1.03]	.163
90 to 105	5,627	1.00	[0.90, 1.11]	.960
≥ 105, referent	6,685	1.00		
Evidence of CKD	4,839	0.90	[0.82, 0.98]	.019
Smoking status				
Never smoker referent	14,860	1.00		
Former smoker	7,444	1.06	[0.98, 1.14]	.148
Current smoker	5,585	0.98	[0.87, 1.10]	.694

Note. ACR = urinary albumin-to-creatinine ratio; BMI = body mass index; CI = confidence interval; eGFR = estimated glomerular filtration rate; HS = High school; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; Set A. = renin-aldosterone inhibitors, calcium channel blockers, beta blockers or any combination of these; Set B. = diuretics plus renin-aldosterone inhibitors, calcium channel blockers, or beta blockers; Set C. = any other antihypertensive agent or any combination of three drugs. Chi-square, Loglinear Chi-square, as appropriate

[a]Estimated glomerular filtration rate using the CKD-Epi equation (Levey et al., 2009)

Subproblem 4

What was the relationship between systolic and diastolic blood pressure and key

a. demographic and
b. clinical characteristics?

A statistically significant correlation with systolic blood pressure was observed for every variable examined except for current smokers vs never smokers (p = .438; Table 15). Compared to the referent group for each category, a lower systolic blood pressure was observed only in participants with a BMI < 18.5 kg/m^2 vs a normal BMI and being Mexican American or of other race or ethnicity vs non-Hispanic White. An overall negative association of eGFR was observed with systolic blood pressure (r = .260, a medium effect size; b = - 0.19, p < .001). The systolic blood pressure increased incrementally with each kidney function level decrease: a 6 mmHg increase in systolic blood pressure for participants with eGFR 90-105 ml/min/1.73m^2 compared to having eGFR >105 ml/min/1.73m^2 and a 21 mmHg increase in systolic blood pressure in those having eGFR 15-29 ml/min/1.73m^2. The variable with the strongest correlation with systolic blood pressure was age (r = .419, a medium effect size; b = 0.44, p < .001. This positive correlation corresponds to a 1 mmHg increase in systolic blood pressure for every 2.3 years increase in age, Table 15).

When evaluating the correlation of variables to systolic blood pressure according to participants who were not prescribed or were prescribed antihypertensive agents, the variables with strongest correlations differed. For participants not prescribed antihypertensive agents, the five variables with strongest positive correlation to systolic blood pressure were, in order: age (r = .375, a medium effect size; b = 0.40, $p < .001$), awareness of high blood pressure (r = .285, a medium effect size; b = 13.47, $p < .001$), BMI (r = .177, a small effect size; b = 0.44, $p < .001$), and gender (males, r = .168, a small effect size; b = 5.27, $p < .001$). A negative correlation was observed for eGFR (r = .230, a small to medium effect size; b = -0.16, $p < .001$). However, the systolic blood pressure increased exponentially for each kidney function group level decrease (Appendix Table C5).

For participants who were prescribed antihypertensive agents, the top five variables for a positive correlation with systolic blood pressure were: age (r = .247, a medium effect size; b = 0.38, $p < .001$), ACR (r = .167, a small effect size; b = 0.01, $p < .001$), awareness of high blood pressure (r = .139, a small effect size; b = 7.74, $p < .001$), education (r = .124, a small effect size; $p < .001$), and income (r = .121, a small effect size; $p < .001$). The relationship of kidney function level groups to systolic blood pressure in participants who were prescribed antihypertensive agents varied in direction (e.g., the direction was negative for participants with kidney function level group 45-59 ml/min/1.73m^2 and 90-105 ml/min/1.73m^2 compared to >105 ml/min/1.73m^2

and the direction was positive for the other kidney function level groups but the systolic blood pressure change was <1 mmHg until kidney function level decreased to <45 ml/min/1.73m^2; Appendix C, Table C5).

Table 15.
The relationship between key demographic and clinical characteristics and systolic blood pressure in U.S. nonpregnant adults in NHANES 2003-2014

Variable	n	*r*	*B*	*SE*	95% CI	*p*-value
Age, years	27,943	.419	0.44	0.01	[0.42, 0.45]	<.001
Gender, females referent	13,849					
Males	14,094	.080	2.82	0.23	[2.37, 3.26]	<.001
Race, ethnicity; Non-Hispanic white referent	13,199	.081				<.001
Non-Hispanic black	5,862		3.49	0.51	[2.47, 4.50]	<.001
Mexican American	4,525		-2.11	0.51	[-3.11, -1.11]	<.001
Other	4,357		-1.72	0.41	[-2.54, -0.91]	<.001
Education, College degree or higher referent	6,018	.122				<.001
Less than HS	7,343		5.97	0.47	[5.04, 6.90]	<.001
HS or equivalent	6,545		4.43	0.45	[3.54, 5.33]	<.001
Some college	8,011		2.40	0.37	[1.66, 3.14]	<.001
Income, ≥ $75,000 referent	6,044	.087				<.001
<$20,000	7,063		3.81	0.45	[2.91, 4.71]	<.001
$20,000 to <$45,000	9,041		3.28	0.36	[2.57, 3.99]	<.001
$45,000 to <$75,000	4,916		2.28	0.44	[1.40, 3.16]	<.001
ACR (mg/g)	27,568	.145	0.01	0.00	[0.009, 0.013]	<.001
BMI (kg/m^2)	27,664	.153	0.41	0.02	[0.36, 0.45]	<.001
BMI category, 18.5-24.9 kg/m^2 referent	7,789	.154				<.001
<18.5	433		-3.72	1.25	[-6.22, -1.23]	.004
25.0 to <30.0	9,344		3.91	0.36	[5.65, 6.96]	<.001
≥30.0	10,098		6.31	0.33	[3.20, 4.62]	<.001
Evidence of diabetes, No evidence referent	21,816	.180				<.001
Yes	5,001		9.06	0.45	[8.17, 9.96]	<.001
High blood pressure awareness	10,029	.356	13.42	0.36	[12.70, 14.15]	<.001

Variable	n	*r*	*B*	*SE*	95% CI	*p*-value
Taking antihypertensive agents, No agents referent	8,786	.279	-11.07	0.37	[-11.80. -10.34]	<.001
Number of antihypertensive agents used, No agents referent	19,157	.280				<.001
1	4,489		10.11	0.38	[9.35, 10.86]	<.001
2	2,540		11.74	0.64	[10.48, 13.00]	<.001
3 or more	1,757		12.98	0.88	[11.23, 14.73]	<.001
Type of antihypertensive agent used, No agents referent	19,157	.280				<.001
Diuretics alone	720		8.65	0.90	[6.87, 10.43]	<.001
Set A	4,086		11.56	0.49	[10.59, 12.53]	<.001
Set B	3,266		11.15	0.55	[10.05, 12.24]	<.001
Set C	714		10.44	1.27	[7.91, 12.97]	<.001
eGFR[a] (ml/min/1.73m^2)	26,590	.260	-0.19	0.01	[-0.20, -0.18]	<.001
Kidney disease awareness	808	.040	4.83	1.05	[2.74, 6.92]	<.001
Kidney function level[a], >105ml/min/1.73m^2 referent	6,685	.260				<.001
<15 or dialysis	117		19.70	3.26	[13.22, 26.18]	<.001
15 to 29	301		21.30	2.08	[17.17, 25.44]	<.001
30 to 44	1,240		16.28	0.71	[14.87, 17.69]	<.001
45 to 59	3,181		12.28	0.46	[11.36, 13.19]	<.001
60 to 74	4,503		8.60	0.42	[7.76, 9.43]	<.001
75 to 89	4,936		8.42	0.41	[7.61, 9.24]	<.001
90 to 105	5,627		6.08	0.43	[5.23, 6.93]	<.001
eGFR[a] <60 ml/min/1.73m^2	4,839	.173	8.10	0.38	[7.34, 8.85]	<.001
Smoking status, Never smoker referent	14,860	.088				<.001
Current smoker	5,585		-0.35	0.45	[-1.25, 0.54]	.438
Former smoker	7,444		3.41	0.36	[2.71, 4.12]	<.001

Note. ACR = urinary albumin-to-creatinine ratio; *B* = parameter estimate; BMI = body mass index; CI = confidence interval; eGFR = estimated glomerular filtration rate; HS = high school; NHANES = National Health and Nutrition Examination Survey;

SE = standard error of the mean; *r* = correlation coefficient; Set A. = renin-aldosterone inhibitors, calcium channel blockers, beta blockers or any combination of these; Set B. = diuretics plus renin-aldosterone inhibitors, calcium channel blockers, or beta blockers; Set C. = any other antihypertensive agent or any combination of three drugs. Student's t-test or One-way Analysis of Variance, as appropriate

[a]Estimated glomerular filtration rate using the CKD-Epi equation (Levey et al., 2009)

Variables with the strongest correlation to diastolic blood pressure were, in order, kidney function level (r = .162, a small effect size; $p < .001$), BMI category (r = 0.136, a small effect size; $p < .001$), BMI as a continuous variable (r = .131, a small effect size; $p < .001$) and gender (males vs females, r = .107, a small effect size; $p < .001$; Table 16). For the kidney function level variable, having kidney function < 45 ml/min/1.73m^2 had a negative relationship to diastolic blood pressure, while eGFR 45 – 105 ml/min/1.73m^2 had a significantly positive relationship to diastolic blood pressure vs participants with highest eGFR (>105 ml/min/1.73m^2); all correlations were >1 mmHg change in diastolic blood pressure. For the BMI categories variable, those with BMI ≥ 25 kg/m^2 had statistically significantly higher diastolic blood pressure than those whose BMI was normal (18.5 to < 25 kg/m^2). Males had a mean (SE) 2.5 (0.2) mmHg higher diastolic blood pressure than females (r = .107, a small effect size; b = 2.53, $p < .001$).

For participants who were not prescribed antihypertensive agents, the five variables with strongest correlation to systolic blood pressure were: awareness of high blood pressure (r = .180, a small effect size; b = 6.02, $p <.001$), BMI (r = .179, a small effect size; b = 0.32, $p < .001$) , eGFR (r = .153, a small effect size; b = -0.07, $p < .001$), age (r = .146, a small effect size; b = 0.11, $p < .001$), and gender (males, r = .125, a small effect size; b = 2.77, $p < .001$; Appendix Table C6).

The most strongly positively correlated variables with diastolic blood pressure for participants who were prescribed antihypertensive agents were: eGFR (r = .218, a small effect size; b = 0.13, $p < .001$), income (r = .119, a small effect size; $p < .001$), having evidence of diabetes (r = .108, a small effect size; $p < .001$), and race/ethnicity (r = .092, a small effect size; $p < .001$; whereas age was negatively correlated (r = .371, a medium effect size; b = -0.38, $p < .001$), Appendix Table C6).

Table 16.
The relationship between key demographic and clinical characteristics and diastolic blood pressure in U.S. nonpregnant adults in NHANES 2003-2014

Variable	n	*r*	*B*	*SE*	95% CI	*p*-value
Age, years	27,943	.021	-0.01	0.01	[-0.027, -0.002]	.020
Gender, females referent	13,849					
Males	14,094	.107	2.53	0.18	[2.18, 2.88]	<.001
Race, ethnicity; Non-Hispanic White referent	13,199	.042				<.001
Non-Hispanic Black	5,862		1.32	0.31	[0.70, 1.95	<.001
Mexican American	4,525		-0.79	0.36	[-1.51, -0.08]	.030
Other	4,357		-0.22	0.35	[-0.91, 0.47]	.526
Education, College degree or higher referent	6,018	.045				<.001
Less than HS	7,343		-1.36	0.27	[-1.90, -0.86]	<.001
HS or equivalent	6,545		-0.06	0.32	[-0.70, 0.58]	. 853
Some college	8,011		0.10	0.24	[-0.38, 0.57]	. 687
Income, ≥ $75,000 referent	6,044	.082				<.001
<$20,000	7,063		-2.30	0.30	[-2.85, -1.67]	<.001
$20,000 to <$45,000	9,041		-2.11	0.27	[-2.66, -1.57]	<.001
$45,000 to <$75,000	4,916		-0.87	0.33	[-1.53, -0.21]	.010
ACR, mg/g	27,568	.023	0.001	0.001	[0.000, 0.002]	.017
BMI, kg/m^2	27,664	.131	0.23	0.01	[0.20, 0.26]	<.001
BMI category, 18.5-24.9 kg/m^2 referent	7,789	.136				<.001
<18.5	433		-0.48	0.63	[-1.74, 0.77]	.448
25.0 to <30.0	9,344		2.32	0.21	[1.91, 2.73]	<.001
≥30.0	10,098		3.89	0.22	[3.44, 4.34]	<.001
Diabetes status, No evidence referent	21,816	.033				.001
Yes	5,001		-1.10	0.34	[-1.77, -0.42]	.002
High blood pressure awareness	10,029	.080	2.02	0.24	[1.54, 2.50]	<.001

Variable	n	*r*	*B*	*SE*	95% CI	*p*-value
Taking antihypertensive agents, No agents referent	8,786	.042	1.12	0.23	[0.66, 1.59]	<.001
Number of antihypertensive agents used	19,157	.102				<.001
1	4,489		0.66	0.27	[-6.02, -3.86]	.015
2	2,540		-2.13	0.41	[-2.96, -1.32]	<.001
3 or more	1,757		-4.94	0.54	[-6.02, -3.86]	<.001
Type of antihypertensive agent used, No agents referent	19,157	.070				<.001
Diuretics alone	720		0.74	0.56	[-0.38, 1.86]	.191
Set A	4,086		-0.17	0.31	[-0.78, 0.44]	.577
Set B	3,266		-2.70	0.31	[-3.31 -2.07]	<.001
Set C	714		-1.68	0.76	[-3.19, -0.17]	.030
eGFR[a], ml/min/1.73m^2	26,590	.020	-0.010	0.004	[-0.017, -0.002]	.011
Kidney disease awareness	808	.035	-2.87	0.59	[-4.03, -1.70]	<.001
Kidney function level[a], >105ml/min/1.73m^2 referent	6,685	.162				<.001
<15 or dialysis	117		-1.89	1.79	[-5.44, 1.66]	.293
15 to 29	301		-8.04	0.98	[-9.98, -6.09]	<.001
30 to 44	1,240		-2.98	0.50	[-3.98, -1.98]	<.001
45 to 59	3,181		2.23	0.35	[1.54, 2.92]	<.001
60 to 74	4,503		3.74	0.29	[3.17, 4.31]	<.001
75 to 89	4,936		2.12	0.28	[1.57, 2.67]	<.001
90 to 105	5,627		3.44	0.25	[2.95, 3.94]	<.001
eGFR[a] <60 ml/min/1.73m^2	4,839	.052	-1.64	0.26	[-2.16, -1.11]	<.001
Smoking status, Never smoker referent	14,860	.008				.521
Current smoker	5,585		-0.23	0.24	[-0.71, 0.25]	.339
Former smoker	7,444		-0.04	0.23	[-0.49, 0.41]	.865

Note. ACR = urinary albumin-to-creatinine ratio; BMI = body mass index; CI = confidence interval; eGFR = estimated glomerular filtration rate; HS = high school; NHANES = National Health and Nutrition Examination Survey; *r* = correlation coefficient; Set A. = renin-aldosterone inhibitors, calcium channel blockers, beta blockers or any combination of these; Set B.

= diuretics plus renin-aldosterone inhibitors, calcium channel blockers, or beta blockers; Set C. = any other antihypertensive agent or any combination of three drugs. Student's t-test or One-way Analysis of Variance, as appropriate
[a]Estimated glomerular filtration rate using the CKD-Epi equation (Levey et al., 2009)

Examining the data by category of blood pressure demonstrated progressively increased odds for each category of blood pressure examined compared to normal blood pressure for most variables (Appendix Table D2). For example, participants with eGFR 45 – 59 ml/min/1.73m^2 were 3.15, 7.81, and 9.43 times more likely to have blood pressure in the categories considered to indicate blood pressure 120-139 mmHg systolic or 80-89 mm Hg diastolic, 140-159 mm Hg systolic or 90-99 mmHg diastolic, or a blood pressure ≥160 mmHg systolic or ≥100 mmHg diastolic, respectively, than to have blood pressure <120/80 mmHg (all p-values < .001). In fact, for kidney function, each successive 15 ml/min/1.73m^2 decrease in eGFR, the odds for having blood pressure in any category above 120/80 mmHg were statistically significantly increased. The width of the 95% CI increased in the lowest kidney function level groups for the two higher blood pressure categories, reflecting the smaller sample size in those groups.

Variables with statistically significant odds for blood pressure of 120-139 / 80-89 mmHg are depicted in Figure 10. For participants who reported not taking or taking antihypertensive agents, variables demonstrating statistically significant odds ratios for blood pressure of 120-139 / 80-89 mmHg are depicted in Appendix Figure C2.

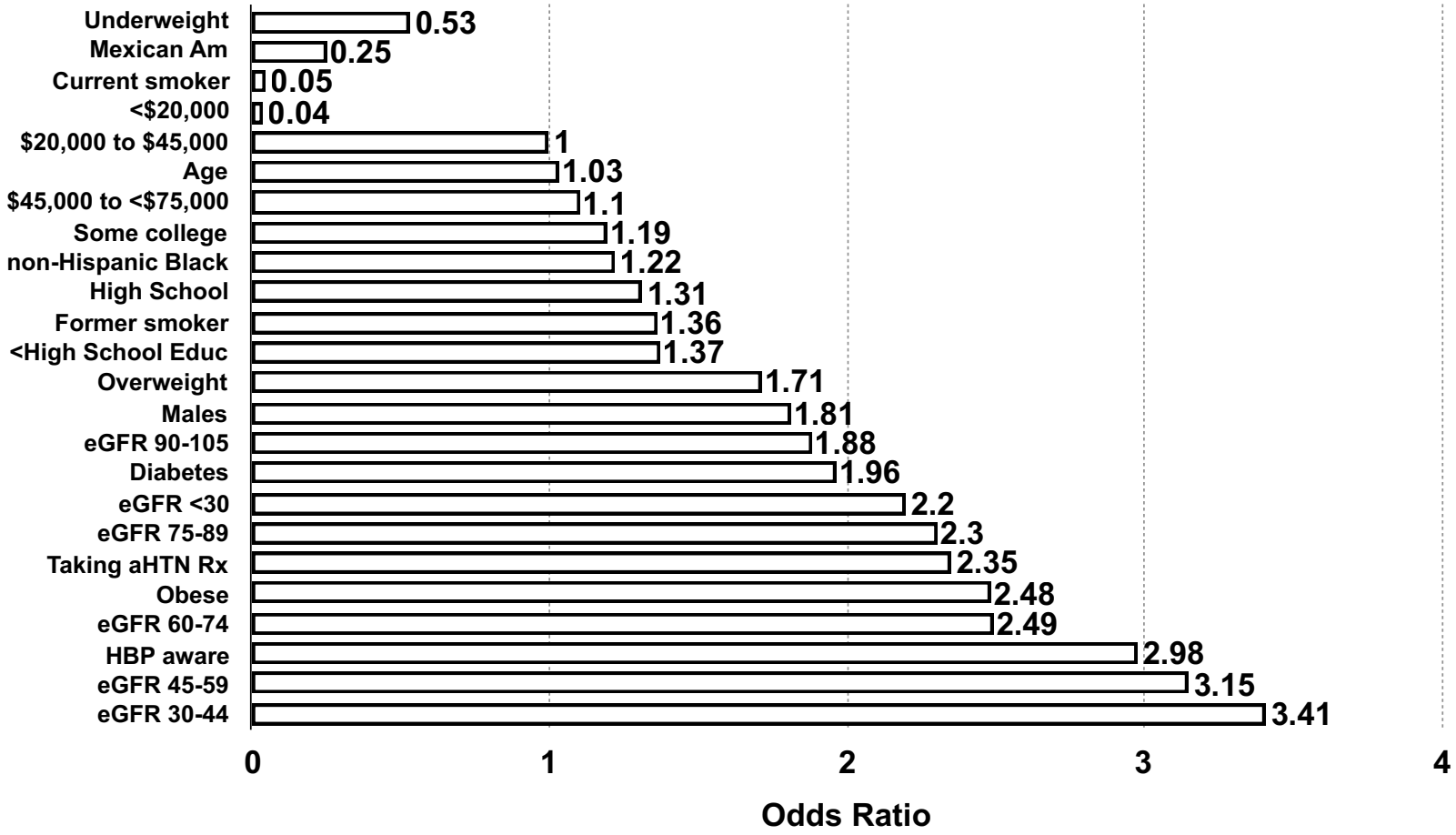

Figure 10. Odds for having blood pressure 120-139 / 80-89 mmHg compared to < 120/80 mmHg, listed by key demographic and clinical characteristics. aHTN Rx = antihypertensive agents, eGFR = estimated glomerular filtration rate in ml/min/1.73m^2, HBP = high blood pressure

Subproblem 5

What was the relationship between dietary sodium intake and systolic and diastolic blood pressure?

Linear Regression

A small, but statistically significant relationship between dietary sodium and systolic (Figure 11 and Table 17) and diastolic blood pressures (Figure 12 and Table 17) was observed. Per mg of dietary sodium increase, there was a 0.0003 mmHg decrease in systolic blood pressure ($p < .001$) and a 0.0005 mmHg increase in diastolic blood pressure ($p < .001$). Two additional units of dietary sodium were applied to the analysis to improve the relevance of the association: a 200 mg increment (obtained by dividing the total mg/day dietary sodium by 200) and a 1 g NaCl increment (obtained by multiplying the total mg/day dietary sodium by 2.5 then dividing by 1000). When applied, the dietary sodium relationship to systolic blood pressure was expressed as follows: for every 200 mg increase in dietary sodium, there was a 0.064 mmHg decrease in systolic blood pressure and a 0.092 increase in diastolic blood pressure; or for every 1 g increase in dietary NaCl, there was a 0.128 mmHg decrease in systolic blood pressure and a 0.184 mmHg increase in diastolic blood pressure.

Reporting the relationship in a more clinically relevant measure of blood pressure (e.g., a 1 mmHg change in systolic or diastolic blood

pressure), for every 5g dietary sodium (or 12.7g dietary NaCl) increase, there was a 1mmHg decrease in systolic blood pressure. For every 10g dietary sodium (or 25.4g dietary NaCl) increase, there was a 1mmHg increase in diastolic blood pressure.

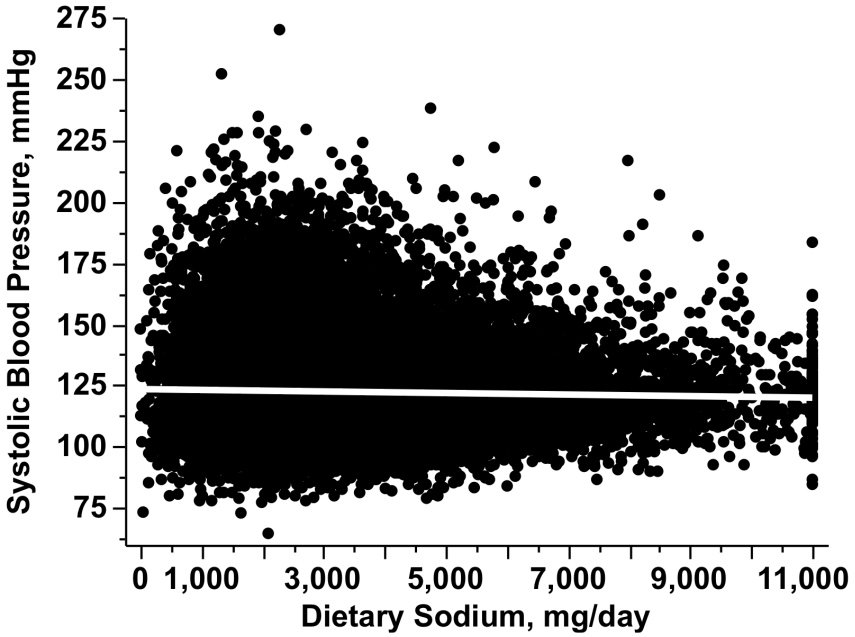

Figure 11. Linear regression of dietary sodium and systolic blood pressure in U.S. nonpregnant adults in NHANES 2003-2014; r = 0.032, a small effect size; B = -0.0003, $p < .001$

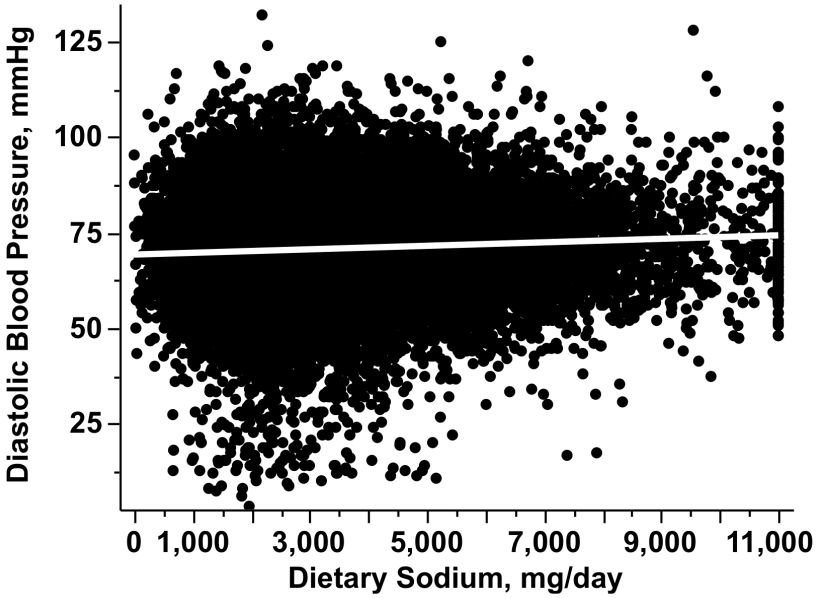

Figure 12. Linear regression of dietary sodium and diastolic blood pressure in U.S. nonpregnant adults in NHANES 2003-2014; r = 0.069, a small effect size; B = 0.0005, $p < .001$

Table 17.
The relationship between dietary sodium intake and blood pressure in U.S. nonpregnant adults in NHANES 2003-2014.

Variable	n	*r*	*B*	*SE*	95% CI	*p*-value
Systolic blood pressure	27,943	.032				<.001
per mg sodium/day			-0.0003	0.0001	[-0.0004, -0.0002]	
per 200 mg sodium/day			-0.06	0.01	[-0.09, -0.04]	
per g NaCl/day			-0.13	0.03	[-0.18, -0.08]	
Diastolic blood pressure	27,943	.069				<.001
per mg sodium/day			0.0005	0.0001	[0.0004, 0.0006]	
per 200 mg sodium/day			0.09	0.01	[0.07, 0.11]	
per g NaCl/day			0.18	0.02	[0.14, 0.23]	

Note. r = correlation coefficient, CI = confidence interval, NaCl = sodium chloride, NHANES = National Health and Nutrition Examination Survey. Linear regression

Logistic Regression

Dietary sodium expressed in mg/day revealed odds ratios of 1.00 for each increase in blood pressure category compared to normal blood pressure. However, expressed as 200 mg increments, the dietary sodium relationship to blood pressure 120-139 systolic or 80-89 diastolic was 1.01 (95% CI: 1.01-1.01, $p < .001$) and expressed as 1 g NaCl, the odds were 1.02 (95% CI: 1.01, 1.02; $p < .001$). Increases in dietary sodium resulted in lower odds for having blood pressure >140 systolic or > 90 diastolic (Table 18).

Table 18.

The relationship between dietary sodium intake and blood pressure categories in U.S. nonpregnant adults in NHANES 2003-2014; odds for having blood pressure <120/80 mmHg

Variable	120-139 mmHg sys. or 80-89 mmHg dias. n = 11,560			140-159 mmHg sys. or 90-99 mmHg dias. n = 2,616			≥ 160 mmHg sys. or ≥ 100 mmHg dias. n = 1,587		
	OR	95% CI	*p*-value	*OR*	95% CI	*p*-value	*OR*	95% CI	*p*-value
Dietary sodium, odds ratio									
per mg sodium/day	1.00	[1.00, 1.00]	<.001	1.00	[1.00, 1.00]	<.001	1.00	[1.00, 1.00]	<.001
per 200 mg sodium/day	1.01	[1.01, 1.01]	<.001	0.98	[0.97, 0.98]	<.001	0.97	[0.96, 0.98]	<.001
per g NaCl/day	1.02	[1.01, 1.02]	<.001	0.95	[0.94, 0.97]	<.001	0.94	[0.92, 0.96]	<.001

Note: CI = confidence interval, dias. = diastolic blood pressure, mmHg = millimeters of mercury, NaCl = sodium chloride, OR = odds ratio, sys. = systolic blood pressure. Multinomial logistic regression

Subproblem 6

What was the relationship between dietary sodium intake and systolic and diastolic blood pressure when controlling for key demographic and clinical characteristics?

Hypothesis 2a. There is no statistically significant relationship between dietary sodium intake on the day prior to blood pressure measurement and systolic and diastolic blood pressure in U.S. nonpregnant adults when controlling for key demographic and clinical characteristics.

Multiple Regression

In standard statistical models, multicollinearity is often assessed as predictor variables having Pearson correlation coefficients ≥ 0.8 (Field, 2013). However, in complex survey analyses, it has been recommended that lower correlations can demonstrate multicollinearity (Liao & Valliant, 2012). Current complex survey statistical software systems are not equipped to test for multicollinearity (Liao & Valliant, 2012). Using standard software for testing for multicollinearity while adjusting for weighted frequencies (but not for strata or sampling unit) in the current study, revealed a collinearity between kidney function and age of 0.59 that increased to 0.63 when gender was added. Variance inflation factors were between 2 and 3 for some kidney function levels when age and kidney function were both in the model. Gender, age and race (specifically, non-Hispanic Black) are variables in the estimation

formula for eGFR such that multicollinearity was anticipated to be present if each variable was included in the model. This is important because multicollinearity can bias the standard errors in a model and result in unstable *p*-values; multicollinearity can also influence the direction of an association. Given that accurate tests for multicollinearity are not currently available in SAS Survey®, a decision was made to perform the models with and without age to assess the effect on significance of the relationship between dietary sodium and blood pressure (systolic and diastolic) as a means to determine whether multicollinearity was a problem.

Dietary sodium was entered into a linear regression model as the primary variable of interest in association with blood pressure. Systolic and diastolic blood pressures were analyzed separately. Covariates were consecutively entered according to an *a priori* order of interest beginning with kidney function in 15 ml/min/1.73m^2 increments, then demographic variables together (age, gender, race, education, income) and finally a set of clinical variables (BMI, evidence of diabetes, use of antihypertensive agents, and smoking status). Each successive addition of variables was considered a model; thus, there are four models each for systolic blood pressure and for diastolic blood pressure. The intent of the modelling was to demonstrate the effect of conditioning of the DAG variables on the dietary sodium to blood pressure relationship, not to build a prediction model of blood pressure.

For the dietary sodium to systolic blood pressure relationship, as the modelling advanced, the relationship of dietary sodium to systolic blood pressure changed direction, changing from a negative relationship to a positive relationship (Table 19; see Appendix Table D3 for the full models) and with each model, the size of the relationship was attenuated. Using the full model (Model 4) without exclusion, the relationship was positive, but not statistically significant and not clinically relevant.

Table 19.
Multiple regression models of the relationship of dietary sodium to systolic blood pressure when conditioned on key demographic and clinical variables in U.S. nonpregnant adults in NHANES 2003-2014; n = 27,943

Parameter	Model 1	Model 2	Model 3	Model 4
R-square	.001	.069	.206	.222
Dietary sodium 200 mg/day				
B (SE)	-0.06 (0.01)	-0.06 (0.01)	0.05 (0.02)	0.03 (0.02)
95% CI	[-0.09, -0.04]	[-0.08, -0.03]	[0.02, 0.08]	[-0.003, 0.066]
p-value	<.001	<.001	.005	.052

Note. B = parameter estimate, CI = confidence interval, NHANES = National Health and Nutrition Examination Survey. Multiple regression
Model 1, only dietary sodium in 200mg/day increments; Model 2, includes Model 1 plus kidney function level groups; Model 3, includes Model 2 plus demographic characteristics (age, gender, race or ethnicity, education level, income status); Model 4, includes Model 3 plus clinical characteristics (BMI, evidence of diabetes, use of antihypertensive agents, smoking status)

When the covariate age was excluded (Table 20; see Appendix Table D4 for the full models), the direction of the full model relationship between dietary sodium and systolic blood pressure was altered and was statistically significant but not clinically relevant. The difference suggests that the inclusion of age along with the kidney function variable was overfitting the model.

Table 20.
Multiple regression models of the relationship of dietary sodium to systolic blood pressure when conditioned on key demographic (excluding age) and clinical variables in U.S. nonpregnant adults in NHANES 2003-2014; n = 27,943

Parameter	Model 1	Model 2	Model 3	Model 4
R-square	.001	.069	.100	.144
Dietary sodium 200 mg/day				
B (SE)	-0.06 (0.01)	-0.06 (0.01)	-0.04 (0.02)	-0.04 (0.02)
95% CI	[-0.09, -0.04]	[-0.08, -0.03]	[-0.07, -0.01]	[-0.07, -0.01]
p-value	<.001	<.001	.025	.018

Note: B = parameter estimate, CI = confidence interval, NHANES = National Health and Nutrition Examination Survey. Multiple regression
Model 1, only dietary sodium in 200mg/day increments; Model 2, includes Model 1 plus kidney function level groups; Model 3, includes Model 2 plus demographic characteristics (gender, race or ethnicity, education level, income status); Model 4, includes Model 3 plus clinical characteristics (BMI, evidence of diabetes, use of antihypertensive agents, smoking status)

For diastolic blood pressure, the relationship between dietary sodium and diastolic blood pressure remained positive with each model but reduced in size. The full model, without exclusions, indicated a dietary sodium to diastolic blood pressure relationship that was not statistically significant nor clinically relevant (Table 21; see Appendix Table D5 for the full models).

Table 21.
Multiple regression models of the relationship of dietary sodium to diastolic blood pressure when conditioned by demographic and clinical variables in U.S. nonpregnant adults in NHANES 2003-2014; n = 27,943

Parameter	Model 1	Model 2	Model 3	Model 4
R-square	.005	.030	.044	.065
Dietary sodium 200 mg/day				
B (SE)	0.09 (0.01)	0.08 (0.01)	0.03 (0.01)	0.02 (0.01)
95% CI	[0.07, 0.11]	[0.06, 0.10]	[0.01, 0.05]	[-0.01, 0.04]
p-value	<.001	<.001	.014	.115

Note: B = parameter estimate, CI = confidence interval, NHANES = National Health and Nutrition Examination Survey. Multiple regression
Model 1, only dietary sodium in 200mg/day increments; Model 2, includes Model 1 plus kidney function level groups; Model 3, includes Model 2 plus demographic characteristics (age, gender, race or ethnicity, education level, income status); Model 4, includes Model 3 plus clinical characteristics (BMI, evidence of diabetes, use of antihypertensive agents, smoking status)

The reduced model (excluding age) for diastolic blood pressure was concordant with the model that included age (Table 22; see Appendix Table D6 for the full models).

Table 22.
Multiple regression models of the relationship of dietary sodium to diastolic blood pressure when conditioned by demographic (excluding age) and clinical variables in U.S. nonpregnant adults in NHANES 2003-2014; n = 27,943

Parameter	Model 1	Model 2	Model 3	Model 4
R-square	.005	.030	.044	.065
Dietary sodium 200 mg/day				
B (SE)	0.09 (0.01)	0.08 (0.01)	0.03 (0.01)	0.02 (0.01)
95% CI	[0.07, 0.11]	[0.06, 0.10]	[0.01, 0.05]	[-0.01, 0.04]
p-value	<.001	<.001	.015	.200

Note: B = parameter estimate, CI = confidence interval, NHANES = National Health and Nutrition Examination Survey. Multiple regression
Model 1, only dietary sodium in 200mg/day increments; Model 2, includes Model 1 plus kidney function level groups; Model 3, includes Model 2 plus demographic characteristics (gender, race or ethnicity, education level, income status); Model 4, includes Model 3 plus clinical characteristics (BMI, evidence of diabetes, use of antihypertensive agents, smoking status)

Sensitivity Analysis

A sensitivity analysis was performed using a multinomial logistic regression of the dietary sodium to blood pressure categories relationship while conditioning on the key demographic and clinical characteristics. As in the linear model, dietary sodium was entered first, followed by kidney function levels, then demographic variables, and finally clinical variables (Table 23; see Appendix Table D7 for the full models).

The logistic regression model was concordant with the linear regression model in that as the model expanded, the relationship of dietary sodium to blood pressure lost statistical significance, with one exception. Compared to having normal blood pressure, as dietary sodium increased, the odds for having blood pressure of 140-159 mmHg systolic or 90-99 mmHg diastolic was reduced by 2% compared to having a normal blood pressure

(<120 mmHg systolic and <80 mmHg diastolic) and was statistically

significant (*p* <.001).

Table 23.
Logistic regression models of the relationship of dietary sodium to blood pressure categories when conditioned on key demographic (excluding age) and clinical variables in U.S. nonpregnant adults in NHANES 2003-2014

Parameter	Model 1	Model 2	Model 3	Model 4
Blood pressure 120-139 mmHg systolic or 80-89 mmHg diastolic, n = 11,560				
Dietary sodium 200 mg/day				
Odds Ratio	0.97	0.97	0.98	0.98
95% CI	[0.97, 0.98]	[0.96, 0.98]	[0.98, 0.99]	[0.98, 1.00]
p-value	<.001	<.001	.030	.055
Blood pressure 140-159 mmHg systolic or 90-99 mmHg diastolic, n = 2,616				
Dietary sodium 200 mg/day				
Odds Ratio	0.98	0.98	0.98	0.98
95% CI	[0.97, 0.98]	[0.97, 0.98]	[0.98, 0.99]	[0.98, 0.99]
p-value	<.001	<.001	<.001	<.001
Blood pressure ≥160 mmHg systolic or ≥ 90 mmHg diastolic, n = 1,587				
Dietary sodium 200 mg/day				
Odds Ratio	1.01	1.01	1.00	1.00
95% CI	[1.00, 1.01]	[1.00, 1.01]	[1.00, 1.01]	[1.00, 1.01]
p-value	<.001	<.001	.565	.938

Note: CI = confidence interval; mmHg = millimeters of mercury, NHANES = National Health and Nutrition Examination Survey. Multinomial logistic regression Referent: normal blood pressure (<120 mmHg systolic and <80 mmHg diastolic) Model 1, only dietary sodium in 200mg/day increments; Model 2, includes Model 1 plus kidney function level groups; Model 3, includes Model 2 plus demographic characteristics (age, gender, race or ethnicity, education level, income status); Model 4, includes Model 3 plus clinical characteristics (BMI, evidence of diabetes, use of antihypertensive agents, smoking status)

Chapter V

DISCUSSION, CONCLUSIONS AND RECOMMENDATIONS

The study aimed to demonstrate that a simple dietary sodium and blood pressure relationship does not exist. Thus, the study evaluated whether a relationship between dietary sodium and blood pressure could be demonstrated when accounting for levels of kidney function and other key demographic and clinical characteristics. The *Dietary Guidelines for Americans* state that all adults should limit dietary sodium to <2,300 mg/day (*Dietary Guidelines for Americans, 2015-2020*, 2015). However, the published research suggests that it is those with salt sensitivity who may have the most benefit or response in blood pressure from a dietary sodium restriction (Barba et al., 2007; Feng et al., 2017; Meng et al., 2014; Rayner et al., 2012; Yazdanpanah et al., 2007). Whereas it was not possible to determine salt sensitivity in this data set, assessing other demographic and clinical characteristics that might influence the relationship between dietary sodium and blood pressure was warranted. Using NHANES, a cross-sectional evaluation of the nutrition and health of U.S. residents, to explore these questions may provide insight into some of the challenges faced in implementing guidelines related to dietary sodium.

This study hypothesized that dietary sodium intake would be lower in people who take antihypertensive agents compared to those who do not take medications for blood pressure control. The data analyses revealed that people taking antihypertensive agents consumed 1 g of salt per day less than people who were not taking antihypertensive agents; thus, supporting the hypothesis and the theoretical approach used in the study. The mean dietary sodium of participants who reported not using antihypertensive agents was 3,624 mg sodium (9.1 g NaCl). This finding was a higher mean value than that estimated by other recent NHANES reports (*Dietary Guidelines for Americans, 2015-2020*, 2015; Hoy et al., 2011; Nothwehr, 2014).

The study also hypothesized that adults with reduced kidney function would consume less dietary sodium than those with normal kidney function. The study findings revealed that people with a kidney function level < 75 ml/min/1.73m^2 consumed statistically significantly different amounts of dietary sodium than those with the best kidney function. However, the differences varied across levels of kidney function with those having kidney function < 45 ml/min/1.73m^2 consuming statistically significantly less dietary sodium and those with 45 – 74 ml/min/1.73m^2 consuming statistically significantly more dietary sodium than people with the best kidney function. The hypothesis and the theoretical approach used in this study were supported by the results.

The third hypothesis was that dietary sodium of people with normal kidney function would be higher than the current dietary sodium being

reported. The study found that people with normal kidney function consumed a mean of 56 mg/day more sodium (or 0.14 g/day more salt) than is currently reported (*Dietary Guidelines for Americans, 2015-2020*, 2015). Importantly, some groups of participants with reduced kidney function (eg, 45-74 ml/min/1.73m^2) who were not taking prescribed antihypertensive agents for blood pressure control reported statistically significantly higher dietary sodium (>400 mg dietary sodium/day or >1 g of NaCl/day) than those with the best kidney function and represent approximately 38 million U.S. adults. The hypothesis and the theoretical approach used in this study were supported by the results.

The next hypothesis was related to the relationship between dietary sodium and blood pressure. It was hypothesized that a statistical relationship between dietary sodium and systolic and diastolic blood pressure would not be apparent after conditioning on key demographic and clinical characteristics. The crude relationship between dietary sodium and systolic blood pressure and dietary sodium and diastolic blood pressure was statistically significant in this study, in contrast to what was originally proposed, but the relationship was very small (ie, for every 1 g of NaCl consumed, a 0.13 mmHg decrease in systolic blood pressure and a 0.18 mmHg increase in diastolic blood pressure was observed), and thus not considered clinically relevant as these differences would not be measureable on a sphygmomanometer. After conditioning on the key demographic and

clinical characteristics, the dietary sodium to systolic blood pressure relationship was attenuated yet remained statistically significant (ie, a 0.08 mmHg decrease in systolic blood pressure for every 1 g dietary NaCl increase). However, a 0.08 mmHg change in blood pressure would not be detectable on a sphygmomanometer and is, therefore, not a clinically relevant decrease. For diastolic blood pressure, the statistically significant relationship observed on crude analysis was no longer apparent after conditioning on the confounder variables and the relationship continued to lack clinical relevance, which supported the hypothesis of no dietary sodium relationship to diastolic blood pressure in this data set.

In a post hoc analysis of the dietary sodium to blood pressure relationship separated by use of antihypertensive agents, the conditioned model demonstrated a negative association of dietary sodium with systolic blood pressure in both groups but neither group demonstrated statistically significant or clinically relevant relationships. For diastolic blood pressure, the dietary sodium to blood pressure relationship was positive in both groups, but not statistically significant or clinically relevant. These observations directionally concurred with the overall, a priori, analysis of the population.

Study Sample

The study sample was comprised of participants in the National Health and Nutrition Examination Survey from six 2-year cycles (2003-2004, 2005-

2006, 2007-2008, 2009-2010, 2011-2012, and 2013-2014). The sample was restricted to adults ≥ 20 years of age who were not pregnant, who had blood pressure measured, and had completed a 24-hour dietary intake assessment prior to blood pressure measurement.

Subproblem 1

In U.S. nonpregnant adults, as represented by data from NHANES 2003-2014, whose kidney function is estimated and who have completed a 24-hour dietary recall on the day prior to blood pressure measurement, what were their demographic characteristics (age, sex, race and ethnicity, education level, income status) and what are their clinical characteristics (albumin-to-creatinine ratio, body mass index, diabetes status, number and type of antihypertensive agents used, kidney disease awareness, kidney function level, smoking status)?

The population studied was representative of U.S. nonpregnant adults. According to the Centers for Disease Control and Prevention (CDC), one in three U.S. adults have high blood pressure (Merai et al., 2016). In the current study, evidence of hypertension was defined as being treated with antihypertensive agents or having a blood pressure >140/90 mmHg and was seen in 35.3% of the study sample, which is similar to the CDC report (Merai et al., 2016).

Chronic kidney disease prevalence in the population has been described by the U.S. Renal Data System (USRDS) as having an eGFR < 60 ml/min/1.73m^2 or an ACR ≥ 30 mg/g ("U.S. Renal Data System," 2016). Using 4-year periods of NHANES data to estimate the burden of kidney disease, the most recent USRDS report estimates CKD at 14.8% of the U.S. adult population during 2011-2014 with CKD stage 3 (eGFR 30-59 ml/min/1.73m^2) at 6.6%. The current study differs from the USRDS report: no estimation of CKD by a single serum creatinine or single spot urine measurement of ACR was employed in the current study, inclusion of 12 years instead of four years for the current study period, exclusion of participants without a valid blood pressure reading or without dietary intake information. Both the USRDS report and the current study consider that CKD is evident if the eGFR is < 60 ml/min/1.73m^2, yet the current study demonstrated 14.0% of U.S. adults had eGFR in the 30-59 ml/min/1.73m^2 range instead of 6.6% as the USRDS report indicated. The most likely explanation for this difference is the population denominator and the study exclusion criteria. In a recent study by Lazo et al (2017) the prevalence of eGFR <60 ml/min/1.73m^2 was 15.0% from NHANES 1999-2012 and was similar to the prevalence in the current study.

The National Center for Health Statistics (NCHS) recently reported that the unadjusted prevalence of obesity in adults was 39.8% (Hales, Carroll, Fryar, & Ogden, 2017). The current study encompassed a period from 2003 to 2014 with an observed obesity prevalence of 34.9% in U.S. adults.

Reviewing the NCHS (Hales et al., 2017) report demonstrated an obesity range of 32.2 to 37.7% during the current study period (2003 to 2014), with a rising trajectory.

Subproblem 2

What was their dietary sodium intake and systolic and diastolic blood pressure?

Dietary sodium

The unadjusted mean dietary sodium of U.S. nonpregnant adults in NHANES 2003-2014 was almost 100 mg per day higher than that reported in the most recent dietary guidelines (*Dietary Guidelines for Americans, 2015-2020*, 2015) and was an overall mean of 3,526 mg of sodium or 8.8 g of NaCl per day. This dietary sodium intake is approximately 1,300 mg/day higher than the amount recommended by the U.S. *Dietary Guidelines for Americans* (*Dietary Guidelines for Americans, 2015-2020*, 2015) and approximately 2,000 mg/day higher than that recommended by the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines guidelines (Whelton et al., 2018). Furthermore, a small proportion (<1%) of the population consumed more than 11,000 mg of sodium or 27 g of NaCl on the day of the dietary interview. Whereas this was a small number for the study, as a population study, the number represents thousands of adults.

The mean dietary sodium reported by participants in this study was more than two times higher than the dietary sodium challenge used in the Blanch et al (2015) study of adults without hypertension. However, remaining studies of adults without hypertension (Allen et al., 2014; Cavka et al., 2015; Lennon-Edwards et al., 2014; Rorije et al., 2018; Selvarajah et al., 2017; Wang et al., 2014; Wenner et al., 2011) that were reviewed for the current study tested dietary sodium that was nearly two to three times greater than the mean dietary sodium reported by participants in the current study. Other than studies that demonstrated increased systolic blood pressure upon dietary sodium challenge in salt-sensitive individuals, the only healthy volunteer study reviewed in the literature for this study that demonstrated a statistically significant increase in systolic blood pressure was by Wang et al. (2014) who pushed the dietary sodium challenge to 15 g NaCl (7,200 mg sodium) higher than the control and observed a 9 mmHg increase in systolic blood pressure in healthy Chinese volunteers whose mean age was 50 years.

The upper quartile of dietary sodium reported by the participants in the current study was greater than 4,400 mg of sodium (11 g of NaCl) and in those not prescribed antihypertensive agents for blood pressure treatment, the upper quartile was > 4,500 mg of sodium (11.4 g of NaCl). Such an amount of dietary sodium was similar to the dietary sodium challenge investigated by Gijsbers et al. (2015) and by Gilbert et al. (2013) who observed an 8 mmHg and 15 mmHg increase in systolic blood pressure,

respectively, using a dietary sodium > 4,500 mg in adults with hypertension or prehypertension.

The recognized cut point of kidney function that depicts chronic kidney disease is eGFR <60 ml/min/1.73m^2 (Kidney Disease: Improving Global Outcomes Workgroup, 2013). Using this cut point, the hypothesis that persons with CKD consumed less dietary sodium than those without CKD was not supported. However, those who reported taking antihypertensive agents had significantly lower dietary sodium if their eGFR was <60 compared to ≥60 ml/min/1.73m^2. Importantly, 25% of participants in the current study who had kidney function estimated to be in the range of 45-59 and 60-74 ml/min/1.73m^2 reported dietary sodium greater than 4,900 mg/day (12 g NaCl). Two studies of patients with chronic kidney disease evaluated a dietary sodium challenge of 4,600 mg/day (11.5 g NaCl) (Kwakernaak et al., 2014; McMahon et al., 2013). Kwakernaak et al. (2014) observed a 6 mmHg increase in systolic blood pressure and McMahon et al. (2013) observed a 10 mmHg increase in systolic blood pressure when dietary sodium was 200 mmol/day (or 11.5 g NaCl) in patients with chronic kidney disease. In these studies, the urinary sodium excretion reached 224 mEq (5,152 mg sodium) on the high sodium diet and 148 mEq (3,404 mg sodium) on the low sodium diet. The urinary sodium excretion (148 mmol/day) on low sodium diet (50 mEq/day or 1,150 mg/day) was higher than planned yet still resulted in

significant differences in systolic and diastolic blood pressure in patients with CKD.

Blood pressure

Fewer than one-half of U.S. adults (46.6%) in the current study had blood pressure considered to be in the normal range (<120 mmHg systolic and <80 mmHg diastolic) and only 28% of those reporting that they took medications for blood pressure control had blood pressure in this range (Appendix C). Having a blood pressure that is between 120 and 139 mmHg systolic or between 80 and 89 mmHg diastolic is considered a major risk factor for developing hypertension (Merai et al., 2016) and was observed in 39% of adults in the current study who did not report having a prescription for medication for their blood pressure. Another 7.6% had blood pressure of 140-159 mmHg systolic or 90-99 mmHg diastolic or had blood pressure ≥160 mmHg systolic or ≥100 mmHg diastolic and did not report having a prescription for medication for high blood pressure treatment.

The participants in the current study who were prescribed antihypertensive agents and had kidney function in the 30-59 ml/min/1.73m^2 had somewhat lower mean systolic blood pressure (130 to 133 mmHg) than that of the participants in most of the studies of chronic kidney disease reported in the literature review (de Brito-Ashurst et al., 2013; Kwakernaak et al., 2014; McMahon et al., 2013) where the means for systolic blood pressure ranged from 141 to 156 mmHg.

Subproblem 3

What was the relationship between dietary sodium intake and key demographic and clinical characteristics?

As anticipated, and described by the DAG, each of the studied demographic and clinical variables also demonstrated statistically significant correlations with dietary sodium. Therefore, the theoretical and statistical findings were concordant. These correlations suggest that studies of the relationship between dietary sodium and blood pressure should account for demographic and clinical variables such as the ones evaluated in the current study. Of the 22 randomized controlled studies reviewed for this report, age was accounted for by restricting enrollment in three studies (Allen et al., 2014; Cavka et al., 2015; Rorije et al., 2018); gender was accounted for by 1) restricting enrollment to only males in two studies (Cavka et al., 2015; Rorije et al., 2018), 2) stratification without separate reporting in three studies (Gijsbers et al., 2015; Hwang et al., 2014; Wang et al., 2014), or 3) equal enrollment and separate reporting in two studies (Lennon-Edwards et al., 2014; Selvarajah et al., 2017). None of the studies controlled for BMI or for race and only the studies in CKD accounted for kidney function. Only two of the studies analyzed the outcomes based on demographic [gender only (Selvarajah et al., 2017)] or clinical characteristics (Lennon-Edwards et al., 2014). Therefore, despite the quality of the study design (eg, randomized, controlled, crossover), these studies are unable to provide information on the

actual dietary sodium relationship with blood pressure since these demographic and clinical characteristics were not considered as influential on the relationship.

In general, men eat more than women and higher dietary sodium in men than women has been reported (*Dietary Guidelines for Americans, 2015-2020*, 2015; Mozaffarian et al., 2015). The current study results indicated that men had 1.2 g sodium (3 g NaCl) higher intake than women. It has also been postulated that persons in lower socioeconomic (SES) strata have higher dietary sodium than high SES groups. In a systematic review by de Mestral et al. (2017), persons in lower SES strata were reported to consume 503 mg/day higher sodium than high SES groups. The study was based on data from trials conducted in high-income countries throughout the world. This finding was not corroborated in the current study that indicated a lower dietary sodium intake in lower education and lower income groups than the higher education and income groups. However, important differences in the evaluation of dietary sodium in the report by de Mestral et al and the current study should be mentioned. The systematic review was reporting dietary intake of sodium as 1) equivalent to the urine sodium reported in some of the studies in the review or 2) as a standardized dietary sodium to the dietary energy (a measure of diet quality or nutrient density) in other studies in the review. The focus of the current study was to assess dietary sodium intake the day before the blood pressure measurement (e.g., dietary sodium

exposure) and, thus, the interest was in evaluating the maximum dietary sodium consumed by participants, not an adjusted dietary sodium. In Figure 8 (and Appendix Table D1) of the current study, the dietary sodium density of the overall study population was shown to be 1,650 mg sodium/1,000 kcal, which is higher than recommended (eg, a 2,000 kcal diet should have a dietary sodium density of 1,150 mg sodium/1000 kcal considering the dietary guideline of <2,300 mg sodium). Evaluation of the demographic and clinical variables for relationship to dietary sodium density reduced the effect size of each relationship.

Due to the method of dietary recall utilized in the NHANES 2003-2014 cycles, the dietary sodium intake reported in this study represents the usual mean dietary sodium intake of U.S. nonpregnant adults (Ahluwalia, Dwyer, Terry, Moshfegh, & Johnson, 2016). The survey was performed on all days of the week, which reduces the day-to-day variability of the dietary report. Additionally, because dietary sodium is not *per se* an episodic nutrient that would be only occasionally consumed, a single-day record of dietary sodium intake in this large population study can be considered an accurate representation of the mean usual intake of dietary sodium.

Subproblem 4

What was the relationship between systolic and diastolic blood pressure and key demographic and clinical characteristics?

All but the smoking status variable were statistically significantly correlated to blood pressure in the crude analysis. For systolic blood pressure, only current smoking vs never smoking was not statistically significantly correlated; all other categories and subcategories within a variable were statistically significantly correlated with systolic blood pressure and were associated with a ≥1 mmHg difference in systolic blood pressure. In contrast, some subcategories within a variable (eg, other races vs non-Hispanic White, high school diploma or some college vs college degree or higher, BMI < 18.5 vs 18.5 - <25 kg/m^2), taking diuretics alone or renin-aldosterone inhibitors vs no antihypertensive agents, having kidney function <15 or dialysis vs eGFR >105 ml/min/1.73m^2) were not statistically significantly correlated to diastolic blood pressure and did not meet the clinical relevance criteria of ≥1 mmHg difference in diastolic blood pressure.

Men have higher blood pressure than women, at least until about age 45; then after age 65, women tend to have higher blood pressure than men (Mozaffarian et al., 2015). In the current study, men had almost 3 mmHg higher systolic blood pressure than women. People with diabetes are known to have higher blood pressure ("American Diabetes Association standards of medical care in diabetes — 2016," 2016) and some reports have suggested that a lower socioeconomic status is associated with higher blood pressure (Cundiff et al., 2015; Leng et al., 2015). The current study concurred with this observation, demonstrating a 9 mmHg increase in systolic blood pressure in

those with diabetes and progressive increases in systolic blood pressure for each decrease in education status as well as income status. A higher systolic blood pressure was also observed in this study in participants who were categorized as overweight and higher still in those who were categorized as obese compared to participants of normal BMI category, which is in agreement with several reports (Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration [BMI Mediated Effects] et al., 2014; Kidney Disease: Improving Global Outcomes Workgroup, 2012; Middlemiss et al., 2016).

Analyses of data from this study demonstrated the progressive increase in systolic blood pressure that is evident as kidney function decreases; an increase that was statistically significant at each level of kidney function compared to the best kidney function in the data set. As early as eGFR 90-105 ml/min/1.73m^2, the systolic blood pressure was 6 mmHg higher than for participants with eGFR > 105 ml/min/1.73m^2 and increased incrementally to > 20 mmHg higher in participants with eGFR 15-29 ml/min/1.73m^2. The Kidney Disease, Improving Global Outcomes (KDIGO) workgroup practice guideline on the “Management of Blood Pressure in CKD” focuses on guidance for blood pressure in the later stages of CKD and does not address the earlier levels of kidney function decline (Kidney Disease: Improving Global Outcomes Workgroup, 2012). In another guideline by KDIGO (Kidney Disease: Improving Global Outcomes Workgroup, 2013),

workgroup members demonstrated a grid of the prognosis of CKD by eGFR decline with levels of albuminuria. A similar grid might be useful in considering the blood pressure risk to further declines in kidney function.

Similar to their relationships with dietary sodium, the DAG variables appear to have important significance for blood pressure studies; however, most studies are not adjusted for these demographic and clinical characteristics. The systematic reviews on the topic of blood pressure, dietary sodium, and outcomes (eg, all-cause mortality, cardiovascular events, or death) have noted confounders (age, sex, BMI, education, and others) with results suggesting that low as well as high dietary sodium confers increased risk (Graudal, Hubeck-Graudal, & Jurgens, 2017; Mente et al., 2016). However, none of the systematic reviews have delineated levels of kidney function in their analyses.

Subproblem 5

What was the relationship between dietary sodium intake and systolic and diastolic blood pressure?

The crude analysis of the correlation between dietary sodium to systolic (a negative correlation) or diastolic blood pressure (a positive correlation) was statistically significant, each at $p < .001$. However, the effect size was very small (B = -0.0003, 95% CI = -0.0004, -0.0002 for systolic blood pressure). Even after accounting for dietary sodium using grams of salt, for

every 1 g increase in dietary salt, a 0.13 mmHg decrease in systolic and a 0.18 mmHg increase in diastolic blood pressure would be expected by this data set. Such changes in blood pressure are unmeasurable on a sphygmomanometer and would not be considered clinically relevant. Additionally, a large proportion of participants in the current study were adults with normal kidney function (44.7%) and normal blood pressure (<120/80 mmHg) was observed in 46.6%. None of the RCTs or cohort studies, or even meta-analyses, contained data from such a large sampling of persons of diverse race and ethnicities with normal blood pressure. However, the large meta-analyses of RCTs should be considered as stronger evidence since they were testing a low vs a high dietary sodium effect on blood pressure and the current study is only cross-sectional.

In the randomized controlled trials reviewed for this study, a dietary sodium challenge resulting in an increase in blood pressure in subjects with normal blood pressure was only observed in participants with salt sensitivity but only a few of the studies reported salt sensitivity. Those who responded with an increase in blood pressure were older or already had increased blood pressure. Furthermore, some of the studies demonstrated a decrease in diastolic blood pressure associated with the dietary sodium challenge in subjects without hypertension (Allen et al., 2014; Carey et al., 2012). Only one of the RCTs examined demonstrated a significant increase in systolic and diastolic blood pressure in the cohort (Wang et al., 2014); a 15g NaCl

challenge (15g higher than the low sodium period of 3g per day) in a study of 42 Chinese participants resulted in a statistically significant ($p < .05$) and clinically relevant increased blood pressure (109 to 117 mmHg systolic and 74 to 78 mmHg diastolic).

Subproblem 6

What was the relationship between dietary sodium intake and systolic and diastolic blood pressure when controlling for key demographic and clinical characteristics?

Both the conditioned multiple regression and logistic regression (sensitivity analysis), as well as the post hoc analysis that separated the participants by use of antihypertensive agents or no antihypertensive agents, demonstrated a very small negative relationship between dietary sodium exposure and systolic blood pressure in this large population sample. Statistical significance was only demonstrated in the overall population multiple regression analysis for systolic blood pressure. In contrast, the dietary sodium-to-diastolic blood pressure relationship, while also very small, was a positive relationship. However, the multiple regression in the overall population sample and in the subgroup of treatment with or without antihypertensive agents was not statistically significant for a dietary sodium to diastolic blood pressure relationship when conditioned on the confounders

applied in this study. Together, these findings suggest that the relationship between dietary sodium exposure and blood pressure is not a simple relationship and is not a clinically relevant relationship across a population demographic such as U.S. nonpregnant adults that includes a large proportion of people with normal kidney function and normal blood pressure.

Study Limitations and Strengths

Limitations

The cross-sectional design of this study limited the ability to determine a causal relationship between dietary sodium and systolic and diastolic blood pressure. A temporal bias exists in cross-sectional designs because it is not possible to establish whether the outcome (systolic and diastolic blood pressure) was caused by the exposure (dietary sodium) or vice versa. In complex relationships, such as the relationships in the current study, it is possible that the correlation of dietary sodium with blood pressure may differ within levels of either variable. The study design attempted to account for this by evaluating different levels of the exposure and outcome (e.g., continuous and categorical), by including confounders of the relationship, and by using a theoretical approach for model-building. The study used a priori knowledge of associations with both the exposure and the outcome to select the variables considered to confound the relationship between dietary sodium and systolic and diastolic blood pressure. However, it is possible that residual confounding

existed (eg, unmeasured confounders such as duration of exposure, stress; the kidney function variable was an estimate; the blood pressure measurements may have been confounded by the “white-coat syndrome” described below), or that some of the confounders confounded each other (eg, if education was confounded by income status, if the use of antihypertensive agents was confounded by education or income or both, if kidney function was confounded by age).

The cross-sectional design also limited the ability to test whether the observations would endure over time. The extremes in dietary sodium, both at the lower end and high end of distribution suggest that individuals would not likely be consuming the reported amount on a regular basis. For example, it may not be physiologically possible for the participants reporting >11,000 mg dietary sodium to maintain that level of dietary sodium continuously. However, it was not the purpose of this study to determine the usual dietary intake of individuals at these extremes. The intent of this study was to assess the blood pressure response by examining the relationship of dietary sodium exposure with blood pressure measured the day after exposure. To determine if the extreme dietary sodium intakes were usual intakes, the second-day 24-hour dietary intake would need to be assessed (Ahluwalia et al., 2016). However, there is no second-day blood pressure measurement in NHANES at the present time. A limitation to assessing the blood pressure response to dietary sodium exposure is that the kidney response to a high sodium diet may occur

over hours to days (Elliott et al., 2016). Whereas the blood pressure may respond in a period of hours to a dietary sodium exposure in some people; others may have little or, perhaps, no apparent immediate response. It is known that the majority of individuals will have an increase in urinary sodium and no change in blood pressure when a high dietary sodium is consumed (R. J. Johnson et al., 2016; Lawton et al., 2016) and that those who are sensitive to dietary sodium loading will not excrete the excess sodium and have a consequent increase in blood pressure. Another response to sodium loading has recently been recognized as an ability by some to store sodium in reservoirs in the skin (as opposed to immediately excreting the excess sodium in the urine), which may be one of the mechanisms of salt resistance (Titze & Luft, 2017). Age is also associated with a decreasing resistance to salt (Anderson et al., 2008) as well as decreasing kidney function. The current study could not assess salt sensitivity, however, which might have provided further insight into the dietary sodium-to-blood pressure response across the demographic studied. It is unknown whether salt loading contributes to development of salt sensitivity in humans (Williams et al., 2014).

A syndrome referred to as the “white coat syndrome” may have been present in this study. The white coat syndrome is a known phenomenon that occurs in approximately 20% of hypertensive individuals when having their blood pressure measured in the clinic or doctor’s office (Lawton et al., 2016) where the blood pressure is higher than when measured in ambulatory

settings or the blood pressure measured while wearing blood pressure monitors. Additionally, blood pressure varies throughout the day related to physical, mental, and emotional factors. Blood pressure can also decrease approximately 20% during sleep (a diurnal effect). Thus, blood pressure measurement on a single day and time of day, despite taking the average of three to four measures, may not accurately reflect the participant's usual blood pressure.

Other variables associated with blood pressure, including other nutrients (eg, potassium, magnesium, calcium, and fats) and physical activity, were not assessed in the current study which may limit the ability to understand the dietary sodium-to-blood pressure relationship and should be evaluated in future studies. The study did not collect information on use of nonsteroidal anti-inflammatory agents which can blunt or block the action of antihypertensive agents and contribute to acute kidney injury during volume depletion. These scenarios may have been present at the time of the laboratory examination in NHANES and influenced the level of kidney function. It is possible that additional unknown variables confound the relationship between dietary sodium and blood pressure or confound the confounders evaluated in the current study.

Finally, assessing dietary sodium using 24-hour diet recalls may have limited the ability to know the actual dietary sodium of participants in this study. Participants may have inaccurately recalled their intake or been

reluctant to report their actual food intake. However, the technique used for collecting dietary sodium of NHANES participants was recently validated in almost 500 adults (men and women) against 24-hour urine collections and found to have a reporting accuracy >0.8 (Rhodes et al., 2013). A 24-hour urine sodium would possibly have been a more accurate assessment of sodium intake, but these were not available from NHANES and may not have been as accurate in the very reduced kidney function level groups.

Strengths

The main strength of this study is the large sample size representing the U.S. nonpregnant adult population who are not actively seeking healthcare on the day of the NHANES examination; they have not been identified as having risk for diseases or conditions of interest prior to participation in the survey. NHANES participants are randomly approached to take part in the survey and, thus, provide insight into the prevalence of the measures of interest (eg, dietary sodium, levels of blood pressure, and levels of kidney function) in the U.S. population across the range of demography. Whereas large sample sizes may deflate p-values when the sample is very large, large sample sizes strengthen the precision of the effect size and confidence intervals of the results (Lantz, 2013), which is the more accurate measure of association. In the current study, the key demographic and clinical

characteristics had clinically relevant associations with systolic and diastolic blood pressure but the dietary sodium association with blood pressure did not demonstrate a clinically relevant relationship when controlling for the key demographic and clinical variables.

Dietary sodium is assessed using the validated automated multiple-pass method for 24-hour dietary recall that has been shown to accurately capture the dietary sodium intake in populations (Rhodes et al., 2013). Also, the dietary assessment in this study encompassed all seven days of the week, which reduces the impact of the known day-to-day variability of eating patterns. Furthermore, the observation that a high dietary sodium intake (>11,000 mg/day) occurs in some participants was present in all six of the 2-year cycles included in this analysis, which suggests that such a high dietary intake is not uncommon in US adults.

Another strength of this study is the use of a DAG approach to accounting for confounding of variables on the association between dietary sodium and blood pressure. A priori knowledge of covariates having a dual relationship between the dietary sodium and blood pressure variables was used to inform the model. Although statistical significance was present for each variable on the exposure (dietary sodium) and outcome (blood pressure), the model described an attenuation of the relationship between the exposure and outcome that should be considered when evaluating and designing future studies of dietary sodium and blood pressure. The variables

selected for the DAG were based upon evidence for relatedness to both the exposure and outcome and upon availability in NHANES and not statistical significance after univariate analyses.

Conclusions

This study found that a clinically relevant relationship between dietary sodium intake on the day prior to blood pressure measurements and systolic and diastolic blood pressure was not apparent. Several demographic and clinical characteristics (kidney function, gender, race, income but not education, BMI, evidence of diabetes) may influence the dietary sodium-to-blood pressure relationship. The demographic and clinical relationships studied should be included in evaluations of the association between dietary sodium and blood pressure.

Additionally, in each 2-year cycle of NHANES included in this study (2003-2014), an appreciable proportion of U.S. nonpregnant adults consumed well over the recommended dietary sodium on the day of the dietary assessment. However, the overall mean of the population was nearer 3,500 mg sodium (8.8 g NaCl). The mean was higher than in most recent reports, which indicates an update on the dietary sodium of U.S. adults may be indicated. The study also found that some subgroups of the population (eg, persons with kidney function between 45 and 74 ml/min/1.73m^2, persons who do not take antihypertensive agents) have significantly higher dietary sodium

which should be considered when estimating the dietary sodium of the population.

Implications for Education

NHANES contains a large repository of information on the cross-sectional status of the U.S. population health and nutrition. Data from NHANES should be used more often to inform students and clinicians on the health of the population. The current study, for example, could be used to better understand the dietary sodium intake and blood pressure of people at each level of kidney function and to see the difference in dietary sodium and of blood pressure in people at levels of education and income in the U.S. This study may also be used to inform dietetic, nursing, and medical students on the prevalence of conditions examined and the combinations of blood pressure medications used as well as the prevalence of blood pressure categories within antihypertensive agent classifications and for persons not taking antihypertensive agents. The study could provide information to students, clinicians, and public policy makers on understanding the use of DAGs in clinical and epidemiologic research and interpreting clinical relevance in the context of statistical significance. The study could be used to encourage other students and clinicians to utilize NHANES for querying their research and clinical interests to improve public health nutrition and clinical practice.

Implications for Research

As no consensus exists for the appropriate assessment of salt sensitivity, there is a need for improved detection of salt sensitivity or salt resistance. Tools should be developed for detection of salt sensitivity in order to appropriately classify the blood pressure response to dietary sodium. For example, the relatively recent observation that the skin may act as a reservoir for sodium (Theodore W. Kurtz et al., 2016) makes the skin a likely target for developing sensors to detect sodium accumulation. Selvarajah et al. (2017) used tissue biopsy in a study to demonstrate that men in their study had significantly more sodium in skin following a high sodium diet, but tissue biopsy would not be appropriate for large population studies. Given that dysregulation of sodium handling may be an early sign of kidney disease and may precede high blood pressure, a method for detecting altered sodium handling in populations would be a public health benefit because the target population for dietary sodium reduction would be better defined.

Some research questions stimulated by this study include:

1) Is there a response to salt that associates with a lowering of blood pressure during salt loading? If so, is this response sustainable or does it convert to increased blood pressure over time?
2) Does salt sensitivity manifest changes in blood pressure differently at different life stages? For example, diastolic blood pressure has been noted to rise to about age 50 (Lawton et al., 2016), then

decreases later in life. The mean age of participants in the current study was 47 years and there was a slight positive correlation between dietary sodium and diastolic blood pressure. Further research would be required to determine if the positive dietary sodium-to-diastolic blood pressure relationship was a marker of salt sensitivity.

3) Is there a salt threshold at which a salt-resistant state may convert to salt sensitive state (eg, salt excess leading to renal injury)?
4) Do other dietary factors (nutrients such as potassium, magnesium, calcium, fats or food patterns) relate to a blood pressure response in a more direct way than dietary sodium across the adult population?
5) Is there an explanation for the higher dietary sodium intake of people with kidney function 45 – 74 ml/min/1.73m^2 compared to participants with better or worse kidney function? Could it be related to medications they take? Are they consuming more foods away from home or likely to have added sodium beyond their control? Is this group more at risk for cardiovascular disease and hypertension and further kidney damage related to the dietary sodium intake?
6) Whereas the study provides information on the dietary sodium intake, it does not provide information on dietary patterns or the

dietary sodium density of the population studied. Additional research on these factors of persons having the kidney function levels studied may benefit these subgroups of the population.

7) Further analyses should be performed to determine if the level of kidney function may influence a dietary sodium-to-blood pressure relationship.
8) A second day of 24-hour dietary intake is provided by a large subset of the NHANES participants. Future studies might consider use of wearable technology that would provide blood pressure measurement for the second 24-hour dietary intake to determine if the findings from the current study endure or would be more revealing than the current study. The monitor would need to be worn for both visits.

Implications for Practice

The current study provides information on the dietary sodium intake of a large sample of the U.S. nonpregnant adult population. The study does not provide information on how much dietary sodium should be consumed to treat elevations in blood pressure or to prevent elevated blood pressure. This study demonstrated that persons with decreasing kidney function appeared to have higher dietary sodium than expected, especially those at levels of kidney

function who might not yet be referred to a nephrologist (eg, eGFR >60 ml/min/1.73m^2). Whether in a primary care setting or a nephrology clinic, this information could be coupled with practice guidelines on the recommended dietary sodium for developing methods of managing nutrient intakes under current guidelines to attenuate kidney damage. For example, in clinical practice, frequent monitoring of both the changes in dietary intake and the physical response (blood pressure, gastrointestinal, weight changes, urinary albumin-to-creatinine ratio) to making dietary changes may be beneficial for determining the best dietary sodium intake for an individual. The information from this study could also be used by public health practitioners and policy makers to better understand the complexity of the dietary sodium-to-blood pressure link.

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Appendices

A – LITERATURE SEARCH STRATEGIES

Appendix Table A1.
Search strategy used for the Medical Literature Analysis and Retrieval System Online (MEDLINE®), through PubMed® from the U.S. National Library of Medicine®, National Center for Biotechnology Information, National Institutes of Health

Search	Query	Items found	Notes
#26	Search (((((((("blood pressure"[Mesh] OR "blood pressure"))) AND ((((((((("sodium, dietary"[Mesh]) OR "dietary sodium") OR "sodium chloride, dietary"[Mesh]) OR "dietary sodium chloride") OR "dietary salt") OR "Diet, Sodium-Restricted"[Mesh]) OR "sodium-restricted diet") OR "salt reduction") OR "dietary sodium reduction")))) AND (("Randomized Controlled Trial"[Publication Type]) OR "randomized controlled trial"))) AND (((((((("Kidney"[Mesh]) OR "kidney") OR "renal") OR "Glomerular Filtration Rate"[Mesh]) OR "glomerular filtration rate") OR "kidney function")))))) NOT "Review"[Publication Type] Filters: Publication date from 2011/10/19 to 2018/11/30	51	Included in #22 below
#25	Search (((((((("blood pressure"[Mesh] OR "blood pressure"))) AND ((((((((("sodium, dietary"[Mesh]) OR "dietary sodium") OR "sodium chloride, dietary"[Mesh]) OR "dietary sodium chloride") OR "dietary salt") OR "Diet, Sodium-Restricted"[Mesh]) OR "sodium-restricted diet") OR "salt reduction") OR "dietary sodium reduction")))) AND (("Randomized Controlled Trial"[Publication Type]) OR "randomized controlled trial"))) AND (((((((("Kidney"[Mesh]) OR "kidney") OR "renal") OR "Glomerular Filtration Rate"[Mesh]) OR "glomerular filtration rate") OR "kidney function")))))) NOT "Review"[Publication Type]	148	Included in #21 below

Search	Query	Items found	Notes
#24	Search (((((((("blood pressure"[Mesh] OR "blood pressure"))) AND ((((((((("sodium, dietary"[Mesh]) OR "dietary sodium") OR "sodium chloride, dietary"[Mesh]) OR "dietary sodium chloride") OR "dietary salt") OR "Diet, Sodium-Restricted"[Mesh]) OR "sodium-restricted diet") OR "salt reduction") OR "dietary sodium reduction")))) AND (("Randomized Controlled Trial"[Publication Type]) OR "randomized controlled trial"))) AND (((((((("Kidney"[Mesh]) OR "kidney") OR "renal") OR "Glomerular Filtration Rate"[Mesh]) OR "glomerular filtration rate") OR "kidney function"))))	152	
#23	Search ((((((((("Kidney"[Mesh]) OR "kidney") OR "renal") OR "Glomerular Filtration Rate"[Mesh]) OR "glomerular filtration rate") OR "kidney function")))	1,045,549	
#22	Search (((((((("blood pressure"[Mesh] OR "blood pressure"))) AND ((((((((("sodium, dietary"[Mesh]) OR "dietary sodium") OR "sodium chloride, dietary"[Mesh]) OR "dietary sodium chloride") OR "dietary salt") OR "Diet, Sodium-Restricted"[Mesh]) OR "sodium-restricted diet") OR "salt reduction") OR "dietary sodium reduction")))) AND (("Randomized Controlled Trial"[Publication Type]) OR "randomized controlled trial") NOT "Review"[Publication Type])) Filters: Publication date from 2011/10/19 to 2018/11/30	139	
#21	Search ((((((("blood pressure"[Mesh] OR "blood pressure"))) AND ((((((((("sodium, dietary"[Mesh]) OR "dietary sodium") OR "sodium chloride, dietary"[Mesh]) OR "dietary sodium chloride") OR "dietary salt") OR "Diet, Sodium-Restricted"[Mesh]) OR "sodium-restricted diet") OR "salt reduction") OR "dietary sodium reduction")))) AND (("Randomized Controlled Trial"[Publication Type]) OR "randomized controlled trial") NOT "Review"[Publication Type])	600	
#20	Search (((((("blood pressure"[Mesh] OR "blood pressure"))) AND ((((((((("sodium, dietary"[Mesh]) OR "dietary sodium") OR "sodium chloride, dietary"[Mesh]) OR "dietary sodium chloride") OR "dietary salt") OR "Diet, Sodium-Restricted"[Mesh]) OR "sodium-restricted diet") OR "salt reduction") OR "dietary sodium reduction")))) AND (("Randomized	612	

Search	Query	Items found	Notes
	Controlled Trial"[Publication Type]) OR "randomized controlled trial")		
#19	Search ("Randomized Controlled Trial"[Publication Type]) OR "randomized controlled trial"	493,394	
#18	Search "randomized controlled trial"	493,021	
#17	Search "Randomized Controlled Trial"[Publication Type]	472,544	
#16	Search ((("blood pressure"[Mesh] OR "blood pressure"))) AND ((((((((("sodium, dietary"[Mesh]) OR "dietary sodium") OR "sodium chloride, dietary"[Mesh]) OR "dietary sodium chloride") OR "dietary salt") OR "Diet, Sodium-Restricted"[Mesh]) OR "sodium-restricted diet") OR "salt reduction") OR "dietary sodium reduction"))	7,186	
#15	Search (((((((("sodium, dietary"[Mesh]) OR "dietary sodium") OR "sodium chloride, dietary"[Mesh]) OR "dietary sodium chloride") OR "dietary salt") OR "Diet, Sodium-Restricted"[Mesh]) OR "sodium-restricted diet") OR "salt reduction") OR "dietary sodium reduction")	21,576	
#14	Search "sodium restricted diet"	6,155	
#13	Search "dietary sodium reduction"	68	
#12	Search "salt reduction"	630	
#11	Search "sodium-restricted diet"	6,155	
#10	Search "Diet, Sodium-Restricted"[Mesh]	6,081	
#9	Search "dietary salt"	1,833	
#8	Search "dietary sodium chloride"	6,387	
#7	Search "sodium chloride, dietary"[Mesh]	6,300	
#6	Search ("sodium, dietary"[Mesh] OR "dietary sodium")	16,230	
#5	Search "dietary sodium"	10,409	
#4	Search "sodium, dietary"[Mesh]	14,521	
#3	Search ("blood pressure"[Mesh] OR "blood pressure")	434,634	
#2	Search "blood pressure"	422,812	
#1	Search "blood pressure"[Mesh]	278,802	

Appendix Table A2.
Search of the Cochrane Library database

Step	Term	Number of records
#1	MeSH descriptor: [Blood Pressure] explode all trees	26,375
#2	“blood pressure”	68,992
#3	#1 or #2	69,595
#4	MeSH descriptor: [Sodium, Dietary] explode all trees	634
#5	MeSH descriptor: [Sodium Chloride, Dietary] explode all trees	270
#6	MeSH descriptor: [Diet, Sodium-Restricted] explode all trees	581
#7	“dietary sodium”	495
#8	“dietary sodium chloride”	15
#9	“sodium-restricted diet”	48
#10	“salt reduction”	106
#11	“dietary sodium reduction”	37
#12	“#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11	1,360
#13	“#3 and #12	841
#14	“systematic review”	12,132
#15	“#13 and #14”	18
#16	“#15” publication year from 2011 to 2017	17
#17	“#16” publication year from 2011 to 2018	17

Appendix Table A3.
Search of the database from Centre for Reviews and Dissemination

Step	Term	Number of records
1	MeSH DESCRIPTOR Blood Pressure EXPLODE ALL TREES	573
2	("blood pressure")	1,743
3	MeSH DESCRIPTOR Sodium, Dietary EXPLODE ALL TREES	30
4	("dietary sodium")	8
5	MeSH DESCRIPTOR Diet, Sodium-Restricted EXPLODE ALL TREES	21
6	("sodium-restricted diet")	2
7	("salt reduction")	16
8	("dietary salt")	13
9	#3 OR #4 OR #5 OR #6 OR #7 OR #8	59
10	#1 OR #2	1,757
11	#9 AND #10	32
12	* FROM 2011 TO 2018	38,823
13	#11 AND #12	12
14	MeSH DESCRIPTOR Kidney EXPLODE ALL TREES	176
15	MeSH DESCRIPTOR Glomerular Filtration Rate EXPLODE ALL TREES	92
16	("glomerular filtration rate") FROM 2011 TO 2018	86
17	#15 OR #16	116
18	#14 AND #17	12
19	#11 AND #18	0

Note. Search selected: #13

B – IRB APPROVAL LETTERS

Rutgers eIRB, Health Sciences IRB - Newark

Rutgers University eIRB: Study Approved

eIRB@ored.rutgers.edu

Wed 11/29/2017 10:43 AM

To: Linda Moore <moorelw@shp.rutgers.edu>; Laura Byham-Gray <byhamgld@shp.rutgers.edu>;

Cc: Claribel Vega <vegacl@ored.rutgers.edu>;

RUTGERS eIRB

Arts & Sciences IRB - New Brunswick
335 George Street
Suite 3100, 3rd Floor
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Phone: 732-235-2866

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New Brunswick, NJ 08901
Phone: 732-235-9806

Health Sciences IRB - Newark
65 Bergen Street
Suite 511, 5th Floor
Newark, NJ 07107
Phone: 973-972-3608

DHHS Federal Wide Assurance Identifier: FWA00003913
IRB Chair Person: Cheryl Kennedy
IRB Director: Carlotta Rodriguez
Effective Date: 11/29/2017
Approval Date: 11/20/2017

eIRB Notice of Approval for Initial Submission # Pro20170001674

STUDY PROFILE

Study ID: Pro20170001674
Title: Blood Pressure, Dietary Sodium, and Kidney Function in U.S. Adults

Principal Investigator:	Linda Moore	**Study Coordinator:**	Linda Moore
Co-Investigator(s):	Laura Byham-Gray Jesse Plascak Diane Rigassio Radler	**Other Study Staff:**	Laura Byham-Gray
Sponsor:	Department Funded		
Risk Determination:	Minimal Risk		
Review Type:	Exempt	**Exempt Category:**	4

Houston Methodist Hospital, Institutional Review Board

HOUSTON Methodist
LEADING MEDICINE

November 9, 2017

TO: Linda Moore

SUBJECT: HMRI Determination of Not Human Subject Research: Blood Pressure, Dietary Sodium, and Kidney Function in U.S. Adults

Purpose: The purpose of this research is to report the relationship between the dietary sodium and the systolic and diastolic blood pressure of U.S. adults according to kidney function level while accounting for potential confounders using NHANES data from 2003-2014. NHANES is the National Health and Nutrition Examination Survey conducted annually across the non-institutionalized U.S. residents and is reported publicly in 2-year cycles.

Data will be stored on Houston Methodist (HM) computer and access to the statistical software is through an HMH server. All data is de-identified when received from the Centers for Disease Control and Prevention website.

Based on a review of the proposal for the above mentioned project, this is Not Human Subject Research and does not require IRB review or approval. The data is not identifiable and therefore is not human subject research per 45CFR46.

Thank you for your question. If the scope of the project changes, and there is any question about the involvement of human subjects, please contact the IRB before proceeding.

If you have any questions, do not hesitate to contact me.

Sincerely,

Mary K Clancy, MSN CCRC CIP
Director, HMRI Research Protections

C – RESULTS TABLES AND FIGURES ACCORDING TO ANTIHYPERTENSIVE AGENTS

Appendix Table C1.
Demographic and clinical characteristics of U.S. nonpregnant adults in NHANES 2003-2014 who were not prescribed or were prescribed antihypertensive agents

Parameter	Not Prescribed Antihypertensive Agents							Prescribed Antihypertensive Agents						
	M	*SE*	*Med*	*IQR*	*n*	Grp, %	Sub, %	*M*	*SE*	*Med*	*IQR*	*n*	Grp, %	Sub, %
Number of participants					19,157	50.6	73.3					8,786	18.4	26.7
Age (years)*	31.4	0.4	41	[30, 52]				61.9	0.2	63	[53, 72]			
Gender*														
Males					9,776	25.3	50.2					4,318	8.6	47.1
Females					9,381	25.0	49.8					4,468	9.7	52.9
Race and ethnicity*														
Non-Hispanic White					8,612	34.2	67.9					4,587	13.8	75.2
Non-Hispanic Black					3,643	5.3	10.5					2,219	2.4	13.0
Mexican American					3,566	4.9	9.7					959	0.8	8.2
Non-Mexican American Hispanic					1,677	2.6	5.2					561	0.5	2.1

Parameter	Not Prescribed Antihypertensive Agents							Prescribed Antihypertensive Agents						
	M	*SE*	*Med*	*IQR*	*n*	Grp, %	Sub, %	*M*	*SE*	*Med*	*IQR*	*n*	Grp, %	Sub, %
Other					1,659	3.4	6.7					460	0.9	4.8
Education level*														
Less than HS diploma					4,725	11.1	16.1					2,618	5.2	20.6
HS or equivalent					4,344	15.8	22.8					2,201	6.5	25.7
Some college					5,686	22.7	32.7					2,325	7.3	29.0
College degree or higher					4,383	19.7	28.5					1,635	6.2	24.7
Income status, annual*														
<$20,000					4,609	9.6	19.1					2,454	3.8	20.4
$20,000 to <$45,000					6,108	14.4	28.6					2,933	6.0	32.9
$45,000 to <$75,000					3,375	10.3	20.4					1,541	3.7	20.4
≥$75,000					4,434	16.1	31.9					1,610	4.8	26.3
BMI (kg/m^2)*	27.8	0.1	26.8	[23.5,31]	19,033			31.0	0.1	29.9	[26.3, 34.4]	8,631		
BMI category*														
<18.5					365	1.0	1.9					68	0.1	0.7
18.5 to <25.0					6,251	18.0	34.6					1,538	3.2	17.2
25 to <30					6,470	17.6	33.8					2,874	6.2	33.0
≥30					5,947	15.5	29.7					4,151	9.3	49.2
Evidence of diabetes*					1,700	4.4	7.2					3,301	7.3	32.6

Parameter	Not Prescribed Antihypertensive Agents							Prescribed Antihypertensive Agents						
	M	*SE*	*Med*	*IQR*	*n*	Grp, %	Sub, %	*M*	*SE*	*Med*	*IQR*	*n*	Grp, %	Sub, %
Evidence of hypertension*					2,601	6.8	11.8							
Sys. blood pressure ≥140 or Dias. pressure ≥90 mmHg*					2,601	6.9	11.8					2,907	6.3	29.8
Awareness of hypertension*					2,594	8.0	12.5					7,435	20.0	85.1
Taking anti-hypertensive agents					0							8,786	18.3	100
Number of anti-hypertensive agents used								1.7	0.0	1	[1, 2]			
Distribution of antihyper-tensive agents														
None					19,157	73.3	100							
1												4,489	10.0	54.4
2												2,540	5.2	28.2
3 or more												1,757	3.2	17.4
Type of antihyper-tensive agents														
None					19,157	73.3	100							

Parameter	Not Prescribed Antihypertensive Agents							Prescribed Antihypertensive Agents						
	M	*SE*	*Med*	*IQR*	*n*	Grp, %	Sub, %	*M*	*SE*	*Med*	*IQR*	*n*	Grp, %	Sub, %
Diuretics alone												720	1.6	8.7
Set A												4,086	8.7	47.7
Set B												3,266	6.5	35.5
Set C												714	1.5	8.1
ACR (mg/g)*	16.7	0.8	5.9	[4.0, 9.8]	18,951			68.2	5.2	8.6	[5.2, 19.7]	8,597		
ACR category*														
<10					13,789	41.8	75.6					4,348	11.2	56.2
10-<30					3,701	10.0	18.2					2,348	5.2	26.2
30-300					1,299	3.1	5.6					1,513	2.9	14.3
>300					162	0.3	0.6					388	0.7	3.3
Kidney disease awareness*					256	0.8	1.1					552	1.3	5.0
Dialysis in previous year[a]**					13	1.0	2.8					68	5.7	9.1
eGFR[b] (ml/min/ 1.73m^2)*	90.2	0.3	91.9	[71.7, 107.4]	18,280			71.2	0.4	70.4	[53.9, 88.8]	8,310		
Kidney function level[b] (ml/min/ 1.73m^2)*														
<30 or dialysis					54	0.1	0.1					364	0.7	3.1
30-44					271	0.7	1.1					969	2.3	10.3
45-59					1,427	5.3	8.7					1,754	4.8	21.5
60-74					2,969	11.9	19.6					1,534	4.5	20.4
75-89					3,202	10.9	17.9					1,734	4.7	21.3
90-105					4,322	14.3	23.5					1,305	3.7	16.5
>105					6,035	17.7	29.0					650	1.5	6.9

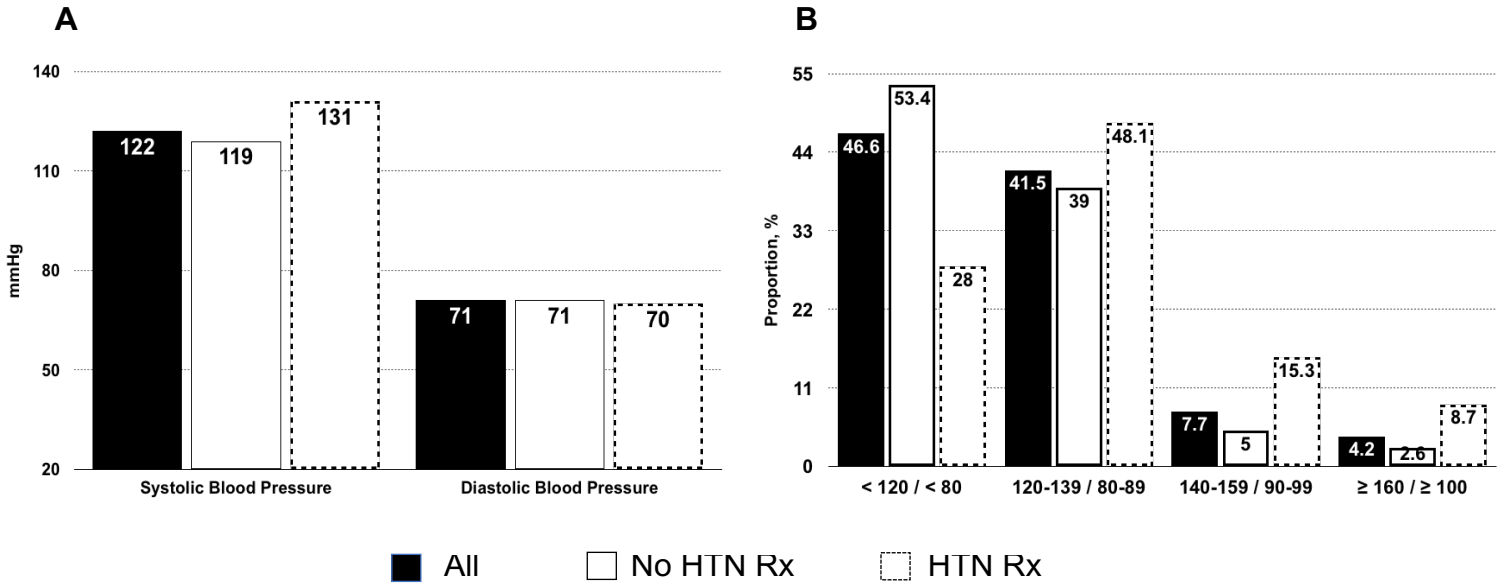
Parameter	Not Prescribed Antihypertensive Agents							Prescribed Antihypertensive Agents						
	M	*SE*	*Med*	*IQR*	*n*	Grp, %	Sub, %	*M*	*SE*	*Med*	*IQR*	*n*	Grp, %	Sub, %
eGFR[a] <60 ml/min/ 1.73m^2*					1,752	6.1	10.0					3,087	7.7	34.9
Smoking status*														
Current					4,354	16.1	23.3					1,231	3.5	14.1
Former					4,201	15.5	22.6					3,243	9.3	37.0
Never					10,556	37.2	54.1					4,304	12.3	48.9

Note. % = survey weighted population proportion; ACR = albumin-to-creatinine ratio; BMI = body mass index; eGFR = estimated glomerular filtration rate; HS = High school; IQR = interquartile range; *M* = mean; *Med* = median; NHANES = National Health and Nutrition Examination Survey; *SE* = standard error of the mean; Set A. = renin-aldosterone inhibitors, calcium channel blockers, beta blockers or any combination of these; Set B. = diuretics plus renin-aldosterone inhibitors, calcium channel blockers, or beta blockers; Set C. = any other antihypertensive agent or any combination of three drugs. Wald Log-Linear Chi-square or One-way Analysis of Variance, as appropriate.

*p-value <.001, **p-value <.05; between not prescribed vs prescribed antihypertensive agents

[a]Denominator is participants who answered “yes” to kidney disease awareness

[b]Estimated glomerular filtration rate using the CKD-Epi equation (Levey et al., 2009)



Appendix C Figure 1. Mean systolic and diastolic blood pressure (A) and proportion of U.S. adults having blood pressure <120 / <90 mmHg, 120-139 / 80-89 mmHg, 140-159 / 90-99 mmHg or ≥ 160 / ≥ 100 mmHg in U.S. non-pregnant adults in NHANES 2003-2014 by whether they were not prescribed or were prescribed antihypertensive agents. HTN Rx = antihypertensive agents, NHANES = National Health and Nutrition Examination Survey

Appendix Table C2.
Descriptors of dietary sodium intake and blood pressure in U.S. nonpregnant adults in NHANES 2003-2014 who were not prescribed or were prescribed antihypertensive agents

Parameter	Not Prescribed Antihypertensive Agents							Prescribed Antihypertensive Agents						
	M	*SE*	*Med*	*IQR*	*n*	Grp, %	Sub, %	*M*	*SE*	*Med*	*IQR*	*n*	Grp, %	Sub, %
Number of participants					19,157	50.6	73.3					8,786	18.4	26.7
Dietary sodium														
mg/day	3,624	17	3,310	[2,362, 4,551]				3,253	28	2,940	[2,115, 4,037]			
mEq/day	158	1	144	[103, 198]				141	1	128	[92, 176]			
g NaCl/day	9.1	0.1	8.3	[5.9, 11.4]				8.1	0.1	7.4	[5.3, 10.1]			
Dietary energy (kcal/day)	2,258	10	2,076	[1,542, 2,782]				1,930	13	1,799	[1,349, 2,368]			
Dietary sodium density (mg sodium/1000 kcal/day)	1,650	6	1,590	[1,298, 1,913]				1,721	9	1,651	[1,348, 1,991]			
Dietary sodium guidelines (mg/day)														
≥2,300					14,187	38.7	76.5					5,772	12.7	69.1
<2,300					4,970	11.9	23.5					3,014	5.7	30.9
Systolic blood pressure, mmHg	119.4	0.2	117.3	[109.3, 127.3]				130.5	0.3	128.7	[117.3, 141.3]			
Diastolic blood pressure, mmHg	71.2	0.2	71.3	[64, 78]				70.1	0.2	70.7	[62, 78.7]			
Blood pressure category														

Parameter	Not Prescribed Antihypertensive Agents							Prescribed Antihypertensive Agents						
	M	*SE*	*Med*	*IQR*	*n*	Grp, %	Sub, %	*M*	*SE*	*Med*	*IQR*	*n*	Grp, %	Sub, %
<120 mmHg systolic and <80 mmHg diastolic					9,937	31.1	53.4					2,243	5.9	28.0
120-139 mmHg sys. or 80-89 mmHg dias.					7,414	22.8	39.0					4,146	10.2	48.1
140-159 mmHg sys. or 90-99 mmHg dias.					1,141	2.9	5.0					1,475	3.2	15.3
≥ 160 mmHg sys. or ≥ 100 mmHg dias.					665	1.5	2.6					922	1.8	8.7

Note. dias. = diastolic, Grp. = survey weighted population group, IQR = interquartile range, *M* = mean, *Med*. = median, mmHg = millimeters of mercury, n = sample count, NHANES = National Health and Nutrition Examination Survey, *SE* = standard error, Sub. = survey weighted population subgroup, sys. = systolic. Wald Log-linear Chi-square or One-way Analysis of Variance, as appropriate. All p-values <.001 for difference between not prescribed vs prescribed antihypertensive agents

Appendix Table C3.
The relationship between key demographic and clinical characteristics and dietary sodium in mg/day intake in U.S. nonpregnant adults in NHANES 2003-2014 who were not prescribed or were prescribed antihypertensive agents

Parameter	Not Prescribed Antihypertensive Agents						Prescribed Antihypertensive Agents					
	n	*r*	*B*	*SE*	95% CI	*p*-value	n	*r*	*B*	*SE*	95% CI	*p*-value
Age, years	19,157	.140	-17	1	[-19, -15]	<.001	8,786	.222	-28	2	[-32, -24]	<.001
Gender		.345				<.001		.316				<.001
Males	9,776		1247	31	[1186, 1308]		4,316		1037	48	[943, 1132]	
Females	9,381		ref				4,468		ref			
Race, ethnicity		.026				<.001		.56				<.001
Non-Hispanic White	8,612		ref				4,587		ref			
Non-Hispanic Black	3,643		-146	50	[-246, -46]	.005	2,219		-288	56	[-398, -177]	<.001
Mexican American	3,566		-63	53	[-168, 41]	.233	959		-210	79	[-366, -53]	.009
Other	3,336		-50	45	[-140, 40]	.277	1,021		-179	76	[-330, -27]	.022
Education		.056				<.001		.100				<.001
Less than HS	4,725		-302	55	[-411, -193]	<.001	2,618		-478	72	[-620, -335]	<.001
HS or equivalent	4,344		-72	54	[-180, 36]	.189	2,201		-257	74	[-404, -109]	<.001
Some college	5,686		-47	48	[-143, 49]	.337	2,325		-157	82	[-320, 5]	.057
College degree or higher	4,383		ref				1,635	ref				
Income		.063				<.001		.159				<.001
<$20,000	4,609		-238	54	[-345, -132]	<.001	2,454		-691	76	[-842, -539]	<.001
$20,000 to <$45,000	6,108		-263	49	[-360, -165]	<.001	2,933		-494	76	[-645, -344]	<.001

Parameter	Not Prescribed Antihypertensive Agents						Prescribed Antihypertensive Agents					
	n	*r*	*B*	*SE*	95% CI	*p*-value	n	*r*	*B*	*SE*	95% CI	*p*-value
$45,000 to <$75,000	3,375		-89	51	[-191, 13]	.085	1,541		-191	88	[-366, -15]	.034
≥ $75,000	4,434		ref				1,610		ref			
BMI (kg/m^2)	19,033	.029	8	3	[3, 13]	.001	8,631	.112	26	4	[19, 34]	<.001
BMI category (kg/m^2)		.034				.002		.106				<.001
<18.5	365		-291	123	[-535, -46]	.020	68		39	180	[-319, 397]	.829
18.5 to <25.0	6,251		ref				1,538		ref			
25.0 to <30.0	6,470		70	48	[-25, 165]	.145	2,874		292	75	[320, 629]	<.001
≥30.0	5,947		91	44	[2, 179]	.045	4,151		475	78	[320, 629]	<.001
Evidence of diabetes		.036				.006		.031				.947
No	16,614		ref				5,202		ref			
Yes	1,700		-175	62	[-298, -53]		3,301		-4	54	[-111, 104]	
High blood pressure awareness	2,594	.002	-10	64	[-136, 116]	.871	7,435	.002	7	76	[-114, 158]	.928
Number of antihypertensive agents used	19,157	0					8,786	.061				.001
1							4,489		ref			
2							2,540		-186	64	[-314, -58]	.005
3 or more							1,757		-219	64	[-346, -92]	<.001

Parameter	Not Prescribed Antihypertensive Agents						Prescribed Antihypertensive Agents					
	n	*r*	*B*	*SE*	95% CI	*p*-value	n	*r*	*B*	*SE*	95% CI	*p*-value
Type of antihypertensive agent used	19,157						8,786	.070				<.001
Diuretics alone							720		ref			
Set A							4,086		342	89	[165, 518]	<.001
Set B							3,266		245	85	[77, 413]	.005
Set C							714		513	128	[258, 767]	<.001
Blood pressure category (mmHg)		.074				<.001		.098				<.001
< 120 sys. and < 80 dias.	9,937		ref				2,243		ref			
120-139 sys. or 80-89 dias.	7,414		228	37	[155, 301]	<.001	4,146		62	59	[-56, 180]	.299
140-159 sys. or 90-99 dias.	1,141		-202	71	[-343, -61]	.005	1,475		-263	60	[-382, -144]	<.001
≥ 160 sys. or ≥ 100 dias.	665		-180	111	[-402, 40]	.108	922		-421	83	[-585, -257]	<.001
eGFR[a] (ml/min/1.73m^2)	18,280	.082	-7	0.8	[-8, -5]	<.001	8,310	.057	4	1	[2, 6]	<.001
ACR (mg/g)	18,951	.017	-0.25	0.11	[-0.47, -0.04]	.023	8,597	.011	-0.06	0.04	[-0.15, 0.03]	.189
Kidney disease awareness	256	.032	-557	199	[-951, -163]	.006	552	.049	-371	74	[-518, -224]	<.001

Parameter	Not Prescribed Antihypertensive Agents						Prescribed Antihypertensive Agents					
	n	*r*	*B*	*SE*	95% CI	*p*-value	n	*r*	*B*	*SE*	95% CI	*p*-value
Kidney function level[a] (ml/min/1.73m^2)	18,280	.113					8,310	.086				<.001
<30 or dialysis	54		-909	165	[-1237, -582]	<.001	364		-592	112	[-815, -369]	<.001
30 to 44	271		-374	165	[-702, -46]	.026	969		-245	120	[-483, -7]	.044
45 to 59	1,427		456	76	[305, 608]	<.001	1,754		8	124	[-237, 254]	.947
60 to 74	2,969		441	56	[331, 553]	<.001	1,534		50	121	[-191, 291]	.680
75 to 89	3,202		31	52	[-72, 135]	.550	1,734		-73	106	[-284, 138]	.493
90 to 105	4,322		30	48	[-64, 125]	.519	1,305		112	121	[-128, 353]	.356
>105	6,035		ref				650		ref			
eGFR[a] (ml/min/1.73m$^{2)}$	18,280						8,310					
< 60	1,752	.039	232	70	[94, 370]	.001	3,087	.041	-140	55	[-249, -31]	.012
≥ 60	16,528		ref				5,223		ref			
Smoking status	19,111	.029				.034	8,778	.042				.036
Never smoker	10,556		ref				4,304		ref			
Former smoker	4,201		119	47	[25, 211]	.013	3,243		148	56	[36, 260]	.010
Current smoker	4,354		83	56	[25, 212]	.013	1,231		77	75	[-72, 225]	.307

Note. ACR = albumin-to-creatinine ratio; *B* = parameter estimate; BMI = body mass index; CI = confidence interval; eGFR = estimated glomerular filtration rate; HS = High school; NHANES = National Health and Nutrition Examination Survey; *r* = correlation coefficient; *SE* = standard error of the mean; Set A. = renin-aldosterone inhibitors, calcium channel blockers, beta blockers or any combination of these; Set B. = diuretics plus renin-aldosterone inhibitors, calcium channel blockers, or beta blockers; Set C. = any other antihypertensive agent or any combination of three drugs. Wald log-linear chi-square or One-way Analysis of Variance, as appropriate

[a]Estimated glomerular filtration rate using the CKD-Epi equation (Levey et al., 2009)

Appendix Table C4.
The relationship between key demographic and clinical characteristics and dietary sodium < 2,300 or ≥ 2,300 mg/day in U.S. nonpregnant adults in NHANES 2003-2014 who were not prescribed or were prescribed antihypertensive agents. Odds for exceeding the U.S. Dietary Guideline of < 2,300 mg dietary sodium/day

Variable	Not Prescribed Antihypertensive Agents				Prescribed Antihypertensive Agents			
	n	Odds Ratio	95% CI	p-value	n	Odds Ratio	95% CI	p-value
Age, years	19,157	1.01	[1.01, 1.02]	<.001	8,786	1.02	[1.02, 1.03]	<.001
Gender, females referent	9,381				4,468			
Males	9,776	1.26	[1.23, 1.28]	<.001	4,318	1.36	[1.31, 1.42]	<.001
Race or ethnicity, non-Hispanic White referent	8,612	1.00			4,587	1.00		
Non-Hispanic Black	3,643	0.81	[0.74, 0.90]	<.001	2,219	0.79	[0.66, 0.90]	<.001
Mexican American	3,566	0.89	[0.80, 0.99]	.037	959	0.89	[0.72, 1.10]	.263
Other Latin or Other races	1,677	0.94	[0.85, 1.04]	.247	561	0.95	[0.78, 1.17]	.649
Education, College degree or higher referent	4,383	1.00			1,635	1.00		
Less than HS	4,725	0.69	[0.63, 0.75]	<.001	2,618	0.72	[0.65, 0.80]	<.001
HS or equivalent	4,344	0.90	[0.83, 0.98]	.020	2,201	1.00	[0.90, 1.12]	.996
Some college	5,686	1.06	[0.99, 1.14]	.071	2,325	1.08	[.98, 1.18]	.104
Income, ≥$75,000 referent	4,434	1.00			1,610	1.00		
<$20,000	4,609	0.74	[0.68, 0.81]	<.001	2,454	0.67	[0.60, 0.74]	<.001
$20,000 to <$45,000	6,108	0.87	[0.81, 0.94]	<.001	2,933	0.89	[0.81, 0.99]	.032
$45,000 to <$75,000	3,375	1.12	[1.01, 1.25]	.037	1,541	1.16	[0.99, 1.36]	.055
BMI (kg/m^2)	19,033	0.99	[0.98, 1.00]	.002	8,631	0.97	[0.96, 0.98]	<.001
BMI category, 18.5 to <25.0 referent	6,251	1.00			1,538	1.00		
<18.5	365	0.57	[0.41, 0.80]	.001	68	1.10	[0.60, 2.04]	.749

Variable	Not Prescribed Antihypertensive Agents				Prescribed Antihypertensive Agents			
	n	Odds Ratio	95% CI	p-value	n	Odds Ratio	95% CI	p-value
25.0 to <30	6,470	1.06	[0.99, 1.14]	.116	2,874	1.00	[0.92, 1.09]	.925
≥30	5,947	1.07	[0.99, 1.15]	.081	4,151	1.14	[1.07, 1.22]	<.001
Evidence of diabetes, no evidence referent	16,614				5,202			
Yes	1,700	0.94	[0.80, 1.10]	.447	3,301	0.98	[0.90, 1.06]	.581
High blood pressure awareness	2,594	0.90	[0.79, 1.03]	.129	7,435	1.01	[0.98, 1.03]	.715
Number of antihypertensive agents used	19,157	0			8.786			
1					4,489	1.06	[0.99, 1.12]	.065
2					2,540	0.98	[0.89, 1.09]	.722
3 or more					1,757	0.88	[0.77, 0.99]	.049
None, ref						1.00		
Type of antihypertensive agent	19,157	0			8,786			
Diuretics alone					720	0.75	[0.61, .93]	<.001
Set A					4,086	1.04	[0.97, 1.11]	.229
Set B					3,266	0.94	[0.87, 1.02]	.142
Set C					714	1.46	[1.17, 1.81]	<.001
ACR (mg/g)	18,951	1.00	[1.00, 1.00]	.199	8,597	1.00	[1.00, 1.00]	.251
Kidney disease awareness	256	0.51	[0.31, 0.82]	.005	552	0.79	[0.62, 1.00]	.053
Kidney function level[a], ml/min/1.73m^2, >105 referent	6,035	1.00			650	1.00		
<30 or dialysis	54	0.50	[0.23, 1.08]	.076	364	0.55	[0.44, 0.70]	<.001

Variable	Not Prescribed Antihypertensive Agents				Prescribed Antihypertensive Agents			
	n	Odds Ratio	95% CI	p-value	n	Odds Ratio	95% CI	p-value
30 to 44	271	0.52	[0.36, 0.75]	<.001	969	0.89	[0.72, 1.01]	.073
45 to 59	1,427	1.48	[1.26, 1.74]	<.001	1,754	1.01	[0.89, 1.14]	.920
60 to 74	2,969	1.29	[1.15, 1.45]	<.001	1,534	1.03	[0.90, 1.18]	.679
75 to 89	3,202	0.93	[0.85, 1.02]	.121	1,734	1.03	[0.91, 1.16]	.619
90 to 105	4,322	0.91	[0.83, 1.01]	.096	1,305	1.19	[1.03, 1.38]	.021
eGFR[a] <60 ml/min/1.73m^2	18,280	1.48	[1.26, 1.74]	<.001	8,310	0.90	[0.84, 0.97]	.005
Smoking status, never smoker referent	10,556	1.00			4,304	1.00		
Former smoker	4,201	1.04	[0.95, 1.15]	.351	3,243	1.15	[1.07, 1.24]	<.001
Current smoker	4,354	0.94	[0.85, 1.04]	.218	1,231	0.98	[0.81, 1.19]	.833

Note. ACR = albumin-to-creatinine ratio; BMI = body mass index; CI = confidence interval; eGFR = estimated glomerular filtration rate; HS = High school; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; Set A. = renin-aldosterone inhibitors, calcium channel blockers, beta blockers or any combination of these; Set B. = diuretics plus renin-aldosterone inhibitors, calcium channel blockers, or beta blockers; Set C. = any other antihypertensive agent or any combination of three drugs. Chi-square, Loglinear Chi-square, as appropriate

[a]Estimated glomerular filtration rate using the CKD-Epi equation (Levey et al., 2009)

Appendix Table C5.
The relationship between key demographic and clinical characteristics and systolic blood pressure in U.S. nonpregnant adults in HNANES 2003-2014 who were not prescribed or were prescribed antihypertensive agents

Systolic blood pressure	Not Prescribed Antihypertensive Agents						Prescribed Antihypertensive Agents					
Variable	n	*r*	*B*	*SE*	95% CI	*p*-value	n	*r*	*B*	*SE*	95% CI	*p*-value
Age, years	19,157	.375	0.40	0.01	[0.38, 0.42]	<.001	8,786	.247	0.38	.012	[0.34, 0.41]	<.001
Gender, males; ref=females	9,381	.168	5.27	0.26	[4.77, 5.79]	<.001	4,468	.073	-2.91	0.52	[-3.94, -1.88]	<.001
Race, ethnicity; ref=Non-Hispanic white	9,776	.072				<.001	4,318	.078				<.001
Non-Hispanic black	8,612	.063	3.22	0.51	[2.21, 4.22]	<.001	4,587	.062	3.66	0.64	[2.39, 4.93]	<.001
Mexican American	3,643	.024	-1.29	0.47	[-2.24, -0.36]	.007	2,219	.026	2.57	1.07	[0.44, 4.69]	.018
Other	3,566	.036	-1.73	0.46	[-2.64, -0.82]	<.001	959	.026	1.96	0.81	[0.35, 3.57]	.018
Education, ref=College degree or higher	3,336	.102				<.001	1,021	.124				<.001
Less than HS	4,383	.063	2.71	0.47	[1.77, 3.64]	<.001	1,635	.082	4.02	0.57	[2.88, 5.16]	<.001
HS or equivalent	4,725	.046	1.70	0.45	[0.81, 2.60]	<.001	2,618	.041	1.85	0.62	[0.62, 3.08]	.004
Some college	4,344	.007	-0.23	0.32	[-0.87, 0.42]	.489	2,201	.010	-0.42	0.62	[-1.64, 0.81]	.502
Income, ref=$75,000/year or higher	5,686	.062				<.001	2,325	.121				<.001
<$20,000	4,434	.019	0.75	0.43	[-0.10, 1.60]	.081	1,610	.094	4.64	0.82	[3.02, 6.26]	<.001
$20,000 to <$45,000	4,609	.031	1.06	0.37	[0.33, 1.79]	.005	2,454	.030	1.28	0.56	[0.18, 2.39]	.024
$45,000 to <$75,000	6,108	.019	0.72	0.39	[-0.06, 1.50]	.072	2,933	.028	-1.46	0.80	[-3.05, 0.13]	.071
BMI, kg/m^2	3,375	.177	0.44	0.03	[0.39, 0.49]	<.001	1,541	.049	-0.14	0.05	[-0.23, -0.05]	.004
BMI category, ref=18.5-24.9 kg/m^2	19,033	.177				<.001	8,631	.074				.001
<18.5	6,251	.061	-6.95	1.27	[-9.48, -4.42]	<.001	1,538	.021	4.98	4.08	[-3.12, 13.08]	.225
25.0 to <30.0	365	.030	0.98	0.32	[0.34, 1.62]	.003	68	.004	0.18	0.55	[-0.93, 1.28]	.752

Systolic blood pressure	Not Prescribed Antihypertensive Agents						Prescribed Antihypertensive Agents					
Variable	n	*r*	*B*	*SE*	95% CI	*p*-value	n	*r*	*B*	*SE*	95% CI	*p*-value
≥30.0	6,470	.138	4.71	0.34	[4.03, 5.40]	<.001	2,874	.056	-2.22	.54	[-3.28, -1.16]	<.001
Diabetes status, ref=no evidence	5,947						4,151					
Yes	16,614	.140	8.44	0.84	[6.77, 10.10]	<.001	5,202	.053	2.24	0.57	[1.11, 3.37]	<.001
High blood pressure awareness	1,700	.285	13.47	0.60	[12.28, 14.66]	<.001	3,301	.139	7.74	0.74	[6.27, 9.20]	<.001
eGFR[a], ml/min/1.73m^2	2,594	.230	-0.16	0.01	[-0.17, -0.14]	<.001	7,435	.084	-0.07	0.01	[-0.09, -0.05]	<.001
Kidney disease awareness	18,280	.014	-2.08	1.39	[-4.83, 0.68]	.138	8,310	.030	2.72	1.30	[0.14, 5.31]	.039
ACR, mg/g	256	.091	0.01	0.00	[0.01, 0.02]	<.001	552	.167	0.01	0.00	[0.01, 0.01]	<.001
Kidney function level[a], ref=>105ml/min/1.73m^2		.230				<.001		.092				<.001
<30 or dialysis	6,035	.037	15.03	4.38	[6.33, 23.74]	<.001	650	.057	6.45	1.74	[2.99, 9.90]	<.001
30 to 44	54	.062	9.04	1.82	[5.43, 12.65]	<.001	364	.041	2.68	0.92	[0.85, 4.51]	.005
45 to 59	271	.121	6.64	0.64	[5.36, 7.92]	<.001	969	.003	-0.13	0.58	[-1.27, 1.02]	.824
60 to 74	1,427	.069	2.70	0.39	[1.92, 3.468]	<.001	1,754	.006	0.31	0.77	[-1.21, 1.84]	.686
75 to 89	2,969	.047	1.90	0.34	[1.22, 2.58]	.600	1,534	.007	0.32	0.62	[-0.91, 1.55]	.603
90 to 105	3,202	.010	0.35	0.49	[-0.57, 1.27]	.452	1,734	.035	-1.85	0.80	[-3.45, -0.25]	.024
eGFR[a] <60 ml/min/1.73m^2	4,322	.140	7.24	0.61	[6.02, 8.46]	<.001	1,305	.045	1.85	0.46	[0.93, 2.76]	<.001
Smoking status, ref=Never smoker	1,752	.087				<.001	3,087	.059				.002
Current smoker	10,556	.011	0.42	0.47	[-0.51, 1.36]	.371	4,304	.055	-3.13	0.93	[-4.97, -1.29]	.001
Former smoker	4,354	.079	2.95	0.39	[2.17, 3.73]	<.001	1,231	.004	-0.14	.62	[-1.37, 1.09]	.820
	4,201						3,243					

Note. ACR = albumin-to-creatinine ratio; BMI = body mass index; CI = confidence interval; eGFR = estimated glomerular filtration rate; HS = High school; NHANES = National Health and Nutrition Examination Survey; Set A. = renin-aldosterone inhibitors, calcium channel blockers, beta blockers or any combination of these; Set B. = diuretics plus renin-aldosterone inhibitors, calcium channel blockers, or beta blockers; Set C. = any other antihypertensive agent or any combination of three drugs. One-way Analysis of Variance

[a]Estimated glomerular filtration rate using the CKD-Epi equation (Levey et al., 2009)

Appendix Table C6.
The relationship between key demographic and clinical characteristics and diastolic blood pressure in U.S. nonpregnant adults in NHANES 2003-2014 who were not prescribed or were prescribed antihypertensive agents

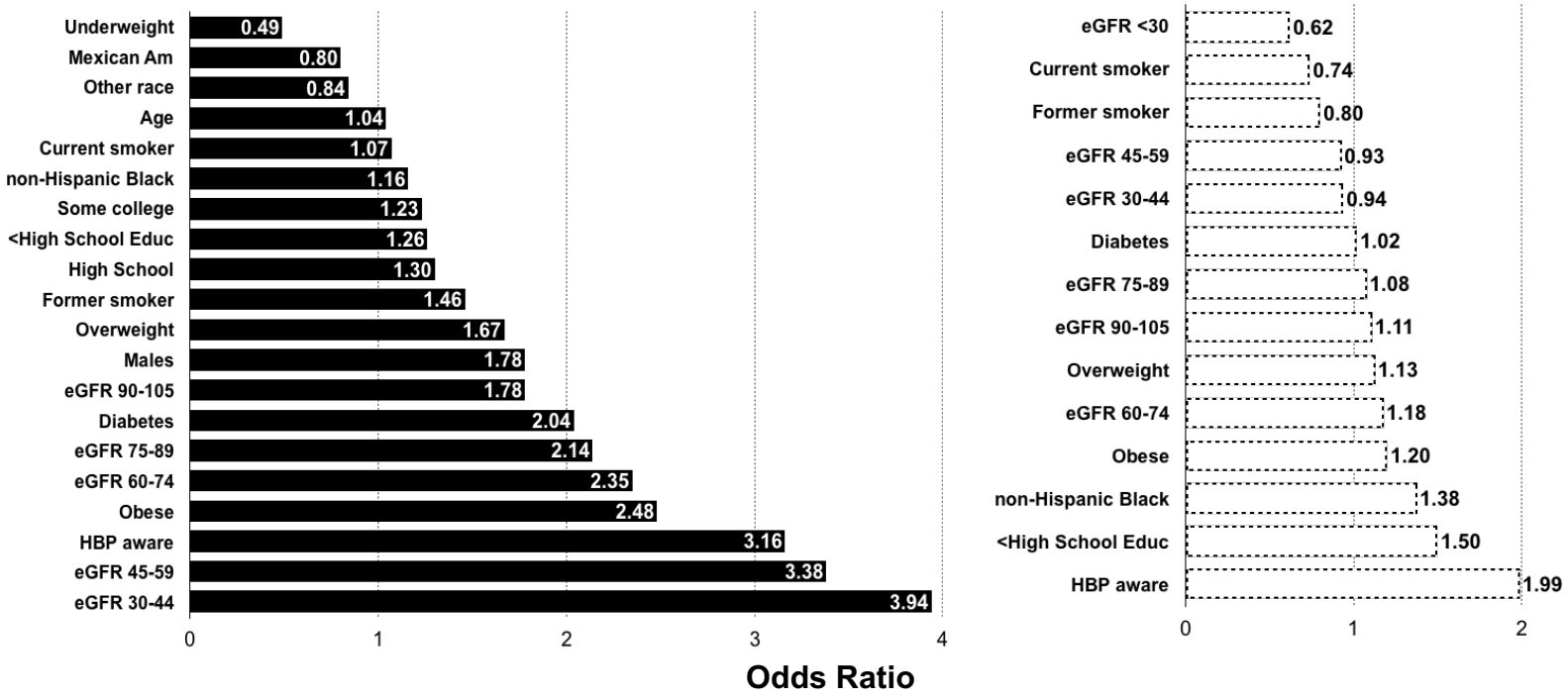
Diastolic blood pressure	Not Prescribed Antihypertensive Agents						Prescribed Antihypertensive Agents					
Variable	n	*r*	*B*	*SE*	95% CI	*p*-value	n	*r*	*B*	*SE*	95% CI	*p*-value
Age, years	19,157	.146	0.11	0.01	[0.10, 0.12]	<.001	8,786	.371	-0.38	0.01	[-0.41, -0.36]	<.001
Gender, females referent	9,381						4,468					
Males	9,776	.125	2.77	0.19	[2.38, 3.15]	<.001	4,318	.066	1.77	0.36	[1.06, 2.49]	<.001
Race, ethnicity; Non-Hispanic white referent	8,612	.048				<.001	4,587	.092				<.001
Non-Hispanic Black	3,643		0.38	0.36	[-0.34, 1.09]	.302	2,219		3.57	0.52	[2.55, 4.60]	<.001
Mexican American	3,566		-1.45	0.41	[-2.26, -0.64]	<.001	959		1.19	0.82	[-0.43, 2.81]	.149
Other	3,336		-0.93	0.41	[-1.74, -0.13]	.024	1,021		1.81	0.61	[0.60, 3.01]	.004
Education, College degree or higher referent	4,383	.030				<.001	1,635	.079				<.001
Less than HS	4,725		-0.67	0.31	[-1.29, -0.05]	.035	2,618		-2.85	0.59	[-4.03, -1.68]	<.001
HS or equivalent	4,344		0.34	0.36	[-0.39, 1.06]	.359	2,201		-0.99	0.59	[-2.16, 0.17]	.095
Some college	5,686		0.18	0.26	[-0.34, 0.70]	.494	2,325		-0.16	0.61	[-1.37, 1.05]	.792
Income, $75,000/year or higher referent	4,434	.063				<.001	1,610	.119				<.001
<$20,000	4,609		-1.66	0.36	[-2.36, -0.95]	<.001	2,454		-3.86	0.50	[-4.86, -2.87]	<.001
$20,000 to <$45,000	6,108		-1.49	0.31	[-2.11, -0.87]	<.001	2,933		-3.67	0.52	[-4.70, -2.63]	<.001
$45,000 to <$75,000	3,375		-0.57	0.40	[-1.36, 0.25]	.169	1,541		-1.77	0.56	[-2.89, -0.65[	.002
BMI, kg/m^2	19,033	.179	0.32	0.02	[0.28, 0.35]	<.001	8,631	.070	0.13	0.03	[0.08, 0.19]	<.001
BMI category, 18.5-24.9 kg/m^2 referent	6,251	.177				<.001	1,538	.062				<.001
<18.5	365		-3.72	1.30	[-6.30, -1.13]	.005	68		-0.59	2.12	[-4.88, 3.70]	.785
25.0 to <30.0	6,470		3.75	0.34	[3.08, 4.42]	<.001	2,874		1.39	0.54	[0.31, 2.47]	.012

Diastolic blood pressure	Not Prescribed Antihypertensive Agents						Prescribed Antihypertensive Agents					
Variable	n	*r*	*B*	*SE*	95% CI	*p*-value	n	*r*	*B*	*SE*	95% CI	*p*-value
≥30.0	5,947		6.42	0.39	[5.65, 7.18]	<.001	4,151		2.24	0.52	[1.22, 3.27]	<.001
Evidence of diabetes, no evidence referent	16,614	.053				<.001	5,202	.108				<.001
Yes	1,700		2.14	0.51	[1.13, 3.14]	<.001	3,301		-3.09	0.42	[-3.93, -2.25]	<.001
High blood pressure awareness	2,594	.180	6.02	0.36	[5.31, 6.73]	<.001	7,435	.090	3.41	0.44	[2.53, 4.28]	<.001
eGFR[a], ml/min/1.73m^2	18,280	.153	-0.07	0.004	[-0.08, -0.07]	<.001	8,310	.218	0.13	0.01	[0.11, 0.14]	<.001
Kidney disease awareness	256	.019	-1.97	0.78	[-3.52, -0.41]	.014	552	.046	-2.85	0.82	[-4.48, -1.21]	<.001
ACR, mg/g		.035	0.003	0.001	[0.001, 0.006]	.013		.024	0.001	0.001	[-0.0002, 0.002]	.107
Kidney function level[a], >105ml/min/1.73m^2 referent	6,035	.179				<.001	650					
<30 or dialysis	54		-4.89	2.15	[-9.16, -0.61]	.026	364		-8.49	0.94	[-10.36, -6.61]	<.001
30 to 44	271		2.43	0.90	[0.64, 4.21]	.008	969		-10.41	0.86	[-12.22, -8.80]	<.001
45 to 59	1,427		5.32	0.42	[4.49, 6.16]	<.001	1,754		-6.70	0.80	[-8.27, -5.12]	<.001
60 to 74	2,969		4.81	0.31	[4.20, 5.42]	<.001	1,534		-3.76	0.80	[-5.36, -2.16]	<.001
75 to 89	3,202		2.66	0.32	[2.02, 3.30]	<.001	1,734		-3.97	0.79	[-5.53, -2.41]	<.001
90 to 105	4,322		3.75	0.27	[3.22, 4.27]	<.001	1,305		-1.77	0.79	[-3.34, -0.20]	.027
eGFR[a] <60 ml/min/1.73m^2	1,752	.064	2.33	0.38	[1.58, 3.09]	<.001	3,087	.194	-5.46	0.37	[-6.19, -4.73]	<.001
Smoking status, Never smoker referent	10,556	.049				<.001	4,304	.072				<.001

Diastolic blood pressure	Not Prescribed Antihypertensive Agents						Prescribed Antihypertensive Agents					
Variable	n	*r*	*B*	*SE*	95% CI	*p*-value	n	*r*	*B*	*SE*	95% CI	*p*-value
Current smoker	4,354		-0.33	0.29	[-0.91, 0.24]	.253	1,231		0.15	0.58	[-0.99, 1.30]	.792
Former smoker	4,201		1.17	0.27	[0.63, 1.70]	<.001	3,243		-1.98	0.36	[-2.68, -1.27]	<.001

Note. ACR = urinary albumin-to-creatinine ratio; BMI = body mass index; CI = confidence interval; eGFR = estimated glomerular filtration rate; HS = high school; NHANES = National Health and Nutrition Examination Survey; Set A. = renin-aldosterone inhibitors, calcium channel blockers, beta blockers or any combination of these; Set B. = diuretics plus renin-aldosterone inhibitors, calcium channel blockers, or beta blockers; Set C. = any other antihypertensive agent or any combination of three drugs. One-way Analysis of Variance

[a]Estimated glomerular filtration rate using the CKD-Epi equation (Levey et al., 2009)



Appendix C Figure 2. Odds for having blood pressure 120-139 / 80-89 mmHg compared to normal blood pressure (< 120 / < 80 mmHg) in participants in NHANES 2003-2014 who were not (■) or were (⬚) prescribed antihypertensive agents.

Note. Educ = education, eGFR = estimated glomerular filtration rate in ml/min/1.73m^2, HBP = high blood pressure, Mexican Am = Mexican American, NHANES = National Health and Nutrition Examination Survey; all *p*-values < .05 from respective referent categories, see Appendix Table C7.

Appendix Table C7.
The relationship between key demographic and clinical characteristics and blood pressure categories in U.S. nonpregnant adults in NHANES 2003-2014 who were not prescribed antihypertensive agents; odds for having blood pressure >120/80 mmHg (n = 9,937)

Variable	120-139 mmHg sys. or 80-89 mmHg dias. n = 7,414				140-159 mmHg sys. or 90-99 mmHg dias. n = 1,141				≥ 160 mmHg sys. or ≥ 100 mmHg dias. n = 665			
	n	*OR*	95% CI	*p*-value	*n*	*OR*	95% CI	*p*-value	*n*	*OR*	95% CI	*p*-value
Age	7,414	1.04	[1.03, 1.04]	<.001	1,141	1.08	[1.08, 1.09]	<.001	665	1.10	[1.09, 1.11]	<.001
Gender, males	2,822	1.78	[1.68, 1.89]	<.001	529	1.20	[1.07, 1.33]	.001	332	0.95	[0.83, 1.09]	.429
Race/ethnicity												
Non-Hispanic Black	1,540	1.16	[1.03, 1.30]	.016	278	1.44	[1.15, 1.81]	.002	186	2.08	[1.55, 2.81]	<.001
Mexican American	1,281	0.80	[0.71, 0.92]	.001	201	0.76	[0.58, 0.99]	.043	130	0.87	[0.59, 1.28]	.469
Other	1,195	0.84	[0.74, 0.95]	.007	142	0.73	[0.56, 0.95]	.018	92	0.93	[0.61, 1.39]	.708
Education												
Less than HS	1,848	1.26	[1.12, 1.42]	<.001	390	2.02	[1.55, 2.64]	<.001	257	3.19	[2.23, 4.57]	<.001
HS or equivalent	1,771	1.30	[1.15, 1.49]	<.001	271	1.48	[1.13, 1.94]	.004	174	2.56	[1.77, 3.71]	<.001
Some college	2,236	1.23	[1.09, 1.39]	<.001	287	1.25	[0.95, 1.65]	.116	136	1.64	[1.11, 2.40]	.012
Income												
<$20,000	1,704	0.90	[0.78, 1.03]	.127	307	1.28	[0.97, 1.69]	.083	239	3.35	[2.25, 4.97]	<.001
$20,000 to <$45,000	2,372	0.98	[0.87, 1.10]	.724	391	1.60	[1.26, 2.02]	<.001	229	2.48	[1.67, 3.67]	<.001
$45,000 to <$75,000	1,387	1.06	[0.93, 1.22]	.366	203	1.58	[1.22, 2.05]	<.001	94	1.97	[1.29, 3.01]	.002
ACR (mg/g)	7,346	1.00	[1.00, 1.00]	.017	1,124	1.00	[1.00, 1.00]	<.001	645	1.00	[1.00, 1.00]	<.001
BMI (kg/m^2)	7,364	1.06	[1.06, 1.07]	<.001	1,130	1.06	[1.05, 1.08]	<.001	658	1.07	[1.05, 1.09]	<.001
BMI categories												

Variable	120-139 mmHg sys. or 80-89 mmHg dias. n = 7,414				140-159 mmHg sys. or 90-99 mmHg dias. n = 1,141				≥ 160 mmHg sys. or ≥ 100 mmHg dias. n = 665			
	n	*OR*	95% CI	*p*-value	*n*	*OR*	95% CI	*p*-value	*n*	*OR*	95% CI	*p*-value
Underweight	78	0.49	[0.33, 0.72]	<.001	21	1.21	[0.64, 2.27]	.563	13	1.07	[0.51, 2.26]	.857
Overweight	2,567	1.67	[1.53, 1.82]	<.001	406	1.83	[1.46, 2.30]	<.001	226	1.33	[1.00, 1.78]	.050
Obese	2,802	2.48	[2.21, 2.77]	<.001	399	2.40	[1.95, 2.95]	<.001	230	2.47	[1.86, 3.29]	<.001
Evidence of diabetes	816	2.04	[1.73, 2.41]	<.001	193	3.62	[2.78, 4.71]	<.001	126	4.93	[3.36, 7.23]	<.001
High blood pressure aware	1,288	3.16	[2.74, 3.64]	<.001	374	7.72	[6.28, 9.49]	<.001	303	12.38	[9.48, 16.16]	<.001
Kidney disease awareness	91	0.62	[0.41, 0.93]	.020	23	1.60	[0.87, 2.97]	.132	5	0.40	[0.14, 1.13]	.082
Kidney function level[a], ml/min/1.73m^2												
<30	18	2.37	[0.98, 5.76]	.056	10	19.88	[6.83, 57.92]	<.001	10	28.45	[10.35, 78.25]	<.001
30 to 44	121	3.94	[2.77, 5.61]	<.001	45	11.69	[6.62, 20.61]	<.001	29	17.00	[8.46, 34.12]	<.001
45 to 59	705	3.38	[2.84, 4.01]	<.001	154	5.80	[4.26, 7.91]	<.001	91	7.26	[4.54, 11.61]	<.001
60-74	1,327	2.35	[2.11, 2.63]	<.001	194	3.43	[2.48, 4.74]	<.001	141	5.16	[3.50, 7.60]	<.001
75-89	1,378	2.14	[1.89, 2.43]	<.001	243	3.37	[2.41, 4.70]	<.001	140	4.13	[2.66, 6.39]	<.001
90-105	1,725	1.78	[1.61, 1.96]	<.001	263	2.84	[2.07, 3.89]	<.001	141	3.52	[2.25, 5.50]	<.001
eGFR[a] <60 ml/min/1.73m^2	844	2.09	[1.78, 2.45]	<.001	209	2.84	[2.29, 3.52]	<.001	130	2.90	[2.06, 4.07]	<.001
Smoking status												

Variable	120-139 mmHg sys. or 80-89 mmHg dias. n = 7,414				140-159 mmHg sys. or 90-99 mmHg dias. n = 1,141				≥ 160 mmHg sys. or ≥ 100 mmHg dias. n = 665			
	n	*OR*	95% CI	*p*-value	*n*	*OR*	95% CI	*p*-value	*n*	*OR*	95% CI	*p*-value
Current smoker	1,688	1.07	[0.95, 1.20]	.299	250	1.17	[0.92, 1.49]	.203	152	1.22	[0.85, 1.75]	.277
Former smoker	1,837	1.46	[1.31, 1.63]	<.001	308	1.54	[1.24, 1.92]	<.001	174	1.68	[1.20, 2.35]	.003

Note. ACR = urinary albumin-to-creatinine ratio, BMI = body mass index, dias = diastolic, eGFR = estimated glomerular filtration rate, HS = high school, NHANES = National Health and Nutrition Examination Survey, OR = odds ratio, sys = systolic

[a]Estimated glomerular filtration rate using the CKD-Epi equation (Levey et al., 2009)

Appendix Table C8.
The relationship between key demographic and clinical characteristics and blood pressure categories in U.S. nonpregnant adults in NHANES 2003-2014 who were prescribed antihypertensive agents; odds for having blood pressure >120/80 mmHg (n=2,243)

Variable	120-139 mmHg sys. or 80-89 mmHg dias. n = 4,146				140-159 mmHg sys. or 90-99 mmHg dias. n = 1,475				≥ 160 mmHg sys. or ≥ 100 mmHg dias. n = 922			
	n	*OR*	95% CI	*p*-value	*n*	*OR*	95% CI	*p*-value	*n*	*OR*	95% CI	*p*-value
Age	4,146	1.00	[0.99, 1.01]	.098	1,475	1.05	[1.04, 1.06]	<.001	922	1.05	[1.04, 1.07]	<.001
Gender, males	2,031	1.07	[0.94, 1.21]	.303	775	0.82	[0.69, 0.98]	.032	561	0.60	[0.48, 0.74]	<.001
Race/ethnicity												
Non-Hispanic Black	1,095	1.38	[1.20, 1.58]	<.001	365	1.20	[0.99, 1.45]	.063	277	2.08	[1.61, 2.70]	<.001
Mexican American	440	1.11	[0.93, 1.32]	.238	171	1.25	[0.89, 1.74]	.193	121	1.45	[1.02, 2.06]	.039
Other	504	1.31	[1.07, 1.61]	.010	172	1.23	[0.92, 1.63]	.158	104	1.70	[1.24, 2.33]	<.001
Non-Hispanic White, referent	2,107	1.00			767	1.00			420	1.00		
Education												
Less than HS	1,244	1.50	[1.22, 1.85]	.001	474	2.10	[1.58, 2.80]	<.001	341	2.94	[2.16, 4.01]	<.001
HS or equivalent	1,002	1.21	[0.96, 1.53]	.112	402	1.88	[1.43, 2.47]	<.001	243	2.08	[1.45, 2.98]	<.001
Some college	1,099	1.10	[0.90, 1.35]	.370	388	1.41	[1.07, 1.85]	.014	221	1.60	[1.13, 1.85]	.009
College degree or higher, referent	797	1.00			210	1.00			116	1.00		
Income												
<$20,000	1,095	1.10	[0.90, 1.35]	.368	448	1.71	[1.27, 2.31]	<.001	336	3.27	[2.17, 4.91]	<.001

Variable	120-139 mmHg sys. or 80-89 mmHg dias. n = 4,146				140-159 mmHg sys. or 90-99 mmHg dias. n = 1,475				≥ 160 mmHg sys. or ≥ 100 mmHg dias. n = 922			
	n	*OR*	95% CI	*p*-value	*n*	*OR*	95% CI	*p*-value	*n*	*OR*	95% CI	*p*-value
$20,000 to <$45,000	1,323	0.91	[0.73, 1.13]	.401	542	1.43	[1.12, 1.84]	.005	305	2.08	[1.48, 2.90]	<.001
$45,000 to <$75,000	792	1.10	[0.85, 1.41]	.469	213	1.12	[0.82, 1.52]	.481	139	1.59	[1.09, 2.30]	.016
≥$75,000, referent	834	1.00			222	1.00			106	1.00		
ACR, mg/g	4,068	1.00	[1.00, 1.00]	.001	1,435	1.00	[1.00, 1.00]	<.001	896	1.00	[1.00, 1.00]	<.001
BMI, kg/m^2	4,086	1.01	[1.00, 1.02]	.006	1,441	0.99	[0.97, 1.00]	.159	897	0.98	[0.96, 0.99]	.028
BMI categories												
Underweight	22	0.49	[0.20, 1.18]	.112	14	1.32	[0.58, 3.00]	.507	16	1.15	[0.53, 2.52]	.725
Normal weight, referent	659	1.00			311	1.00			220	1.00		
Overweight	1,331	1.13	[0.88, 1.46]	.338	482	0.80	[0.60, 1.07]	.124	309	0.73	[0.53, 1.01]	.058
Obese	2,074	1.20	[0.97, 1.49]	.096	634	0.78	[0.58, 1.04]	.093	352	0.57	[0.42, 0.77]	<.001
Evidence of diabetes	1,520	1.02	[0.88, 1.18]	.781	600	1.28	[1.07, 1.54]	.008	362	1.36	[1.10, 1.69]	.005
High blood pressure aware	3,578	1.99	[1.69, 2.35]	<.001	1,281	2.26	[1.75, 2.93]	<.001	852	3.74	[2.70, 5.18]	<.001
Number of antihypertensive agents												
1, referent	2,262	1.00			706	1.00			393	1.00		
2	1,170	0.92	[0.75, 1.11]	.367	443	0.98	[0.79, 1.22]	.853	284	1.44	[1.15, 1.81]	.002
3 or more	714	0.76	[0.65, 0.90]	.002	326	1.14	[0.89, 1.46]	.304	245	1.75	[1.33, 2.31]	<.001

Variable	120-139 mmHg sys. or 80-89 mmHg dias. n = 4,146				140-159 mmHg sys. or 90-99 mmHg dias. n = 1,475				≥ 160 mmHg sys. or ≥ 100 mmHg dias. n = 922			
	n	*OR*	95% CI	*p*-value	*n*	*OR*	95% CI	*p*-value	*n*	*OR*	95% CI	*p*-value
Type of antihypertensive agents												
Diuretics alone, referent	375	1.00			114	1.00			44	1.00		
Set A	1,969	0.91	[0.69, 1.21]	.519	686	1.01	[0.70, 1.47]	.940	448	1.87	[1.19, 2.94]	.007
Set B	1,478	0.86	[0.65, 1.14]	.288	552	0.96	[0.65, 1.41]	.833	358	1.89	[1.17, 3.06]	.010
Set C	324	0.75	[0.54, 1.04]	.088	123	0.95	[0.59, 1.51]	.814	72	1.76	[0.95, 3.28]	.074
Kidney disease awareness	217	0.84	[0.61, 1.16]	.280	106	1.33	[0.93, 1.90]	.124	84	1.48	[1.01, 2.17]	.046
Kidney function level[a], ml/min/1.73m^2												
<30 or dialysis	114	0.62	[0.41, 0.91]	.016	73	2.49	[1.39, 4.46]	.002	75	4.05	[2.35, 7.00]	<.001
30 to 44	418	0.94	[0.68, 1.29]	.689	187	2.38	[1.45, 3.89]	<.001	115	2.51	[1.62, 3.89]	<.001
45 to 59	767	0.93	[0.67, 1.29]	.669	314	1.92	[1.29, 2.85]	.001	197	1.92	[1.24, 2.98]	.004
60-74	783	1.18	[0.67, 1.62]	.293	242	1.92	[1.18, 3.12]	.008	135	1.78	[1.06, 3.00]	.030
75-89	834	1.08	[0.80, 1.46]	.611	314	1.81	[1.13, 2.90]	.014	173	1.99	[1.28, 3.10]	.002
90-105	689	1.11	[0.79, 1.57]	.545	176	1.39	[0.81, 2.36]	.229	111	1.53	[0.92, 2.55]	.104
>105, referent	359	1.00			72	1.00			42	1.00		
eGFR <60 ml/min/1.73m^2	1,299	0.82	[0.70, 0.95]	.009	574	1.28	[1.09, 1.51]	.003	387	1.35	[1.10, 1.66]	.004
Smoking status												
Never smoker	2,073	1.00			716	1.00			507	1.00		

Variable	120-139 mmHg sys. or 80-89 mmHg dias. n = 4,146				140-159 mmHg sys. or 90-99 mmHg dias. n = 1,475				≥ 160 mmHg sys. or ≥ 100 mmHg dias. n = 922			
	n	*OR*	95% CI	*p*-value	*n*	*OR*	95% CI	*p*-value	*n*	*OR*	95% CI	*p*-value
Current smoker	579	0.74	[0.60, 0.90]	.003	164	0.62	[0.48, 0.81]	<.001	111	0.61	[0.45, 0.83]	.002
Former smoker	1,490	0.80	[0.67, 0.96]	.016	594	0.96	[0.77, 1.20]	.732	303	0.69	[0.55, 0.85]	<.001

Note. ACR = urinary albumin-to-creatinine ratio; BMI = body mass index; CI = confidence interval; eGFR = estimated glomerular filtration rate; HS = high school; NHANES = National Health and Nutrition Examination Survey; Set A. = renin-aldosterone inhibitors, calcium channel blockers, beta blockers or any combination of these; Set B. = diuretics plus renin-aldosterone inhibitors, calcium channel blockers, or beta blockers; Set C. = any other antihypertensive agent or any combination of three drugs.

[a]Estimated glomerular filtration rate using the CKD-Epi equation (Levey et al., 2009)

Appendix Table C9.

The relationship between dietary sodium intake and blood pressure in U.S. nonpregnant adults in NHANES 2003-2014 who were not prescribed or were prescribed antihypertensive agents

	Not Prescribed Antihypertensive Agents						Prescribed Antihypertensive Agents					
Variable	n	*r*	*B*	*SE*	95% CI	*p*-value	n	*r*	*B*	*SE*	95% CI	*p*-value
Systolic blood pressure	19,157	.023				.013	8,786	.078				<.001
per mg sodium/day			0.0002	0.0001	[0.00004, 0.0004]				-0.001	0.0002	[-0.001, -0.0006]	
per 200 mg sodium/day			0.04	0.02	[0.01, 0.07]				-0.19	0.03	[-0.26, -0.12]	
per g NaCl/day			0.08	0.03	[0.02, 0.14]				-0.38	0.07	[-0.51, -0.24]	
Diastolic blood pressure	19,157	.057				<.001	8,786	.089				<.001
per mg sodium/day			0.0003	0.0000	[0.0002, 0.0005]				0.001	0.0001	[0.0005, 0.0009]	
per 200 mg sodium/day			0.05	0.01	[0.03, 0.08]				0.15	0.02	[0.10, 0.19]	
per g NaCl/day			0.14	0.02	[0.09, 0.19]				0.29	0.04	[0.21, 0.38]	

Note. CI = confidence interval, NaCl = sodium chloride, NHANES = National Health and Nutrition Examination Survey, OR = odds ratio

Appendix Table C10.

Dietary sodium relationship to blood pressure categories in U.S. nonpregnant adults in NHANES 2003-2014 who were not prescribed antihypertensive agents; odds for having blood pressure >120/80 mmHg (n = 9,937)

Variable	120-139 mmHg sys. or 80-89 mmHg dias. n = 7,414			140-159 mmHg sys. or 90-99 mmHg dias. n = 1,141			≥ 160 mmHg sys. or ≥ 100 mmHg dias. n = 665		
	OR	95% CI	*p*-value	*OR*	95% CI	*p*-value	*OR*	95% CI	*p*-value
Dietary sodium, odds ratio									
per mg sodium/day	1.00	[1.00, 1.00]	<.001	1.00	[1.00, 1.00]	.007	1.00	[1.00, 1.00]	.124
per 200 mg sodium/day	1.01	[1.01, 1.02]	<.001	0.99	[0.98, 0.99]	.007	0.99	[0.97, 1.00]	.124
per g NaCl/day	1.03	[1.02, 1.04]	<.001	0.97	[0.95, 0.99]	.007	0.98	[0.95, 1.01]	.124

Note. CI = confidence interval, dias. = diastolic, mmHg = millimeters of mercury, NaCl = sodium chloride, NHANES = National Health and Nutrition Examination Survey, OR = odds ratio, sys. = systolic

Appendix Table C11.

Dietary sodium relationship to blood pressure categories in U.S. nonpregnant adults in NHANES 2013-2014 who were prescribed antihypertensive agentsodds for having blood pressure >120/80 mmHg (n = 2,243)

Variable	120-139 mmHg sys. or 80-89 mmHg dias. n = 4,146			140-159 mmHg sys. or 90-99 mmHg dias. n = 1,475			≥ 160 mmHg sys. or ≥ 100 mmHg dias. n = 922		
	OR	95% CI	*p*-value	*OR*	95% CI	*p*-value	*OR*	95% CI	*p*-value
Dietary sodium, odds ratio									
per mg sodium/day	1.00	[1.00, 1.00]	.301	1.00	[1.00, 1.00]	<.001	1.00	[1.00, 1.00]	<.001
per 200 mg sodium/day	1.00	[1.00, 1.01]	.301	0.98	[0.97, 0.99]	<.001	0.96	[0.97, 0.99]	<.001
per g NaCl/day	1.01	[0.99, 1.03]	.301	0.94	[0.94, 0.96]	<.001	0.93	[0.90, 0.96]	<.001

Note. CI = confidence interval, dias. = diastolic, mmHg = millimeters of mercury, NaCl = sodium chloride, NHANES = National Health and Nutrition Examination Survey, OR = odds ratio, sys. = systolic

Appendix Table C12.
The relationship between dietary sodium intake and systolic blood pressure when controlling for key demographic and clinical characteristics in U.S. nonpregnant adults in NHANES 2003-2014 who were not prescribed or were prescribed antihypertensive agents

Systolic:	Not Prescribed Antihypertensive Agents						Prescribed Antihypertensive Agents					
Variables	n	R^2	*B*	*SE*	95% CI	*p*-value	n	R^2	*B*	*SE*	95% CI	*p*-value
Model 1		.0005						.006				
Dietary sodium	19,157						8,786					
per mg/day			0.0002	0.0001	[0.00004, 0.0004]	.013			-0.001	0.0002	[-0.001, -0.0006]	<.001
per 200 mg/day			0.04	0.02	[0.01, 0.07]	.013			-0.19	0.03	[-0.26, -0.12]	<.001
per g NaCl/day			0.08	0.03	[0.02, 0.14]	.013			-0.38	0.07	[-0.51, -0.24]	<.001
Model 2		.053						.013				
Dietary sodium	19,157						8,786					
per mg/day			0.0001	0.0001	[-0.0001, 0.0003]	.223			-0.001	0.0002	[-0.001, -0.0005]	<.001
per 200 mg/day			0.02	0.02	[-0.01, 0.06]	.223			-0.17	0.04	[-0.24, -0.10]	<.001
per g NaCl/day			0.04	0.04	[-0.03, 0.11]	.223			-0.34	0.07	[-0.49, -0.20]	<.001
Kidney function level[a], ml/min/1.73m^2												

Systolic:	Not Prescribed Antihypertensive Agents						Prescribed Antihypertensive Agents					
Variables	n	R^2	*B*	*SE*	95% CI	*p*-value	n	R^2	*B*	*SE*	95% CI	*p*-value
<30 or dialysis	54		20.00	4.36	[11.35, 28.65]	<.001	364		9.65	1.87	[5.93, 13.37]	<.001
30-44	271		13.87	1.82	[10.26, 17.48]	<.001	969		6.10	1.17	[3.78, 8.43]	<.001
45-59	1,427		10.90	0.66	[9.60, 12.21]	<.001	1,754		3.81	1.07	[1.69, 5.94]	<.001
60-74	2,969		7.02	0.42	[6.18, 7.85]	<.001	1,534		4.20	1.22	[1.77, 6.62]	<.001
75-89	3,202		6.45	0.41	[5.62, 7.85]	<.001	1,734		4.10	1.13	[1.86, 6.34]	<.001
90-105	4,322		5.16	0.47	[4.23, 6.09]	<.001	1,305		2.46	1.21	[0.07, 4.85]	.044
Model 3		.088						.040				
Dietary sodium	19,157						8,786					
per mg/day			-0.0001	0.0001	[-0.0003, 0.0001]	.288			-0.0003	0.0002	[-0.0007, 0.0001]	.106
per 200 mg/day			-0.02	0.02	[-0.06, 0.02]	.288			-0.07	0.04	[-0.14, 0.01]	.106
per g NaCl/day			-0.04	0.04	[-0.11, 0.04]	.288			-0.13	0.08	[-0.29, 0.03]	.106
Kidney function level[a], ml/min/1.73m^2												
<30 or dialysis	54		17.13	4.30	[8.59, 25.67]	<.001	364		11.41	1.81	[7.81, 15.00]	<.001
30-44	271		12.68	1.83	[9.06, 16.31]	<.001	969		9.41	1.12	[7.19, 11.64]	<.001
45-59	1,427		10.63	0.73	[9.18, 12.07]	<.001	1,754		7.29	1.12	[5.06, 9.51]	<.001
60-74	2,969		7.04	0.47	[6.10, 7.98]	<.001	1,534		7.03	1.21	[4.62, 9.44]	<.001
75-89	3,202		6.62	0.43	[5.76, 7.48]	<.001	1,734		6.30	1.08	[4.16, 8.44]	<.001
90-105	4,322		5.54	0.45	[4.64, 6.44]	<.001	1,305		4.26	1.17	[1.94, 6.57]	<.001
Gender, male	9,776		3.24	0.35	[2.54, 3.94]	<.001	4,318		-2.85	0.63	[-4.11, -1.59]	<.001

Systolic:	Not Prescribed Antihypertensive Agents						Prescribed Antihypertensive Agents					
Variables	n	R^2	*B*	*SE*	95% CI	*p*-value	n	R^2	*B*	*SE*	95% CI	*p*-value
Non-Hispanic Black	3,643		4.34	0.53	[3.28, 5.39]	<.001	2,219		4.66	0.68	[3.30, 6.02]	<.001
Mexican American	3,566		-1.05	0.54	[-2.11, 0.02]	.054	959		3.06	1.09	[0.90, 5.22]	.006
Other race	3,336		-0.68	0.49	[-1.65, 0.28]	.163	1,021		2.88	0.80	[1.30, 4.46]	<.001
Education												
<HS	4,725		4.69	0.55	[3.59, 5.79]	<.001	2,618		4.01	0.88	[2.28, 5.76]	<.001
HS or equivalent	4,344		3.43	0.56	[2.32, 4.55]	<.001	2,201		3.50	0.81	[1.88, 5.12]	<.001
Some college	5,686		2.25	0.43	[1.39, 3.10]	<.001	2,325		2.31	0.78	[0.77, 3.85]	.004
Income												
<$20,000	4,609		1.35	0.46	[0.36, 2.33]	.008	2,454		3.18	0.97	[1.26, 5.11]	.031
$20,000-<$45,000	6,108		1.48	0.46	[0.57, 2.39]	.002	2,933		1.60	0.73	[0.15, 3.05]	.031
$45,000-<$75,000	3,375		1.38	0.46	[0.47, 2.29]	.003	1,541		0.87	0.90	[-0.92, 2.66]	.337
Model 4		.126						.046				
Dietary sodium	19,157						8,786					
per mg/day			-0.0001	0.0001	[-0.0003, 0.0001]	.149			-0.0002	0.0003	[-0.0007, 0.0001]	.120
per 200 mg/day			-0.03	0.02	[-0.06, 0.01]	.149			-0.07	0.04	[-0.14, 0.02]	.120
per g NaCl/day			-0.05	0.04	[-0.13, 0.02]	.149			-0.12	0.08	[-0.28, 0.03]	.120

Systolic:	Not Prescribed Antihypertensive Agents						Prescribed Antihypertensive Agents					
Variables	n	R^2	*B*	*SE*	95% CI	*p*-value	n	R^2	*B*	*SE*	95% CI	*p*-value
Kidney function level[a], ml/min/1.73m^2												
<30 or dialysis	54		15.70	3.71	[8.34, 23.06]	<.001	364		10.32	1.81	[6.73, 13.91]	<.001
30-44	271		11.66	1.91	[7.87, 15.45]	<.001	969		8.02	1.14	[5.76, 10.28]	<.001
45-59	1,427		9.80	0.73	[8.35, 11.26]	<.001	1,754		6.25	1.16	[3.96, 8.55]	<.001
60-74	2,969		6.49	0.48	[5.54, 7.45]	<.001	1,534		6.28	1.21	[3.87, 8.69]	<.001
75-89	3,202		6.27	0.43	[5.42, 7.12]	<.001	1,734		5.69	1.10	[3.50, 7.88]	<.001
90-105	4,322		5.16	0.42	[4.32, 5.99]	<.001	1,305		4.04	1.22	[1.62, 6.50]	.001
Gender, male	9,776		3.22	0.36	[2.50, 3.94]	<.001	4,318		-2.40	0.60	[-3.60, -1.20]	<.001
Non-Hispanic Black	3,643		3.55	0.52	[2.52, 4.58]	<.001	2,219		4.54	0.68	[3.19, 5.90]	<.001
Mexican American	3,566		-1.75	0.54	[-2.82, -0.67]	.002	959		2.36	1.09	[0.19, 4.53]	.034
Other race	3,336		-0.62	0.49	[-1.59, 0.35]	.207	1,021		2.34	0.78	[0.79, 3.88]	<.001
Education												
<HS	4,725		3.65	0.54	[2.57, 4.73]	<.001	2,618		4.28	0.89	[2.30, 5.51]	<.001
HS or equivalent	4,344		2.48	0.54	[1.41, 3.55]	<.001	2,201		3.91	0.81	[2.30, 5.51]	<.001
Some college	5,686		1.39	0.41	[0.57, 2.22]	.001	2,325		2.82	0.80	[1.24, 4.40]	<.001
Income												
<$20,000	4,609		1.41	0.47	[0.48, 2.34]	.003	2,454		3.52	1.00	[1.53, 5.51]	<.001
$20,000-<$45,000	6,108		1.45	0.43	[0.59, 2.30]	.001	2,933		1.97	0.73	[0.51, 3.43]	.009

Systolic:	Not Prescribed Antihypertensive Agents						Prescribed Antihypertensive Agents					
Variables	n	R^2	*B*	*SE*	95% CI	*p*-value	n	R^2	*B*	*SE*	95% CI	*p*-value
$45,000-<$75,000	3,375		1.25	0.45	[0.36, 2.15]	.007	1,541		1.18	0.91	[-0.62, 2.98]	.196
BMI, kg/m^2	19,033		0.39	0.02	[0.34, 0.44]	<.001	8,631		-0.16	0.05	[-0.26, -0.07]	.001
Evidence of diabetes			5.49	0.85	[3.79, 7.18]	<.001	3,301		1.48	0.65	[0.18, 2.78]	.026
Former smoker	4,201		1.63	0.38	[0.86, 2.39]	<.001	3,243		-0.72	0.58	[-1.87, 0.43]	.219
Current smoker	4,354		0.32	0.42	[-0.52, 1.16]	.447	1,231		-4.15	1.04	[-6.22, -2.08]	<.001

Note: BMI = body mass index, CI = confidence interval, HS = high school, NaCl = sodium chloride, NHANES = National Health and Nutrition Examination Survey, OR = odds ratio

[a]Estimated glomerular filtration rate using the CKD-Epi equation (Levey et al., 2009)

Appendix Table C13.
The relationship between dietary sodium intake and diastolic blood pressure when controlling for key demographic and clinical characteristics in U.S. nonpregnant adults in NHANES 2003-2014 who were not prescribed or were prescribed antihypertensive agents

Diastolic:	Not Prescribed Antihypertensive Agents						Prescribed Antihypertensive Agents					
Variables	n	R^2	*B*	*SE*	95% CI	*p*-value	n	R^2	*B*	*SE*	95% CI	*p*-value
Model 1		.003						.008				
Dietary sodium	19,157						8,786					
per mg/day			0.0003	0.0001	[0.0002, 0.0005]	<.001			0.001	0.0001	[0.0005, 0.0009]	<.001
per 200 mg/day			0.05	0.01	[0.03, 0.08]	<.001			0.15	0.02	[0.10, 0.19]	<.001
per g NaCl/day			0.14	0.02	[0.09, 0.19]	<.001			0.29	0.04	[0.21, 0.38]	<.001
Model 2		.034						.059				
Dietary sodium	19,157						8,786					
per mg/day			0.0003	0.0001	[0.0001, 0.0004]	<.001			0.0006	0.0001	[0.0004, 0.0008]	<.001
per 200 mg/day			0.05	0.01	[0.03, 0.08]	<.001			0.12	0.02	[0.08, 0.17]	<.001
per g NaCl/day			0.10	0.02	[0.05, 0.15]	<.001			0.25	0.04	[0.16, 0.34]	<.001
Kidney function level[a],												

Diastolic:	Not Prescribed Antihypertensive Agents						Prescribed Antihypertensive Agents					
Variables	n	R^2	*B*	*SE*	95% CI	*p*-value	n	R^2	*B*	*SE*	95% CI	*p*-value
ml/min/1.73 m^2												
<30 or dialysis	54		-1.86	2.17	[-6.17, 2.46]	.400	364		-12.69	1.19	[-15.04, -10.34]	<.001
30-44	271		2.52	0.92	[0.70, 4.34]	.007	969		-10.35	0.89	[-12.12, -8.59]	<.001
45-59	1,427		5.20	0.42	[4.38, 6.03]	<.001	1,754		-6.70	0.80	[-8.29, -5.11]	<.001
60-74	2,969		4.69	0.31	[4.08, 5.31]	<.001	1,534		-3.79	0.82	[-5.42, -2.16]	<.001
75-89	3,202		2.65	0.32	[2.01, 3.29]	<.001	1,734		-3.93	0.80	[-5.52, -2.23]	<.001
90-105	4,322		3.74	0.26	[3.21, 4.26]	<.001	1,305		-1.84	0.80	[-3.43, -0.24]	.024
Model 3		.043						.084				
Dietary sodium	19,157						8,786					
per mg/day			0.0001	0.0001	[-0.00003, 0.0002]	.127			0.0003	0.0001	[0.0000, 0.0005]	.037
per 200 mg/day			0.02	0.01	[-0.01, 0.05]	.127			0.05	0.03	[0.003, 0.10]	.037
per g NaCl/day			0.04	0.03	[-0.02, 0.10]	.127			0.11	0.05	[0.01, 0.21]	.037
Kidney function level[a], ml/min/1.73 m^2												
<30 or dialysis	54		-2.84	2.15	[-7.11, 1.44]	.191	364		-12.89	1.18	[-15.22, -10.55]	<.001

Diastolic:	Not Prescribed Antihypertensive Agents						Prescribed Antihypertensive Agents					
Variables	n	R^2	*B*	*SE*	95% CI	*p*-value	n	R^2	*B*	*SE*	95% CI	*p*-value
30-44	271		-1.62	0.96	[-0.28, 3.52]	.094	969		-10.74	0.94	[-12.62, -8.86]	<.001
45-59	1,427		4.33	0.45	[3.43, 5.23]	<.001	1,754		-7.47	0.86	[-9.17, -5.76]	<.001
60-74	2,969		4.05	0.35	[3.36, 4.74]	<.001	1,534		-4.11	0.80	[-5.69, -2.53]	<.001
75-89	3,202		2.34	0.33	[1.68, 3.00]	<.001	1,734		-4.02	0.78	[-5.57, -2.47]	<.001
90-105	4,322		3.49	0.27	[2.95, 4.03]	<.001	1,305		-2.09	0.77	[-3.63, -0.56]	.008
Gender, male	9,776		1.65	0.25	[1.17, 2.16]	<.001	4,318		3.00	0.44	[2.12, 3.89]	<.001
Non-Hispanic Black	3,643		1.54	0.40	[0.75, 2.33]	<.001	2,219		2.68	0.53	[1.62, 3.74]	<.001
Mexican American	3,566		-0.41	0.46	[-1.33, 0.50]	.371	959		0.79	0.73	[-0.65, 2.23]	.280
Other race	3,336		-0.21	0.42	[-1.04, 0.63]	.621	1,021		1.77	0.64	[0.49, 3.04]	.007
Education												
<HS	4,725		0.50	0.36	[-0.22, 1.22]	.170	2,618		-1.13	0.69	[-2.50, 0.25]	.107
HS or equivalent	4,344		1.06	0.37	[0.33, 1.79]	.005	2,201		0.11	0.68	[-1.24, 1.46]	.875
Some college	5,686		0.92	0.26	[0.41, 1.44]	<.001	2,325		0.70	0.64	[-0.57, 1.98]	.275
Income												
<$20,000	4,609		-1.29	0.41	[-2.11, -0.47]	.002	2,454		-2.56	0.63	[-3.81, -1.31]	<.001

Diastolic:	Not Prescribed Antihypertensive Agents						Prescribed Antihypertensive Agents					
Variables	n	R^2	*B*	*SE*	95% CI	*p*-value	n	R^2	*B*	*SE*	95% CI	*p*-value
$20,000-<$45,000	6,108		-1.38	0.34	[-2.04, -0.71]	<.001	2,933		-2.74	0.60	[-3.94, -1.54]	<.001
$45,000-<$75,000	3,375		-0.80	0.40	[-1.38, 0.17]	.125	1,541		-1.57	0.63	[-2.82, -0.33]	.014
Model 4		.076						.098				
Dietary sodium	19,157						8,786					
per mg/day			0.0001	0.0001	[-0.0001, 0.0002]	.313			0.0002	0.0001	[-0.0001, 0.0004]	.126
per 200 mg/day			0.01	0.01	[-0.01, 0.04]	.313			0.04	0.03	[-0.01, 0.09]	.126
per g NaCl/day			0.03	0.03	[-0.03, 0.08]	.313			0.08	0.05	[-0.02, 0.18]	.126
Kidney function level, ml/min/1.73 m^2												
<30 or dialysis	54		-2.21	2.21	[-6.60, 2.17]	.318	364		-11.68	1.21	[-14.08, -9.27]	<.001
30-44	271		1.35	0.95	[-0.53, 3.24]	.157	969		-9.97	0.99	[-11.95, -8.00]	<.001
45-59	1,427		3.98	0.45	[3.06, 4.84]	<.001	1,754		-6.99	0.90	[-8.77, -5.21]	<.001
60-74	2,969		3.75	0.36	[3.04, 4.47]	<.001	1,534		-3.67	0.82	[-5.29, -2.04]	<.001
75-89	3,202		2.25	0.33	[1.60, 2.91]	<.001	1,734		-3.62	0.82	[-5.24, -2.00]	<.001
90-105	4,322		3.39	0.28	[2.83, 3.94]	<.001	1,305		-1.81	0.79	[-3.37, -0.25]	.024

Diastolic:	Not Prescribed Antihypertensive Agents						Prescribed Antihypertensive Agents					
Variables	n	R^2	*B*	*SE*	95% CI	*p*-value	n	R^2	*B*	*SE*	95% CI	*p*-value
Gender, male	9,776		1.71	0.26	[1.20, 2.20]	<.001	4,318		3.44	0.44	[2.65, 4.39]	<.001
Non-Hispanic Black	3,643		0.87	0.40	[0.07, 1.67]	.034	2,219		2.56	0.53	[1.51, 3.61]	<.001
Mexican American	3,566		-1.04	0.47	[-1.98, -0.10]	.030	959		0.93	0.72	[-0.49, 2.36]	.196
Other race	3,336		-0.14	0.40	[-0.93, 0.66]	.734	1,021		2.12	0.66	[0.82, 3.43]	.002
Education												
<HS	4,725		0.03	0.35	[-0.67, 0.73]	.940	2,618		-0.61	0.73	-2.05, 0.83]	.401
HS or equivalent	4,344		0.54	0.36	[-0.17, 1.25]	.134	2,201		0.21	0.71	[-1.19, 1.62]	.764
Some college	5,686		0.46	0.26	[-0.06, 0.97]	.084	2,325		0.85	0.65	[-0.43, 2.14]	.192
Income												
<$20,000	4,609		-1.12	0.40	[-1.92, -0.32]	.007	2,454		-2.28	0.63	[-3.54, -1.03]	<.001
$20,000-<$45,000	6,108		-1.36	0.33	[-2.02, -0.70]	<.001	2,933		-2.39	0.59	[-3.57, -1.22]	<.001
$45,000-<$75,000	3,375		-0.70	0.38	[-1.46, 0.05]	.066	1,541		-1.45	0.63	[-2.70, -0.20]	.024
BMI (kg/m^2)	19,033		0.32	0.02	[0.28, 0.35]	<.001	8,631		0.13	0.03	[0.08, 0.18]	<.001
Evidence of diabetes			0.86	0.54	[-0.21, 1.93]	.113	3,301		-3.07	0.48	[-4.02, -2.13]	<.001

Diastolic:	Not Prescribed Antihypertensive Agents						Prescribed Antihypertensive Agents					
Variables	n	R^2	*B*	*SE*	95% CI	*p*-value	n	R^2	*B*	*SE*	95% CI	*p*-value
Former smoker	4,201		0.41	0.27	[-0.12, 0.94]	.130	3,243		-1.54	0.36	[-2.25, -0.84]	<.001
Current smoker	4,354		-0.31	0.28	[-0.87, 0.25]	.271	1,231		-0.36	0.63	[-1.61, 0.89]	.566

Note. BMI = body mass index, CI = confidence interval, HS = high school, NaCl = sodium chloride, NHANES = National Health and Nutrition Examination Survey, OR = odds ratio

[a]Estimated glomerular filtration rate using the CKD-Epi equation (Levey et al., 2009)

D – RESULTS TABLES SUPPLEMENTAL TO CHAPTER IV

Appendix Table D1.
Descriptors of dietary sodium and blood pressure in U.S. nonpregnant adults in NHANES 2003-2014.

	Result						
Characteristic	*M*	*SE*	*Med*	*Q1, Q3*	*N*	Grp., %	Sub., %
Dietary sodium (mg/day)					27,943		
mg/day	3,526	16	3,206	[2,281, 4,417]			
mEq/day	153.3	0.7	139.4	[99.2, 192.0]			
g NaCl/day	8.8	0.1	8.0	[5.7, 11.0]			
Dietary energy (kcal/day)	2,170	9	1,989	[1,480, 2,668]	27,943		
Dietary sodium density (mg/1000 kcal/day)	1,669	5	1,604	[1,311, 1,935]			
Dietary sodium guidelines (mg/day)							
≥2,300					19,959	51.5	74.5
<2,300					7,984	17.6	25.5
Systolic blood pressure, mmHg	122.4	0.2	119.3	[110.7, 131.3]	27,943		
Diastolic blood pressure, mmHg	70.9	0.2	71.3	[64.0, 78.0]	27,943		
Blood pressure category							
<120 mmHg sys. and <80 mmHg dias.					12,180	37.1	46.6
120-139 mmHg sys. or 80-89 mmHg dias.					11,560	33.0	41.5
140-159 mmHg sys. or 90-99 mmHg dias.					2,616	6.1	7.7
≥ 160 mmHg sys. or ≥ 100 mmHg dias.					1,587	3.3	4.2

Note. dias. = diastolic, Grp. = survey weighted population group, *M* = mean, *Med*. = median, mEq = milliequivalents, mmHg = millimeters of mercury, *N* = sample count, NaCl = sodium chloride, Q1,Q3 = interquartile range, *SE* = standard error, Sub. = survey weighted population subgroup, sys. = systolic. Wald Log-linear Chi-square; One-way Analysis of Variance. All *p*-values <.001

Appendix Table D2.

The relationship between key demographic and clinical characteristics and blood pressure categories in U.S. nonpregnant adults in NHANES 2003-2014; odds for having blood pressure >120/80 mmHg (n = 12,180)

Variable	120-139 mmHg sys. or 80-89 mmHg dias. n = 11,560				140-159 mmHg sys. or 90-99 mmHg dias. n = 2,616				≥ 160 mmHg sys. or ≥ 100 mmHg dias. n = 1,587			
	n	*OR*	95% CI	*p*-value	*n*	*OR*	95% CI	*p*-value	*n*	*OR*	95% CI	*p*-value
Age	11,560	1.03	[1.03, 1.04]	<.001	2,616	1.08	[1.08, 1.09]	<.001	1,587	1.09	[1.09, 1.10]	<.001
Gender, males	6,707	1.81	[1.69, 1.93]	<.001	1,312	1.21	[1.08, 1.37]	.001	694	0.99	[0.86, 1.13]	.676
Race/ethnicity												
Non-Hispanic Black	5,505	1.22	[1.11, 1.34]	<.001	1,287	1.29	[1.09, 1.53]	.003	677	2.05	[1.67, 2.52]	<.001
Mexican American	1,721	0.75	[0.67-, 0.84]	<.001	372	0.64	[0.52, 0.78]	<.001	251	0.72	[0.54, 0.96]	.022
Other	1,699	0.84	[0.75, 0.93]	.001	314	0.69	[0.56, 0.85]	<.001	296	0.91	[0.74, 1.12]	.345
Education												
Less than HS	3,092	1.37	[1.24, 1.52]	<.001	864	2.17	[1.81, 2.59]	<.001	598	3.23	[2.54, 4.11]	<.001
HS or equivalent	2,773	1.31	[1.16, 1.46]	<.001	673	1.78	[1.48, 2.15]	<.001	417	2.43	[1.92, 3.08]	<.001
Some college	3,335	1.19	[1.08, 1.32]	<.001	675	1.33	[1.12, 1.57]	<.001	357	1.61	[1.26, 2.07]	<.001
Income												
<$20,000	2,799	0.96	[0.86, 1.07]	<.001	755	1.52	[1.23, 1.87]	<.001	575	3.35	[2.60, 4.30]	<.001
$20,000 to <$45,000	3,695	1.00	[0.91, 1.10]	.473	933	1.69	[1.44, 1.97]	<.001	534	2.53	[2.00, 3.20]	<.001
$45,000 to <$75,000	2,179	1.10	[0.98, 1.23]	.092	416	1.41	[1.17, 1.70]	<.001	233	1.86	[1.43, 2.43]	<.001
ACR (mg/g)	11,414	1.002	[1.001, 1.003]	<.001	2,559	1.003	[1.002, 1.004]	<.001	1,541	1.003	[1.002, 1.004]	<.001

Variable	120-139 mmHg sys. or 80-89 mmHg dias. n = 11,560				140-159 mmHg sys. or 90-99 mmHg dias. n = 2,616				≥ 160 mmHg sys. or ≥ 100 mmHg dias. n = 1,587			
	n	*OR*	95% CI	*p*-value	*n*	*OR*	95% CI	*p*-value	*n*	*OR*	95% CI	*p*-value
BMI (kg/m^2)	11,450	1.09	[1.09, 1.10]	<.001	2,571	1.10	[1.09, 1.11]	<.001	1,555	1.09	[1.08, 1.10]	<.001
BMI categories												
Underweight	269	0.47	[0.33, 0.66]	<.001	100	1.10	[0.69, 1.76]	.700	29	0.96	[0.61, 1.51]	.730
Overweight	3,898	1.71	[1.58, 1.86]	<.001	888	1.71	[1.45, 2.03]	<.001	535	1.43	[1.17, 1.74]	.001
Obese	4,876	2.48	[2.26, 2.71]	<.001	1,033	2.43	[2.09, 2.81]	<.001	582	2.01	[1.72, 2.50]	<.001
Evidence of diabetes	2,336	1.96	[1.78, 2.15]	<.001	793	3.66	[3.19, 4.21]	<.001	488	4.32	[3.67, 5.09]	<.001
High blood pressure aware	4,866	2.98	[2.71, 3.27]	<.001	1,655	7.84	[6.83, 9.00]	<.001	1,155	11.56	[9.80, 13.64]	<.001
Antihypertensive Agents Use	4,146	2.35	[2.16, 2.56]	<.001	1,475	5.85	[5.15, 6.66]	<.001	922	6.45	[5.45, 7.64]	<.001
Number of antihypertensive agents												
1	2,262	1.93	[1.65, 2.25]	<.001	706	6.54	[5.20, 8.21]	<.001		8.96	[6.84, 11.73]	<.001
2	1,170	2.31	[1.98, 2.69]	<.001	443	5.63	[4.54, 6.98]	<.001	284	7.38	[5.94, 9.16]	<.001
3 or more	714	2.52	[2.25, 2.83]	<.001	326	5.74	[4.97, 6.63]	<.001	245	5.12	[4.21, 6.22]	<.001
Type of antihypertensive agents												
Diuretics alone	375	2.66	[2.07, 3.41]	<.001	114	5.93	[4.23, 8.32]	<.001	44	3.60	[2.29, 5.66]	<.001
Set A	1,969	2.42	[2.14, 2.74]	<.001	686	6.02	[5.09, 7.10]	<.001	448	6.72	[5.41, 8.35]	<.001
Set B	1,478	2.28	[2.01, 2.59]	<.001	552	5.69	[4.72, 6.86]	<.001	358	6.80	[5.51, 8.40]	<.001

Variable	120-139 mmHg sys. or 80-89 mmHg dias. n = 11,560				140-159 mmHg sys. or 90-99 mmHg dias. n = 2,616				≥ 160 mmHg sys. or ≥ 100 mmHg dias. n = 1,587			
	n	*OR*	95% CI	*p*-value	*n*	*OR*	95% CI	*p*-value	*n*	*OR*	95% CI	*p*-value
Set C	324	1.99	[1.58, 2.51]	<.001	123	5.61	[4.16, 7.56]	<.001	72	6.34	[4.11, 9.79]	<.001
Kidney disease awareness	308	0.98	[0.74, 1.30]	.979	129	2.39	[1.81, 3.18]	<.001	89	2.28	[1.59, 3.27]	<.001
CKD-Epi group												
<30 or dialysis	132	2.20	[1.62, 2.97]	<.001	83	16.13	[10.79, 24.12]	<.001	85	31.01	[20.38, 47.18]	<.001
30 to 44	539	3.41	[2.83, 4.09]	<.001	232	13.86	[9.88, 19.45]	<.001	144	18.14	[12.99, 25.34]	<.001
45 to 59	1,472	3.15	[2.81, 3.64]	<.001	468	7.81	[6.28, 9.71]	<.001	288	9.43	[6.97, 12.78]	<.001
60-74	2,110	2.49	[2.26, 2.73]	<.001	436	4.40	[3.37, 5.75]	<.001	276	5.57	[4.11, 7.54]	<.001
75-89	2,212	2.30	[2.08, 2.54]	<.001	557	4.42	[3.33, 5.86]	<.001	313	5.52	[4.01, 7.61]	<.001
90-105	2,414	1.88	[1.72, 2.07]	<.001	439	3.03	[2.35, 3.97]	<.001	252	3.70	[2.71, 5.06]	<.001
eGFR[b] <60 ml/min/1.73m^2	2,143	1.79	[1.62, 1.98]	<.001	783	3.33	[2.98, 3.72]	<.001	517	3.56	[2.98, 4.25]	<.001
Smoking status												
Current smoker	2,267	0.95	[0.86, 1.06]	<.001	414	0.86	[0.72, 1.03]	.099	263	0.84	[0.67, 1.04]	.107
Former smoker	3,327	1.36	[1.25, 1.48]	<.001	902	1.68	[1.49, 1.94]	<.001	477	1.43	[1.20, 1.70]	<.001

Note. AA = Associate of Arts degree; ACR = albumin-to-creatinine ratio; BMI = body mass index; CI = confidence interval; eGFR = estimated glomerular filtration rate; HS = High school; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; Set A. = renin-aldosterone inhibitors, calcium channel blockers, beta blockers or any combination of these; Set B. = diuretics plus renin-aldosterone inhibitors, calcium channel blockers, or beta blockers; Set C. = any other antihypertensive agent or any combination of three drugs. Chi-square or Loglinear Chi-square, as appropriate

[a]Estimated glomerular filtration rate using the CKD-Epi equation (Levey et al., 2009)

Appendix Table D3.
The relationship between dietary sodium intake and systolic blood pressure when controlling for key demographic and clinical characteristics in U.S. nonpregnant adults in NHANES 2003-2014, n = 27,943

Systolic Blood Pressure Model #	Variables	n	Model R^2	*B*	*SE*	95% CI	*p*-value
1		27,943	.001				
	Dietary sodium as:						
	per mg/day			-0.0003	0.0001	[-0.0004, -0.0002]	<.001
	per 200 mg/day			-0.06	0.01	[-0.09, -0.04]	<.001
	per g NaCl/day			-0.13	0.03	[-0.18, -0.08]	<.001
2		27,943	.069				
	Dietary sodium						
	per mg/day			-0.0003	0.00007	[-0.00040, -0.00013]	<.001
	per 200 mg/day			-0.06	0.01	[-0.08, -0.03]	<.001
	per g NaCl/day			-0.11	0.03	[-0.17, -0.06]	<.001
	Kidney function level[a], ml/min/1.73m^2						
	<15 or dialysis	117		19.46	3.26	[12.99, 25.93]	<.001
	15-29	301		21.09	2.08	[16.96, 25.22]	<.001
	30-44	1,240		16.16	0.70	[14.77, 17.56]	<.001
	45-59	3,181		12.32	0.46	[11.40, 13.23]	<.001
	60-74	4,503		8.68	0.42	[7.84, 9.52]	<.001
	75-89	4,936		8.41	0.41	[7.59, 9.23]	<.001
	90-105	5,627		6.09	0.43	[5.24, 6.94]	<.001
3		27,943	.206				
	Dietary sodium						

Systolic Blood Pressure Model #	Variables	n	Model R^2	*B*	*SE*	95% CI	*p*-value
	per mg/day			0.0003	0.0001	[0.0001, 0.0004]	.005
	per 200 mg/day			0.05	0.02	[0.02, 0.08]	.005
	per g NaCl/day			0.10	0.03	[0.03, 0.17]	.005
	Kidney function level[a], ml/min/1.73m^2						
	>105 ml/min/1.73m^2 referent						
	<15 or dialysis	117		3.73	3.48	[-3.17, 10.63]	.286
	15-29	301		0.57	2.16	[-3.72, 4.87]	.792
	30-44	1,240		-1.71	0.95	[-3.59, 0.17]	.075
	45-59	3,181		-0.79	0.68	[-2.13, 0.55]	.247
	60-74	4,503		0.91	0.52	[-0.12, 1.94]	.083
	75-89	4,936		0.63	0.40	[-0.17, 1.43]	.124
	90-105	5,627		0.69	0.38	[-0.07, 1.44]	.074
	Age, years	14,094		0.46	0.01	[0.43, 0.48]	<.001
	Gender, females referent	5,862					
	Males	4,525		3.86	0.35	[3.16, 4.55]	<.001
	Race or ethnicity, non-Hispanic White referent	4,357					
	Non-Hispanic Black			4.54	0.45	[3.64, 5.43]	<.001
	Mexican American	7,343		0.43	0.44	[-0.44, 1.31]	.327
	Other race	6,545		0.70	0.37	[-0.03, 1.43]	.061

Systolic Blood Pressure Model #	Variables	n	Model R^2	*B*	*SE*	95% CI	*p*-value
	Education, College degree or higher referent	8,011					
	<HS			3.34	0.42	[2.51, 4.16]	<.001
	HS or equivalent	7,063		3.22	0.45	[2.33, 4.10]	<.001
	Some college	9,041		2.86	0.34	[2.18, 3.53]	<.001
	Income, ≥ $75,000 referent	4,916					
	<$20,000	27,943		2.69	0.39	[1.92, 3.46]	<.001
	$20,000-<$45,000			1.46	0.36	[0.74, 2.17]	.001
	$45,000-<$75,000			1.45	0.36	[0.74, 2.17]	<.001
4			.222				
	Dietary sodium						
	per mg/day			0.0002	0.0001	[0.0000, 0.0003]	.052
	per 200 mg/day	117		0.03	0.02	[-0.003, 0.066]	.052
	per g NaCl/day	301		0.07	0.03	[-0.001, 0.132]	.052
	Kidney function level[a], ml/min/1.73m^2 > 105 ml/min/1.73m^2 referent	1,240					
	<15 or dialysis	3,181		4.21	3.26	[-2.26, 10.68]	.200
	15-29	4,503		-0.45	2.21	[-4.83, 3.93]	.839
	30-44	4,936		-2.59	0.98	[-4.54, -0.64]	.010
	45-59	5,627		-1.26	0.68	[-2.62, 0.09]	.068
	60-74	14,094		0.56	0.52	[-0.47, 1.59]	.282

Systolic Blood Pressure Model #	Variables	n	Model R^2	*B*	*SE*	95% CI	*p*-value
	75-89	5,862		0.43	0.39	[-0.34, 1.21]	.268
	90-105	4,525		0.59	0.35	[-0.11, 1.29]	.099
	Age, years	4,357		0.43	0.01	[0.40, 0.45]	<.001
	Gender, females referent						
	Males	7,343		4.20	0.34	[3.52, 4.88]	<.001
	Race or ethnicity, non-Hispanic White referent	6,545					
	Non-Hispanic Black	8,011		3.55	0.44	[2.69, 4.42]	<.001
	Mexican American			-0.06	0.45	[-0.97, 0.84]	.887
	Other race	7,063		0.73	0.38	[-0.02, 1.47]	.057
	Education, College degree or higher referent	9,041					
	<HS	4,916		2.87	0.43	[2.01, 3.73]	<.001
	HS or equivalent	27,664		2.69	0.44	[1.82, 3.56]	<.001
	Some college	5,001		2.36	0.33	[1.70, 3.02]	<.001
	Income, ≥ $75,000 referent	8,786					
	<$20,000	7,444		2.58	0.38	[1.83, 3.32]	<.001
	$20,000-<$45,000	5,585		1.39	0.34	[0.70, 2.07]	.001
	$45,000-<$75,000			1.21	0.35	[0.51, 1.91]	<.001
	BMI, kg/m^2			0.28	0.02	[0.23, 0.33]	<.001
	Evidence of diabetes			0.95	0.48	[0.00, 1.89]	.050

Systolic Blood Pressure Model #	Variables	n	Model R^2	*B*	*SE*	95% CI	*p*-value
	Antihypertensive agents			1.71	0.44	[0.83, 2.60]	<.001
	Smoking status, never smoker referent						
	Former smoker			-0.80	0.31	[-1.42, -0.18]	.012
	Current smoker			-0.21	0.37	[-0.94, 0.51]	.558

Note: BMI = body mass index, CI = confidence interval, HS = high school, NaCl = sodium chloride, NHANES = National Health and Nutrition Examination Survey

[a]Estimated glomerular filtration rate using the CKD-Epi equation (Levey et al., 2009)

Appendix Table D4.
The relationship between dietary sodium intake and systolic blood pressure when controlling for key demographic (excluding age) and clinical characteristics in U.S. nonpregnant adults in NHANES 2003-2014

Model # Systolic:	Variables	n	Model R^2	*B*	*SE*	95% CI	*p*-value
1		27,943	.001				
	Dietary sodium						
	per mg/day			-0.0003	0.0001	[-0.0004, -0.0002]	<.001
	per 200 mg/day			-0.06	0.01	[-0.09, -0.04]	<.001
	per g NaCl/day			-0.13	0.03	[-0.18, -0.08]	<.001
2		27,943	.069				
	Dietary sodium						
	per mg/day			-0.0003	0.00007	[-0.00042, -0.00014]	<.001
	per 200 mg/day			-0.06	0.01	[-0.08, -0.03]	<.001
	per g NaCl/day			-0.11	0.03	[-0.17, -0.06]	<.001
	Kidney function level[a], ml/min/1.73m^2						
	<15 or dialysis	117		19.46	3.26	[12.99, 25.93]	<.001
	15-29	301		21.09	2.08	[16.96, 25.22]	<.001
	30-44	1,240		16.16	0.70	[14.77, 17.56]	<.001
	45-59	3,181		12.32	0.46	[11.40, 13.23]	<.001
	60-74	4,503		8.68	0.42	[7.84, 9.52]	<.001
	75-89	4,936		8.41	0.41	[7.59, 9.23]	<.001
	90-105	5,627		6.09	0.43	[5.24, 6.94]	<.001
3		27,943	.100				
	Dietary sodium						
	per mg/day			-0.0002	0.0001	[-0.0004, -0.00003]	.025
	per 200 mg/day			-0.04	0.02	[-0.07, -0.01]	.025
	per g NaCl/day			-0.08	0.03	[-0.15, -0.01]	.025

Model # Systolic:	Variables	n	Model R^2	*B*	*SE*	95% CI	*p*-value
	Kidney function level[a], ml/min/1.73m^2						
	<15 or dialysis	117		18.58	3.34	[11.94, 25.21]	<.001
	15-29	301		19.91	2.08	[15.77, 24.04]	<.001
	30-44	1,240		16.60	0.70	[15.21, 17.99]	<.001
	45-59	3,181		13.47	0.54	[12.40, 14.54]	<.001
	60-74	4,503		10.03	0.46	[9.11, 10.95]	<.001
	75-89	4,936		9.17	0.39	[8.38, 9.95]	<.001
	90-105	5,627		6.95	0.41	[6.13, 9.95]	<.001
	Gender, male	14,094		0.62	0.35	[-0.07, 1.32]	.079
	Non-Hispanic Black	5,862		5.55	0.50	[4.56, 6.54]	<.001
	Mexican American	4,525		-0.90	0.51	[-1.91, 0.11]	.082
	Other race	4,357		-0.19	0.40	[-0.99, 0.60]	.633
	Education						
	<HS	7,343		5.35	0.47	[4.41, 6.29]	<.001
	HS or equivalent	6,545		3.99	0.48	[3.04, 4.93]	<.001
	Some college	8,011		2.47	0.38	[1.72, 3.23]	<.001
	Income						
	<$20,000	7,063		2.21	0.43	[1.36, 3.06]	<.001
	$20,000-<$45,000	9,041		1.86	0.38	[1.11, 2.62]	<.001
	$45,000-<$75,000	4,916		1.45	0.39	[0.67, 2.23]	<.001
4		27,943	.144				
	Dietary sodium						
	per mg/day			-0.0002	0.0001	[-0.0004, -0.00003]	.018
	per 200 mg/day			-0.04	0.02	[-0.07, -0.01]	.018
	per g NaCl/day			-0.08	0.03	[-0.14, -0.01]	.018

Model # Systolic:	Variables	n	Model R^2	*B*	*SE*	95% CI	*p*-value
	Kidney function level[a], ml/min/1.73m^2						
	<15 or dialysis	117		13.14	3.24	[6.70, 19.57]	<.001
	15-29	301		12.51	2.19	[8.16, 16.86]	<.001
	30-44	1,240		10.19	0.84	[8.52, 11.85]	<.001
	45-59	3,181		9.41	0.57	[8.28, 10.53]	<.001
	60-74	4,503		7.64	0.46	[6.72, 8.58]	<.001
	75-89	4,936		6.95	0.39	[6.18, 7.72]	<.001
	90-105	5,627		5.55	0.40	[4.75, 6.34]	<.001
	Gender, male	14,094		1.60	0.33	[0.95, 2.26]	<.001
	Non-Hispanic Black	5,862		4.05	0.47	[3.12, 4.98]	<.001
	Mexican American	4,525		-0.96	0.50	[-1.94, 0.02]	.056
	Other race	4,357		0.05	0.41	[-0.75, 0.86]	.899
	Education						
	<HS	7,343		4.26	0.45	[3.37, 5.15]	<.001
	HS or equivalent	6,545		3.20	0.45	[2.30, 4.10]	<.001
	Some college	8,011		1.92	0.37	[1.18, 2.65]	<.001
	Income						
	<$20,000	7,063		2.07	0.43	[1.22, 2.92]	<.001
	$20,000-<$45,000	9,041		1.58	0.35	[0.87, 2.28]	<.001
	$45,000-<$75,000	4,916		1.25	0.39	[0.47, 2.02]	.002
	BMI, kg/m^2	27,664		0.23	0.02	[0.18, 0.28]	<.001
	Evidence of diabetes	5,001		2.90	0.54	[1.83, 3.97]	<.001
	Antihypertensive agents	8,786		6.30	0.44	[5.43, 7.18]	<.001
	Former smoker	7,444		0.82	0.33	[0.16, 1.47]	.015
	Current smoker	5,585		-0.63	0.42	[-1.46, 0.20]	.137

Note: BMI = body mass index, CI = confidence interval, HS = high school, NaCl = sodium chloride, NHANES = National Health and Nutrition Examination Survey

[a]Estimated glomerular filtration rate using the CKD-Epi equation (Levey et al., 2009)

Appendix Table D5.
The relationship between dietary sodium intake and diastolic blood pressure when controlling for key demographic and clinical characteristics in U.S. nonpregnant adults in NHANES 2003-2014

Diastolic Blood Pressure Model #	Variables	n	Model R^2	*B*	*SE*	95% CI	*p*-value
1		27,943	.005				
	Dietary sodium						
	per mg/day			0.0005	0.0001	[0.0004, 0.0006]	<.001
	per 200 mg/day			0.09	0.01	[0.07, 0.11]	<.001
	per g NaCl/day			0.18	0.02	[0.14, 0.23]	<.001
2		27,943	.030				
	Dietary sodium						
	per mg/day			0.0004	0.0001	[0.0003, 0.0005]	<.001
	per 200 mg/day			0.08	0.01	[0.06, 0.10]	<.001
	per g NaCl/day			0.15	0.02	[0.11, 0.20]	<.001
	Kidney function level[a], ml/min/1.73m^2						
	> 105 ml/min/1.73m^2 referent						
	<15 or dialysis	117		-1.57	1.81	[-5.15, 2.02]	.389
	15-29	301		-7.74	0.97	[-9.67, -5.81]	<.001
	30-44	1,240		-2.82	0.50	[-3.1, -1.82]	<.001
	45-59	3,181		2.17	0.35	[1.48, 2.85]	<.001
	60-74	4,503		3.63	0.29	[3.06, 4.20]	<.001
	75-89	4,936		2.14	0.27	[1.59, 2.68]	<.001
	90-105	5,627		3.43	0.25	[2.94, 3.92]	<.001
3		27,943	.044				

Diastolic Blood Pressure Model #	Variables	n	Model R^2	*B*	*SE*	95% CI	*p*-value
	Dietary sodium						
	per mg/day			0.0002	0.0001	[0.00003, 0.0003]	.014
	per 200 mg/day			0.03	0.01	[0.01, 0.05]	.014
	per g NaCl/day			0.06	0.02	[0.01, 0.11]	.014
	Kidney function level[a], ml/min/1.73m^2 > 105 ml/min/1.73m^2 referent						
	<15 or dialysis	117		-2.52	1.88	[-6.24, 1.20]	.183
	15-29	301		-7.98	0.98	[-9.91, -6.04]	<.001
	30-44	1,240		-3.44	0.72	[-4.87, -2.01]	<.001
	45-59	3,181		1.21	0.51	[0.19, 2.23]	.020
	60-74	4,503		2.89	0.35	[2.20, 3.59]	<.001
	75-89	4,936		1.82	0.37	[1.07, 2.56]	<.001
	90-105	5,627		3.13	0.28	[2.57, 3.68]	<.001
	Age, years	14,094		-0.0004	0.010	[-0.02, 0.02]	.963
	Gender, females referent	5,862					
	Males	4,525		2.24	0.24	[1.77, 2.71]	<.001
	Race or ethnicity, non-Hispanic White referent	4,357					
	Non-Hispanic Black			2.00	0.35	[1.30, 2.69]	<.001
	Mexican American	7,343		-0.12	0.41	[-0.93, 0.69]	.774
	Other race	6,545		0.18	0.36	[-0.52, 0.90]	.606
	Education, College degree or higher referent	8,011					
	<HS			-0.13	0.31	[-0.74, 0.47]	.663

Diastolic Blood Pressure Model #	Variables	n	Model R^2	*B*	*SE*	95% CI	*p*-value
	HS or equivalent	7,063		0.72	0.34	[0.04, 1.40]	.037
	Some college	9,041		0.80	0.25	[0.31, 1.29]	.002
	Income, ≥ $75,000 referent	4,916					
	<$20,000	27,943		-1.78	0.36	[-2.49, -1.08]	<.001
	$20,000-<$45,000			-1.88	0.30	[-2.48, -1.29]	<.001
	$45,000-<$75,000			-0.90	0.33	[-1.55, -0.24]	.008
4			.065				
	Dietary sodium						
	per mg/day			0.0001	0.0001	[-0.00002, 0.00021]	.115
	per 200 mg/day	117		0.02	0.01	[-0.005, 0.04]	.115
	per g NaCl/day	301		0.04	0.02	[-0.01, 0.08]	.115
	Kidney function level[a], ml/min/1.73m^2	1,240					
	> 105 ml/min/1.73m^2 referent						
	<15 or dialysis	3,181		-1.17	1.95	[-5.04, 2.71]	.551
	15-29	4,503		-7.58	0.99	[-9.54, -5.59]	<.001
	30-44	4,936		-3.34	0.72	[-4.76, -1.91]	<.001
	45-59	5,627		1.02	0.49	[0.06, 1.99]	.037
	60-74	14,094		2.64	0.34	[1.97, 3.32]	<.001
	75-89	5,862		1.71	0.36	[1.00, 2.42]	<.001
	90-105	4,525		2.98	0.27	[2.44, 3.51]	<.001
	Age, years	4,357		0.02	0.01	[-0.00, 0.04]	.061
	Gender, females referent						
	Males	7,343		2.41	0.23	[1.95, 2.87]	<.001

Diastolic Blood Pressure Model #	Variables	n	Model R^2	*B*	*SE*	95% CI	*p*-value
	Race or ethnicity, non-Hispanic White referent	6,545					
	Non-Hispanic Black	8,011		1.49	0.35	[0.80, 2.19]	<.001
	Mexican American			-0.59	0.42	[-1.41, 0.24]	.160
	Other race	7,063		0.35	0.34	[-0.32, 1.03]	.303
	Education, College degree or higher referent	9,041					
	<HS	4,916		-0.28	0.31	[-0.91, 0.34]	.368
	HS or equivalent	27,664		0.41	0.34	[-0.28, 1.09]	.241
	Some college	5,001		0.52	0.25	[0.02, 1.02]	.041
	Income, ≥ $75,000 referent	8,786					
	<$20,000	7,444		-1.61	0.34	[-2.28, -0.93]	<.001
	$20,000-<$45,000	5,585		-1.85	0.29	[-2.43, -1.27]	<.001
	$45,000-<$75,000			-0.96	0.32	[-1.59, -0.32]	.004
	BMI (kg/m^2)			0.27	0.01	[0.24, 0.30]	<.001
	Evidence of diabetes			-1.42	0.38	[2.17, -0.67]	<.001
	Antihypertensive agents			-1.29	0.30	[-1.89, -0.70]	<.001
	Smoking status, never smoker referent						
	Former smoker			-0.21	0.23	[-0.68, 0.25	.358
	Current smoker			-0.23	0.24	[-0.70, 0.23]	.319

Note: BMI = body mass index, CI = confidence interval, HS = high school, NaCl = sodium chloride, NHANES = National Health and Nutrition Examination Survey

[a]Estimated glomerular filtration rate using the CKD-Epi equation (Levey et al., 2009)

Appendix Table D6.
The relationship between dietary sodium intake and diastolic blood pressure when controlling for key demographic (excluding age) and clinical characteristics in U.S. nonpregnant adults in NHANES 2003-2014

Model # Diastolic:	Variables	n	Model R^2	*B*	*SE*	95% CI	*p*-value
1		27,943	.005				
	Dietary sodium						
	per mg/day			0.0005	0.0001	[0.0004, 0.0006]	<.001
	per 200 mg/day			0.09	0.01	[0.07, 0.11]	<.001
	per g NaCl/day			0.18	0.02	[0.14, 0.23]	<.001
2		27,943	.030				
	Dietary sodium						
	per mg/day			0.0004	0.0001	[0.0003, 0.0005]	<.001
	per 200 mg/day			0.08	0.01	[0.06, 0.10]	<.001
	per g NaCl/day			0.15	0.02	[0.11, 0.20]	<.001
	Kidney function level[a], ml/min/1.73m^2						
	<15 or dialysis	117		-1.56	1.81	[-5.15, 2.02]	.389
	15-29	301		-7.74	0.97	[-9.67, -5.81]	<.001
	30-44	1,240		-2.82	0.50	[-3.1, -1.82]	<.001
	45-59	3,181		2.17	0.35	[1.48, 2.85]	<.001
	60-74	4,503		3.63	0.29	[3.06, 4.20]	<.001
	75-89	4,936		2.14	0.27	[1.59, 2.68]	<.001
	90-105	5,627		3.43	0.25	[2.94, 3.92]	<.001
3		27,943	.044				
	Dietary sodium						

Model # Diastolic:	Variables	n	Model R^2	*B*	*SE*	95% CI	*p*-value
	per mg/day			0.0002	0.0001	[0.00003, 0.0003]	.015
	per 200 mg/day			0.03	0.01	[0.01, 0.05]	.015
	per g NaCl/day			0.06	0.02	[0.01, 0.11]	.015
	Kidney function level[a], ml/min/1.73m^2						
	<15 or dialysis	117		-2.53	1.84	[-6.18, 1.11]	.171
	15-29	301		-8.00	0.97	[-9.93, -6.06]	<.001
	30-44	1,240		-3.46	0.55	[-4.55, -2.37]	<.001
	45-59	3,181		1.20	0.38	[0.44, 1.95]	.002
	60-74	4,503		2.88	0.29	[2.30, 3.46]	<.001
	75-89	4,936		1.81	0.28	[1.25, 2.37]	<.001
	90-105	5,627		3.12	0.26	[2.61, 3.63]	<.001
	Gender, male	14,094		2.25	0.22	[1.80, 2.69]	<.001
	Non-Hispanic Black	5,862		2.00	0.35	[1.29, 2.70]	<.001
	Mexican American	4,525		-0.12	0.41	[-0.92, 0.69]	.777
	Other race	4,357		0.18	0.35	[-0.52, 0.89]	.603
	Education						
	<HS	7,343		-0.14	0.30	[-0.74, 0.47]	.655
	HS or equivalent	6,545		0.72	0.34	[0.05, 1.40]	.036
	Some college	8,011		0.80	0.25	[0.31, 1.29]	.002
	Income						
	<$20,000	7,063		-1.78	0.36	[-2.49, -1.08]	<.001
	$20,000-<$45,000	9,041		-1.88	0.30	[-2.47, -1.30]	<.001
	$45,000-<$75,000	4,916		-0.90	0.33	[-1.55, -0.24]	.008
4		27,943	.065				
	Dietary sodium						

Model # Diastolic:	Variables	n	Model R^2	*B*	*SE*	95% CI	*p*-value
	per mg/day			0.0001	0.0001	[-0.00004, 0.0002]	.200
	per 200 mg/day			0.02	0.01	[-0.008, 0.04]	.200
	per g NaCl/day			0.03	0.02	[-0.02, 0.08]	.200
	Kidney function level[a], ml/min/1.73m^2						
	<15 or dialysis	117		-0.78	1.91	[-4.57, 3.02]	.685
	15-29	301		-7.00	1.02	[-9.01, -4.98]	<.001
	30-44	1,240		-2.78	0.59	[-3.95, -1.61]	<.001
	45-59	3,181		1.50	0.38	[0.74, 2.26]	<.001
	60-74	4,503		2.95	0.29	[2.38, 3.53]	<.001
	75-89	4,936		2.00	0.30	[1.41, 2.58]	<.001
	90-105	5,627		3.19	0.26	[2.68, 3.71]	<.001
	Gender, male	14,094		2.30	0.22	[1.86, 2.74]	<.001
	Non-Hispanic Black	5,862		1.52	0.35	[0.81, 2.22]	<.001
	Mexican American	4,525		-0.63	0.41	[-1.45, 0.19]	.133
	Other race	4,357		0.32	0.34	[-0.35, 1.00]	.344
	Education						
	<HS	7,343		-0.22	0.31	[-0.83, 0.39]	.470
	HS or equivalent	6,545		0.43	0.34	[-0.25, 1.11]	.213
	Some college	8,011		0.50	0.25	[-0.00, 1.00]	.051
	Income						
	<$20,000	7,063		-1.63	0.34	[-2.31, -0.95]	<.001
	$20,000-<$45,000	9,041		-1.84	0.29	[-2.42, -1.26]	<.001
	$45,000-<$75,000	4,916		-0.96	0.32	[-1.59, -0.32]	.004
	BMI (kg/m^2)	27,664		0.27	0.01	[0.24, 0.30]	<.001
	Evidence of diabetes	5,001		-1.33	0.38	[-2.08, -0.59]	<.001

Model # Diastolic:	Variables	n	Model R^2	*B*	*SE*	95% CI	*p*-value
	Antihypertensive agents	8,786		-1.09	0.29	[-1.67, -0.51]	<.001
	Former smoker	7,444		-0.14	0.23	[-0.61, 0.32]	0.543
	Current smoker	5,585		-0.25	0.24	[-0.72, 0.21]	0.283

Note: BMI = body mass index, CI = confidence interval, HS = high school, NaCl = sodium chloride, NHANES = National Health and Nutrition Examination Survey

[a]Estimated glomerular filtration rate using the CKD-Epi equation (Levey et al., 2009)

Appendix Table D7.
The relationship between dietary sodium intake and blood pressure categories when controlling for key demographic (excluding age) and clinical characteristics in U.S. nonpregnant adults in NHANES 2003-2014

Variable	120-139 mmHg sys. or 80-89 mmHg dias. n = 11,560				140-159 mmHg sys. or 90-99 mmHg dias. n = 2,616				≥ 160 mmHg sys. or ≥ 100 mmHg dias. n = 1,587			
	n	*OR*	95% CI	*p*-value	*n*	*OR*	95% CI	*p*-value	*n*	*OR*	95% CI	*p*-value
Model 1												
Dietary sodium, odds ratio	11,560				2,616				1,587			
per mg sodium/day		1.00	[1.00, 1.00]	<.001		1.00	[1.00, 1.00]	<.001		1.00	[1.00, 1.00]	<.001
per 200 mg sodium/day		0.97	[0.96, 0.98]	<.001		0.98	[0.97, 0.98]	<.001		1.01	[1.00, 1.01]	<.001
per g NaCl/day		0.94	[0.92, 0.96]	<.001		0.95	[0.94, 0.97]	<.001		1.02	[1.01, 1.02]	<.001
Model 2												
Dietary sodium, odds ratio	11,560				2,616				1,587			
per mg sodium/day		1.00	[1.00, 1.00]	<.001		1.00	[1.00, 1.00]	<.001		1.00	[1.00, 1.00]	<.001
per 200 mg sodium/day		0.97	[0.96, 0.98]	<.001		0.98	[0.97, 0.98]	<.001		1.01	[1.00, 1.01]	<.001
per g NaCl/day		0.94	[0.92, 0.96]	<.001		0.96	[0.94, 0.97]	<.001		1.02	[1.01, 1.02]	<.001
Kidney function level[a], ml/min/1.73m^2												

Variable	120-139 mmHg sys. or 80-89 mmHg dias. n = 11,560				140-159 mmHg sys. or 90-99 mmHg dias. n = 2,616				≥ 160 mmHg sys. or ≥ 100 mmHg dias. n = 1,587			
	n	*OR*	95% CI	*p*-value	*n*	*OR*	95% CI	*p*-value	*n*	*OR*	95% CI	*p*-value
> 105 ml/min/1.73m^2 referent												
<15 or dialysis	38	28.02	[13.28, 59.13]	<.001	19	7.26	[3.27, 16.11]	<.001	26	2.14	[1.15, 3.98]	.016
15-29	94	28.28	[13.28, 59.13]	<.001	64	18.07	[11.53, 28.31]	<.001	59	2.31	[1.65, 3.22]	<.001
30-44	539	17.28	[12.40, 24.09]	<.001	232	13.34	[9.45, 18.82]	<.001	144	3.46	[2.86, 4.17]	<.001
45-59	1,472	9.68	[7.12, 13.15]	<.001	468	8.00	[6.39, 9.94]	<.001	288	3.13	[2.79, 3.52]	<.001
60-74	2,110	5.79	[4.25, 7.90]	<.001	436	4.55	[3.47, 5.95]	<.001	276	2.46	[2.23, 2.70]	<.001
75-89	2,212	5.50	[3.97, 7.60]	<.001	557	4.40	[3.31, 5.84]	<.001	313	2.31	[2.08, 2.55]	<.001
90-105	2,414	3.71	[2.70, 5.09]	<.001	439	3.04	[2.35, 3.93]	<.001	252	1.88	[1.71, 2.07]	<.001
Model 3 Dietary sodium, odds ratio	11,560				2,616				1,587			
per mg sodium/day		1.00	[1.00, 1.00]	.030		1.00	[1.00, 1.00]	<.001		1.00	[1.00, 1.00]	.565
per 200 mg sodium/day		0.98	[0.98, 0.99]	.030		0.98	[0.98, 0.99]	<.001		1.00	[1.00, 1.01]	.565

Variable	120-139 mmHg sys. or 80-89 mmHg dias. n = 11,560				140-159 mmHg sys. or 90-99 mmHg dias. n = 2,616				≥ 160 mmHg sys. or ≥ 100 mmHg dias. n = 1,587			
	n	*OR*	95% CI	*p*-value	*n*	*OR*	95% CI	*p*-value	*n*	*OR*	95% CI	*p*-value
per g NaCl/day		0.97	[0.95, 0.99]	.030		0.97	[0.95, 0.98]	<.001		1.00	[0.99, 1.01]	.565
Kidney function level[a], ml/min/1.73m^2 > 105 ml/min/1.73m^2 referent												
<15 or dialysis	38	29.64	[12.87, 68.25]	<.001	19	6.87	[2.91, 16.18]	<.001	26	1.77	[0.93, 3.40]	.084
15-29	94	32.02	[20.37, 50.34]	<.001	64	17.66	[11.23, 27.77]	<.001	59	2.025	[1.41, 2.90]	<.001
30-44	539	25.33	[17.36, 36.96]	<.001	232	15.09	[10.59, 21.50]	<.001	144	3.088	[2.48, 3.84]	<.001
45-59	1,472	16.24	[11.33, 23.28]	<.001	468	9.84	[7.90, 12.27]	<.001	288	2.89	[2.52, 3.31]	<.001
60-74	2,110	9.41	[6.73, 13.17]	<.001	436	5.60	[4.30, 7.30]	<.001	276	2.39	[2.14, 2.66]	<.001
75-89	2,212	7.40	[5.34, 10.24]	<.001	557	4.91	[3.68, 6.55]	<.001	313	2.33	[2.09, 2.60]	<.001
90-105	2,414	4.85	[3.49, 6.74]	<.001	439	3.41	[2.65, 4.38]	<.001	252	1.93	[1.75, 2.13]	<.001
Gender, male	6,707	0.73	[0.58 0.90]	.005	1,312	0.94	[0.80, 1.10]	.425	694	1.50	[1.38, 1.64]	<.001

Variable	120-139 mmHg sys. or 80-89 mmHg dias. n = 11,560				140-159 mmHg sys. or 90-99 mmHg dias. n = 2,616				≥ 160 mmHg sys. or ≥ 100 mmHg dias. n = 1,587			
	n	*OR*	95% CI	*p*-value	*n*	*OR*	95% CI	*p*-value	*n*	*OR*	95% CI	*p*-value
Non-Hispanic Black	5,505	2.99	[2.41, 3.72]	<.001	1,287	2.02	[1.65, 2.46]	<.001	677	1.58	[1.40, 1.78]	<.001
Mexican American	1,721	0.97	[0.73, 1.29]	.834	372	0.75	[0.58, 0.96]	.023	251	0.84	[0.73, 0.96]	.013
Other race	1,699	1.17	[0.91, 1.50]	.225	314	0.88	[0.71, 1.10]	.258	296	0.95	[0.85, 1.08]	.437
Education												
<HS	3,092	2.27	[1.76, 2.93]	<.001	864	2.22	[1.82, 2.70]	<.001	598	1.68	[1.49, 1.90]	<.001
HS or equivalent	2,773	1.96	[1.51, 2.55]	<.001	673	1.75	[1.44, 2.13]	<.001	417	1.43	[1.25, 1.64]	<.001
Some college	3,335	1.42	[1.09, 1.86]	.011	675	1.39	[1.17, 1.66]	<.001	357	1.33	[1.19, 1.48]	<.001
Income												
<$20,000	2,799	2.36	[1.82, 3.06]	<.001	755	1.23	[1.00, 1.52]	.048	575	0.91	[0.80, 1.05]	.192
$20,000-<$45,000	3,695	1.91	[1.49, 2.44]	<.001	933	1.39	[1.17, 1.65]	<.001	534	0.93	[0.83, 1.04]	.200
$45,000-<$75,000	2,179	1.53	[1.17, 2.00]	.002	416	1.31	[1.06, 1.62]	.014	233	1.05	[0.93, 1.18]	.416
Model 4 Dietary sodium, odds ratio	11,560				2,616				1,587			

Variable	120-139 mmHg sys. or 80-89 mmHg dias. n = 11,560				140-159 mmHg sys. or 90-99 mmHg dias. n = 2,616				≥ 160 mmHg sys. or ≥ 100 mmHg dias. n = 1,587			
	n	*OR*	95% CI	*p*-value	*n*	*OR*	95% CI	*p*-value	*n*	*OR*	95% CI	*p*-value
per mg sodium/day		1.00	[1.00, 1.00]	0.055		1.00	[1.00, 1.00]	<.001		1.00	[1.00, 1.00]	.938
per 200 mg sodium/day		0.98	[0.98, 1.00]	.055		0.98	[0.98, 0.99]	<.001		1.00	[1.00, 1.01]	.938
per g NaCl/day		0.98	[0.95, 1.01]	.055		0.97	[0.95, 0.99]	<.001		1.00	[0.99, 1.01]	.938
Kidney function level[a], ml/min/1.73m^2												
> 105 ml/min/1.73m^2 referent												
<15 or dialysis	38	11.17	[4.90, 25.47]	<.001	19	2.89	[1.13, 7.40]	.028	26	1.27	[0.64, 2.53]	.492
15-29	94	9.41	[5.55, 15.95]	<.001	64	5.68	[3.45, 9.36]	<.001	59	1.17	[0.78, 1.74]	.450
30-44	539	8.79	[5.74, 13.49]	<.001	232	5.33	[3.58, 7.94]	<.001	144	1.87	[1.48, 2.38]	<.001
45-59	1,472	7.95	[5.44, 11.62]	<.001	468	5.09	[3.98, 6.50]	<.001	288	2.16	[1.87, 2.50]	<.001
60-74	2,110	6.11	[4.34, 8.59]	<.001	436	3.81	[2.91, 4.98]	<.001	276	2.02	[1.80, 2.27]	<.001
75-89	2,212	5.03	[3.62, 6.97]	<.001	557	3.47	[2.60, 4.64]	<.001	313	2.03	[1.82, 2.27]	<.001

Variable	120-139 mmHg sys. or 80-89 mmHg dias. n = 11,560				140-159 mmHg sys. or 90-99 mmHg dias. n = 2,616				≥ 160 mmHg sys. or ≥ 100 mmHg dias. n = 1,587			
	n	*OR*	95% CI	*p*-value	*n*	*OR*	95% CI	*p*-value	*n*	*OR*	95% CI	*p*-value
90-105	2,414	3.81	[2.73, 5.32]	<.001	439	2.78	[2.14, 3.61]	<.001	252	1.77	[1.60, 1.95]	<.001
Gender, male	6,707	0.90	[0.73, 1.11]	.310	1,312	1.13	[0.95, 1.35]	.166	1,312	1.66	[1.51, 1.82]	<.001
Non-Hispanic Black	5,505	2.41	[1.92, 3.03]	<.001	1,287	1.62	[1.32, 2.00]	<.001	1,287	1.36	[1.20, 1.54]	<.001
Mexican American	1,721	0.93	[0.68, 1.28]	.659	372	0.75	[0.59, 0.97]	.026	372	0.79	[0.68, 0.92]	.003
Other race	1,699	1.17	[0.90, 1.53]	.236	314	0.91	[0.73, 1.15]	.424	314	0.99	[0.87, 1.13]	.905
Education												
<HS	3,092	1.99	[1.52, 2.59]	<.001	864	1.89	[1.54, 2.32]	<.001	864	1.55	[1.37, 1.77]	<.001
HS or equivalent	2,773	1.79	[1.37, 2.34]	<.001	673	1.59	[1.30, 1.95]	<.001	673	1.32	[1.14, 1.52]	<.001
Some college	3,335	1.35	[1.02, 1.78]	.034	675	1.29	[1.08, 1.55]	.006	675	1.24	[1.10, 1.39]	<.001
Income												
<$20,000	2,799	2.28	[1.74, 2.98]	<.001	755	1.21	[0.97, 1.50]	.084	755	0.92	[0.80, 1.06]	.232
$20,000-<$45,000	3,695	1.82	[1.42, 2.35]	<.001	933	1.32	[1.11, 1.56]	.002	933	0.91	[0.81, 1.01]	.082
$45,000-<$75,000	2,179	1.491	[1.13, 1.96]	.005	416	1.261	[1.02, 1.56]	.033	416	1.025	[0.91, 1.16]	.688

Variable	120-139 mmHg sys. or 80-89 mmHg dias. n = 11,560				140-159 mmHg sys. or 90-99 mmHg dias. n = 2,616				≥ 160 mmHg sys. or ≥ 100 mmHg dias. n = 1,587			
	n	*OR*	95% CI	*p*-value	*n*	*OR*	95% CI	*p*-value	*n*	*OR*	95% CI	*p*-value
BMI (kg/m^2)	11,450	1.027	[1.01, 1.04]	.003	2,571	1.033	[1.02, 1.05]	<.001	1,555	1.050	[1.04, 1.06]	<.001
Evidence of diabetes	2,336	1.710	[1.35, 2.17]	<.001	793	1.543	[1.28, 1.86]	<.001	488	1.183	[1.04, 1.34]	.007
Antihypertensive agents	4,146	2.93	[2.35, 3.67]	<.001	1,475	3.015	[2.52, 3.61]	<.001	922	1.683	[1.51, 1.88]	<.001
Former smoker	3,327	1.018	[0.84, 1.24]	.857	902	1.150	[0.98, 1.35]	.084	477	1.071	[0.97, 1.19]	.188
Current smoker	2,267	0.80	[0.63, 1.02]	.069	414	0.90	[0.71, 1.13]	.356	263	0.94	[0.83, 1.05]	.268

Note: BMI = body mass index, CI = confidence interval, dias = diastolic blood pressure, HS = high school, NaCl = sodium chloride, NHANES = National Health and Nutrition Examiniation Survey, OR = odds ratio, sys = systolic blood pressure

[a]Estimated glomerular filtration rate using the CKD-Epi equation (Levey et al., 2009)

E – DIETARY SODIUM AND BLOOD PRESSURE ACCORDING TO KIDNEY FUNCTION LEVEL GROUPING

Appendix Table E1.
Dietary sodium according to kidney function level grouping of adults in NHANES 2003-2014

Kidney function, ml/min/1.73m^2	N	Mean (SE)	[95% CI]	Median	[IQR]
<15	117	2,638 (137)	[2,367, 2,910]	2,330	[1,728, 3,307]
15 to 29	301	2,707 (75)	[2,558, 2,856]	2,587	[1,780, 3,352]
30 to 44	1,240	3,067 (67)	[2,934, 3,201]	2,825	[1,997, 3,842]
45 to 59	3,181	3,648 (54)	[3,542, 3,755]	3,388	[2,364, 4,562]
60 to 74	4,503	3,779 (39)	[3,701, 3,858]	3,402	[2,431, 4,755]
75 to 89	4,936	3,439 (33)	[3,374, 3,503]	3,126	[2,252, 4,285]
90 to 105	5,627	3,507 (30)	[3,447, 3,503]	3,161	[2,289, 4,309]
>105	6,685	3,485 (30)	[3,426, 3,545]	3,207	[2,266, 4,373]

Note. CI = confidence interval, IQR=interquartile range, NHANES = National Health and Nutrition Examination Survey

Appendix Table E2.
Dietary sodium according to kidney function level grouping of adults in NHANES 2003-2014 who were not prescribed antihypertensive agents

Kidney function, ml/min/1.73m^2	N	Mean (SE)	[95% CI]	Median	[IQR]
<30	54	2,593 (164)	[2,266, 2,919]	2,425	[2,130, 3,341]
30 to 44	271	3,128 (161)	[2,809, 3,447]	3,031	[1,840, 4,012]
45 to 59	1,427	3,958 (74)	[3,811, 4,105]	3,734	[2,713, 4,905]
60 to 74	2,969	3,943 (46)	[3,851, 4,035]	3,580	[2,598, 4,927]
75 to 89	3,202	3,533 (41)	[3,452, 3,614]	3,204	[2,308, 4,452]
90 to 105	4,322	3,532 (33)	[3,466, 3,560]	3,208	[2,309, 4,333]
>105	6,035	3,502 (30)	[3,442, 3,562]	3,230	[2,290, 4,391]

Note. CI = confidence interval, IQR=interquartile range, NHANES = National Health and Nutrition Examination Survey

Appendix Table E3.
Dietary sodium according to kidney function level grouping of adults in NHANES 2003-2014 who were prescribed antihypertensive agents

Kidney function, ml/min/1.73m^2	N	Mean (SE)	[95%CI]	Median	[IQR]
<30	364	2,703 (76)	[2,551, 2,854]	2,517	[1,760, 3,353]
30 to 44	969	3,049 (69)	[2,912, 3,187]	2,796	[2,040, 3,774]
45 to 59	1,754	3,303 (66)	[3,171, 3,434]	3,013	[2,107, 4,136]
60 to 74	1,534	3,344 (62)	[3,222, 3,467]	2,990	[2,141, 4,142]
75 to 89	1,734	3,221 (50)	[3,121, 3,321]	2,929	[2,143, 3,944]
90 to 105	1,305	3,407 (72)	[3,264, 3,550]	3,030	[2,231, 4,177]
>105	650	3,294 (101)	[3,095, 3,494]	2,960	[2,066, 4,242]

Note. CI = confidence interval, IQR=interquartile range, NHANES = National Health and Nutrition Examination Survey

Appendix Table E4.
Blood pressure according to kidney function level grouping of adults in NHANES 2003-2014

Kidney function, ml/min/1.73m^2	N	Mean (SE)	[95% CI]	Median	[IQR]
		Systolic blood pressure, mmHg			
<15	117	135.1 (3.3)	[128.6, 141.6]	133.8	[113.4, 153.0]
15 to 29	301	136.7 (2.0)	[132.7, 140.7]	135.7	[117.5, 153.4]
30 to 44	1,240	131.7 (0.7)	[130.3, 133.0]	129.0	[116.6, 142.4]
45 to 59	3,181	127.7 (0.5)	[126.7, 128.6]	125.1	[115.1, 137.6]
60 to 74	4,503	124.0 (0.4)	[123.2, 124.8]	121.2	[113.1, 131.9]
75 to 89	4,936	123.8 (0.4)	[123.1, 124.5]	121.2	[111.7, 133.1]
90 to 105	5,627	121.5 (0.4)	[120.6, 122.3]	119.1	[109.7, 129.8]
>105	6,685	115.4 (0.3)	[114.9, 115.9]	113.3	[105.8, 122.1]
		Diastolic blood pressure, mmHg			
<15	117	67.0 (1.8)	[63.4, 70.6]	66.1	[54.4, 75.6]
15 to 29	301	60.8 (1.0)	[58.8, 62.9]	60.1	[52.5, 70.3]
30 to 44	1,240	65.9 (0.5)	[64.9, 66.9]	65.5	[57.3, 73.9]
45 to 59	3,181	71.1 (0.3)	[70.5, 71.7]	71.3	[63.7, 79.3]
60 to 74	4,503	72.6 (0.3)	[72.1, 73.2]	72.5	[65.3, 79.2]
75 to 89	4,936	71.0 (0.3)	[70.4, 71.6]	71.2	[63.6, 77.6]
90 to 105	5,627	72.3 (0.3)	[71.8, 72.9]	71.9	[65.2, 78.5]
>105	6,685	68.9 (0.2)	[68.4, 69.3]	68.5	[61.7, 75.3]

Note. CI = confidence interval, IQR=interquartile range, NHANES = National Health and Nutrition Examination Survey

Appendix Table E5.
Blood pressure according to kidney function level grouping of adults in NHANES 2003-2014 who were not prescribed antihypertensive agents

Kidney function, ml/min/1.73m^2	N	Mean (SE)	[95% CI]	Median	[IQR]
		Systolic blood pressure			
<30	54	134.4 (4.3)	[125.7, 143.0]	130.1	[112.7, 146.2]
30 to 44	271	128.3 (1.8)	[124.7, 131.9]	124.2	[115.9, 137.8]
45 to 59	1,427	125.4 (0.7)	[124.1, 126.7]	121.9	[114.2, 133.1]
60 to 74	2,969	121.5 (0.4)	[120.8, 122.3]	119.2	[111.6, 128.2]
75 to 89	3,202	120.9 (0.4)	[120.2, 121.6]	118.4	[110.1, 108.6]
90 to 105	4,322	119.6 (0.5)	[118.7, 120.6]	117.1	[108.6, 127.5]
>105	6,035	114.5 (0.3)	[114.0, 115.0]	112.6	[105.4, 121.1]
		Diastolic blood pressure			
<30	54	66.3 (2.2)	[62.0, 70.6]	65.7	[58.9, 75.3]
30 to 44	271	70.8 (0.9)	[69.0, 72.6]	70.7	[63.4, 77.5]
45 to 59	1,427	73.7 (0.3)	[72.9, 74.4]	73.6	[67.2, 81.2]
60 to 74	2,969	73.2 (0.3)	[72.6, 73.7]	73.0	[65.9, 79.2]
75 to 89	3,202	71.0 (0.4)	[70.3, 71.7]	71.1	[63.7, 77.4]
90 to 105	4,322	72.1 (0.3)	[71.5, 72.7]	71.6	[65.1, 78.2]
>105	6,035	68.4 (0.2)	[67.9, 68.8]	67.9	[61.4, 74.6]

Note. CI = confidence interval, IQR=interquartile range, NHANES = National Health and Nutrition Examination Survey

Appendix Table E6.
Blood pressure according to kidney function level grouping of adults in NHANES 2003-2014 who were prescribed antihypertensive agents

Kidney function, ml/min/1.73m^2	N	Mean (SE)	[95% CI]	Median	[IQR]
		Systolic blood pressure			
<30	364	136.6 (1.7)	[133.2, 139.9]	135.8	[116.0, 153.6]
30 to 44	969	132.7 (0.8)	[131.1, 134.3]	130.4	[117.5, 143.9]
45 to 59	1,754	130.2 (0.6)	[129.0, 131.4]	128.5	[116.3, 140.8]
60 to 74	1,534	130.6 (0.8)	[129.1, 132.1]	129.1	[117.7, 140.2]
75 to 89	1,734	130.6 (0.6)	[129.4, 131.7]	128.3	[117.2, 141.1]
90 to 105	1,305	128.8 (0.7)	[127.4, 130.2]	126.0	[116.3, 137.3]
>105	650	126.4 (0.9)	[124.6, 128.2]	123.6	[113.8, 135.2]
		Diastolic blood pressure			
<30	364	61.9 (1.0)	[59.9, 63.8]	60.7	[53.0, 71.0]
30 to 44	969	64.4 (0.5)	[63.4, 65.5]	64.0	[55.6, 72.4]
45 to 59	1,754	68.2 (0.4)	[67.4, 69.1]	68.4	[59.5, 77.1]
60 to 74	1,534	71.2 (0.5)	[70.1, 72.2]	71.6	[63.6, 79.3]
75 to 89	1,734	71.0 (0.4)	[70.1, 71.8]	71.5	[63.6, 78.2]
90 to 105	1,305	73.2 (0.4)	[72.4, 74.0]	73.4	[65.4, 79.7]
>105	650	74.9 (0.7)	[73.6, 76.3]	74.7	[67.3, 81.7]

Note. CI = confidence interval, IQR=interquartile range, NHANES = National Health and Nutrition Examination Survey

F – DIETARY SODIUM DENSITY REPORT

The relationship between key demographic and clinical characteristics and dietary sodium density in U.S. nonpregnant adults in NHANES 2003-2014

Variable	n	*r*	*B*	*SE*	95% CI	*p*-value
Age, years	27,943	.024	0.79	0.25	[0.29, 1.29]	.002
Gender, females referent	13,849					
Males	14,094	.014	-15.29	8.88	[-32.92, 2.34]	.088
Race, ethnicity; Non-Hispanic White referent	13,199	.080				<.001
Non-Hispanic black	5,862		-61.93	12.23	[-86.21, -37.66]	<.001
Mexican American	4,525		-60.49	14.72	[-89.73, -31.26]	<.001
Other	4,357		111.57	18.61	[74.62, 148.53]	<.001
Education, College degree or higher referent	6,018	.047				<.001
Less than HS	7,343		-77.56	12.78	[-102.94, -52.19]	<.001
HS or equivalent	6,545		-50.29	15.11	[-80.29, -20.29]	.001
Some college or AA	8,011		-35.98	12.80	[-61.40, -10.55]	.006
Income, $75,000/year or higher referent	6,044	.054				<.001
<$20,000	7,063		-76.26	13.53	[-103.13, -49.40]	<.001
$20,000 to <$45,000	9,041		-61.37	14.16	[-83.48, -33.25]	<.001
$45,000 to <$75,000	4,916		-22.52	16.60	[-55.48, 10.45]	.178
ACR (mg/g)	27,568	.016	0.04	0.02	[0.01, 0.07]	.024
BMI (kg/m^2)	27,664	.061	5.25	0.78	[3.71, 6.79]	<.001

Variable	n	*r*	*B*	*SE*	95% CI	*p*-value
BMI category, 18.5-24.9 kg/m^2 referent	7,789	.060				<.001
<18.5	433		-128.63	35.17	[-198.45, -58.81]	<.001
25.0 to <30.0	9,344		8.38	13.08	[-17.60, 34.35]	.524
≥30.0	10,098		63.53	13.42	[36.88, 90.17]	<.001
Evidence of diabetes, No evidence referent	21,816	.071				<.001
Yes	5,001		116.87	12.99	[91.08, 142.66]	<.001
High blood pressure awareness	10,029	.031	37.71	10.48	[16.90, 58.53]	<.001
Taking antihypertensive agents, None referent	8,786	.055	70.93	11.85	[47.41, 94.45]	<.001
Number of antihypertensive agents used, None referent	19,157	.057				<.001
1	4,489		64.44	13.97	[36.71, 92.17]	<.001
2	2,540		66.58	16.22	[34.38, 98.77]	<.001
3 or more	1,757		98.16	21.50	[55.47, 140.85]	<.001
Type of antihypertensive agent used, None referent	19,157	.064				<.001
Diuretics alone	720		-26.72	24.43	[-75.23, 21.78]	.277
Set A	4,086		75.75	15.35	[45.29, 106.22]	<.001
Set B	3,266		96.93	15.07	[67.01, 126.86]	<.001
Set C	714		33.36	29.09	[-24.40, 91.11]	.254
Blood pressure category, 120/80 mmHg referent	12,180	.013				.025
120-139 mmHg sys. or 80-89 mmHg dias.	11,560		-13.77	11.38	[-36.36, 8.82]	.229
140-159 mmHg sys. or 90-99 mmHg dias.	2,616		1.38	17.12	[-32.60, 35.36]	.936
≥ 160 mmHg sys. or ≥ 100 mmHg dias.	1,587		9.02	21.87	[-34.40, 52.45]	.681
eGFR (ml/min/1.73m^2)	26,590	.015	-0.35	0.21	[-0.75, 0.06]	.096
Kidney disease awareness	808	.004	15.97	26.35	[-36.35, 68.29]	.546

Variable	n	*r*	*B*	*SE*	95% CI	*p*-value
Kidney function level, >105ml/min/1.73m^2 referent	6,685	.024				<.001
<15 or dialysis	117		136.61	50.49	[36.37, 236.86]	.008
15 to 29	301		87.43	42.07	[3.90, 170.97]	.040
30 to 44	1,240		28.77	20.46	[-11.85, 69.40]	.163
45 to 59	3,181		27.60	17.13	[-6.41, 61.61]	.110
60 to 74	4,503		23.78	13.44	[-2.90, 50.45]	.080
75 to 89	4,936		6.06	13.38	[-20.52, 32.63]	.652
90 to 105	5,627		14.78	14.51	[-14.03, 43.60]	.311
Evidence of CKD	4,839	.014	21.03	12.92	[-4.61, 46.68]	.107
Smoking status, Never smoker referent	14,860	.079				<.001
Former smoker	7,444		-5.05	10.26	[-25.42, 15.32]	.624
Current smoker	5,585		-111.18	11.07	[-133.16, -89.20]	<.001

Note. AA = Associate of Arts degree; ACR = albumin-to-creatinine ratio; *B* = parameter estimate; BMI = body mass index; CI = confidence interval; dias. = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HS = high school; NHANES = National Health and Nutrition Examination Survey; *r* = correlation coefficient; *SE* = standard error of the mean; Set A. = renin-aldosterone inhibitors, calcium channel blockers, beta blockers or any combination of these; Set B. = diuretics plus renin-aldosterone inhibitors, calcium channel blockers, or beta blockers; Set C. = any other antihypertensive agent or any combination of three drugs; sys. = systolic blood pressure. Student's t-test or One-way Analysis of Variance, as appropriate

[a]Estimated glomerular filtration rate using the CKD-Epi equation (Levey et al., 2009)